DRI

DIETARY REFERENCE INTAKES

FOR

Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids

Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes

Food and Nutrition Board

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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Dedication

The Panel on Macronutrients dedicates this report to the late Peter Reeds, a diligent and enthusiastic member of the panel who made significant contributions to this study. His expertise in protein and amino acid metabolism was a special asset to the panel's work, as well as a contribution to the understanding of protein and amino acid requirements.

Preface

This report is one in a series that presents a comprehensive set of reference values for nutrient intakes for healthy U.S. and Canadian individuals and populations. It is a product of the Food and Nutrition Board of the Institute of Medicine (IOM), working in cooperation with Canadian scientists.

The report establishes a set of reference values for dietary energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids to expand and replace previously published Recommended Dietary Allowances (RDAs) and Recommended Nutrient Intakes (RNIs) for the United States and Canada, respectively. Close attention was given throughout the report to the evidence relating macronutrient intakes to risk reduction of chronic disease and to amounts needed to maintain health. Thus, the report includes guidelines for partitioning energy sources (Acceptable Macronutrient Distribution Ranges) compatible with decreasing risks of various chronic diseases. It also provides a definition for dietary fiber.

The groups responsible for developing this report, the Panel on Macronutrients, the Panel on the Definition of Dietary Fiber, the Subcommittee on Upper Reference Levels of Nutrients (UL Subcommittee), the Subcommittee on Interpretation and Uses of Dietary Reference Intakes (Uses Subcommittee), and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee), have analyzed the evidence on risks and beneficial effects of nutrients and other food components included in this review.

Although all reference values are based on data, available data were often sparse or drawn from studies with significant limitations in address-

ing various questions confronted by the panel and subcommittees. Thus, although governed by scientific rationales, informed judgments were often required in setting reference values. The reasoning used for each nutrient is described in Chapters 5 through 11. Chapter 13 addresses major conceptual issues related to the uses of the DRIs that were included in the early stages of the DRI process and have been developed further by the Uses Subcommittee.

The quality and quantity of information on overt deficiency diseases for protein, amino acids, and essential fatty acids available to the committee were substantial. Unfortunately, information regarding other nutrients for which their primary dietary importance relates to their roles as energy sources was limited most often to alterations in chronic disease biomarkers that follow dietary manipulations of energy sources.

Given the uniqueness of the nutrients considered in this report (i.e., they or their precursors serve as energy sources and, for this purpose, can substitute for each other in the diet), the inability to determine an Estimated Average Requirement (EAR) or a Tolerable Upper Intake Level (UL) in many cases is not surprising. Also, for most of the nutrients in this report (with a notable exception of protein and some amino acids), there is no direct information that permits estimating the amounts required by children, adolescents, the elderly, or pregnant and lactating women. Similarly, data were exceptionally sparse for setting ULs for the macronutrients. Dose–response studies were either not available or were suggestive of very low intake levels that could result in inadequate intakes of other nutrients. These information gaps and inconsistencies often precluded setting reliable estimates of upper intake levels that can be ingested safely.

The report's attention to energy would be incomplete without its substantial review of the role of daily physical activity in achieving and sustaining fitness and optimal health (Chapter 12). The report provides recommended levels of energy expenditure that are considered most compatible with minimizing risks of several chronic diseases and provides guidance for achieving recommended levels of energy expenditure. Inclusion of these recommendations avoids the tacit false assumption that light sedentary activity is the expected norm in the United States and Canada.

Readers are urged to recognize that the Dietary Reference Intakes (DRI) process is iterative in character. The Food and Nutrition Board and the DRI Committee and its subcommittees and panels fully expect that the DRI conceptual framework will evolve and be improved as novel information becomes available and is applied to an expanding list of nutrients and other food components. Thus, because the DRI activity is ongoing, comments were solicited widely and received on the published reports of this series. Refinements that resulted from this iterative process were included in the general information regarding approaches used (Chapters 1

through 4) and in the discussion of uses of DRIs (Chapter 13). With more experience, the proposed models for establishing reference intakes of nutrients and other food components that play significant roles in promoting and sustaining health and optimal functioning will be refined. Also, as new information or new methods of analysis are adopted, these reference values undoubtedly will be reassessed.

Many of the questions that were raised about requirements and recommended intakes could not be answered satisfactorily for the reasons given above. Thus, among the panel's major tasks was to outline a research agenda addressing information gaps uncovered in its review (Chapter 14). The research agenda is anticipated to help future policy decisions related to these and future recommendations. This agenda and the critical, comprehensive analyses of available information are intended to assist the private sector, foundations, universities, governmental and international agencies and laboratories, and other institutions in the development of their respective research priorities for the next decade.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Arne Astrup, The Royal Veterinary and Agricultural University; George Blackburn, Beth Israel Deaconess Medical Center; Elsworth Buskirk, Pennsylvania State University; William Connor, Oregon Health and Science University; John Hathcock, Council for Responsible Nutrition; Satish Kalhan, Case Western Reserve University School of Medicine; Martijn Katan, Wageningen Agricultural University; David Kritchevsky, The Wistar Institute; Shiriki Kumanyika, University of Pennsylvania School of Medicine; William Lands, National Institutes of Health; Geoffrey Livesey, Independent Nutrition Logic; Ross Prentice, Fred Hutchinson Cancer Research Center; Barbara Schneeman, University of California, Davis; Christopher Sempos, State University of New York, Buffalo; Virginia Stallings, Children's Hospital of Philadelphia; Steve Taylor, University of Nebraska; Daniel Tomé, Institut National Agronomique Paris-Grinon; and Walter Willett, Harvard School of Public Health.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Catherine Ross, Pennsylvania State University and Irwin Rosenberg, Tufts University, appointed by the Institute of Medicine, who were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The Food and Nutrition Board gratefully acknowledges the Canadian government's support and Canadian scientists' participation in this initiative. This close collaboration represents a pioneering first step in the harmonization of nutrient reference intakes in North America. A description of the overall DRI project and of the panel's task is given in Appendix B.

The Food and Nutrition Board joins the DRI Committee, the Panel on Macronutrients, the Panel on the Definition of Dietary Fiber, the UL Subcommittee, and the Uses Subcommittee in extending sincere appreciation to the many experts who assisted with this report by giving presentations to the various groups charged with its development, providing written materials, participating in the groups' open discussions, analyzing data, and other means. Many, but far from all, of these individuals are named in Appendix C. Special gratitude is extended to the staff at ENVIRON International Corporation for providing national survey data.

The respective chairs and members of the Panel on Macronutrients and subcommittees performed their work under great time pressures. Their dedication made the report's timely completion possible. All gave their time and hard work willingly and without financial reward; the public and the science and practice of nutrition are among the major beneficiaries of their dedication. The Food and Nutrition Board thanks these individuals, and especially the staff responsible for its development—in particular, Paula Trumbo for coordinating this complex report, and Sandra Schlicker, who served as a program officer for the study. The intellectual and managerial contributions made by these individuals to the report's comprehensiveness and scientific base were critical to fulfilling the project's mandate. Sincere thanks also go to other FNB staff, including Alice Vorosmarti, Kimberly Stitzel, Carrie Holloway, Gail Spears, Sandra Amamoo-Kakra, and Michele Ramsey, all of whom labored over nearly three years of work to complete this document.

And last, but certainly not least, the Food and Nutrition Board wishes to extend special thanks to Sandy Miller, who initially served as chair of the Panel on Macronutrients; Joanne Lupton, who subsequently assumed the role of chair of the panel and continued in that role through the

study's completion; and Vernon Young, who served as chair of the DRI Committee since the inception of the overall DRI activity. Professor Young's dedication to this and earlier DRI activities and his uncompromising standards for scientific rigor are most gratefully acknowledged.

Cutberto Garza
Chair, Food and Nutrition Board

Contents

SUMMARY **1**

1 INTRODUCTION TO DIETARY REFERENCE INTAKES **21**
What Are Dietary Reference Intakes? 21
Categories of Dietary Reference Intakes, 22
Determination of Adequacy, 28
Parameters for Dietary Reference Intakes, 29
Summary, 36
References, 36

2 METHODS AND APPROACHES USED **38**
Overview, 38
Types of Data Used, 39
Methods to Determine the Adequate Intake for Infants, 44
Methods to Determine the Dietary Requirements for Children and Adults, 46
Estimates of Nutrient Intake, 48
Dietary Intakes in the United States and Canada, 49
Summary, 50
References, 50

3 RELATIONSHIP OF MACRONUTRIENTS AND PHYSICAL ACTIVITY TO CHRONIC DISEASE **53**
Overview, 53
Cancer, 53
Heart Disease, 57

Dental Caries, 61
Type 2 Diabetes Mellitus, 62
Obesity, 64
Skeletal Health, 66
Summary, 66
References, 66

4 A MODEL FOR THE DEVELOPMENT OF TOLERABLE UPPER INTAKE LEVELS 84
Background, 84
A Model for the Derivation of Tolerable Upper Intake Levels, 85
Risk Assessment and Food Safety, 86
Application of the Risk Assessment Model to Nutrients, 91
Steps in the Development of the Tolerable Upper Intake Level, 94
Intake Assessment, 104
Risk Characterization, 104
References, 105

5 ENERGY 107
Summary, 107
Background Information, 108
Selection of Indicators for Estimating the Requirement for Energy, 117
Factors Affecting Energy Expenditure and Requirements, 131
Approach Used to Determine Total Energy Expenditure, 151
Findings by Life Stage and Gender Group, 164
Adverse Effects of Overconsumption of Energy, 223
Research Recommendations, 225
References, 240

6 DIETARY CARBOHYDRATES: SUGARS AND STARCHES 265
Summary, 265
Background Information, 265
Evidence Considered for Estimating the Average Requirement for Carbohydrate, 277
Findings by Life Stage and Gender Group, 280
Intake of Carbohydrates, 294
Adverse Effects of Overconsumption, 295
Research Recommendations, 323
References, 324

7 DIETARY, FUNCTIONAL, AND TOTAL FIBER 339
Summary, 339
Background Information, 340
Evidence Considered for Estimating the Requirement for *Dietary Fiber* and *Functional Fiber*, 362
Findings by Life Stage and Gender Group, 384
Intake of *Dietary Fiber*, 390
Adverse Effects of Overconsumption, 391
Research Recommendations, 399
References, 400

8 DIETARY FATS: TOTAL FAT AND FATTY ACIDS 422
Summary, 422
Background Information, 424
Evidence Considered for Estimating the Requirements for Total Fat and Fatty Acids, 440
Factors Affecting the Requirements, 447
Findings by Life Stage and Gender Group, 456
Intakes of Total Fat and Fatty Acids, 473
Adverse Effects of Overconsumption, 481
Research Recommendations, 505
References, 515

9 CHOLESTEROL 542
Summary, 542
Background Information, 543
Findings by Life Stage and Gender Group, 546
Intake of Cholesterol, 549
Adverse Effects of Overconsumption, 549
Risk Characterization, 573
Research Recommendations, 574
References, 578

10 PROTEIN AND AMINO ACIDS 589
Summary, 589
Background Information, 590
Selection of Indicators for Estimating the Requirement for Protein (Nitrogen), 610
Selection of Indicators for Estimating the Requirement for Individual Amino Acids, 613
Findings by Life Stage and Gender Group for Total Protein, 619
Findings by Life Stage and Gender Group for Indispensable Amino Acids, 662

Intake of Total Protein and Amino Acids, 682
Tolerable Upper Intake Levels for Protein, 692
Tolerable Upper Intake Levels for Individual Amino Acids, 695
Research Recommendations, 737
References, 738

11 MACRONUTRIENTS AND HEALTHFUL DIETS 769
Summary, 769
Introduction, 770
Dietary Fat and Carbohydrate, 772
n-9 Monounsaturated Fatty Acids, 816
n-6 Polyunsaturated Fatty Acids, 820
n-3 Polyunsaturated Fatty Acids, 826
Saturated Fatty Acids, *Trans* Fatty Acids, and Cholesterol, 835
Conjugated Linoleic Acid, 836
Dietary Fiber and Functional Fiber, 838
Dietary Protein, 839
References, 845

12 PHYSICAL ACTIVITY 880
Summary, 880
Background Information, 881
Physical Activity Level and Energy Balance, 884
Evidence for Healthful Effects of Physical Activity, 912
Balance of Carbohydrate and Lipid Oxidation During Exercise and Recovery, 917
Physical Fitness, 923
Adverse Effects of Excessive Physical Activity, 926
Research Recommendations, 929
References, 929

13 APPLICATIONS OF DIETARY REFERENCE INTAKES FOR MACRONUTRIENTS 936
Overview, 936
Assessing Nutrient Intakes of Individuals, 937
Assessing Nutrient Intakes of Groups, 941
Planning Nutrient Intakes of Individuals, 946
Planning Nutrient Intakes of Groups, 947
Nutrient-Specific Considerations, 949
Integrated Example, 963
Summary, 964
References, 965

14 A RESEARCH AGENDA **968**
Approach, 968
Major Knowledge Gaps, 969
The Research Agenda, 971

APPENDIXES
A Glossary and Acronyms 973
B Origin and Framework of the Development of Dietary Reference Intake 978
C Acknowledgments 985
D Dietary Intake Data from the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 988
E Dietary Intake Data from the Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998 1028
F Canadian Dietary Intake Data, 1990–1997 1066
G Special Analyses for Dietary Fats 1076
H Body Composition Data Based on the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 1078
I Doubly Labeled Water Data Used to Predict Energy Expenditure 1104
J Association of Added Sugars Intake and Intake of Other Nutrients, 1203
K Data Comparing Carbohydrate Intake to Intake of Other Nutrients from the Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998 1226
L Options for Dealing with Uncertainties 1244
M Nitrogen Balance Studies Used to Estimate the Protein Requirements in Adults 1250

BIOGRAPHICAL SKETCHES OF PANEL AND SUBCOMMITTEE MEMBERS 1259

INDEX 1275

SUMMARY TABLES, DIETARY REFERENCE INTAKES 1319

Summary

This is one volume in a series of reports that presents dietary reference values for the intake of nutrients by Americans and Canadians. This report provides Dietary Reference Intakes (DRIs) for energy and the macronutrients carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. While the role of ethanol in macronutrient metabolism and energy is briefly discussed in this report, its role in chronic diseases will be reviewed in a future DRI report.

The development of DRIs expands and replaces the series of reports called *Recommended Dietary Allowances* (RDAs) published in the United States and *Recommended Nutrient Intakes* (RNIs) in Canada. A major impetus for the expansion of this review is the growing recognition of the many uses to which RDAs and RNIs have been applied and the growing awareness that many of these uses require the application of statistically valid methods that depend on reference values other than RDAs. This report includes a review of the roles that macronutrients are known to play in traditional deficiency diseases as well as chronic diseases.

The overall project is a comprehensive effort undertaken by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, the National Academies, in collaboration with Health Canada (see Appendix B for a description of the overall process and its origins). This study was requested by the Federal Steering Committee for Dietary Reference Intakes, which is coordinated by the Office of Disease Prevention and Health Promotion of the U.S. Department of Health and Human Services, in collaboration with Health Canada.

Major new approaches and findings in this report include the following:

- The establishment of Estimated Energy Requirements (EER) at four levels of energy expenditure (Chapter 5).
- Recommendations for levels of physical activity associated with a normal body mass index range (Chapter 12).
- The establishment of RDAs for dietary carbohydrate (Chapter 6) and protein (Chapter 10).
- The development of the definitions *Dietary Fiber*, *Functional Fiber*, and *Total Fiber* (Chapter 7).
- The establishment of Adequate Intakes (AI) for *Total Fiber* (Chapter 7).
- The establishment of AIs for linoleic and α-linolenic acids (Chapter 8).
- Acceptable Macronutrient Distribution Ranges as a percent of energy intake for fat, carbohydrate, linoleic and α-linolenic acids, and protein (Chapter 11).
- Research recommendations for information needed to advance the understanding of human energy and macronutrient requirements and the adverse effects associated with intake of higher amounts (Chapter 14).

APPROACH FOR SETTING DIETARY REFERENCE INTAKES

The scientific data used to develop Dietary Reference Intakes (DRIs) have come from observational and experimental studies. Studies published in peer-reviewed journals were the principal source of data. Life stage and gender were considered to the extent possible, but the data did not provide a basis for proposing different requirements for men, for pregnant and nonlactating women, and for nonpregnant and nonlactating women in different age groups for many of the macronutrients. Three of the categories of reference the values—the Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), and Estimated Energy Requirement (EER)—are defined by specific criteria of nutrient adequacy; the third, the Tolerable Upper Intake Level (UL), is defined by a specific endpoint of adverse effect, when one is available (see Box S-1). In all cases, data were examined closely to determine whether a functional endpoint could be used as a criterion of adequacy. The quality of studies was examined by considering study design; methods used for measuring intake and indicators of adequacy; and biases, interactions, and confounding factors.

Although the reference values are based on data, the data were often scanty or drawn from studies that had limitations in addressing the various questions that confronted the panel. Therefore, many of the questions raised about the requirements for, and recommended intakes of, these macronutrients cannot be answered fully because of inadequacies in the present database. Apart from studies of overt deficiency diseases, there is a

BOX S-1
Dietary Reference Intakes

Recommended Dietary Allowance (RDA): *the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group.*

Adequate Intake (AI): *the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate—used when an RDA cannot be determined.*

Tolerable Upper Intake Level (UL): *the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.*

Estimated Average Requirement (EAR): *the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group.*[a]

[a] In the case of energy, an Estimated Energy Requirement (EER) is provided. The EER is the average dietary energy intake that is predicted to maintain energy balance in a healthy adult of a defined age, gender, weight, height, and level of physical activity consistent with good health. In children and pregnant and lactating women, the EER is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.

dearth of studies that address specific effects of inadequate intakes on specific indicators of health status, and a research agenda is proposed (see Chapter 14). The reasoning used to establish the values is described for each nutrient in Chapters 5 through 10. While the various recommendations are provided as single-rounded numbers for practical considerations, it is acknowledged that these values imply a precision not fully justified by the underlying data in the case of currently available human studies.

Except for fiber, the scientific evidence related to the prevention of chronic degenerative disease was judged to be too nonspecific to be used as the basis for setting any of the recommended levels of intake for the nutrients. The indicators used in deriving the EARs, and thus the RDAs, are described below.

NUTRIENT FUNCTIONS AND THE INDICATORS USED TO ESTIMATE REQUIREMENTS

Energy is required to sustain the body's various functions, including respiration, circulation, physical work, and protein synthesis. This energy is supplied by carbohydrates, proteins, fats, and alcohol in the diet. The energy balance of an individual depends on his or her dietary energy intake and energy expenditure. The Estimated Energy Requirement (EER) is defined as the average dietary energy intake that is predicted to maintain energy balance in a healthy adult of a defined age, gender, weight, height, and level of physical activity, consistent with good health (Table S-1). In children and pregnant and lactating women, the EER is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health. While EERs can be estimated for four levels of activity from the equations provided, the *active* physical activity level is recommended to maintain health.

Carbohydrates (sugars and starches) provide energy to cells in the body, particularly the brain, which is a carbohydrate-dependent organ. An Estimated Average Requirement (EAR) for carbohydrate is established based on the average amount of glucose utilized by the brain. The Recommended Dietary Allowance (RDA) for carbohydrate is set at 130 g/d for adults and children (Table S-2). There was insufficient evidence to set a daily intake of sugars or added sugars that individuals should aim for.

Dietary Fiber is defined as nondigestible carbohydrates and lignin that are intrinsic and intact in plants. *Functional Fiber* is defined as isolated, nondigestible carbohydrates that have been shown to have beneficial physiological effects in humans. *Total Fiber* is the sum of *Dietary Fiber* and *Functional Fiber*. Viscous fibers delay the gastric emptying of ingested foods into the small intestine, which can result in a sensation of fullness. This delayed emptying effect also results in reduced postprandial blood glucose concentrations. Viscous fibers can also interfere with the absorption of dietary fat and cholesterol, as well as the enterohepatic recirculation of cholesterol and bile acids, which may result in reduced blood cholesterol concentrations. An Adequate Intake (AI) for *Total Fiber* is set at 38 and 25 g/d for men and women ages 19 to 50, respectively (Table S-3).

Fat is a major source of fuel energy for the body and aids in the absorption of fat-soluble vitamins and other food components such as carotenoids. Because the percent of energy that is consumed as fat can vary greatly while still meeting daily energy needs, neither an AI nor EAR is set for adults (the AI for infants is given in Table S-4). *Saturated fatty acids*, *monounsaturated fatty acids*, and *cholesterol* are synthesized by the body and have no known beneficial role in preventing chronic diseases, and thus are not required in the diet. Therefore, no AI, EAR, or RDA is set. The *n-6*

TABLE S-1 Criteria and Dietary Reference Intake Values for Energy by Active Individuals by Life Stage Group[a]

		Active PAL EER[b] (kcal/d)	
Life Stage Group	Criterion	Male	Female
0 through 6 mo	Energy expenditure plus energy deposition	570	520 (3 mo)
7 through 12 mo	Energy expenditure plus energy deposition	743	676 (9 mo)
1 through 2 y	Energy expenditure plus energy deposition	1,046	992 (24 mo)
3 through 8 y	Energy expenditure plus energy deposition	1,742	1,642 (6 y)
9 through 13 y	Energy expenditure plus energy deposition	2,279	2,071 (11 y)
14 through 18 y	Energy expenditure plus energy deposition	3,152	2,368 (16 y)
> 18 y	Energy expenditure	3,067[c]	2,403[c] (19 y)
Pregnancy			
14 through 18 y	Adolescent female EER plus change in Total Energy Expenditure (TEE) plus pregnancy energy deposition		
1st trimester			2,368 (16 y)
2nd trimester			2,708 (16 y)
3rd trimester			2,820 (16 y)
19 through 50 y	Adult female EER plus change in TEE plus pregnancy energy deposition		
1st trimester			2,403[c] (19 y)
2nd trimester			2,743[c] (19 y)
3rd trimester			2,855[c] (19 y)
Lactation			
14 through 18 y	Adolescent female EER plus milk energy output minus weight loss		
1st 6 mo			2,698 (16 y)
2nd 6 mo			2,768 (16 y)
19 through 50 y	Adult female EER plus milk energy output minus weight loss		
1st 6 mo			2,733[c] (19 y)
2nd 6 mo			2,803[c] (19 y)

[a] For healthy active Americans and Canadians. Based on the cited age, an active physical activity level, and the reference heights and weights cited in Table 1-1. Individualized EERs can be determined by using the equations in Chapter 5.
[b] PAL = Physical Activity Level, EER = Estimated Energy Requirement. The intake that meets the average energy expenditure of individuals at the reference height, weight, and age (see Table 1-1).
[c] Subtract 10 kcal/d for males and 7 kcal/d for females for each year of age above 19 years.

polyunsaturated fatty acid, linoleic acid, is an essential fatty acid. A deficiency of *n*-6 polyunsaturated fatty acids is characterized by rough and scaly skin, dermatitis, and an elevated eicosatrienoic acid:arachidonic acid (triene:tetraene) ratio. The AI for linoleic acid is based on the median

TABLE S-2 Criteria and Dietary Reference Intake Values for Carbohydrate by Life Stage Group

		EAR[a] (g/d)		RDA[b] (g/d)		
Life Stage Group	Criterion	Male	Female	Male	Female	AI[c] (g/d)
0 through 6 mo	Average content of human milk					60
7 through 12 mo	Average intake from human milk plus complementary foods					95
1 through 3 y	Extrapolation from adult data	100	100	130	130	
4 through 8 y	Extrapolation from adult data	100	100	130	130	
9 through 13 y	Extrapolation from adult data	100	100	130	130	
14 through 18 y	Extrapolation from adult data	100	100	130	130	
> 18 y	Brain glucose utilization	100	100	130	130	
Pregnancy						
14 through 18 y	Adolescent female EAR plus fetal brain glucose utilization		135		175	
19 through 50 y	Adult female EAR plus fetal brain glucose utilization		135		175	
Lactation						
14 through 18 y	Adolescent female EAR plus average human milk content of carbohydrate		160		210	
19 through 50 y	Adult female EAR plus average human milk content of carbohydrate		160		210	

[a] EAR = Estimated Average Requirement. The intake that meets the estimated nutrient needs of half the individuals in a group.
[b] RDA = Recommended Dietary Allowance. The intake that meets the nutrient need of almost all (97–98 percent) individuals in a group.
[c] AI = Adequate Intake: the observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an EAR. For healthy infants receiving human milk, the AI is the mean intake. **The AI is not equivalent to an RDA.**

TABLE S-3 Criteria and Dietary Reference Intake Values for *Total Fiber* by Life Stage Group

Life Stage Group	Criterion	AI[a] (g/d) Male	AI[a] (g/d) Female
0 through 6 mo		ND[b]	ND
7 through 12 mo		ND	ND
1 through 3 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)	19	19
4 through 8 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)	25	25
9 through 13 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)	31	26
14 through 18 y		38	26
19 through 30 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)	38	25
31 through 50 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)	38	25
51 through 70 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)	30	21
> 70 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)	30	21

continued

TABLE S-3 Continued

Life Stage Group	Criterion	AI[a] (g/d) Male	AI[a] (g/d) Female
Pregnancy			
14 through 18 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)		28
19 through 50 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)		28
Lactation			
14 through 18 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)		29
19 through 50 y	Intake level shown to provide the greatest protection against coronary heart disease (14 g/1,000 kcal) × median energy intake level (kcal/1,000 kcal/d)		29

[a] AI = Adequate Intake. Based on 14 g/1,000 kcal of required energy. The AI is the observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an Estimated Average Requirement (EAR). For healthy infants receiving human milk, the AI is the mean intake. **The AI is not equivalent to a Recommended Dietary Allowance (RDA).**
[b] ND = not determined.

intake of linoleic acid by different life stage and gender groups in the United States, where the presence of *n*-6 polyunsaturated fatty acid deficiency is nonexistent. The AI for linoleic acid is 17 and 12 g/d for men and women 19 through 50 years of age, respectively (Table S-5). *n-3 Polyunsaturated fatty acids* play an important role as structural membrane lipids, particularly in nerve tissue and the retina of the eye. These fatty acids also modulate the metabolism of *n*-6 polyunsaturated fatty acids and thereby influence the balance of *n*-6 and *n*-3 fatty acid-derived eicosanoids. The AI is based on the median intakes of α-linolenic acid in the United States

TABLE S-4 Criteria and Dietary Reference Intake Values for Total Fat by Life Stage Group

Life Stage Group	Criterion	AI[a] (g/d) Male	AI[a] (g/d) Female
0 through 6 mo	Average consumption of total fat from human milk	31	31
7 through 12 mo	Average consumption of total fat from human milk and complementary foods	30	30
1 through 3 y		ND[b]	ND
4 through 8 y		ND	ND
9 through 13 y		ND	ND
14 through 18 y		ND	ND
> 18 y		ND	ND
Pregnancy		ND	ND
14 through 18 y		ND	ND
19 through 50 y		ND	ND
Lactation		ND	ND
14 through 18 y		ND	ND
19 through 50 y		ND	ND

[a] AI = Adequate Intake: the observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an Estimated Average Requirement (EAR). For healthy infants receiving human milk, the AI is the mean intake. **The AI is not equivalent to a Recommended Dietary Allowance (RDA).**
[b] ND = not determined.

where the presence of *n*-3 polyunsaturated fatty acid deficiency is nonexistent. The AI for α-linolenic acid is 1.6 and 1.1 g/d for men and women, respectively (Table S-6). Eicosapentaenoic acid and docosahexaenoic acid contribute approximately 10 percent of the total *n*-3 fatty acid intake and therefore this percent contributes toward the AI for α-linolenic acid.

Proteins form the major structural components of all the cells of the body. Along with amino acids, they function as enzymes, membrane carriers, and hormones. The RDA for both men and women is 0.8 g/kg of body weight/d of protein and is based on meta-analysis of nitrogen balance studies (Table S-7). *Amino acids* are dietary components of protein; nine amino acids are considered indispensable and thus dietary sources must be provided. The relative ratio of indispensable amino acids in a food protein and its digestibility determines the quality of the dietary protein (see Table S-8).

TABLE S-5 Criteria and Dietary Reference Intake Values for *n*-6 Polyunsaturated Fatty Acids (Linoleic Acid) by Life Stage Group

Life Stage Group	Criterion	AI (g/d)[a] Male	AI (g/d)[a] Female
0 through 6 mo	Average consumption of total *n*-6 fatty acids from human milk	4.4	4.4
7 through 12 mo	Average consumption of total *n*-6 fatty acids from human milk and complementary foods	4.6	4.6
1 through 3 y	Median intake of linoleic acid from CSFII[b]	7	7
4 through 8 y	Median intake of linoleic acid from CSFII	10	10
9 through 13 y	Median intake of linoleic acid from CSFII	12	10
14 through 18 y	Median intake of linoleic acid from CSFII	16	11
19 through 30 y	Median intake of linoleic acid from CSFII	17	12
31 through 50 y	Median intake of linoleic acid from CSFII for 19 to 30 y group	17	12
51 through 70 y	Median intake of linoleic acid from CSFII	14	11
> 70 y	Median intake of linoleic acid from CSFII for 51 through 70 y group	14	11
Pregnancy			
14 through 18 y	Median intake of linoleic acid from CSFII for all pregnant women		13
19 through 50 y	Median intake of linoleic acid from CSFII for all pregnant women		13
Lactation			
14 through 18 y	Median intake of linoleic acid from CSFII for all lactating women		13
19 through 50 y	Median intake of linoleic acid from CSFII for all lactating women		13

[a] AI = Adequate Intake: the observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an Estimated Average Requirement (EAR). For healthy infants receiving human milk, the AI is the mean intake. **The AI is not equivalent to a Recommended Dietary Allowance (RDA).**

[b] CSFII = Continuing Survey of Food Intake by Individuals.

TABLE S-6 Criteria and Dietary Reference Intake Values for *n*-3 Polyunsaturated Fatty Acids (α-Linolenic Acid) by Life Stage Group

		AI[a] (g/d)	
Life Stage Group	Criterion	Male	Female
0 through 6 mo	Average consumption of total *n*-3 fatty acids from human milk	0.5	0.5
7 through 12 mo	Average consumption of total *n*-3 fatty acids from human milk and complementary foods	0.5	0.5
1 through 3 y	Median intake of α-linolenic acid from CSFII[b]	0.7	0.7
4 through 8 y	Median intake of α-linolenic acid from CSFII	0.9	0.9
9 through 13 y	Median intake of α-linolenic acid from CSFII	1.2	1.0
14 through 18 y	Median intake of α-linolenic acid from CSFII	1.6	1.1
19 through 30 y	Highest median intake of α-linolenic acid from CSFII for all adult age groups	1.6	1.1
31 through 50 y	Highest median intake of α-linolenic acid from CSFII for all adult age groups	1.6	1.1
51 through 70 y	Highest median intake of α-linolenic acid from CSFII for all adult age groups	1.6	1.1
> 70 y	Highest median intake of α-linolenic acid from CSFII for all adult age groups	1.6	1.1
Pregnancy			
14 through 18 y	Median intake of α-linolenic acid from CSFII for all pregnant women		1.4
19 through 50 y	Median intake of α-linolenic acid from CSFII for all pregnant women		1.4
Lactation			
14 through 18 y	Median intake of α-linolenic acid from CSFII for all lactating women		1.3
19 through 50 y	Median intake of α-linolenic acid from CSFII for all lactating women		1.3

[a] AI = Adequate Intake: the observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an Estimated Average Requirement (EAR). For healthy infants receiving human milk, the AI is the mean intake. **The AI is not equivalent to a Recommended Dietary Allowance (RDA).**

[b] CSFII = Continuing Survey of Food Intake by Individuals.

TABLE S-7 Criteria and Dietary Reference Intake Values for Protein by Life Stage Group

Life Stage Group	Criterion
0 through 6 mo	Average consumption of protein from human milk
7 through 12 mo	Nitrogen equilibrium plus protein deposition
1 through 3 y	Nitrogen equilibrium plus protein deposition
4 through 8 y	Nitrogen equilibrium plus protein deposition
9 through 13 y	Nitrogen equilibrium plus protein deposition
14 through 18 y	Nitrogen equilibrium plus protein deposition
> 18 y	Nitrogen equilibrium
Pregnancy	
14 through 18 y	Nitrogen equilibrium plus protein deposition
19 through 50 y	Nitrogen equilibrium plus protein deposition
Lactation	
14 through 18 y	Nitrogen equilibrium plus milk nitrogen
19 through 50 y	Nitrogen equilibrium plus milk nitrogen

[a] AI = Adequate Intake, RDA = Recommended Dietary Allowance. The AI is the observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. It is used if sufficient scientific evidence is not available to derive an EAR. For healthy infants receiving human milk, the AI is the mean intake. **The AI is not equivalent to an RDA.** The RDA is the intake that meets the nutrient need of almost all (97–98 percent) individuals in a group.
[b] EAR = Estimated Average Requirement. The intake that meets the estimated nutrient needs of half the individuals in a group.

CRITERIA AND PROPOSED VALUES FOR TOLERABLE UPPER INTAKE LEVELS

A risk assessment model is used to derive Tolerable Upper Intake Levels (ULs). The model consists of a systematic series of scientific considerations and judgments. The hallmark of the risk assessment model is the requirement to be explicit in all of the evaluations and judgments made.

There were insufficient data to use the model of risk assessment to set a UL for total fat, monounsaturated fatty acids, *n*-6 and *n*-3 polyunsaturated fatty acids, protein, or amino acids. While increased serum low density lipoprotein cholesterol concentrations, and therefore risk of coronary heart disease, may increase at high intakes of saturated fatty acids, *trans* fatty acids, or cholesterol, a UL is not set for these fats because the level at which risk begins to increase is very low and cannot be achieved by usual

AI or RDA for Reference Individual[a] (g/d)		EAR[b] (g/kg/d)		RDA (g/kg/d)		AI
Males	Females	Males	Females	Males	Females	(g/kg/d)[c]
9.1 (AI)	9.1 (AI)					1.52
11.0	11.0	1.0	1.0	1.2	1.2	
13	13	0.87	0.87	1.05	1.05	
19	19	0.76	0.76	0.95	0.95	
34	34	0.76	0.76	0.95	0.95	
52	46	0.73	0.71	0.85	0.85	
56	46	0.66	0.66	0.80	0.80	
	71[c]		0.88		1.1	
	71		0.88		1.1	
	71		1.05		1.3	
	71		1.05		1.3	

[c] The EAR and RDA for pregnancy are only for the second half of pregnancy. For the first half of pregnancy, the protein requirements are the same as those of the nonpregnant woman.

NOTE: Due to a calculation error in the prepublication copy, values are changed for: RDA for reference infants 7 through 12 mo from 13.5 g/d to 11.0 g/d; EAR for infants 7 through 12 mo from 1.1 g/kg/d to 1.0 g/kg/d; RDA for infants 7 through 12 mo from 1.5 g/kg/d to 1.2 g/kg/d; EAR for children 1 through 3 y from 0.88 g/kg/d to 0.87 g/kg/d; RDA for children 1 through 3 y from 1.10 g/kg/d to 1.05 g/kg/d; RDA for lactating women from 1.1 g/kg/d to 1.3 g/kg/d.

diets and still have adequate intakes of all other required nutrients. It is thus recommended that saturated fatty acid, *trans* fatty acid, and cholesterol consumption be as low as possible while consuming a nutritionally adequate diet. Although there were insufficient data to set a UL for added sugars, a maximal intake level of 25 percent or less of energy is suggested to prevent the displacement of foods that are major sources of essential micronutrients (see Chapter 11).

Although a specific UL was not set for any of the macronutrients, the absence of definitive data does not signify that people can tolerate chronic intakes of these substances at high levels. Like all chemical agents, nutrients and other food components can produce adverse effects if intakes are excessive. Therefore, when data are extremely limited or conflicting, extra caution may be warranted in consuming levels significantly above that found in typical food-based diets.

TABLE S-8 FNB/IOM Protein Quality Scoring Pattern (mg/g protein)

Indispensable Amino Acid	Recommended FNB/IOM Pattern[a]
Histidine	18
Isoleucine	25
Leucine	55
Lysine	51
Methionine + cysteine	25
Phenylalanine + tyrosine	47
Threonine	27
Tryptophan	7
Valine	32

[a] Based on Estimated Average Requirements for 1- to 3-year-old children for both indispensable amino acids and total protein.

ACCEPTABLE MACRONUTRIENT DISTRIBUTION RANGES FOR HEALTHY DIETS

Dietary Reference Intakes have been set for carbohydrate, *n*-6 and *n*-3 polyunsaturated fatty acids, protein, and amino acids based on controlled studies in which the actual amount of nutrient provided or utilized is known, or based on median intakes from national survey data. A growing body of evidence has shown that macronutrients, particularly fats and carbohydrate, play a role in the risk of chronic diseases.

Although various guidelines have been established that suggest a maximal intake level of fat and fatty acids (e.g., American Heart Association [Krauss et al., 1996], Dietary Guidelines for Americans [USDA/HHS, 2000]), the scientific evidence suggests that individuals can consume moderate levels without risk of adverse health effects, while increased risk may occur with the chronic consumption of diets that are too low or too high in these macronutrients. Much of this evidence is based on clinical endpoints (e.g., risk of coronary heart disease (CHD), diabetes, cancer, and obesity), which are associations rather than distinct endpoints. Furthermore, because there may be factors other than diet that may contribute to chronic diseases, it is not possible to determine a defined level of intake at which chronic diseases may be prevented or may develop.

Based on the evidence to suggest a role in chronic diseases, as well as information to ensure sufficient intakes of essential nutrients, Acceptable Macronutrient Distribution Ranges (AMDR) have been estimated for individuals (see Chapter 11). An AMDR is defined as a range of intakes for a particular energy source that is associated with reduced risk of chronic

diseases while providing adequate intakes of essential nutrients. The AMDR is expressed as a percentage of total energy intake because its requirement, in a classical sense, is *not* independent of other energy fuel sources or of the total energy requirement of the individual. Each must be expressed in terms relative to each other. A key feature of each AMDR is that it has a lower and upper boundary, some determined mainly by the lowest or highest value judged to have an expected impact on health. If an individual consumes below or above this range, there is a potential for increasing the risk of chronic diseases shown to affect long-term health, as well as increasing the risk of insufficient intakes of essential nutrients.

When fat intakes are low and carbohydrate intakes are high, intervention studies, with the support of epidemiological studies, demonstrate a reduction in plasma high density lipoprotein (HDL) cholesterol concentration, an increase in the plasma total cholesterol:HDL cholesterol ratio, and an increase in plasma triacylglycerol concentration, all consistent with an increased risk of CHD. Conversely, interventional studies show that when fat intakes are high, many individuals gain additional weight. Weight gain on high fat diets can be detrimental to individuals already susceptible to obesity and will worsen the metabolic consequences of obesity, particularly risk of CHD. Moreover, high fat diets are usually accompanied by increased intakes of saturated fatty acids, which can raise plasma low density lipoprotein cholesterol concentrations and further heighten risk for CHD. Based on the apparent risk for CHD that may occur on both low and high fat diets, and the increased risk for CHD at higher carbohydrate intakes, an AMDR for fat and carbohydrate is estimated to be 20 to 35 and 45 to 65 percent of energy, respectively, for all adults. By consuming fat and carbohydrate within these ranges, the risk for CHD, as well as obesity and diabetes, may be kept at a minimum. Furthermore, these ranges allow for sufficient intakes of essential nutrients, while keeping the intake of saturated fat at moderate levels. To complement these ranges, the AMDR for protein is 10 to 35 percent of energy.

Based on usual median intakes of energy, it is estimated that a lower boundary level of 5 percent of energy will meet the Adequate Intake (AI) for linoleic acid (Chapter 8). An upper boundary for linoleic acid is set at 10 percent of energy for three reasons: (1) individual dietary intakes of linoleic acid in the North American population rarely exceed 10 percent of energy, (2) epidemiological evidence for safety of intakes greater than 10 percent of energy are generally lacking, and (3) high intakes of linoleic acid create a pro-oxidant state that may predispose to several chronic diseases, such as CHD and cancer. Therefore, an AMDR of 5 to 10 percent of energy is suggested for linoleic acid.

The AMDR for α-linolenic acid is set at 0.6 to 1.2 percent of energy. Ten percent of this range can be consumed as eicosapentaenoic acid

(EPA) and/or docosahexaenoic acid (DHA). The lower boundary of the range meets the AI for α-linolenic acid (Chapter 8). The upper boundary corresponds to the highest intakes from foods consumed by individuals in the United States and Canada. A growing body of literature suggests that diets higher in α-linolenic acid, EPA, and DHA may afford some degree of protection against CHD. Because the physiological potency of EPA and DHA is much greater than that for α-linolenic acid, it is not possible to estimate one AMDR for all *n*-3 fatty acids.

No more than 25 percent of energy from added sugars should be consumed. This maximal intake level is based on ensuring sufficient intakes of essential micronutrients that are, for the most part, present in relatively low amounts in foods and beverages that are major sources of added sugars in North American diets.

USING DIETARY REFERENCE INTAKES TO ASSESS NUTRIENT INTAKES OF GROUPS

Suggested uses of Dietary Reference Intakes (DRIs) appear in Box S-2. The transition from using previously published Recommended Dietary Allowances (RDAs) and Reference Nutrient Intakes (RNIs) to using each of the DRIs appropriately will require time and effort by health professionals and others.

For statistical reasons that are addressed briefly in Chapter 13 and in more detail in the report *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000), the Estimated Average Requirement (EAR) is the appropriate reference intake to use in assessing the nutrient intake of groups, whereas the RDA is not. When assessing nutrient intakes of groups, it is important to consider the variation in intake in the same individuals from day to day, as well as underreporting. With these considerations, the prevalence of inadequacy for a given nutrient may be estimated by using national survey data and determining the percentage of the population below the EAR (see Chapter 13).

Assuming a normal distribution of requirements, the percentage of surveyed individuals whose intake is less than the EAR equals the percentage of individuals whose diets are considered inadequate based on the criteria of inadequacy chosen to determine the requirement. For example, intake data from the Continuing Survey of Food Intakes by Individuals (1994–1996, 1998), which collected 24-hour diet recalls for 1 or 2 days, indicate that:

- Less than 5 percent of adults at that time consumed dietary carbohydrate at a level less than the EAR.

BOX S-2
Uses of Dietary Reference Intakes for Healthy Individuals and Groups

Type of Use	*For an Individual*[a]	*For a Group*[b]
Assessment	**EAR**: use to examine the probability that usual intake is inadequate.	**EAR**: use to estimate the prevalence of inadequate intakes within a group.
	EER[d]**:** use to examine the probability that usual energy intake is inadequate.	**EER:** use to estimate the prevalence of inadequate energy intakes within a group.
	RDA: usual intake at or above this level has a low probability of inadequacy.	**RDA:** do not use to assess intakes of groups.
	AI[c]**:** usual intake at or above this level has a low probability of inadequacy.	**AI**[c]**:** mean usual intake at or above this level implies a low prevalence of inadequate intakes.
	UL: usual intake above this level may place an individual at risk of adverse effects from excessive nutrient intake.	**UL:** use to estimate the percentage of the population at potential risk of adverse effects from excess nutrient intake.
Planning	**RDA**: aim for this intake.	**EAR:** use to plan an intake distribution with a low prevalence of inadequate intakes.
		EER: use to plan an energy intake distribution with a low prevalence of inadequate intakes.
	AI[c]**:** aim for this intake.	**AI**[c]**:** use to plan mean intakes.
	UL: use as a guide to limit intake; chronic intake of higher amounts may increase the potential risk of adverse effects.	**UL:** use to plan intake distributions with a low prevalence of intakes potentially at risk of adverse effects.

RDA = Recommended Dietary Allowance
EER = Estimated Energy Requirement
EAR = Estimated Average Requirement
AI = Adequate Intake
UL = Tolerable Upper Level

[a] Evaluation of true status requires clinical, biochemical, and anthropometric data.
[b] Requires statistically valid approximation of distribution of usual intakes.
[c] For the nutrients in this report, AIs are set for infants for all nutrients, and for other age groups for fiber and *n*-6 and *n*-3 fatty acids. The AI may be used as a guide for infants as it reflects the average intake from human milk. Infants consuming formulas with the same nutrient composition as human milk are consuming an adequate amount after adjustments are made for differences in bioavailability. When the AI for a nutrient is not based on mean intakes of healthy populations, this assessment is made with less confidence.
[d] The EER may be used as the EAR for these applications.

- Less than 5 percent of children and adults consumed protein at levels less than the EAR.
- Less than 5 percent of adults consumed *Dietary Fiber* at levels greater than the AI.

RESEARCH RECOMMENDATIONS

Four major types of information gaps were noted: (1) a lack of data designed specifically to estimate average requirements for fiber and fat in presumably healthy humans, (2) a lack of data on the needs of macronutrients of infants, children, adolescents, the elderly, and pregnant women, (3) a lack of multidose, long-term studies to determine the role of specific macronutrients in reducing the risk of certain chronic diseases, and (4) a lack of studies designed to detect adverse effects of chronic high intakes of specific macronutrients.

Highest priority is thus given to studies that address the following research topics:

- long-term, dose–response studies to help identify the requirement of individual macronutrients that are essential in the diet (e.g., essential amino acids and *n*-6 and *n*-3 polyunsaturated fats) for all life stage and gender groups. It is recognized that it is not possible to identify a defined intake level of fat for maintaining health and decreasing risk of disease; however, it is recognized that further information is needed to identify acceptable ranges of intake for fat, as well as for protein and carbohydrate that are based on prevention of chronic diseases and maintaining health;
- studies to further understand the beneficial roles of *Dietary* and *Functional Fibers* in human health;
- studies during pregnancy designed to determine protein and energy needs;
- information on the form, frequency, intensity, and duration of exercise and physical activity that is successful in managing body weight in both children and adults;
- long-term studies on the role of glycemic response in preventing chronic diseases, such as diabetes and coronary heart disease, in healthy individuals, and;
- studies to investigate the levels at which adverse effects occur with chronic high intakes of specific macronutrients. For some nutrients, such as saturated fat and cholesterol, biochemical indicators of adverse effects can occur at very low intakes. Thus, more information is needed to ascertain defined levels of intakes at which onset of relevant health risks (e.g., obesity, coronary heart disease, and diabetes) occur.

REFERENCES

IOM (Institute of Medicine). 2000. *Dietary Reference Intakes: Applications in Dietary Assessment*. Washington, DC: National Academy Press.

Krauss RM, Deckelbaum RJ, Ernst N, Fisher E, Howard BV, Knopp RH, Kotchen T, Lichtenstein AH, McGill HC, Pearson TA, Prewitt TE, Stone NJ, Horn LV, Weinberg R. 1996. Dietary guidelines for healthy American adults. A statement for health professionals from the Nutrition Committee, American Heart Association. *Circulation* 94:1795–1800.

USDA/HHS (U.S. Department of Agriculture/Department of Health and Human Services). 2000. *Nutrition and Your Health: Dietary Guidelines for Americans*. Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

1

Introduction to Dietary Reference Intakes

Dietary Reference Intakes (DRIs) comprise a set of reference values for specific nutrients, each category of which has special uses. The development of DRIs expands on the periodic reports called *Recommended Dietary Allowances,* published from 1941 to 1989 by the National Academy of Sciences, and *Recommended Nutrient Intakes,* published by the Canadian government. This comprehensive effort is being undertaken by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, the National Academies, in collaboration with Health Canada. See Appendix B for a description of the overall process, its origins, and other relevant issues that developed as a result of this new process.

WHAT ARE DIETARY REFERENCE INTAKES?

The reference values, collectively called the Dietary Reference Intakes (DRIs), include the Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), Adequate Intake (AI), and Tolerable Upper Intake Level (UL) (Box 1-1). Establishment of these reference values requires that a criterion of nutritional adequacy be carefully chosen for each nutrient, and that the population for whom these values apply be carefully defined.

A requirement is defined as the lowest continuing intake level of a nutrient that, for a specific indicator of adequacy, will maintain a defined level of nutriture in an individual. The chosen criterion or indicator of nutritional adequacy upon which EARs and AIs are based is identified for each nutrient. The criterion may differ for individuals at different life stages. Particular attention is given throughout this report to the choice

BOX 1-1
Dietary Reference Intakes

Recommended Dietary Allowance (RDA): *the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group.*

Adequate Intake (AI): *the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate—used when an RDA cannot be determined.*

Tolerable Upper Intake Level (UL): *the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.*

Estimated Average Requirement (EAR): *the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group.*[a]

[a] In the case of energy, an Estimated Energy Requirement (EER) is provided. The EER is the average dietary energy intake that is predicted to maintain energy balance in a healthy adult of a defined age, gender, weight, height, and level of physical activity consistent with good health. In children and pregnant and lactating women, the EER is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.

and justification of the criterion used to establish requirement values and the intake levels beyond which the potential for increased risk of adverse effects may occur.

CATEGORIES OF DIETARY REFERENCE INTAKES

Estimated Average Requirement[1]

The *Estimated Average Requirement* (EAR) is the daily intake value that is estimated to meet the requirement, as defined by the specified indicator

[1]The definition of EAR implies a median as opposed to a mean, or average. The median and average would be the same if the distribution of requirements followed a symmetrical distribution and would diverge if a distribution were skewed.

or criterion of adequacy, in half of the apparently healthy individuals in a life stage or gender group (see Figure 1-1). A normal or symmetrical distribution (median and mean are similar) is usually assumed for setting the EAR. At an intake level equal to the EAR, half of a specified group would not have their nutritional needs met. This is equivalent to saying that randomly chosen individuals from the population would have a 50:50 chance of having their requirement met at this intake level. This use follows the precedent set by others who have used the term "Estimated Average Requirement" for reference values similarly derived but meant to be applied to population intakes (COMA, 1991).

The EAR's usefulness as a predictor of an individual's requirement depends on the appropriateness of the choice of the nutritional status indicator or criterion and the type and amount of data available. The general method used to set the EAR is the same for all nutrients. The specific approaches, which are provided in Chapters 5 through 10, differ since each nutrient has its own indicator(s) of adequacy, and different amounts and types of data are available for each.

The EAR serves three major functions: as the basis for the Recommended Dietary Allowance (RDA), as the primary reference point for

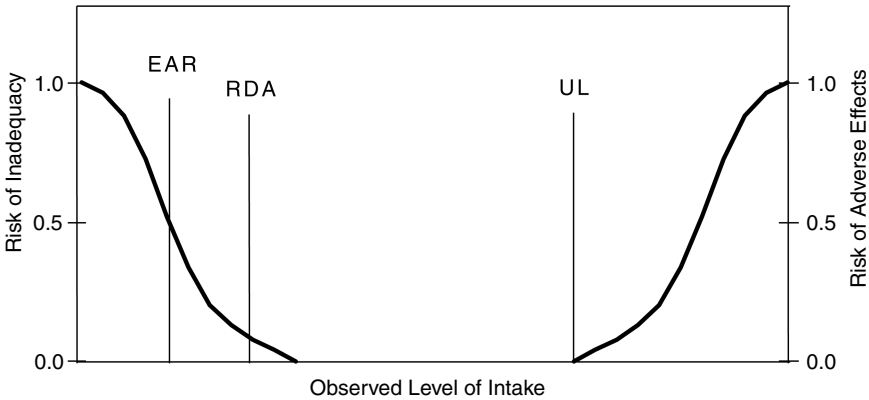

FIGURE 1-1 Dietary Reference Intakes. This figure shows that the Estimated Average Requirement (EAR) is the intake at which the risk of inadequacy is estimated to be 0.5 (50 percent) to an individual. The Recommended Dietary Allowance (RDA) is the intake at which the risk of inadequacy would be very small—only 0.02 to 0.03 (2 to 3 percent). At intakes between the RDA and the Tolerable Upper Intake Level (UL), the risk of inadequacy and of excess are both estimated to be close to 0.0. At intakes above the UL, the potential risk of adverse effects may increase.

assessing the adequacy of estimated nutrient intakes of groups (IOM, 2000a), and, together with estimates of the variance of intake, in planning for the intake of groups (see Chapter 13).

Recommended Dietary Allowance

The *Recommended Dietary Allowance* (RDA) is an estimate of the minimum daily average dietary intake level that meets the nutrient requirements of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group (see Figure 1-1). The RDA is intended to be used as a goal for daily intake by individuals as this value estimates an intake level that has a high probability of meeting the requirement of a randomly chosen individual (about 97.5 percent). The process for setting the RDA is described below; it depends on being able to set an EAR and estimating the variance of the requirement itself. Note that if an EAR cannot be set due to limitations of the data available, no RDA will be set.

This approach differs somewhat from that used by the World Health Organization, Food and Agriculture Organization, and International Atomic Energy Agency (WHO/FAO/IAEA) Expert Consultation on *Trace Elements in Human Nutrition and Health* (WHO, 1996). That publication uses the term *basal requirement* to indicate the level of intake needed to prevent pathologically relevant and clinically detectable signs of a dietary inadequacy. The term *normative requirement* indicates the level of intake sufficient to maintain a desirable body store, or reserve. In developing an RDA (and Adequate Intake [AI], see below), emphasis is placed instead on the reasons underlying the choice of the criterion of nutritional adequacy used to establish the requirement. It is not designated as basal or normative.

Method for Setting the RDA When Nutrient Requirements Are Normally Distributed

When the distribution of a requirement among individuals in a group can be assumed to be approximately normal (or symmetrical), and a standard deviation (SD) of requirement ($SD_{requirement}$) can be determined, the EAR can be used to set the RDA as follows:

$$RDA = EAR + 2 \times SD_{requirement}.$$

If data about variability in requirements are insufficient to calculate an $SD_{requirement}$ for that specific nutrient in that population group, but normality or symmetry can be assumed, then a coefficient of variation (CV) of 10 percent will be assumed and the calculation becomes:

$$RDA = EAR + 2\ (0.1 \times EAR) = 1.2 \times EAR.$$

The assumption of a 10 percent CV is based on extensive data on the variation in basal metabolic rate (FAO/WHO/UNA, 1985; Garby and Lammert, 1984) and the CV of 12.5 percent estimated for the protein requirements in adults (FAO/WHO/UNA, 1985). If there is evidence of greater variation, a larger CV will be used. In all cases, the method used to derive the RDA from the EAR is stated.

Since it is derived from the EAR, the RDA's usefulness as a goal depends on the choice of nutritional status indicator or criterion and the type and amount of data available. Its applicability also depends on the accuracy of the form of the requirement distribution and the estimate of the variance of requirements for the nutrient in the population subgroup for which it is developed.

For many of the macronutrients, there are few direct data on the requirements of children. In this case, EARs and RDAs for children are based on extrapolations from adult values. The methods for extrapolation are described in Chapter 2.

Method for Setting the RDA When Nutrient Requirements Are Not Normally Distributed

If the requirement of a nutrient is not normally distributed but can be transformed to normality, its EAR and RDA can be estimated by transforming the data, calculating the 50th (for the EAR) and the 97.5th percentiles (for the RDA), and transforming these percentiles back into the original units. In this case, the difference between the EAR and RDA cannot be used to obtain an estimate of the variance in the requirement (the SD or CV) since skewing is present.

Where factorial modeling is used to estimate the distribution of a requirement from the distributions of the individual components of the requirement (maintenance and growth), as was done in the case of protein and amino acid recommendations for children, it is necessary to add (termed *convolve*) the individual distributions. Estimating the convolution of two distributions in general is very difficult. However, this is easy to do with normal distributions since the average requirement is simply the sum of the averages of the individual component distributions, and an SD of the combined distribution can be estimated by standard statistical techniques. The 97.5th percentile can then be estimated. (For a discussion of the method, see Appendix B.)

Adequate Intake

If sufficient scientific evidence is not available to calculate an EAR, a reference intake called an *Adequate Intake (*AI) is provided instead of an RDA. The AI is a value based on experimentally determined approximations or estimates of observed median nutrient intakes by a group (or groups) of healthy people. In the judgment of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, the AI is expected to meet or exceed the amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of a specific, apparently healthy, population. Examples of defined nutritional states include normal growth, maintenance of normal circulating nutrient values, or other aspects of nutritional well-being or general health.

For young infants for whom human milk is the recommended sole source of food for most nutrients for the first 4 to 6 months of life, the AI is based on the daily mean nutrient intake of human milk in healthy, full-term infants who are exclusively fed human milk. The goal may be different for infants consuming infant formula for which the bioavailability of a nutrient may be different from that in human milk. For adults, the AI may be based on data from a single experiment, on estimated dietary intakes in apparently healthy population groups, or on a review of data from different approaches that, when considered alone, do not permit a reasonably confident estimate of an EAR.

Comparison of the Recommended Dietary Allowance and the Adequate Intake

There is much less certainty about an AI value than about an RDA value. Because AIs depend on a greater degree of judgment than is applied in estimating an EAR and subsequently an RDA, an AI may deviate significantly from, and may be numerically higher than, an RDA. For this reason, AIs must be used with greater care than is the case for RDAs. Also, an RDA is usually calculated from an EAR by using a formula that takes into account the expected variation in the requirement for the nutrient.

Both the AI and RDA are to be used as a goal for individual intake. In general, the values are intended to cover the needs of nearly all apparently healthy individuals in a life stage group. (For infants, the AI is the mean intake when infants in the age group are consuming human milk. Larger infants may have greater needs, which they meet by consuming more milk.) The AI for a nutrient is expected to exceed the RDA for that nutrient, and thus it should cover the needs of more than 97 to 98 percent of individuals. The degree to which the AI exceeds the RDA is likely to differ among nutrients and population groups. As with RDAs, AIs for children and ado-

lescents may be extrapolated from adult values if no other usable data are available.

For people who have diseases that increase specific nutrient requirements or who have other special health needs, the RDA and AI each may serve as the basis for adjusting individual recommendations. Qualified health professionals should adapt the recommended intake to cover higher or lower needs.

Tolerable Upper Intake Level

The *Tolerable Upper Intake Level* (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the specified life stage group (see Figure 1-1). As intake increases above the UL, there is the potential for an increased risk of adverse effects. The term *tolerable* was chosen to avoid implying a possible beneficial effect. Instead, the term is intended to connote a level of intake that can, with high probability, be tolerated biologically. The UL is not intended to be a recommended level of intake, as there is no established benefit for healthy individuals if they consume a nutrient in amounts exceeding the recommended intake (the RDA or AI).

The UL is based on an evaluation conducted by using the methodology for risk assessment of nutrients (see Chapter 4). The need for setting ULs has arisen as a result of the increased fortification of foods with nutrients and the use of dietary supplements by more people and in larger doses. The UL applies to chronic daily use and is usually based on the total intake of a nutrient from food, water, and supplements if adverse effects have been associated with total intake. However, if adverse effects have been associated with intake from supplements or food fortificants only, the UL is based on nutrient intake from one or both of those sources only, rather than on total intake. As in the case of applying AIs, professionals should avoid very rigid application of ULs and first assess the characteristics of the individual or group of concern (e.g., source of nutrient, physiological state of the individual, length of sustained high intakes, etc.).

For some nutrients, data may not be sufficient for developing a UL. This indicates the need for caution in consuming amounts greater than the recommended intake; it does not mean that high intake poses no potential risk of adverse effects.

The safety of routine, long-term intake above the UL is not well documented. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged as long as subjects participating in these trials have signed informed consent documents regarding pos-

sible toxicity and as long as these trials employ appropriate, safe monitoring of trial subjects.

DETERMINATION OF ADEQUACY

Adequacy

In the derivation of Estimated Average Requirements (EARs) or Adequate Intakes (AIs), close attention has been paid to the determination of the most appropriate indicators of adequacy. A key question is, Adequate for what? In many cases, a continuum of benefits may be ascribed to various levels of intake of the same nutrient. One criterion may be deemed the most appropriate to determine the risk that an individual will become deficient in the nutrient, whereas another may relate to reducing the risk of a chronic degenerative disease, such as certain neurodegenerative diseases, cardiovascular disease, cancer, diabetes mellitus, or age-related macular degeneration.

Each EAR and AI is described in terms of the selected criterion or indicator of adequacy. The potential role of the macronutrients in the reduction of disease risk was considered in developing the EARs. With the acquisition of additional data relating intake more directly to chronic disease or disability, more sensitive and reliable indicators or criteria may be validated and thus the criterion for setting the EAR may change.

Role in Health

Unlike other nutrients, energy-yielding macronutrients can be used somewhat interchangeably (up to a point) to meet energy requirements of an individual. In this report, EARs or AIs have been provided for specific macronutrients or components of these classes of macronutrients where the data were adequate to establish a causal relationship between intake and a specific function or chosen criterion of adequacy. However, for the general classes of nutrients and some of their subunits, this was not always possible; the data do not support a specific number, but rather trends between intake and chronic disease identify a range. Given that energy needs vary with individuals, a specific number was not deemed appropriate to serve as the basis for developing diets that would be considered to decrease risk of disease, including chronic diseases, to the fullest extent possible. Thus Acceptable Macronutrient Distribution Ranges (AMDRs) have been established for macronutrients as percentages of total energy intake. These are ranges of macronutrient intakes that are associated with reduced risk of chronic disease, while providing recommended intakes of other essential nutrients.

Because much of this evidence is based on clinical endpoints (e.g., coronary heart disease, diabetes, cancer, and obesity), which point to trends rather than distinct endpoints, and because there may be factors other than diet that may contribute to chronic disease, it is not possible to determine a defined level of intake at which chronic disease may be prevented or may develop. Therefore, an AMDR is not considered to be a Dietary Reference Intake (DRI) that provides a defined intake level. An AMDR is provided to give guidance in dietary planning by taking into account the trends related to decreased risk of disease identified in epidemiological and clinical studies.

AMDRs are expressed as percentages of total energy intake because their requirements, in a classical sense, are *not* independent of each other or of the total energy requirement of the individual. Each must be expressed in terms relative to the others. A key feature of each AMDR is that it has a lower and upper boundary, some determined mainly by the lowest or highest value judged to have an expected impact on health. Above or below these boundaries there is a potential for increasing the risk of chronic diseases shown to effect long-term health. The macronutrients and their role in health are discussed in Chapter 3, as well as in Chapters 5 through 11.

PARAMETERS FOR DIETARY REFERENCE INTAKES

Nutrient Intakes

Each type of Dietary Reference Intake (DRI) refers to the average daily nutrient intake of individuals over time. The amount consumed may vary substantially from day-to-day without ill effects in most cases. Moreover, unless otherwise stated, all values given for Estimated Average Requirements (EARs), Recommended Dietary Allowances (RDAs), Adequate Intakes (AIs), or Acceptable Macronutrient Distribution Ranges (AMDRs) represent the quantity of the nutrient or food component to be supplied by foods from diets similar to those consumed in Canada and the United States. Healthy subgroups of the population often have different requirements, so special attention has been given to the differences due to gender and age, and often separate reference intakes are estimated for specified subgroups.

For some nutrients (e.g., trace elements), a higher intake may be needed for healthy people if the degree of absorption of the nutrient is unusually low on a chronic basis (e.g., because of very high fiber intake). If the primary source of a nutrient is a supplement, a higher or lower percentage may be absorbed and so a smaller or greater intake may be required, or an adverse effect may be demonstrated at a lower level of

intake. When this is an issue, it is discussed for the specific nutrient in the section "Special Considerations."

The DRIs apply to the apparently healthy population, and while the RDAs and AIs are levels of intake recommended for individuals, meeting these levels would not necessarily be sufficient for individuals who are already malnourished. People with diseases that result in malabsorption syndrome or who are undergoing treatment such as hemo- or peritoneal dialysis may have increased requirements for some nutrients. Special guidance should be provided for those with greatly increased nutrient needs or for those with decreased needs such as energy due to disability or decreased mobility. Although the RDA or AI may serve as the basis for such guidance, qualified medical and nutrition personnel should make necessary adaptations for specific situations.

Life Stage Groups

The life stage groups described below were chosen while keeping in mind all the nutrients to be reviewed, not only those included in this report. Additional subdivisions within these groups may be added in later reports. If data are too sparse to distinguish differences in requirements by life stage or gender group, the analysis provided in establishing the DRI may be presented for a larger grouping.

Infancy

Infancy covers the period from birth through 12 months of age and is divided into two 6-month intervals. Except for energy, the first 6-month interval was not subdivided further because intake is relatively constant during this time. That is, as infants grow, they ingest more food; however, on a body-weight basis their intake remains nearly the same. During the second 6 months of life, growth velocity slows, and thus daily nutrient needs on a body-weight basis may be less than those during the first 6 months of life.

For protein, amino acids, carbohydrate, fat, and *n*-6 and *n*-3 polyunsaturated fatty acids, the average intake by full-term infants who are born to healthy, well-nourished mothers and exclusively fed human milk has been adopted as the primary basis for deriving the AI during the first 6 months of life. This is the model used for other nutrients as well. The value established is thus not an EAR. The extent to which intake of human milk may result in exceeding the actual requirements of the infant is not known, and ethics of human experimentation preclude testing the levels known to be potentially inadequate. Therefore, the AI, while determined from the average composition of an average volume of milk consumed by

this age group, is not an EAR in which only half of the group would be expected to have their needs met.

Using the infant fed human milk as a model is in keeping with the basis for estimating nutrient allowances of infants developed in the last revisions of the RDAs (NRC, 1989) and Recommended Nutrient Intakes (RNIs) (Health Canada, 1990). It also supports the recommendation that exclusive human-milk feeding is the preferred method of feeding for normal, full-term infants for the first 4 to 6 months of life. This recommendation has also been made by the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), and in the Food and Nutrition Board report, *Nutrition During Lactation* (IOM, 1991).

In general, for this report, special consideration was not given to possible variations in physiological need during the first month after birth, or to the variations in intake of nutrients from human milk that result from differences in milk volume and nutrient concentration during early lactation. Specific DRIs to meet the needs of formula-fed infants are not proposed in this report. The previously published RDAs and RNIs for infants have led to much misinterpretation of the adequacy of human milk because of a lack of understanding about their derivation for young infants. Although they were based on human-milk composition and volume of intake, the previous RDA and RNI values allowed for lower bioavailability of nutrients from nonhuman milk. However, where warranted, information discussing specific changes in bioavailability or source of nutrients for use in developing formulations is included in the "Special Considerations" section of each chapter.

Ages 0 Through 6 Months. To determine the AI value for infants ages 0 through 6 months, the mean intake of a nutrient was calculated by multiplying the average concentration of the nutrient in human milk produced during the second through sixth month of lactation (derived from consensus values from several reported studies [Atkinson et al., 1995]) by the average volume of milk intake of 0.78 L/d as reported from studies of full-term infants by test weighing (Butte et al., 1984; Chandra, 1984; Hofvander et al., 1982; Neville et al., 1988). Because there is variation in both of these measures, the computed value represents the mean. It is assumed that infants will have adequate access to human milk and that they will consume increased volumes as needed to meet their requirements for maintenance and growth.

Ages 7 Through 12 Months. The reference body-weight method that has been used in previous DRI reports to extrapolate the AI for infants 0 through 6 months to an AI for older infants in the absence of direct data

on older infants (IOM, 1997) is not appropriate for dietary fats or carbohydrates. This is because the amount of energy required on a body-weight basis is significantly lower during the second 6 months of life, due largely to the slower rate of weight gain/kg of body weight. Therefore, the basis of the AI values derived for this age category for dietary fats and carbohydrates was the sum of the specific nutrient provided by 0.6 L/d of human milk, which is the average volume of milk reported from studies in this age category (Heinig et al., 1993), and that provided by the usual intake of complementary weaning foods consumed by infants in this age category (Specker et al., 1997). This approach is in keeping with the current recommendations of the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), and *Nutrition During Lactation* (IOM, 1991) for continued feeding of human milk to infants through 9 to 12 months of age with appropriate introduction of solid foods.

Toddlers: Ages 1 Through 3 Years

Two points were primary in dividing early childhood into two groups. First, the greater velocity of growth in height during ages 1 through 3 years compared with ages 4 through 5 years provides a biological basis for dividing this period of life. Second, because children in the United States and Canada begin to enter the public school system starting at age 4 years, ending this life stage prior to age 4 years seemed appropriate so that food and nutrition policy planners have appropriate targets and cutoffs for use in program planning.

Data are sparse for indicators of nutrient adequacy on which to derive DRIs for these early years of life. In these cases, extrapolation using the methods described in Chapter 2 has been employed.

Early Childhood: Ages 4 Through 8 Years

Major biological changes in velocity of growth and changing endocrine status occur during ages 4 through 8 or 9 years (the latter depending on onset of puberty in each gender); therefore, the category of 4 through 8 years of age is appropriate. For many nutrients, a reasonable amount of data is available on nutrient intake and various criteria for adequacy (such as nutrient balance measured in children 5 through 7 years of age) that can be used as the basis for the EARs and AIs for this life stage group.

Puberty/Adolescence: Ages 9 Through 13 Years and 14 Through 18 Years

Because current data support younger ages for pubertal development, it was determined that the adolescent age group should begin at 9 years. The mean age of onset of breast development (Tanner Stage 2) for white girls in the United States is 10.0 ± 1.8 (standard deviation) years; this is a physical marker for the beginning of increased estrogen secretion (Herman-Giddens et al., 1997). In African-American girls, onset of breast development is earlier (mean 8.9 years ± 1.9). The reason for the observed racial differences in the age at which girls enter puberty is unknown. The onset of the growth spurt in girls begins before the onset of breast development (Tanner, 1990). The age group of 9 through 13 years allows for this early growth spurt of girls.

For boys, the mean age of initiation of testicular development is 10.5 to 11 years, and their growth spurt begins two years later (Tanner, 1990). Thus, to begin the second age category at 14 years and to have different EARs and AIs for girls and boys for some nutrients at this age seems biologically appropriate. All children continue to grow to some extent until as late as age 20 years; therefore, having these two age categories span the period of 9 through 18 years of age seems justified.

Young Adulthood and Middle-Aged Adults: Ages 19 Through 30 Years and 31 Through 50 Years

The recognition of the possible value of higher nutrient intakes during early adulthood on achieving optimal genetic potential for peak bone mass was the reason for dividing adulthood into ages 19 through 30 years and 31 through 50 years. Moreover, mean energy expenditure decreases during this 30-year period, and needs for nutrients related to energy metabolism may also decrease. For some nutrients, the DRIs may be the same for the two age groups. However, for other nutrients, especially those related to energy metabolism, EARs (and RDAs) are likely to differ for these two age groups.

Adulthood and Older Adults: Ages 51 Through 70 Years and Over 70 Years

The age period of 51 through 70 years spans the active work years for most adults. After age 70, people of the same age increasingly display variability in physiological functioning and physical activity. A comparison of people over age 70 who are the same chronological age may demonstrate as much as a 15- to 20-year age-related difference in level of reserve

capacity and functioning. This is demonstrated by age-related declines in nutrient absorption and renal function. Because of the high variability in functional capacity of older adults, the EARs and AIs for this age group may reflect a greater variability in requirements for the older age categories. This variability may be most applicable to nutrients for which requirements are related to energy expenditure.

Pregnancy and Lactation

Recommendations for pregnancy and lactation may be subdivided because of the many physiological changes and changes in nutrient need that occur during these life stages. In setting EARs and AIs for these life stages, however, consideration is given to adaptations to increased nutrient demand, such as increased absorption and greater conservation of many nutrients. Moreover, nutrients may undergo net losses due to physiological mechanisms regardless of the nutrient intake. Thus, for some nutrients, there may not be a basis for EAR values that are different during these life stages than those for nonpregnant or nonlactating women of comparable age.

Reference Heights and Weights

Use of Reference Heights and Weights

Reference heights and weights are useful when more specificity about body size and nutrient requirements are needed than that provided by life stage categories. For example, while the EAR may be developed for the 4- to 8-year-old age group, a small 4-year-old child may be assumed to require less than the EAR for that age group, whereas a large 8-year-old may require more than the EAR. Based on the model for establishing RDAs, however, the RDA (and for that matter, an AI) should meet the needs of both.

In some cases, where data regarding nutrient requirements are reported on a body-weight basis, it is necessary to have reference heights and weights to transform the data for comparison purposes. Frequently, where data regarding adult requirements represent the only available data (e.g., on adverse effects of chronic high intakes for establishing Tolerable Upper Intake Levels [ULs]), extrapolating on the basis of body weight or size becomes a possible option to providing ULs for other age groups. Thus, for this and other reports, when data are not available, the EAR or UL for children or pregnant women may be established by extrapolation from adult values on the basis of body weight.

TABLE 1-1 New Reference Heights and Weights for Children and Adults in the United States

Sex	Age	Previous Median Body Mass Index[a] (kg/m^2)	New Median Body Mass Index[b] (kg/m^2)	New Median Reference Height,[b] cm (in)	New Reference Weight,[c] kg (lb)
Male, Female	2–6 mo	—	—	62 (24)	6 (13)
	7–12 mo	—	—	71 (28)	9 (20)
	1–3 y	—	—	86 (34)	12 (27)
	4–8 y	15.8	15.3	115 (45)	20 (44)
Male	9–13 y	18.5	17.2	144 (57)	36 (79)
	14–18 y	21.3	20.5	174 (68)	61 (134)
	19–30 y	24.4	22.5	177 (70)	70 (154)
Female	9–13 y	18.3	17.4	144 (57)	37 (81)
	14–18 y	21.3	20.4	163 (64)	54 (119)
	19–30 y	22.8	21.5	163 (64)	57 (126)

[a] Taken from male and female median body mass index and height-for-age data from the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; used in earlier DRI reports (IOM, 1997, 1998, 2000a, 2000b, 2001).
[b] Taken from new data on male and female median body mass index and height-for-age data from the Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics (NCHS) Growth Charts (Kuczmarski et al., 2000).
[c] Calculated from CDC/NCHS Growth Charts (Kuczmarski et al., 2000); median body mass index and median height for ages 4 through 19 years.

New Reference Heights and Weights

As is described in Appendix B, the DRI framework is an iterative process that was undertaken in 1994. At that time, reference heights and weights used in the DRI reports for the U.S. and Canadian populations were developed based on data from the Third National Health and Nutrition Examination Survey on body mass index (BMI) for children and young adults (IOM, 1997). With the recent publication of new U.S.-based growth charts for infants and children and the introduction of BMI recommendations for adults (Kuczmarski et al., 2000), reference heights and weights for adults and children have been updated. Besides being more current, these new reference heights and weights are more representative of the U.S. population. Table 1-1 provides these updated values. Appendix B includes information about the reference values that were used in the earlier DRI reports.

SUMMARY

Dietary Reference Intakes (DRIs) is a generic term for a set of nutrient reference values that include the Estimated Average Requirement, Recommended Dietary Allowance, Adequate Intake, and Tolerable Upper Intake Level. In addition, to provide guidance on the appropriate macronutrient distribution thought to decrease risk of disease, including chronic disease, Acceptable Macronutrient Distribution Ranges are established for the macronutrients. These reference values have been developed for life stage and gender groups in a joint U.S. and Canadian activity.

This report—one volume in a series—covers the DRIs for the dietary macronutrients: carbohydrate, fiber, fat, cholesterol, protein, and amino acids. It also provides recommendations for physical activity and energy expenditure to maintain health and decrease risk of disease.

REFERENCES

AAP (American Academy of Pediatrics). 1997. Breastfeeding and the use of human milk. *Pediatrics* 100:1035–1039.

Atkinson SA, Alston-Mills BP, Lonnerdal B, Neville MC, Thompson M. 1995. Major minerals and ionic constituents of human and bovine milk. In: Jensen RJ, ed. *Handbook of Milk Composition.* San Diego, CA: Academic Press. Pp. 593–619.

Butte NF, Garza C, Smith EO, Nichols BL. 1984. Human milk intake and growth in exclusively breast-fed infants. *J Pediatr* 104:187–195.

Chandra RK. 1984. Physical growth of exclusively breast-fed infants. *Nutr Res* 2:275–276.

COMA (Committee on Medical Aspects of Food Policy). 1991. *Dietary Reference Values for Food Energy and Nutrients in the United Kingdom.* Report on Health and Social Subjects, No. 41. London: HMSO.

FAO/WHO/UNA (Food and Agriculture Organization of the United Nations/World Health Organization/United Nations Association). 1985. *Energy and Protein Requirements. Report of a Joint FAO/WHO/UNA Expert Consultation.* Technical Report Series. No. 724. Geneva: WHO.

Garby L, Lammert O. 1984. Within-subjects between-days-and-weeks variation in energy expenditure at rest. *Hum Nutr Clin Nutr* 38:395–397.

Health Canada. 1990. *Nutrition Recommendations. The Report of the Scientific Review Committee 1990.* Ottawa: Canadian Government Publishing Centre.

Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B, Dewey KG. 1993. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: The DARLING Study. *Am J Clin Nutr* 58:152–161.

Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. 1997. Secondary sexual characteristics and menses in young girls seen in office practice: A study from the Pediatric Research in Office Settings Network. *Pediatrics* 99:505–512.

Hofvander Y, Hagman U, Hillervik C, Sjolin S. 1982. The amount of milk consumed by 1–3 months old breast- or bottle-fed infants. *Acta Paediatr Scand* 71:953–958.

IOM (Institute of Medicine). 1991. *Nutrition During Lactation.* Washington, DC: National Academy Press.

IOM. 1997. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academy Press.

IOM. 1998. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline.* Washington, DC: National Academy Press.

IOM. 2000a. *Dietary Reference Intakes: Applications in Dietary Assessment.* Washington, DC: National Academy Press.

IOM. 2000b. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.* Washington, DC: National Academy Press.

IOM. 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academy Press.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. 2000. CDC growth charts: United States. *Adv Data* 314:1–28.

Neville MC, Keller R, Seacat J, Lutes V, Neifert M, Casey C, Allen J, Archer P. 1988. Studies in human lactation: Milk volumes in lactating women during the onset of lactation and full lactation. *Am J Clin Nutr* 48:1375–1386.

NRC (National Research Council). 1989. *Recommended Dietary Allowances,* 10th ed. Washington, DC: National Academy Press.

Specker BL, Beck A, Kalkwarf H, Ho M. 1997. Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. *Pediatrics* 99:E12.

Tanner JM. 1990. *Growth at Adolescence.* Oxford: Oxford University Press.

WHO (World Health Organization). 1996. *Trace Elements in Human Nutrition and Health.* Geneva: WHO.

2
Methods and Approaches Used

OVERVIEW

Carbohydrate, fat, and protein all have two major functions as classes of nutrients: they are required for many normal biological functions, and they serve as energy sources for body fuel. Physical activity can modulate the amount of energy required by the body. Specific subcomponents, such as some amino acids and fatty acids, are required for normal growth and development. Other subcomponents, such as fiber, play a role in decreasing risk of chronic disease.

Carbohydrate and fat are the primary fuel sources. For this purpose they can be largely utilized interchangeably. On the other hand, many metabolic processes favor one source over another. For example, under normal circumstances the brain functions almost exclusively on glucose (Dienel and Hertz, 2001). Conversely, membranes are composed of specific lipids. To a large extent, the body can synthesize de novo the lipids and carbohydrates it needs for these specialized functions. An exception is the requirement for small amounts of carbohydrate and *n*-6 and *n*-3 polyunsaturated fatty acids. Otherwise, there are no specific "dietary requirements"[1] for fat or carbohydrate for specific functions. Of course, some mixture of fat and carbohydrate is required as a source of fuel to meet the energy requirements of the body.

In order to apply the Dietary Reference Intake (DRI) process and approach to energy-yielding macronutrients, it was necessary to separate

[1]A requirement is defined as the lowest continuing intake level of a nutrient that, for a specific indicator of adequacy, will maintain a defined level of nutriture in an individual.

out the metabolic requirements for specific nutrients for which Estimated Average Requirements (EARs) or Adequate Intakes (AIs) have been derived. It was also necessary to provide quantitative guidance on proportions of specific sources of required energy based on evidence of decreased risk of disease (which, in most cases, is chronic disease).

Thus, a fundamental question to be addressed when reviewing the role of these nutrients in health is, What is the most desirable mix of energy sources that maximizes both health and longevity? Because individuals can live apparently healthy lives for long periods with a wide range of intakes of specific energy nutrients, it is not surprising that this optimal mix of such sources may be difficult to define. There are no clinical trials that compare various energy sources with longevity in humans. For this reason, recommendations about the desirable composition of energy sources must be based on either short-term trials that address specific health or disease endpoints, or surrogate markers (biomarkers) that correlate well with these endpoints. A large number of research studies have been carried out to examine the effects of the composition of energy sources on surrogate markers, and these have provided a basis for making recommendations.

Because diets with specific ratios of carbohydrate to fat, or specific ratios of subcomponents of each, have associations with the risk of various clinical endpoints (e.g., coronary heart disease, diabetes), Acceptable Macronutrient Distribution Ranges (AMDRs) have been proposed that consider these endpoints, as well as the need to consume diets that meet recommended intakes for micronutrients and essential fatty acids. These ranges are given as percentages of total energy intake. For any given diet consumed by an individual, the sum of the contribution to energy intake as a percentage of total intake for carbohydrate, fat, protein, and alcohol must equal 100 percent. The acceptable range of macronutrient intake is a range of intakes for a particular nutrient or class of nutrients that will confer decreased risk of disease and provide the most desirable long-term health benefits to apparently healthy individuals.

TYPES OF DATA USED

A number of disciplines have made key contributions to the evidence linking energy-yielding nutrients to outcomes that may relate to human health. Basic biological research, often involving animal models, provides critical information on mechanisms that may link nutrient consumption to beneficial or adverse health outcomes. While results from animal experiments are generally not used when establishing Dietary Reference Intakes (DRIs), selected animal studies are considered in the absence of human data.

Observational studies in humans include single-case and case-series reports and cross-sectional, cohort, and case-control studies. Experimental studies include randomized and nonrandomized therapeutic or prevention trials and controlled dose–response, balance, turnover, factorial, and depletion–repletion physiological studies. Clinical and epidemiological observational studies play a valuable role in generating hypotheses concerning the health risks and benefits of nutrient intake patterns. Randomized clinical trials in population groups of interest have the potential to provide definitive comparisons between selected nutrient intake patterns and subsequent health-related outcomes. Note, however, that randomized trials attempting to relate diet to disease states also have important limitations, which are elaborated in the discussion below.

Animal Models

Basic research using experimental animals affords considerable advantage in terms of control of nutrient exposures, environmental factors, and even genetics. In contrast, the relevance to free-living humans is often unclear. In addition, dose levels and routes of administration that are practical in animal experiments may differ greatly from those relevant to humans. Nevertheless, due to the opportunity to elaborate specific mechanisms of action, evidence from animal feeding experiments regarding protein, fat, and carbohydrate were included in the evidence reviewed when developing the decisions concerning the ability to specify the DRIs for these nutrients.

Human Feeding Studies

Controlled feeding studies, usually in a confined setting such as a metabolic unit, can yield valuable information on the relationship between nutrient consumption and health-related biomarkers. Much of the understanding of human nutrient requirements to prevent deficiencies is based on studies of this type. Studies in which the subjects are confined allow for close control of intake and activities and complete collection of nutrient or metabolite losses through urine and feces. Recurring sampling of biological materials, such as blood and skin sloughing, is also possible in this type of setting.

Nutrient balance studies measure nutrient status in relation to intake at various levels. Depletion–repletion studies, by contrast, measure nutrient status while subjects are maintained on diets containing marginally low or deficient levels of a nutrient; the deficit is then corrected with measured amounts of the nutrient under study over a period of time. However, these two types of studies have several limitations. Typically, due to

resource constraints, they are limited in time to a few days or weeks, so longer-term outcomes cannot be measured with the same level of accuracy. In addition, since subjects are often confined, findings cannot necessarily be generalized to free-living individuals. Finally, the time and expense involved in such studies usually limit the number of subjects and the number of doses or intake levels that can be tested.

In spite of these limitations, feeding studies have played an important role in understanding nutrient needs and metabolism. Such data were considered in the DRI process and were given particular attention in the absence of reliable data to directly relate nutrient intake to disease risk in free-living individuals.

Observational Studies

In comparison to human feeding studies, observational epidemiological studies are frequently of direct relevance to free-living humans, but they lack the controlled setting. Hence, they are useful in establishing evidence of an association between the consumption of a nutrient and disease risk, but are limited in their ability to ascribe a causal relationship. A judgment of causality may be supported by a consistency of association among studies in diverse populations under various conditions, and it may be strengthened by the use of laboratory-based tools to measure exposures and confounding factors, rather than other means of data collection such as personal interviews.

In recent years, rapid advances in laboratory technology have made possible the increased use of biomarkers of exposure, susceptibility, and disease outcome in molecular epidemiological research. For example, one area of great potential in advancing current knowledge of the effects of diet on health is the study of genetic markers of disease susceptibility (especially polymorphisms in genes that encode metabolizing enzymes) in relation to dietary exposures. This development is expected to provide more accurate assessments of the risk associated with different levels of intake of nutrients and other food constituents.

While analytic epidemiological studies (studies that relate exposure to disease outcomes in individuals) have provided convincing evidence of an associative relationship between selected nondietary exposures and disease risk, there are a number of other factors that limit study reliability in research relating nutrient intakes to disease risk (Sempos et al., 1999). First, the variation in nutrient intake may be rather limited in the population selected for study. This feature alone may yield modest relative risk across intake categories in the population, even if the nutrient is an important factor in explaining large disease-rate variations among populations.

A second factor, one that gives rise to particular concerns about con-

founding, is the human diet's complex mixture of foods and nutrients that include many substances that may be highly correlated. Third, many cohort and case-control studies have relied on self-reports of diet, typically from food records, 24-hour recalls, or diet history questionnaires. Repeated application of such instruments to the same individuals shows considerable variation in nutrient consumption estimates from one time period to another with correlations often in the 0.3 to 0.8 range (Willett et al., 1985).

In addition, there may be systematic bias in nutrient consumption estimates from self-reports, as the reporting of food intakes and portion sizes may depend on individual characteristics such as body mass, ethnicity, and age. For example, some have demonstrated more pronounced and substantial underreporting of total energy consumption among obese persons than among lean persons (Heitmann and Lissner, 1995; Schoeller et al., 1990). Such systematic bias, in conjunction with random measurement error and limited intake range, has the potential to greatly impact analytical epidemiological studies based on self-reported dietary habits. Cohort studies using objective (biomarker) measures of nutrient intake may have an important advantage in the avoidance of systematic bias, though important sources of bias (e.g., confounding) may remain.

Finally, there can be the problem of multicollinearity, in which two independent variables are related to each other, resulting in a low p value for an association with a dependent variable, when in fact each of the independent variables have no relationship to the dependent variable (Sempos et al., 1999).

Randomized Clinical Trials

By randomly allocating subjects to the nutrient exposure level of interest, clinical trials eliminate the confounding that may be introduced in observational studies by self-selection. The unique strength of randomized trials is that, if the sample is large enough, the study groups will be similar not only with respect to those confounding variables known to the investigators, but also to other unknown factors that might be related to risk of the disease. Thus, randomized trials achieve a degree of control of confounding that is simply not possible with any observational design strategy, and thus they allow for the testing of small effects that are beyond the ability of observational studies to detect reliably.

Although randomized controlled trials represent the accepted standard for studies of nutrient consumption in relation to human health, they too possess important limitations. Specifically, individuals agreeing to be randomized may be a select subset of the population of interest, thus limiting the generalization of trial results. For practical reasons, only a small number of nutrients or nutrient combinations at a single intake level

are generally studied in a randomized trial (although a few intervention trials to compare specific dietary patterns have been initiated in recent years). In addition, the follow-up period will typically be short relative to the preceding time period of nutrient consumption; the chronicity of intake may be relevant to the health outcomes under study, particularly if chronic disease endpoints are sought. Also, dietary intervention or supplementation trials tend to be costly and logistically difficult, and the maintenance of intervention adherence can be a particular challenge.

Many complexities arise in conducting studies among free-living human populations. The totality of the evidence from observational and intervention studies, appropriately weighted and corroborated by an understanding of the underlying mechanisms of action, must form the basis for conclusions about causal relationships between particular exposures and disease outcomes.

Weighing the Evidence

As a principle, only studies published in peer-reviewed journals have been used in this report. However, raw data or studies published in other scientific journals or readily available reports were considered if they appeared to provide important information not documented elsewhere.

For estimating requirements for energy, doubly labeled water data was collected from various investigators and subject to statistical analysis (see Appendix I). For other nutrients, to the extent possible, original scientific studies have been used to derive the DRIs. On the basis of a thorough review of the scientific literature, clinical, functional, and biochemical indicators of nutritional adequacy and excess were identified for each nutrient.

The quality of the studies was considered in weighing the evidence. The characteristics examined included the study design and the representativeness of the study population; the validity, reliability, and precision of the methods used for measuring intake and indicators of adequacy or excess; the control of biases and confounding factors; and the power of the study to demonstrate a given difference or correlation. Publications solely expressing opinions were not used in setting DRIs. Each assessment acknowledged the inherent reliability of each type of study design as described above, and standard criteria concerning the strength and dose–response and temporal pattern of estimated nutrient–disease or adverse effect associations, the consistency of associations among studies of various types, and the specificity and biological plausibility of the suggested relationships were applied (Hill, 1971). For example, biological plausibility would not be sufficient in the presence of a weak association and lack of evidence that exposure preceded the effect.

Data were examined to determine whether similar estimates of the requirement resulted from the use of different indicators and different types of studies. For a single nutrient, the criterion or indicator of adequacy for setting the Estimated Average Requirement (EAR) may differ from one life stage group to another because the critical function, the risk of a disease, or its biomarker may be different. When very poor or no data were available for a given life stage group, extrapolation was made from the EAR, Adequate Intake (AI), or Tolerable Upper Intake Level (UL) set for another group; explicit and logical assumptions on relative requirements or potential risk of adverse effects were made. Because EARs can be used for multiple purposes, they were established whenever sufficient supporting data were available.

Data Limitations

Although the reference values are based on data, the data were often scanty or drawn from studies that had limitations in addressing the various questions that arose in reviewing the data. Therefore, many of the questions raised about the requirements for, and recommended intakes of, these nutrients cannot be answered fully because of inadequacies in the present database. Apart from studies of overt deficiency diseases, there is a dearth of studies that address specific effects of inadequate intakes on specific indicators of health status, and thus a research agenda is proposed (see Chapter 14). For many of these nutrients, estimated requirements are based on balance, biochemical indicators, and clinical deficiency data because there is little information relating health status indicators to functional sufficiency or insufficiency.

Thus, after careful review and analysis of the evidence, including examination of the extent of congruent findings, scientific judgment was used to determine the basis for establishing the values. The reasoning used in developing the values is described for each nutrient in Chapters 5 through 11.

METHODS TO DETERMINE THE ADEQUATE INTAKE FOR INFANTS

As for other nutrients in previous Dietary Reference Intake (DRI) reports, the Adequate Intake (AI) for young infants (ages 0 through 6 months) is generally estimated to be the average intake by full-term infants who are born to healthy, well-nourished mothers and who are exclusively fed human milk. The extent to which intake of a nutrient from human milk may exceed the actual requirements of infants is not known, and ethics of human experimentation preclude the testing of levels known to

be potentially inadequate. Using the infant exclusively fed human milk as a model is in keeping with the basis for earlier recommendations for intake (e.g., Health Canada, 1990; IOM, 1991). It also supports the recommendation that exclusive intake of human milk is the preferred method of feeding for normal, full-term infants for the first 4 to 6 months of life. This recommendation has been made by the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), the Institute of Medicine (IOM, 1991), and many other expert groups, even though most infants in the United States no longer receive human milk by the age of 6 months.

In general, this report does not cover possible variations in physiological need during the first month after birth or the variations in intake of nutrients from human milk that result from differences in milk volume and nutrient concentration during early lactation. In keeping with the decision made by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, specific DRIs to meet the needs of formula-fed infants have not been proposed in this report. The use of formula introduces a large number of complex issues, one of which is the bioavailability of different forms of the nutrient in different formula types. Where data are available regarding adjustments that should be made for various formulas, they are included in the "Special Considerations" sections of the nutrient chapters.

Ages 0 Through 6 Months

Except for energy, the AI for infants ages 0 through 6 months was based on: (1) the average concentration of the nutrient in human milk from mothers who had been lactating from 2 to 6 months (using consensus values from several reported studies, if possible), and (2) an average volume of milk intake of 0.78 L/d. This volume was reported from studies that used test weighing of full-term infants. In this procedure, the infant is weighed before and after each feeding (Allen et al., 1991; Hofvander et al., 1982; Michaelsen et al., 1994; Neville et al., 1988). Because there is variation in both the composition of milk and the volume consumed, the computed value represents the mean. It is assumed that infants will consume increased volumes of human milk during growth spurts to meet their needs for maintenance, as well as for growth.

Ages 7 Through 12 Months

There is evidence for different nutrient needs for energy, protein, and amino acids during the period of infant growth and gradual weaning to a

mixed diet of human milk and solid foods from ages 7 through 12 months. There is little evidence, however, of markedly different needs for carbohydrate, fat, and *n*-6 and *n*-3 polyunsaturated fatty acids.

In previous DRI reports, some Estimated Average Requirements (EARs) for this age group were determined by extrapolating down from the EAR for young adults by adjusting for metabolic or total body size and growth. The AI was extrapolated up for infants ages 0 through 6 months by using the same type of adjustment (IOM, 2000). However, for the energy-yielding nutrients, these methods were not appropriate because the amount of energy required per body weight is significantly lower during the second 6 months, due largely to the slower rate of weight gain/kg of body weight.

Instead, the basis of the AIs derived for this age category for carbohydrate, fat, *n*-6 and *n*-3 polyunsaturated fatty acids, and protein was the sum of: (1) the content of the nutrient provided by 0.6 L/d of human milk, which is the average volume of milk reported from studies of infants receiving human milk in this age category (Dewey et al., 1984; Heinig et al., 1993), and (2) the content of the nutrient provided by the usual intakes of complementary weaning foods consumed by infants in this age category. Such an approach is in keeping with the current recommendations of the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), and the Institute of Medicine (IOM, 1991) for continued feeding of infants with human milk through 9 to 12 months of age with appropriate introduction of solid foods. This method has also been used for some nutrients in previous DRI reports.

The amounts of fat and carbohydrate consumed from complementary foods were determined by using data from the Third National Health and Nutrition Examination Survey. One problem encountered in deriving intake data in infants was the lack of available data on total nutrient intake from a combination of human milk and solid foods in the second 6 months of life. Most intake survey data do not identify the milk source, but the published values indicate that cow milk and cow milk formula were most likely consumed. Thus, it is assumed in deriving the AIs for infants 7 through 12 months of age that complementary food intake is similar in both infants consuming human milk and formula-fed infants.

METHODS TO DETERMINE THE DIETARY REQUIREMENTS FOR CHILDREN AND ADULTS

Setting Estimated Average Requirements for Children and Adults

As described previously, various types of studies can be considered for estimating an average requirement. As discussed in Chapter 1, additional

analysis of the data (e.g., transformation of data when nutrient requirements are not normally distributed) may be required. For determining estimated energy requirements using a doubly labeled water database, equations using stepwise multiple linear regressions were generated to predict total energy expenditure based on age, gender, height, and weight.

Extrapolating Data from Adults to Children

When data are lacking to set an Estimated Average Requirement (EAR) or Adequate Intake (AI) for children and adolescents, the EAR or AI can be extrapolated down by scaling requirements to the 0.75 power of body mass (IOM, 2001), which adjusts for metabolic differences demonstrated to be related to body weight, as described by Kleiber (1947) and explored further by West and coworkers (1997). Other approaches include extrapolating down based on the reference body weights, which has been done in developing Tolerable Upper Intake Levels (ULs) for some nutrients (IOM, 1997). Neither of these approaches, however, was used for setting an EAR or AI for the macronutrients under review as adequate data were available to develop Dietary Reference Intakes (DRIs) directly for the younger age groups.

Setting the Recommended Dietary Allowance for Children and Adults

To account for variability in requirements because of growth rates and other factors, a 10 percent coefficient of variation (CV) for the requirement is assumed unless data are available to support another value, as described in Chapter 1. For carbohydrate, protein, and the indispensable amino acids where EARs have been established, the CV was determined to be greater than 10 percent.

Methods to Determine Increased Needs for Pregnancy

It is known that the placenta actively transports certain nutrients from the mother to the fetus against a concentration gradient (Hay, 1994). However, for many nutrients, experimental data that could be used to set an EAR or AI for pregnancy are lacking. In these cases, the potential for increased need for these nutrients during pregnancy is based on theoretical considerations, including obligatory fetal transfer, if data are available, and on increased maternal needs related to increases in energy or protein metabolism, as applicable. Thus, in some cases, the EAR can be determined by the additional weight gained during pregnancy. Carmichael and colleagues (1997) reported that the median weight gain of women who

had good pregnancy outcomes was approximately 16 kg. In six studies of U.S. women, no consistent relationship between maternal age and weight gain was observed (IOM, 1990). Therefore, as is the case for protein, 16 kg is added to the reference weight for nonpregnant adolescent girls and women for setting the EAR.

Methods to Determine Increased Needs for Lactation

For the nutrients under study, it is assumed that the total requirement of lactating women equals the requirement for the nonpregnant, nonlactating woman of similar age plus an increment to cover the amount needed for milk production. To allow for inefficiencies in use of certain nutrients, the increment may be greater than the amount of the nutrient contained in the milk produced. Details are provided in each nutrient chapter.

ESTIMATES OF NUTRIENT INTAKE

Reliable and valid methods of food composition analysis are crucial in determining the intake of a nutrient needed to meet a requirement. While data regarding total fat, cholesterol, protein, and amino acid content of various foods have been available for many years, data for individual fatty acids have only recently been available. For nutrients such as energy, fiber, and *trans* fatty acids, analytical methods to determine the content of the nutrient in food have serious limitations.

Methodological Considerations

The quality of nutrient intake data varies widely across studies. The most valid intake data are those collected from the metabolic study protocols in which all food is provided by the researchers, amounts consumed are measured accurately, and the nutrient composition of the food is determined by reliable and valid laboratory analyses. Such protocols are usually possible with only a few subjects. Thus, in many studies, intake data are self-reported (e.g., through 24-hour recalls of food intake, diet records, or food frequency questionnaires).

Potential sources of error in estimating intake from self-reported intake data include over- or underreporting of portion sizes and frequency of intake, omission of foods, and inaccuracies related to the use of food composition tables (IOM, 2000; Lichtman et al., 1992; Mertz et al., 1991). In addition, because a high percentage of the food consumed in the United States and Canada is not prepared from scratch in the home, errors can occur due to a lack of information on how a food was manufactured,

prepared, and served. Therefore, the values reported by nationwide surveys or studies that rely on self-reporting are often inaccurate and possibly biased, with a greater tendency to underestimate actual intake (IOM, 2000).

It is well known that energy intake is underreported in national surveys (Cook et al., 2000; Mertz et al., 1991; Schoeller et al., 1990). Estimates of underreporting of energy intake in the Third National Health and Nutrition Examination Survey were 18 percent of the adult men and 28 percent of the adult women participating (Briefel et al., 1997). Underreporters indicated that their fat intake was approximately 30.5 percent calories, whereas "adequate" reporters indicated a fat intake of 35 percent of calories. In addition, alcohol intake, which accounted for approximately 4 percent of the total energy intake in men and 2 percent in women, is thought to be routinely underreported as well (McDowell et al., 1994).

Adjusting for Day-to-Day Variation

Because of day-to-day variation in dietary intakes, the distribution of 1-day (or 2-day) intakes for a group is wider than the distribution of usual intakes, even though the mean of the intakes may be the same (for further elaboration, see Chapter 13). To reduce this problem, statistical adjustments have been developed (NRC, 1986; Nusser et al., 1996) that require at least 2 days of dietary data from a representative subsample of the population of interest. However, no accepted method is available to adjust for the underreporting of intake, which may average as much as 18 to 28 percent for energy (Briefel et al., 1997; Mertz et al., 1991).

DIETARY INTAKES IN THE UNITED STATES AND CANADA

Sources of Dietary Intake Data

The major sources of current dietary intake data for the U.S. population include the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted from 1988 to 1994 by the U.S. Department of Health and Human Services, and the Continuing Survey of Food Intakes by Individuals (CSFII), which was conducted by the U.S. Department of Agriculture (USDA) from 1994 to 1996. NHANES III examined 30,000 individuals aged 2 months and older. A single 24-hour diet recall was collected for all participants. A second recall was collected for a 5 percent nonrandom subsample to allow adjustment of intake estimates for day-to-day variation. The CSFII collected two nonconsecutive 24-hour recalls from approximately 16,000 individuals of all ages. Both surveys used the food composition database developed by USDA to calculate nutrient

intakes (Perloff et al., 1990) and were adjusted by the method of Nusser and colleagues (1996).

Appendix D provides the mean and the 1st through 99th percentiles of intake for added sugars and amino acids from NHANES III, adjusted by methods described by the National Research Council (NRC, 1986) and by Feinleib and coworkers (1993) for persons aged 6 years and older. Appendix E provides similar data for energy, carbohydrate, dietary fiber, fat, fatty acids, cholesterol, protein, and alcohol by life stage group from the first phase of the CSFII, adjusted for day-to-day variation by the method of Nusser and colleagues (1996).

Survey data from 1990 to 1997 for several Canadian provinces are available for energy, carbohydrate, fat, saturated fat, and protein intake (Appendix F).

Food Sources

For some nutrients, two types of information are provided about food sources: identification of the foods that are the major contributors of the nutrients to diets in the United States, and the food sources that have the highest content of the nutrient. The determination of foods that are major contributors depends on both nutrient content of a food and the total consumption of the food (amount and frequency). Therefore, a food that has a relatively low concentration of a nutrient might still be a large contributor to total intake if that food is consumed in relatively large amounts.

SUMMARY

General methods for examining and interpreting the evidence for establishing reference intakes for macronutrients are presented in this chapter, with special attention given to infants, children, and pregnant and lactating women. Methodological problems and sources of dietary intake data are also discussed. Relevant details are provided in the nutrient chapters that follow.

REFERENCES

AAP (American Academy of Pediatrics). 1997. Breastfeeding and the use of human milk. *Pediatrics* 100:1035–1039.

Allen JC, Keller RP, Archer P, Neville MC. 1991. Studies in human lactation: Milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutr* 54:69–80.

Briefel RR, Sempos CT, McDowell MA, Chien S, Alaimo K. 1997. Dietary methods research in the Third National Health and Nutrition Examination Survey: Underreporting of energy intake. *Am J Clin Nutr* 65:1203S–1209S.

Carmichael S, Abrams B, Selvin S. 1997. The pattern of maternal weight gain in women with good pregnancy outcomes. *Am J Public Health* 87:1984–1988.

Cook A, Pryer J, Shetty P. 2000. The problem of accuracy in dietary surveys. Analysis of the over 65 UK National Diet and Nutrition Survey. *J Epidemiol Community Health* 54:611–616.

Dewey KG, Finley DA, Lönnerdal B. 1984. Breast milk volume and composition during late lactation (7–20 months). *J Pediatr Gastroenterol Nutr* 3:713–720.

Dienel GA, Hertz L. 2001. Glucose and lactate metabolism during brain activation. *J Neurosci Res* 66:824–838.

Feinleib M, Rifkind B, Sempos C, Johnson C, Bachorik P, Lippel K, Carroll M, Ingster-Moore L, Murphy R. 1993. Methodological issues in the measurement of cardiovascular risk factors: Within-person variability in selected serum lipid measures—Results from the Third National Health and Nutrition Survey (NHANES III). *Can J Cardiol* 9:87D–88D.

Hay WW. 1994. Placental transport of nutrients to the fetus. *Horm Res* 42:215–222.

Health Canada. 1990. *Nutrition Recommendations. The Report of the Scientific Review Committee 1990.* Ottawa: Canadian Government Publishing Centre.

Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B, Dewey KG. 1993. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: The DARLING Study. *Am J Clin Nutr* 58:152–161.

Heitmann BL, Lissner L. 1995. Dietary underreporting by obese individuals—Is it specific or non-specific? *Br Med J* 311:986–989.

Hill AB. 1971. *Principles of Medical Statistics*, 9th ed. New York: Oxford University Press.

Hofvander Y, Hagman U, Hillervik C, Sjolin S. 1982. The amount of milk consumed by 1–3 months old breast- or bottle-fed infants. *Acta Paediatr Scand* 71:953–958.

IOM (Institute of Medicine). 1990. *Nutrition During Pregnancy.* Washington, DC: National Academy Press.

IOM. 1991. *Nutrition During Lactation.* Washington, DC: National Academy Press.

IOM. 1997. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academy Press.

IOM. 2000. *Dietary Reference Intakes: Applications in Dietary Assessment.* Washington, DC: National Academy Press.

IOM. 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academy Press.

Kleiber M. 1947. Body size and metabolic rate. *Physiol Rev* 27:511–541.

Lichtman SW, Pisarska K, Berman ER, Pestone M, Dowling H, Offenbacher E, Weisel H, Heshka S, Matthews DE, Heymsfield SB. 1992. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med* 327:1893–1898.

McDowell MA, Briefel RR, Alaimo K, Bischof AM, Caughman CR, Carroll MD, Loria CM, Johnson CL. 1994. Energy and macronutrient intakes of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. *Adv Data* 255:1–24.

Mertz W, Tsui JC, Judd JT, Reiser S, Hallfrisch J, Morris ER, Steele PD, Lashley E. 1991. What are people really eating? The relation between energy intake derived from estimated diet records and intake determined to maintain body weight. *Am J Clin Nutr* 54:291–295.

Michaelsen KF, Larsen PS, Thomsen BL, Samuelson G. 1994. The Copenhagen Cohort Study on Infant Nutrition and Growth: Breast-milk intake, human milk macronutrient content, and influencing factors. *Am J Clin Nutr* 59:600–611.

Neville MC, Keller R, Seacat J, Lutes V, Neifert M, Casey C, Allen J, Archer P. 1988. Studies in human lactation: Milk volumes in lactating women during the onset of lactation and full lactation. *Am J Clin Nutr* 48:1375–1386.

NRC (National Research Council). 1986. *Nutrient Adequacy: Assessment Using Food Consumption Surveys.* Washington, DC: National Academy Press.

Nusser SM, Carriquiry AL, Dodd KW, Fuller WA. 1996. A semiparametric transformation approach to estimating usual daily intake distributions. *J Am Stat Assoc* 91:1440–1449.

Perloff BP, Rizek RL, Haytowitz DB, Reid PR. 1990. Dietary intake methodology. II. USDA's Nutrient Data Base for Nationwide Dietary Intake Surveys. *J Nutr* 120:1530–1534.

Schoeller DA, Bandini LG, Dietz WH. 1990. Inaccuracies in self-reported intake identified by comparison with the doubly labelled water method. *Can J Physiol Pharmacol* 68:941–949.

Sempos CT, Liu K, Ernst ND. 1999. Food and nutrient exposures: What to consider when evaluating epidemiologic evidence. *Am J Clin Nutr* 69:1330S–1338S.

West GB, Brown JH, Enquist BJ. 1997. A general model for the origin of allometric scaling laws in biology. *Science* 276:122–126.

Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. 1985. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 122:51–65.

3

Relationship of Macronutrients and Physical Activity to Chronic Disease

OVERVIEW

Over the last 40 years, a growing body of evidence has accumulated regarding the relationships among consumption of dietary fat, carbohydrate, protein, and energy and risk of chronic disease. The fact that diets are usually composed of a variety of foods that include varying amounts of carbohydrate, protein, and various fats imposes some limits on the type of research that can be conducted to ascertain causal relationships. The available data regarding the relationships among major chronic diseases that have been linked with consumption of dietary energy and macronutrients (fats, carbohydrates, fiber, and protein), as well as physical inactivity, are discussed below and are reviewed in greater detail in the specific nutrient chapters (Chapters 5 through 11) and the chapter on physical activity (Chapter 12).

CANCER

Diet has long been suspected as a cancer-causing agent. Early studies in animals showed that diet could influence carcinogenesis (Tannenbaum, 1942; Tannenbaum and Silverstone, 1957). Cross-cultural studies that compare incidence rates of specific cancers across populations have found great differences in cancer incidence, and dietary factors, at least in part, have been implicated as causes of these differences (Armstrong and Doll, 1975; Gray et al., 1979; Rose et al., 1986). In addition, observational studies have found strong correlations among dietary components and incidence and mortality rates of cancer (Armstrong and Doll, 1975).

Associations among dietary fat, carbohydrates, and protein and cancer have been hypothesized. Many of these associations, however, have not been supported by clinical and interventional studies in humans.

Increased intakes of energy, total fat, *n*-6 polyunsaturated fatty acids, cholesterol, sugars, protein, and some amino acids have been thought to increase the risk of various cancers, whereas intakes of *n*-3 fatty acids, dietary fiber, and physical activity are thought to be protective. The major findings and potential mechanisms for these relationships are discussed below.

Energy

Animal studies suggest that restriction of energy intake may inhibit cell proliferation (Zhu et al., 1999) and tumor growth (Wang et al., 2000). A risk of mortality from cancer has been associated with increased energy intakes during childhood (Frankel et al., 1998; Must and Lipman, 1999). Excess energy intake is a contributing factor to obesity, which is thought to increase the risk of certain cancers (Carroll, 1998). To support this concept, a number of studies have observed a positive association between energy intake during adulthood and risk of cancer (Andersson et al., 1996; Lissner et al., 1992; Lyon et al., 1987), whereas other studies did not find an association (Stemmermann et al., 1985).

Dietary Fat

High intakes of dietary fat have been implicated in the development of certain cancers. Early cross-cultural and case-control studies reported strong associations between total fat intake and breast cancer (Howe et al., 1991; Miller et al., 1978; van't Veer et al., 1990), yet a number of epidemiological studies, most in the last 15 years, have found little or no association (Hunter et al., 1996; Jones et al., 1987; Kushi et al., 1992; van den Brandt et al., 1993; Velie et al., 2000; Willett et al., 1987, 1992). Evidence from epidemiological studies on the relationship between fat intake and colon cancer has been mixed as well (De Stefani et al., 1997b; Giovannucci et al., 1994; Willett et al., 1990). Howe and colleagues (1997) reported no association between fat intake and risk of colorectal cancer from the combined analysis of 13 case-control studies. Epidemiological studies tend to suggest that dietary fat intake is not associated with prostate cancer (Ramon et al., 2000; Veierød et al., 1997b). Giovannucci and coworkers (1993), however, reported a positive association between total fat consumption, primarily animal fat, and risk of advanced prostate cancer. Findings on the association between fat intake and lung cancer have been mixed (De Stefani et al., 1997a; Goodman et al., 1988; Veierød et al., 1997a; Wu et al.,

1994). Numerous mechanisms for the carcinogenic effect of dietary fat have been proposed, including eiconasanoid metabolism, cellular proliferation, and alteration of gene expression (Birt et al., 1999).

Experimental evidence suggests several mechanisms in which *n*-3 fatty acids may protect against cancer. *n*-3 Fatty acids, particularly docosahexaenoic acid and eicosapentaenoic acid, have been shown to suppress neoplastic transformation (Takahashi et al., 1992), inhibit cell growth and proliferation (Anti et al., 1992; Calviello et al., 1998; Grammatikos et al., 1994), induce apoptosis (Calviello et al., 1998; Lai et al., 1996), and inhibit angiogenesis (Rose and Connolly, 2000), which may occur by suppressing *n*-6 fatty acid eicosanoid production. Epidemiological studies have shown an inverse relationship between fish consumption and the risk of breast and colorectal cancer (Caygill and Hill, 1995; Caygill et al., 1996; Kaizer et al., 1989; Sasaki et al., 1993; Willett et al., 1990).

Monounsaturated fatty acids have been reported as being protective against breast, colon, and possibly prostate cancer (Bartsch et al., 1999). However, there is also some epidemiological evidence for a positive association between these fatty acids and breast cancer risk in women with no history of benign breast disease (Velie et al., 2000) and prostate cancer in men (Schuurman et al., 1999). There may be protective effects associated with olive oil (Rose, 1997; Trichopoulou et al., 1995; Willett, 1997); however, these benefits may reflect constituents other than monounsaturated fatty acids.

Dietary Carbohydrate

While the data on sugar intake and cancer are limited and insufficient, several case-control studies have shown an increased risk of colorectal cancer among individuals with high intakes of sugar-rich foods (Benito et al., 1990; Macquart-Moulin et al., 1986, 1987; Tuyns et al., 1988). Additionally, high vegetable and fruit consumption and avoidance of foods containing highly refined sugars were shown to be negatively correlated to the risk of colon cancer (Giovannucci and Willett, 1994).

Dietary Fiber

There is some evidence based on observational and case-control studies that fiber-rich diets are protective against colorectal cancer (Lanza, 1990; Trock et al., 1990). There is also some epidemiological evidence of a protective effect of cereals and cereal fiber against colon carcinogenesis (Hill, 1997). Despite these and other positive findings, a number of important studies (Fuchs et al., 1999; Giovannucci and Willett, 1994) and three recent clinical intervention trials (Alberts et al., 2000; Bonithon-Kopp et al., 2000;

Schatzkin et al., 2000) do not support a protective effect of dietary fiber against colon cancer, and the issue remains to be resolved.

High-fiber diets may also be protective against the development of colonic adenomas (Giovannucci et al., 1992; Hoff et al., 1986; Little et al., 1993; Macquart-Moulin et al., 1987; Neugut et al., 1993). However, not all studies have found a significant association between the dietary intake of total, cereal, or vegetable fiber and colorectal adenomas, although a slight reduction in risk was observed with increasing intake of fruit fiber (Platz et al., 1997).

There are numerous hypotheses as to how fiber might protect against the development of colon cancer. These include the dilution of carcinogens, procarcinogens, and tumor promoters in a bulky stool; a more rapid rate of transit through the colon with high-fiber diets; a reduction in the ratio of secondary bile acids to primary bile acids by acidifying colonic contents; the production of butyrate from the fermentation of dietary fiber by the colonic microflora; and the reduction of ammonia, which is known to be toxic to cells (Harris and Ferguson, 1993; Jacobs, 1986; Klurfeld, 1992; Van Munster and Nagengast, 1993; Visek, 1978).

Fiber has been shown to lower serum estrogen concentrations (Rose et al., 1991), and therefore may have a protective effect against hormone-related cancers. Recent studies have shown a decreased risk of endometrial cancer (Barbone et al., 1993; Goodman et al., 1997), ovarian cancer (Risch et al., 1994; Tzonou et al., 1993), and prostate cancer (Andersson et al., 1996) with high fiber intakes. More research is needed before conclusions can be drawn on these relationships.

Although fiber has the ability to decrease blood estrogen concentrations by a variety of different mechanisms (Rose et al., 1991), it is not yet known whether this action is sufficient to decrease the risk of breast cancer. Half of the epidemiological studies attempting to link low dietary fiber intake to breast cancer have failed to show this relationship (Gerber, 1998). The data on cereal intake and breast cancer risk are considerably stronger than overall fiber intake (Rohan et al., 1993), suggesting that certain cereal foods are protective or that only certain types and stages of breast cancer respond to these interventions.

Physical Activity

Regular exercise, as recommended in this report, has been shown to be negatively correlated with the risk of colon cancer (Colbert et al., 2001; White et al., 1996). This is, in part, due to the reduction in obesity, which is positively related to cancer (Carroll, 1998). In men and women who are physically active, the risk of colon cancer is reduced by 30 to 40 percent compared with those who are sedentary. A plausible mechanism for the

effect of physical activity on colon cancer is the shortening of intestinal transit time, thus reducing contact time between intestinal mucosa and carcinogens and mutagens in the diet that are carried in the fecal stream (Batty and Thune, 2000).

Examination of more than 30 epidemiological studies concluded that regular physical activity decreased the risk of breast cancer by 20 to 40 percent (IARC, 2002). However, relatively few studies found a consistent association between physical activity and decreased incidence of endometrial cancer. For prostate cancer, results of about 20 studies were less consistent, with only moderately strong relationships. As endogenous sex steroids have been implicated in the development of breast, endometrial, and prostrate cancers, a plausible explanation for the inverse relationship among physical activity and reproductive organ cancers may involve the effect of exercise on the binding and turnover of sex steroids and glucoregulatory hormones, as well as the overall effect of exercise on body fat (IARC, 2002; Vainio and Bianchini, 2001).

With regard to the possible effect of exercise on other forms of cancer, such as pancreatic cancer (Michaud et al., 2001), exercise may also play a beneficial role by compensating for effects of excess energy intake; by modifying the effects of carcinogens, cocarcinogens, and cancer promoters; or by decreasing body fat and lessening the accumulation of cancer-causing substances in body tissues (Shephard, 1990, 1996). Regular activity may also bolster the immune system (Bruunsgaard et al., 1999; Mazzeo et al., 1998).

HEART DISEASE

The known risk factors for coronary heart disease (CHD) include high serum low density lipoprotein (LDL) cholesterol concentration, low serum high density lipoprotein (HDL) cholesterol concentration, a family history of CHD, hypertension, diabetes mellitus, cigarette smoking, advancing age, and obesity (Castelli, 1996; Hennekens, 1998; Parmley, 1997). There is a positive linear relationship between serum total cholesterol and LDL cholesterol concentrations and risk of CHD or mortality from CHD (Jousilahti et al., 1998; Neaton and Wentworth, 1992; Sorkin et al., 1992; Stamler et al., 1986). A low concentration of HDL cholesterol is positively correlated with risk of CHD, independent of other risk factors (Austin et al., 2000).

High concentrations of serum triacylglycerol may also contribute to CHD (Austin, 1989), but the evidence is less clear. Most studies show a positive relationship between serum triacylglycerol and CHD (Bainton et al., 1992; Carlson and Böttiger, 1972; Gordon et al., 1977; Hulley et al., 1980; Stampfer et al., 1996); however, Gordon and coworkers (1977) found

that the statistical significance of this relationship disappears after controlling for total cholesterol, LDL cholesterol, or HDL cholesterol.

The role of diet in the promotion or prevention of heart disease is the subject of considerable research. New studies investigating dietary energy sources and physical activity for their potential to alter some of the risk factors for heart disease are underway (i.e., plasma cholesterol, hypertension, obesity, and diabetes).

Dietary Fat

Increasing the intake of saturated fat can increase serum total cholesterol and LDL cholesterol concentrations (Clarke et al., 1997; Hegsted et al., 1993; Kasim et al., 1993; Krauss and Dreon, 1995; Mensink and Katan, 1992). Furthermore, a meta-analysis of 37 intervention studies showed that a reduction in plasma total cholesterol and LDL cholesterol concentrations was correlated with reductions in percentages of total dietary fat that also included a decrease in saturated fats (Yu-Poth et al., 1999). The correlation between total fat and serum cholesterol concentration is due, in part, to the strong positive association between total fat and saturated fat intake and the weak association between total fat and polyunsaturated fat intake (Masironi, 1970; Stamler, 1979). Furthermore, the impact of saturated fats in increasing LDL cholesterol concentration is twofold greater than the impact of polyunsaturated fats in reducing LDL cholesterol (Hegsted et al., 1993; Mensink and Katan, 1992). This effect, however, is not seen with all saturated fatty acids. While lauric, myristic, and palmitic acids increase cholesterol concentration (Mensink et al., 1994), stearic acid has been shown to have a neutral effect (Bonanome and Grundy, 1988; Denke, 1994; Yu et al., 1995).

Similar to saturated fat, increasing intakes of *trans* fatty acids and cholesterol increase serum total cholesterol and LDL cholesterol concentrations (Ascherio et al., 1999; Clarke et al., 1997; Hegsted, 1986; Howell et al., 1997). Epidemiological studies have generally demonstrated a positive association between *trans* fatty acid intake and increased risk of heart disease (Ascherio et al., 1994, 1996b; Hu et al., 1997; Pietinen et al., 1997; Willett et al., 1993); however, the risk with cholesterol intake has been mixed (Ascherio et al., 1996b; Hu et al., 1997, 1999b; Kushi et al., 1985; Mann et al., 1997; Pietinen et al., 1997). There is wide interindividual variation in serum cholesterol response to dietary cholesterol (Hopkins, 1992), which may be due to genetic factors.

Monounsaturated and polyunsaturated fatty acids decrease serum total cholesterol and LDL cholesterol concentrations (Gardner and Kraemer, 1995). The epidemiological data indicate that monounsaturated fats are either not associated or are positively associated with risk of CHD (Hu et

al., 1997; Kromhout and de Lezenne Coulander, 1984; Pietinen et al., 1997). High intakes of *n*-6 polyunsaturated fats have been associated with the reduced total cholesterol and LDL cholesterol concentrations that are associated with low risk of CHD (Arntzenius et al., 1985; Becker et al., 1983; Sonnenberg et al., 1996). In general, epidemiological studies have demonstrated an inverse association between *n*-6 polyunsaturated fatty acid intake and risk of CHD (Arntzenius et al., 1985; Gartside and Glueck, 1993).

n-3 Polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) have been shown to reduce the risk of CHD and stroke by a multitude of mechanisms: by preventing arrhythmias (Billman et al., 1999; Kang and Leaf, 1996; McLennan, 1993), reducing atherosclerosis (von Schacky et al., 1999), decreasing platelet aggregation (Harker et al., 1993), lowering plasma triacylglycerol concentrations (Harris, 1989), decreasing proinflammatory eicosanoids (James et al., 2000), modulating endothelial function (De Caterina et al., 2000), and decreasing blood pressure in hypertensive individuals (Morris et al., 1993). Many epidemiological studies have used fish or fish oil intake as a surrogate for *n*-3 fatty acid intake because of the high content of EPA and DHA found in fish. A number of these studies have concluded that fish consumption reduced the risk of CHD mortality (Daviglus et al., 1997; Dolecek, 1992; Kromhout et al., 1985, 1995), while others found no association (Albert et al., 1998; Ascherio et al., 1995).

Dietary Carbohydrate

High carbohydrate (low fat) intakes tend to increase plasma triacylglycerol and decrease plasma HDL cholesterol concentrations (Borkman et al., 1991; Brussaard et al., 1982; Marckmann et al., 2000; West et al., 1990; Yost et al., 1998). This effect has been observed especially for increased sugar intake (Mann et al., 1973; Rath et al., 1974; Reiser et al., 1979; Yudkin et al., 1986). Fructose is a better substrate for de novo lipogenesis than glucose or starches (Cohen and Schall, 1988; Reiser and Hallfrisch, 1987), and Parks and Hellerstein (2000) concluded that hypertriacylglycerolemia is more extreme if the carbohydrate content of the diet consists primarily of monosaccharides, particularly fructose.

Dietary Fiber

Evidence supports a protective effect of dietary fiber for CHD, particularly viscous fibers that occur naturally in foods, which reduce total cholesterol and LDL cholesterol concentrations (see Chapter 7). Reduced rates of CHD were observed in individuals consuming high fiber diets (Jacobs et al., 1998; Kushi et al., 1985; Pietinen et al., 1996). These studies used fiber-

containing foods; fiber supplements may not have the same effects. The type of fiber is important; oat bran (viscous fiber) significantly reduces total cholesterol, but wheat bran (primarily nonviscous fiber) may not (Behall, 1990). Viscous fibers are thought to lower serum cholesterol concentrations by interfering with absorption and recirculation of bile acids and cholesterol in the intestine and thus decreasing the concentration of circulating cholesterol. These fibers may also work by delaying absorption of fat and carbohydrate, which could result in increased insulin sensitivity (Hallfrisch et al., 1995) and lower triacylglycerol concentrations (Rivellese et al., 1980). Dietary fiber intake has also been shown to be negatively associated with hypertension in men (Ascherio et al., 1992), but not women (Ascherio et al., 1996a). Fiber intake was shown to have an inverse relationship with systolic and diastolic pressures (Ashcerio et al., 1996a).

Dietary Protein

An inverse relationship between protein intake and risk of CHD has been observed (Hu et al., 1999a). High protein intake has been shown to lower blood pressure (Obarzanek et al., 1996), and substitution of carbohydrate with protein resulted in lower LDL cholesterol and triacylglycerol concentrations (Wolfe and Piché, 1999). These results may, however, be confounded by the fact that dietary animal protein and dietary fat tend to be highly correlated. Independent effects of protein on CHD mortality have not been shown (Gordon et al., 1981; Keys et al., 1986). Soy-based protein may reduce serum cholesterol concentrations, but the evidence has been mixed (Anderson et al., 1995; Bakhit et al., 1994; Meinertz et al., 1989; van Raaij et al., 1982).

Physical Activity

Exercise improves and maintains vessel function. An inverse relationship between exercise and CHD mortality has been observed in numerous studies (Arraiz et al., 1992; Kannel et al., 1986; Lindsted et al., 1991; Paffenbarger et al., 1984). Regular exercise increases serum HDL cholesterol, decreases serum triacylglycerol, decreases blood pressure, enhances fibrinolysis, lessens platelet adherence, enhances glucose effectiveness and insulin sensitivity, and decreases risk of cardiac arrhythmias (Araújo-Vilar et al., 1997; Arroll and Beaglehole, 1992; El-Sayed, 1996; Hinkle et al., 1988; Huttunen et al., 1979).

The mechanisms by which exercise serves to mitigate progression of cardiovascular disease (CVD) and coronary artery disease (CAD) are numerous. For instance, patients with CAD who participated in exercise training showed improved endothelium-dependent vasodilatation in epi-

cardial coronary vessels and in resistance vessels (Hambrecht et al., 2000). Thus, exercise serves to maintain conduit function in vessels impacted by CAD. An inverse dose–response relationship between physical activity and physical fitness and CVD mortality has been documented (Arraiz et al., 1992; Blair et al., 1993; Kannel and Sorlie, 1979; Kannel et al., 1986; Lindsted et al., 1991; Paffenbarger et al., 1984).

Activity may also influence CVD indirectly via an influence on lipoprotein metabolism. Vigorous physical activity increases plasma HDL cholesterol, HDL_2, and apolipoprotein A-I and decreases plasma triacylglycerol, very low density lipoprotein, and atherogenic small, dense LDL concentrations (Williams et al., 1986, 1990, 1992; Wood et al., 1988). Gradient gel electrophoresis shows that the protective HDL_{2b} subclass is increased while the HDL_{3b} subclass is decreased through exercise (Williams et al., 1992). The distribution of LDL is shifted toward larger and more buoyant particles of lower density that result in a decrease in the prevalence of the small, dense LDL phenotype among vigorously active men (Williams et al., 1990). Cross-sectional comparisons of high mileage and low mileage runners suggest that the benefits of vigorous exercise on the lipoprotein profile increase linearly with exercise dose through at least 40 mi (64 km)/wk for both HDL cholesterol and triacylglycerol (Williams, 1997). Physical activity prevents the rise in plasma triacylglycerols in individuals who consume high carbohydrate diets (Koutsari et al., 2001).

Many of the exercise-induced changes in lipoproteins may arise from the effects of lipolytic enzymes on lipoprotein size and composition, namely increases in lipoprotein lipase activity and decreases in hepatic lipase activity (Williams et al., 1986). Runners have significantly higher lipoprotein lipase activity in both muscle and adipose tissue (Nikkilä et al., 1978). Weight loss is known to both increase lipoprotein lipase and reduce hepatic lipase (Marniemi et al., 1990; Purnell et al., 2000). This may explain, in part, why increases in HDL cholesterol and HDL_2 mass in sedentary men who begin exercising vigorously are strongly associated with loss of body fat (Williams et al., 1983). Lipoprotein lipase activity may also explain why HDL cholesterol concentrations in sedentary men predict their success at running (Williams et al., 1994). Specifically, the enzyme's activity is positively correlated with HDL cholesterol concentrations and is higher in slow-twitch red muscle fibers. Thus, high HDL concentrations may be a marker for muscle fiber composition that facilitates endurance exercise.

DENTAL CARIES

Sugars play an important role in dental caries development (Walker and Cleaton-Jones, 1992). Sugars provide a favorable environment for bac-

teria in the mouth, and the presence of these sugars increases the rate and volume of plaque formation (Depaola et al., 1999). However, because development of caries involves other factors such as fluoride intake, oral hygiene, food composition, and frequency of meals and snacks, sugar intake alone is not the only cause of caries.

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus is characterized by a genetic predisposition to the disorder, decreased tissue sensitivity to insulin (insulin resistance), and impaired function of pancreatic β-cells, which control the timely release of insulin (Anderson, 1999). Obesity, physical inactivity, and advancing age are primary risk factors for insulin resistance and development of type 2 diabetes (Barrett-Connor, 1989; Colditz et al., 1990; Helmrich et al., 1991; Manson et al., 1991). Dietary factors have also been suggested as playing a major role in the development of insulin resistance and type 2 diabetes.

Dietary Fat

Intervention studies that have evaluated the effect of the level of fat intake on biochemical risk factors for diabetes have been mixed (Abbott et al., 1989; Borkman et al., 1991; Coulston et al., 1983; Fukagawa et al., 1990; Howard et al., 1991; Jeppesen et al., 1997; Leclerc et al., 1993; Straznicky et al., 1999; Swinburn et al., 1991; Thomsen et al., 1999; Yost et al., 1998). Some epidemiological studies have shown a correlation between higher fat intakes and insulin resistance (Marshall et al., 1991; Mayer-Davis et al., 1997; Parker et al., 1993). It is not clear, however, whether the correlation is due to fat in the diet or to obesity. Obesity, particularly abdominal obesity, is a risk factor for type 2 diabetes (Vessby, 2000). Decreased physical activity is also a significant predictor of higher postprandial insulin concentrations and may confound some studies (Feskens et al., 1994; Parker et al., 1993).

Findings from intervention studies tend to suggest a lack of adverse effect of saturated fat on risk indictors of diabetes in healthy individuals (Fasching et al., 1996; Roche et al., 1998; Thomsen et al., 1999). However, it was recently reported that the consumption of saturated fatty acids can significantly impair insulin sensitivity (Vessby et al., 2001).

Because of the favorable effects of *n*-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) on risk indicators of coronary heart disease, they are often used in patients with lipid disorders. There has been concern about the use of these fatty acids for lipid disorders because many of these patients also have type 2 diabetes. A number of studies have sug-

gested that *n*-3 polyunsaturated fatty acid intake may have adverse effects in individuals with type 2 diabetes (Glauber et al., 1988; Kasim et al., 1988), requiring increased doses of hypoglycemic agents (Friday et al., 1989; Stacpoole et al., 1989; Zambon et al., 1992).

Dietary Carbohydrate

There is little evidence that total dietary carbohydrate intake is associated with type 2 diabetes (Colditz et al., 1992; Lundgren et al., 1989). There may be an increased risk, however, when the glycemic index of a meal is considered instead of total carbohydrates (Salmerón et al., 1997a, 1997b). Some studies have found that reducing the glycemic index of a meal can result in short-term improved glucose tolerance and insulin sensitivity in healthy individuals (Frost et al., 1998; Jenkins et al., 1988; Liljeberg et al., 1999; Wolever et al., 1988). Additional long-term studies are needed to elucidate the true relationship between glycemic index and the development of type 2 diabetes and to determine its effect on glucose tolerance and insulin.

Dietary Fiber

Certain dietary fibers may attenuate the insulin response and thus be protective against type 2 diabetes. There is good epidemiological evidence for the protective effect of fiber against type 2 diabetes (Colditz et al., 1992; Meyer et al., 2000; Salmerón et al., 1997a, 1997b). Viscous soluble fibers, such as pectin and guar gum, have been found to produce a significant reduction in glycemic response in the majority of studies reviewed by Wolever and Jenkins (1993). It is believed that viscous soluble fibers reduce the glycemic response of food by delaying gastric emptying and therefore delaying the absorption of glucose (Jenkins et al., 1978; Wood et al., 1994).

Physical Activity

Increased levels of physical activity have been found to improve insulin sensitivity in individuals with type 2 diabetes (Horton, 1986; Mayer-Davis et al., 1998; Schneider et al., 1984). Physical inactivity was found to be associated with increased incidence of type 2 diabetes in cross-sectional (King et al., 1984; Taylor et al., 1983), cohort (Helmrich et al., 1991; Manson et al., 1991, 1992), and longitudinal training studies (Tuomilehto et al., 2001). Short- and long-term effects of physical activity on glucose tolerance, insulin action, and muscle glucose uptake show that contracting muscle has an "insulin-like" effect on promoting glucose uptake and metabolism (Bergman et al., 1999; Horton, 1991; Richter et al., 1981). This synergistic

effect of contractions on insulin action is thought to increase insulin action and decrease circulating glucose and insulin concentrations. Further, by increasing muscle mass, decreasing total and abdominal obesity (Björntorp et al., 1979; Després et al., 1988), and diverting dietary carbohydrate to muscle for oxidation and glycogen repletion (Brooks et al., 2000), physical activity reduces the potential for energy intakes exceeding expenditures, leading to fat accumulation. Physical activity can reduce the risk of type 2 diabetes (Diabetes Prevention Program Research Group, 2002; Tuomilehto et al., 2001), and can also reduce total and abdominal obesity, both of which are risk factors for type 2 diabetes (Vessby, 2000).

OBESITY

Obesity results from an imbalance between energy intake and energy expenditure. The health risks associated with obesity include increased mortality, hypertension, cardiovascular disease, diabetes mellitus, gallbladder disease, some cancers, and changes in endocrine function and metabolism (NHLBI/NIDDK, 1998). The risk factors for becoming obese are not entirely understood but are thought to include genetics, food intake, physical inactivity, and some rare metabolic disorders (NHLBI/NIDDK, 1998).

Dietary Fat

The available data on whether diets high in total fat increase the risk for obesity are conflicting and are complicated by underreporting of food intake, notably fat intake (Bray and Popkin, 1998; Lissner and Heitmann, 1995; Lissner et al., 2000; Willett, 1998). Intervention studies have shown that high-fat diets, as compared with low-fat diets with equivalent energy intake, are not intrinsically fattening (Davy et al., 2001), whereas cross-cultural, animal, and some human studies have provided support for the theory that diets with a high percentage of fat increase the risk of obesity (Astrup et al., 1997; Lissner and Heitmann, 1995; West and York, 1998). Other studies have shown that as the proportion of fat in the diet increases, so does energy intake (Kendall et al., 1991; Lissner et al., 1987; Stubbs et al., 1995). Because energy density was not kept separate from fat content in these studies, recent investigators have questioned the conclusions of these studies and have found differing results. Further studies have shown that fat content does not affect energy intake (Saltzman et al., 1997; Stubbs et al., 1996; van Stratum et al., 1978), and that energy density has an effect on energy intake independent of the fat content of the diet (Bell et al., 1998).

Dietary Carbohydrate

A negative correlation between total sugars intake and body mass index has been reported in adults (Dreon et al., 1988; Dunnigan et al., 1970; Fehily et al., 1984; Gibson, 1993, 1996b; Miller et al., 1990). Increased added sugars intakes have been shown to result in increased energy intakes of children and adults (see Chapter 6) (Bowman, 1999; Gibson, 1996a, 1997; Lewis et al., 1992). In spite of this, a negative correlation between added sugars intake and body mass index has been observed in children (Bolton-Smith and Woodward, 1994; Gibson, 1996a; Lewis et al., 1992). Published reports disagree about whether a direct link exists between the trend toward higher intakes of sugars and increased rates of obesity. Any association between added sugars intake and body mass index is, in all likelihood, masked by the pervasive and serious problem of underreporting, which is more prevalent and severe among the obese population. In addition, foods and beverages high in added sugars are more likely to be underreported compared to other foods that may be perceived as "healthy" (Johnson, 2000).

Dietary Fiber

Consumption of soluble fibers, which are low in energy, delays gastric emptying (Roberfroid, 1993), which in turn can cause an extended feeling of fullness and therefore satiety (Bergmann et al., 1992). A number of intervention studies suggest that diets high in fiber may assist in weight loss (Birketvedt et al., 2000; Eliasson et al., 1992; Rigaud et al., 1990; Rössner et al., 1987; Ryttig et al., 1989), although other studies have not found this effect (Astrup et al., 1990; Baron et al., 1986). Thus, the evidence to support a role of fiber in the prevention of obesity is unclear at this time.

Physical Activity

Energy expenditure by physical activity (see Chapters 5 and 12) varies considerably between individuals, affecting the energy balance and the body composition by which energy balance and weight maintenance are achieved (Ballor and Keesey, 1991; Williamson et al., 1993). Indeed, physical inactivity is a major risk factor for development of obesity in children and adults (Astrup, 1999; Goran, 2001). In one study, increasing the level of physical activity in obese individuals appeared to have no effect on food intake, whereas in normal-weight individuals an increase in activity was coupled with an increase in food intake (Pi-Sunyer and Woo, 1985).

SKELETAL HEALTH

Physical activity has a beneficial effect on bone health in individuals of all ages (Anderson, 2000; French et al., 2000; Hurley and Roth, 2000; Khan et al., 2000; Layne and Nelson, 1999; Madsen et al., 1998). Physical activity increases bone mass in children and adolescents and maintains bone mass in adults (French et al., 2000; Khan et al., 2000). In elderly individuals, bone mineral density has been found to be higher in those who exercise than in those who do not (Hurley and Roth, 2000). The same is true for young athletes compared to nonathletes (Madsen et al., 1998). Physical activity results in muscle strength, coordination, and flexibility that may benefit elderly individuals by preventing falls and fractures.

SUMMARY

Many causal relationships among over- or underconsumption of macronutrients, physical inactivity, and chronic disease have been proposed. When the diet is modified for one energy-yielding nutrient, it invariably changes the intake of other nutrients, which makes it extremely difficult to have adequate substantiating evidence for providing clear and specific nutritional guidance. Acceptable Macronutrient Distribution Ranges can be estimated, however, by considering risk of chronic disease, as well as in the context of consuming adequate amounts of essential macronutrients and micronutrients. This information is provided in detail in Chapter 11.

REFERENCES

Abbott WGH, Boyce VL, Grundy SM, Howard BV. 1989. Effects of replacing saturated fat with complex carbohydrate in diets of subjects with NIDDM. *Diabetes Care* 12:102–107.

Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN, Manson JE. 1998. Fish consumption and risk of sudden cardiac death. *J Am Med Assoc* 279:23–28.

Alberts DS, Martínes ME, Roe DJ, Guillén-Rodríguez JM, Marshall JR, van Leeuwen JB, Reid ME, Ritenbaugh C, Vargas PA, Bhattacharyya AB, Earnest DL, Sampliner RE. 2000. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. *N Engl J Med* 342:1156–1162.

Anderson JJB. 2000. The important role of physical activity in skeletal development: How exercise may counter low calcium intake. *Am J Clin Nutr* 71:1384–1386.

Anderson JW. 1999. Nutritional management of diabetes mellitus. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease,* 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 1365–1394.

Anderson JW, Johnstone BM, Cook-Newell ME. 1995. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 333:276–282.

Andersson S-O, Wolk A, Bergström R, Giovannucci E, Lindgren C, Baron J, Adami H-O. 1996. Energy, nutrient intake and prostate cancer risk: A population-based case-control study in Sweden. *Int J Cancer* 68:716–722.

Anti M, Marra G, Armelao F, Bartoli GM, Ficarelli R, Percesepe A, De Vitis I, Maria G, Sofo L, Rapaccini GL. 1992. Effect of omega-3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. *Gastroenterology* 103:883–891.

Araújo-Vilar D, Osifo E, Kirk M, García-Estévez DA, Cabezas-Cerrato J, Hockaday TDR. 1997. Influence of moderate physical exercise on insulin-mediated and non-insulin-mediated glucose uptake in healthy subjects. *Metabolism* 46:203–209.

Armstrong B, Doll R. 1975. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 15:617–631.

Arntzenius AC, Kromhout D, Barth JD, Reiber JHC, Bruschke AVG, Buis B, van Gent CM, Kempen-Voogd N, Strikwerda S, van der Velde EA. 1985. Diet, lipoproteins, and the progression of coronary atherosclerosis. The Leiden Intervention Trial. *N Engl J Med* 312:805–811.

Arraiz GA, Wigle DT, Mao Y. 1992. Risk assessment of physical activity and physical fitness in the Canada Health Survey Mortality Follow-up Study. *J Clin Epidemiol* 45:419–428.

Arroll B, Beaglehole R. 1992. Does physical activity lower blood pressure: A review of the clinical trials. *J Clin Epidemiol* 45:439–447.

Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ. 1992. A prospective study of nutritional factors and hypertension among US men. *Circulation* 86:1475–1484.

Ascherio A, Hennekens CH, Buring JE, Master C, Stampfer MJ, Willett WC. 1994. *Trans*-fatty acids intake and risk of myocardial infarction. *Circulation* 89:94–101.

Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. 1995. Dietary intake of marine *n*-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med* 332:977–982.

Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, Witteman J, Stampfer MJ. 1996a. Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* 27:1065–1072.

Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. 1996b. Dietary fat and risk of coronary heart disease in men: Cohort follow up study in the United States. *Br Med J* 313:84–90.

Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. 1999. Trans fatty acids and coronary heart disease. *N Engl J Med* 340:1994–1998.

Astrup A. 1999. Macronutrient balances and obesity: The role of diet and physical activity. *Public Health Nutr* 2:341–347.

Astrup A, Vrist E, Quaade F. 1990. Dietary fibre added to very low calorie diet reduces hunger and alleviates constipation. *Int J Obes* 14:105–112.

Astrup A, Toubro S, Raben A, Skov AR. 1997. The role of low-fat diets and fat substitutes in body weight management: What have we learned from clinical studies? *J Am Diet Assoc* 97:S82–S87.

Austin MA. 1989. Plasma triglyceride as a risk factor for coronary heart disease. The epidemiologic evidence and beyond. *Am J Epidemiol* 129:249–259.

Austin MA, Rodriguez BL, McKnight B, McNeely MJ, Edwards KL, Curb DJ, Sharp DS. 2000. Low-density lipoprotein particle size, triglycerides, and high-density lipoprotein cholesterol as risk factors for coronary heart disease in older Japanese-American men. *Am J Cardiol* 86:412–416.

Bainton D, Miller NE, Bolton CH, Yarnell JWG, Sweetnam PM, Baker IA, Lewis B, Elwood PC. 1992. Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischaemic heart disease in British men. The Caerphilly and Speedwell Collaborative Heart Disease Studies. *Br Heart J* 68:60–66.

Bakhit RM, Klein BP, Essex-Sorlie D, Ham JO, Erdman JW, Potter SM. 1994. Intake of 25 g of soybean protein with or without soybean fiber alters plasma lipids in men with elevated cholesterol concentrations. *J Nutr* 124:213–222.

Ballor DL, Keesey RE. 1991. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *Int J Obes* 15:717–726.

Barbone F, Austin H, Partridge EE. 1993. Diet and endometrial cancer: A case-control study. *Am J Epidemiol* 137:393–403.

Baron JA, Schori A, Crow B, Carter R, Mann JI. 1986. A randomized controlled trial of low carbohydrate and low fat/high fiber diets for weight loss. *Am J Public Health* 76:1293–1296.

Barrett-Connor E. 1989. Epidemiology, obesity, and non-insulin-dependent diabetes mellitus. *Epidemiol Rev* 11:172–181.

Bartsch H, Nair J, Owen RW. 1999. Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: Emerging evidence for their role as risk modifiers. *Carcinogenesis* 20:2209–2218.

Batty D, Thune I. 2000. Does physical activity prevent cancer? Evidence suggests protection against colon cancer and probably breast cancer. *Br Med J* 321:1424–1425.

Becker N, Illingworth R, Alaupovic P, Connor WE, Sundberg EE. 1983. Effects of saturated, monounsaturated, and ω-6 polyunsaturated fatty acids on plasma lipids, lipoproteins, and apoproteins in humans. *Am J Clin Nutr* 37:355–360.

Behall KM. 1990. Effect of soluble fibers on plasma lipids, glucose tolerance and mineral balance. *Adv Exp Med Biol* 270:7–16.

Bell EA, Castellanos VH, Pelkman CL, Thorwart ML, Rolls BJ. 1998. Energy density of foods affects energy intake in normal-weight women. *Am J Clin Nutr* 67:412–420.

Benito R, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Muñoz N, Kaldor J. 1990. A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* 45:69–76.

Bergman BC, Butterfield GE, Wolfel EE, Lopaschuk GD, Casazza GA, Horning MA, Brooks GA. 1999. Muscle net glucose uptake and glucose kinetics after endurance training in men. *Am J Physiol* 277:E81–E92.

Bergmann JF, Chassany O, Petit A, Triki R, Caulin C, Segrestaa JM. 1992. Correlation between echographic gastric emptying and appetite: Influence of psyllium. *Gut* 33:1042–1043.

Billman GE, Kang JX, Leaf A. 1999. Prevention of sudden cardiac death by dietary pure ω-3 polyunsaturated fatty acids in dogs. *Circulation* 99:2452–2457.

Birketvedt GS, Aaseth J, Florholmen JR, Ryttig K. 2000. Long term effect of fibre supplement and reduced energy intake on body weight and blood lipids in overweight subjects. *Acta Medica (Hradec Králové)* 43:129–132.

Birt DF, Shull JD, Yaktine AL. 1999. Chemoprevention of cancer. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease,* 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 1263–1295.

Björntorp P, Sjöström L, Sullivan L. 1979. The role of physical exercise in the management of obesity. In: Munro JF, ed. *The Treatment of Obesity.* Baltimore, MD: University Park Press. Pp. 123–138.

Blair SN, Kohl HW, Barlow CE. 1993. Physical activity, physical fitness, and all-cause mortality in women: Do women need to be active? *J Am Coll Nutr* 12:368–371.

Bolton-Smith C, Woodward M. 1994. Dietary composition and fat to sugar ratios in relation to obesity. *Int J Obes Relat Metab Disord* 18:820–828.

Bonanome A, Grundy SM. 1988. Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels. *N Engl J Med* 318:1244–1248.

Bonithon-Kopp C, Kronborg O, Giacosa A, Räth U, Faivre J. 2000. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: A randomised intervention trial. *Lancet* 356:1300–1306.

Borkman M, Campbell LV, Chisholm DJ, Storlien LH. 1991. Comparison of the effects on insulin sensitivity of high carbohydrate and high fat diets in normal subjects. *J Clin Endocrinol Metab* 72:432–437.

Bowman SA. 1999. Diets of individuals based on energy intakes from added sugars. *Fam Econ Nutr Rev* 12:31–38.

Bray GA, Popkin BM. 1998. Dietary fat intake does affect obesity! *Am J Clin Nutr* 68:1157–1173.

Brooks GA, Fahey TD, White TP, Baldwin KM. 2000. *Exercise Physiology: Human Bioenergetics and its Applications*, 3rd ed. Mountain View, CA: Mayfield Publishing.

Brussaard JH, Katan MB, Groot PHE, Havekes LM, Hautvast JGAJ. 1982. Serum lipoproteins of healthy persons fed a low-fat diet or a polyunsaturated fat diet for three months. A comparison of two cholesterol-lowering diets. *Atherosclerosis* 42:205–219.

Bruunsgaard H, Jensen MS, Schjerling P, Halkjaer-Kristensen J, Ogawa K, Skinhøj P, Pedersen BK. 1999. Exercise induces recruitment of lymphocytes with an activated phenotype and short telomeres in young and elderly humans. *Life Sci* 65:2623–2633.

Calviello G, Palozza P, Piccioni E, Maggiano N, Frattucci A, Franceschelli P, Baroli GM. 1998. Dietary supplementation with eicosapentaenoic and docosahexaenoic acid inhibits growth of Morris hepatocarcinoma 3924A in rats: Effects on proliferation and apoptosis. *Int J Cancer* 75:699–705.

Carlson LA, Böttiger LE. 1972. Ischaemic heart-disease in relation to fasting values of plasma triglycerides and cholesterol. Stockholm Prospective Study. *Lancet* 1:865–868.

Carroll KK. 1998. Obesity as a risk factor for certain types of cancer. *Lipids* 33:1055–1059.

Castelli WP. 1996. Lipids, risk factors and ischaemic heart disease. *Atherosclerosis* 124:S1–S9.

Caygill CPJ, Hill MJ. 1995. Fish, *n*-3 fatty acids and human colorectal and breast cancer mortality. *Eur J Cancer Prev* 4:329–332.

Caygill CPJ, Charlett A, Hill MJ. 1996. Fat, fish, fish oil and cancer. *Br J Cancer* 74:159–164.

Clarke R, Frost C, Collins R, Appleby P, Peto R. 1997. Dietary lipids and blood cholesterol: Quantitative meta-analysis of metabolic ward studies. *Br Med J* 314:112–117.

Cohen JC, Schall R. 1988. Reassessing the effects of simple carbohydrates on the serum triglyceride responses to fat meals. *Am J Clin Nutr* 48:1031–1034.

Colbert LH, Hartman TJ, Malila N, Limburg PJ, Pietinen P, Virtamo J, Taylor PR, Albanes D. 2001. Physical activity in relation to cancer of the colon and rectum in a cohort of male smokers. *Cancer Epidemiol Biomarkers Prev* 10:265–268.

Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE. 1990. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 132:501–513.

Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. 1992. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023.

Coulston AM, Liu GC, Reaven GM. 1983. Plasma glucose, insulin and lipid responses to high-carbohydrate low-fat diets in normal humans. *Metabolism* 32:52–56.

Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB. 1997. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 336:1046–1053.

Davy KP, Horton T, Davy BM, Bessessen D, Hill JO. 2001. Regulation of macronutrient balance in healthy young and older men. *Int J Obes Relat Metab Disord* 25:1497–1502.

De Caterina R, Liao JK, Libby P. 2000. Fatty acid modulation of endothelial activation. *Am J Clin Nutr* 71:213–223.

Denke MA. 1994. Effects of cocoa butter on serum lipids in humans: Historical highlights. *Am J Clin Nutr* 60:1014S–1016S.

Depaola DP, Faine MP, Palmer CA. 1999. Nutrition in relation to dental medicine. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease,* 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 1099–1124.

Després J-P, Tremblay A, Nadeau A, Bouchard C. 1988. Physical training and changes in regional adipose tissue distribution. *Acta Med Scand Suppl* 723: 205–212.

De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Carzoglio JC, Ronco A. 1997a. Dietary fat and lung cancer: A case-control study in Uruguay. *Cancer Causes Control* 8:913–921.

De Stefani E, Mendilaharsu M, Deneo-Pellegrini H, Ronco A. 1997b. Influence of dietary levels of fat, cholesterol, and calcium on colorectal cancer. *Nutr Cancer* 29:83–89.

Diabetes Prevention Program Research Group. 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403.

Dolecek TA. 1992. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial. *Proc Soc Exp Med Biol* 200:177–182.

Dreon DM, Frey-Hewitt B, Ellsworth N, Williams PT, Terry RB, Wood PD. 1988. Dietary fat:carbohydrate ratio and obesity in middle-aged men. *Am J Clin Nutr* 47:995–1000.

Dunnigan MG, Fyfe T, McKiddie MT, Crosbie SM. 1970. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. *Clin Sci* 38:1–9.

Eliasson K, Ryttig KR, Hylander B, Rossner S. 1992. A dietary fibre supplement in the treatment of mild hypertension. A randomized, double-blind, placebo-controlled trial. *J Hypertens* 10:195–199.

El-Sayed MS. 1996. Effects of exercise on blood coagulation, fibrinolysis and platelet aggregation. *Sports Med* 22:282–298.

Fasching P, Ratheiser K, Schneeweiss B, Rohac M, Nowotny P, Waldhausl W. 1996. No effect of short-term dietary supplementation of saturated and poly- and monounsaturated fatty acids on insulin secretion and sensitivity in healthy men. *Ann Nutr Metab* 40:116–122.

Fehily AM, Phillips KM, Yarnell JWG. 1984. Diet, smoking, social class, and body mass index in the Caerphilly Heart Disease Study. *Am J Clin Nutr* 40:827–833.

Feskens EJM, Loeber JG, Kromhout D. 1994. Diet and physical activity as determinants of hyperinsulinemia: The Zutphen Elderly Study. *Am J Epidemiol* 140: 350–360.

Frankel S, Gunnell DJ, Peters TJ, Maynard M, Smith GD. 1998. Childhood energy intake and adult mortality from cancer: The Boyd Orr Cohort Study. *Br Med J* 316:499–504.

French SA, Fulkerson JA, Story M. 2000. Increasing weight-bearing physical activity and calcium intake for bone mass growth in children and adolescents: A review of intervention trials. *Prev Med* 31:722–731.

Friday KE, Childs MT, Tsunehara CH, Fujimoto WY, Bierman EL, Ensinck JW. 1989. Elevated plasma glucose and lowered triglyceride levels from omega-3 fatty acid supplementation in type II diabetes. *Diabetes Care* 12:276–281.

Frost G, Leeds A, Trew G, Margara R, Dornhorst A. 1998. Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic diet. *Metabolism* 47:1245–1251.

Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, Speizer FE, Willett WC. 1999. Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med* 340:169–176.

Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL. 1990. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. *Am J Clin Nutr* 52:524–528.

Gardner CD, Kraemer HC. 1995. Monounsaturated versus polyunsaturated dietary fat and serum lipids. A meta-analysis. *Arterioscler Thromb Vasc Biol* 15:1917–1927.

Gartside PS, Glueck CJ. 1993. Relationship of dietary intake to hospital admission for coronary heart and vascular disease: The NHANES II National Probability Study. *J Am Coll Nutr* 6:676–684.

Gerber M. 1998. Fibre and breast cancer. *Eur J Cancer Prev* 7:S63–S67.

Gibson SA. 1993. Consumption and sources of sugars in the diets of British schoolchildren: Are high-sugar diets nutritionally inferior? *J Hum Nutr Diet* 6:355–371.

Gibson SA. 1996a. Are diets high in non-milk extrinsic sugars conducive to obesity? An analysis from the Dietary and Nutritional Survey of British Adults. *J Hum Nutr Diet* 9:283–292.

Gibson SA. 1996b. Are high-fat, high-sugar foods and diets conducive to obesity? *Int J Food Sci Nutr* 47:405–415.

Gibson SA. 1997. Non-milk extrinsic sugars in the diets of pre-school children: Association with intakes of micronutrients, energy, fat and NSP. *Br J Nutr* 78:367–378.

Giovannucci E, Willett WC. 1994. Dietary factors and risk of colon cancer. *Ann Med* 26:443–452.

Giovannucci E, Stampfer MJ, Colditz G, Rimm EB, Willett WC. 1992. Relationship of diet to risk of colorectal adenoma in men. *J Natl Cancer Inst* 84:91–98.

Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. 1993. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 85:1571–1579.

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. 1994. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54:2390–2397.

Glauber H, Wallace P, Griver K, Brechtel G. 1988. Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 108:663–668.

Goodman MT, Kolonel LN, Yoshizawa CN, Hankin JH. 1988. The effect of dietary cholesterol and fat on the risk of lung cancer in Hawaii. *Am J Epidemiol* 128:1241–1255.

Goodman MT, Wilkens LR, Hankin JH, Lyu L-C, Wu AH, Kolonel LN. 1997. Association of soy and fiber consumption with the risk of endometrial cancer. *Am J Epidemiol* 146:294–306.

Goran MI. 2001. Metabolic precursors and effects of obesity in children: A decade of progress, 1990–1999. *Am J Clin Nutr* 73:158–171.

Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. 1977. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med* 62:707–714.

Gordon T, Kagan A, Garcia-Palmieri M, Kannel WB, Zukel WJ, Tillotson J, Sorlie P, Hjortland M. 1981. Diet and its relation to coronary heart disease and death in three populations. *Circulation* 63:500–515.

Grammatikos SI, Subbaiah PV, Victor TA, Miller WM. 1994. *n*-3 And *n*-6 fatty acid processing and growth effects in neoplastic and non-cancerous human mammary epithelial cell lines. *Br J Cancer* 70:219–227.

Gray GE, Pike MC, Henderson BE. 1979. Breast-cancer incidence and mortality rates in different countries in relation to known risk factors and dietary practices. *Br J Cancer* 39:1–7.

Hallfrisch J, Scholfield DJ, Behall KM. 1995. Diets containing soluble oat extracts improve glucose and insulin responses of moderately hypercholesterolemic men and women. *Am J Clin Nutr* 61:379–384.

Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, Schoene N, Schuler G. 2000. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Eng J Med* 342:454–460.

Harker LA, Kelly AB, Hanson SR, Krupski W, Bass A, Osterud B, Fitzgerald GA, Goodnight SH, Connor WE. 1993. Interruption of vascular thrombus formation and vascular lesion formation by dietary *n*-3 fatty acids in fish oil in nonhuman primates. *Circulation* 87:1017–1029.

Harris PJ, Ferguson LR. 1993. Dietary fibre: Its composition and role in protection against colorectal cancer. *Mutat Res* 290:97–110.

Harris WS. 1989. Fish oils and plasma lipid and lipoprotein metabolism in humans: A critical review. *J Lipid Res* 30:785–807.

Hegsted DM. 1986. Serum-cholesterol response to dietary cholesterol: A reevaluation. *Am J Clin Nutr* 44:299–305.

Hegsted DM, Ausman LM, Johnson JA, Dallal GE. 1993. Dietary fat and serum lipids: An evaluation of the experimental data. *Am J Clin Nutr* 57:875–883.

Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS. 1991. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152.

Hennekens CH. 1998. Risk factors for coronary heart disease in women. *Cardiol Clin* 16:1–8.

Hill MJ. 1997. Cereals, cereal fibre and colorectal cancer risk: A review of the epidemiological literature. *Eur J Cancer Prev* 6:219–225.

Hinkle LE, Thaler HT, Merke DP, Renier-Berg D, Morton NE. 1988. The risk factors for arrhythmic death in a sample of men followed for 20 years. *Am J Epidemiol* 127:500–515.

Hoff G, Moen IE, Trygg K, Frølich W, Sauar J, Vatn M, Gjone E, Larsen S. 1986. Epidemiology of polyps in the rectum and sigmoid colon. Evaluation of nutritional factors. *Scand J Gastroenterol* 21:199–204.

Hopkins PN. 1992. Effects of dietary cholesterol on serum cholesterol: A meta-analysis and review. *Am J Clin Nutr* 55:1060–1070.

Horton ES. 1986. Exercise and physical training: Effects on insulin sensitivity and glucose metabolism. *Diabetes Metab Rev* 2:1–17.

Horton ES. 1991. Exercise and decreased risk of NIDDM. *N Engl J Med* 325: 196–197.

Howard BV, Abbott WGH, Swinburn BA. 1991. Evaluation of metabolic effects of substitution of complex carbohydrates for saturated fat in individuals with obesity and NIDDM. *Diabetes Care* 14:786–795.

Howe GR, Friedenreich CM, Jain M, Miller AB. 1991. A cohort study of fat intake and risk of breast cancer. *J Natl Cancer Inst* 83:336–340.

Howe GR, Aronson KJ, Benito E, Castelleto R, Cornée J, Duffy S, Gallagher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA, Kune S, Lee HP, Lee M, Miller AB, Peters RK, Potter JD, Riboli E, Slattery ML, Trichopoulos D, Tuyns A, Tzonou A, Watson LF, Whittemore AS, Wu-Willimas AH, Shu Z. 1997. The relationship between dietary fat intake and risk of colorectal cancer: Evidence from the combined analysis of 13 case-control studies. *Cancer Causes Control* 8:215–228.

Howell WH, McNamara DJ, Tosca MA, Smith BT, Gaines JA. 1997. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: A meta-analysis. *Am J Clin Nutr* 65:1747–1764.

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. 1997. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 337:1491–1499.

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Speizer FE, Hennekens CH, Willett WC. 1999a. Dietary protein and risk of ischemic heart disease in women. *Am J Clin Nutr* 70:221–227.

Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, Rosner BA, Spiegelman D, Speizer FE, Sacks FM, Hennekens CH, Willett WC. 1999b. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *J Am Med Assoc* 281:1387–1394.

Hulley SB, Rosenman RH, Bawol RD, Brand RJ. 1980. Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. *N Engl J Med* 302:1383–1389.

Hunter DJ, Spiegelman D, Adami H-O, Beeson L, van den Brandt PA, Folsom AR, Fraser GE, Goldbohn A, Graham S, Howe GR, Kushi LH, Marshall JR, McDermott A, Miller AB, Speizer FE, Wolk A, Yaun S-S, Willett W. 1996. Cohort studies of fat intake and the risk of breast cancer—A pooled analysis. *N Engl J Med* 334:356–361.

Hurley BR, Roth SM. 2000. Strength training in the elderly. Effects on risk factors for age-related diseases. *Sports Med* 30:249–268.

Huttunen JK, Länsimies E, Voutilainen E, Ehnholm C, Hietanen E, Penttilä I, Siitonen O, Rauranaa R. 1979. Effect of moderate physical exercise on serum lipoproteins. A controlled clinical trial with special reference to serum high-density lipoproteins. *Circulation* 60:1220–1229.

IARC (International Agency for Research on Cancer). 2002. *IARC Handbooks of Cancer Prevention. Volume 6: Weight Control and Physical Activity.* Lyon, France: IARC Press.

Jacobs DR, Meyer KA, Kushi LH, Folsom AR. 1998. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: The Iowa Women's Health Study. *Am J Clin Nutr* 68:248–257.

Jacobs LR. 1986. Relationship between dietary fiber and cancer: Metabolic, physiologic, and cellular mechanisms. *Proc Soc Exp Biol Med* 183:299–310.

James MJ, Gibson RA, Cleland LG. 2000. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 71:343S–348S.

Jenkins DJA, Wolever TMS, Leeds AR, Gassull MA, Haisman P, Dilawari J, Goff DV, Metz GL, Alberti KGMM. 1978. Dietary fibres, fibre analogues, and glucose tolerance: Importance of viscosity. *Br Med J* 1:1392–1394.

Jenkins DJA, Wolever TMS, Buckley G, Lam KY, Giudici S, Kalmusky J, Jenkins AL, Patten RL, Bird J, Wong GS, Josse RG. 1988. Low-glycemic-index starchy food in the diabetic diet. *Am J Clin Nutr* 48:248–254.

Jeppesen J, Schaaf P, Jones C, Zhou M-Y, Chen Y-DI, Reaven GM. 1997. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. *Am J Clin Nutr* 65:1027–1033.

Johnson RK. 2000. What are people really eating and why does it matter? *Nutr Today* 35:40–45.

Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, Hoover R, Taylor PR. 1987. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I. Epidemiologic follow-up study. *J Natl Cancer Inst* 79:465–471.

Jousilahti P, Vartiainen E, Pekkanen J, Tuomilehto J, Sundvall J, Puska P. 1998. Serum cholesterol distribution and coronary heart disease risk. Observations and predictions among middle-aged population in eastern Finland. *Circulation* 97:1087–1094.

Kaizer L, Boyd NF, Kriukov V, Tritchler D. 1989. Fish consumption and breast cancer risk: An ecologic study. *Nutr Cancer* 12:61–68.

Kang JX, Leaf A. 1996. Antiarrhythmic effects of polyunsaturated fatty acids: Recent studies. *Circulation* 94:1774–1780.

Kannel WB, Sorlie P. 1979. Some health benefits of physical activity. The Framingham Study. *Arch Intern Med* 139:857–861.

Kannel WB, Belanger A, D'Agostino R, Israel I. 1986. Physical activity and physical demand on the job and risk of cardiovascular disease and death: The Framingham Study. *Am Heart J* 112:820–825.

Kasim SE, Stern B, Khilnani S, McLin P, Baciorowski S, Jen K-LC. 1988. Effects of omega-3 fish oils on lipid metabolism, glycemic control, and blood pressure in type II diabetic patients. *J Clin Endocrinol Metab* 67:1–5.

Kasim SE, Martino S, Kim P-N, Khilnani S, Boomer A, Depper J, Reading BA, Heilbrun LK. 1993. Dietary and anthropometric determinants of plasma lipoproteins during a long-term low-fat diet in healthy women. *Am J Clin Nutr* 57:146–153.

Kendall A, Levitsky DA, Strupp BJ, Lissner L. 1991. Weight loss on a low-fat diet: Consequence of the imprecision of the control of food intake in humans. *Am J Clin Nutr* 53:1124–1129.

Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH, Kromhout D, Nedeljkovic S, Punsar S, Seccareccia F, Toshima H. 1986. The diet and 15-year death rate in the seven countries study. *Am J Epidemiol* 124:903–915.

Khan K, McKay HA, Haapasalo H, Bennell KL, Forwood MR, Kannus P, Wark JD. 2000. Does childhood and adolescence provide a unique opportunity for exercise to strengthen the skeleton? *J Sci Med Sport* 3:150–164.

King H, Taylor R, Zimmet P, Pargeter K, Raper LR, Beriki T, Tekanene J. 1984. Non-insulin-dependent diabetes (NIDDM) in a newly independent Pacific nation: The Republic of Kiribati. *Diabetes Care* 7:409–415.

Klurfeld DM. 1992. Dietary fiber-mediated mechanisms in carcinogenesis. *Cancer Res* 52:2055S–2059S.

Koutsari C, Karpe F, Humphreys SM, Frayn KN, Hardman AE. 2001. Exercise prevents the accumulation of triglyceride-rich lipoproteins and their remnants seen when changing to a high-carbohydrate diet. *Arterioscler Thromb Vasc Biol* 21:1520–1525.

Krauss RM, Dreon DM. 1995. Low-density-lipoprotein subclasses and response to a low-fat diet in healthy men. *Am J Clin Nutr* 62:478S–487S.

Kromhout D, de Lezenne Coulander C. 1984. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men. *Am J Epidemiol* 119:733–741.

Kromhout D, Bosschieter EB, de Lezenne Coulander C. 1985. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 312:1205–1209.

Kromhout D, Feskens EJM, Bowles CH. 1995. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *Int J Epidemiol* 24:340–345.

Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. 1985. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. *N Engl J Med* 312:811–818.

Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, Folsom AR. 1992. Dietary fat and postmenopausal breast cancer. *J Natl Cancer Inst* 84:1092–1099.

Lai PBS, Ross JA, Fearson KCH, Anderson JD, Carter DC. 1996. Cell cycle arrest and induction of apoptosis in pancreatic cancer cells exposed to eicosapentaenoic acid in vitro. *Br J Cancer* 74:1375–1383.

Lanza E. 1990. National Cancer Institute Satellite Symposium on Fiber and Colon Cancer. In: Kritchevsky D, Bonfield C, Anderson JW, eds. *Dietary Fiber: Chemistry, Physiology, and Health Effects.* New York: Plenum Press. Pp. 383–387.

Layne JE, Nelson ME. 1999. The effects of progressive resistance training on bone density: A review. *Med Sci Sports Exerc* 21:25–30.

Leclerc I, Davignon I, Lopez D, Garrel DR. 1993. No change in glucose tolerance and substrate oxidation after a high-carbohydrate, low-fat diet. *Metabolism* 42:365–370.

Lewis CJ, Park YK, Dexter PB, Yetley EA. 1992. Nutrient intakes and body weights of persons consuming high and moderate levels of added sugars. *J Am Diet Assoc* 92:708–713.

Liljeberg HGM, Åkerberg AKE, Björck IME. 1999. Effect of the glycemic index and content of indigestible carbohydrates of cereal-based breakfast meals on glucose tolerance at lunch in healthy subjects. *Am J Clin Nutr* 69:647–655.

Lindsted KD, Tonstad S, Kuzma JW. 1991. Self-report of physical activity and patterns of mortality in Seventh-day Adventist men. *J Clin Epidemiol* 44:355–364.

Lissner L, Heitmann BL. 1995. Dietary fat and obesity: Evidence from epidemiology. *Eur J Clin Nutr* 49:79–90.

Lissner L, Levitsky DA, Strupp BJ, Kalkwarf HJ, Roe DA. 1987. Dietary fat and the regulation of energy intake in human subjects. *Am J Clin Nutr* 46:886–892.

Lissner L, Helgesson Ö, Bengtsson C, Lapidus L, Hultén B, Branehög I, Holmberg E. 1992. Energy and macronutrient intake in relation to cancer incidence among Swedish women. *Eur J Clin Nutr* 46:501–507.

Lissner L, Heitmann BL, Bengtsson C. 2000. Population studies of diet and obesity. *Br J Nutr* 83:S21–S24.

Little J, Logan RFA, Hawtin PG, Hardcastle JD, Turner ID. 1993. Colorectal adenomas and diet: A case-control study of subjects participating in the Nottingham Faecal Occult Blood Screening Programme. *Br J Cancer* 67:177–84.

Lundgren H, Bengtsson C, Blohmé G, Isaksson B, Lapidus L, Lenner RA, Saaek A, Winther E. 1989. Dietary habits and incidence of noninsulin-dependent diabetes mellitus in a population study of women in Gothenburg, Sweden. *Am J Clin Nutr* 49:708–712.

Lyon JL, Mahoney AW, West DW, Gardner JW, Smith KR, Sorenson AW, Stanish W. 1987. Energy intake: Its relationship to colon cancer risk. *J Natl Cancer Inst* 78:853–861.

Macquart-Moulin G, Riboli E, Cornée J, Charnay B, Berthezène P, Day N. 1986. Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* 38:183–191.

Macquart-Moulin G, Riboli E, Cornée J, Kaaks R, Berthezène P. 1987. Colorectal polyps and diet: A case-control study in Marseilles. *Int J Cancer* 40:179–188.

Madsen KL, Adams WC, Van Loan MD. 1998. Effects of physical activity, body weight and composition, and muscular strength on bone density in young women. *Med Sci Sports Exerc* 30:114–120.

Mann JI, Watermeyer GS, Manning EB, Randles J, Truswell AS. 1973. Effects on serum lipids of different dietary fats associated with a high sucrose diet. *Clin Sci* 44:601–604.

Mann JI, Appleby PN, Key TJ, Thorogood M. 1997. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart* 78:450–455.

Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE. 1991. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778.

Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH. 1992. A prospective study of exercise and incidence of diabetes among US male physicians. *J Am Med Assoc* 268:63–67.

Marckmann P, Raben A, Astrup A. 2000. Ad libitum intake of low-fat diets rich in either starchy foods or sucrose: Effects on blood lipids, factor VII coagulant activity, and fibrinogen. *Metabolism* 49:731–735.

Marniemi J, Seppänen A, Hakala P. 1990. Long-term effects on lipid metabolism of weight reduction on lactovegetarian and mixed diet. *Int J Obes* 14:113–125.

Marshall JA, Hamman RF, Baxter J. 1991. High-fat, low-carbohydrate diet and the etiology of non-insulin-dependent diabetes mellitus: The San Luis Valley Diabetes Study. *Am J Epidemiol* 134:590–603.

Masironi R. 1970. Dietary factors and coronary heart disease. *Bull World Health Organ* 42:103–114.

Mayer-Davis EJ, Monaco JH, Hoen HM, Carmichael S, Vitolins MZ, Rewers MJ, Haffner SM, Ayad MF, Bergman RN, Karter AJ. 1997. Dietary fat and insulin sensitivity in a triethnic population: The role of obesity. The Insulin Resistance Arteriosclerosis Study (IRAS). *Am J Clin Nutr* 65:79–87.

Mayer-Davis EJ, D'Agostino R, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN. 1998. Intensity and amount of physical activity in relation to insulin sensitivity. The Insulin Resistance Atherosclerosis Study. *J Am Med Assoc* 279:669–674.

Mazzeo RS, Rajkumar C, Rolland J, Blaher B, Jennings G, Esler M. 1998. Immune response to a single bout of exercise in young and elderly subjects. *Mech Ageing Dev* 100:121–132.

McLennan PL. 1993. Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats. *Am J Clin Nutr* 57:207–212.

Meinertz H, Nilausen K, Faergeman O. 1989. Soy protein and casein in cholesterol-enriched diets: Effects on plasma lipoproteins in normolipidemic subjects. *Am J Clin Nutr* 50:786–793.

Mensink RP, Katan MB. 1992. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler Thromb* 12:911–919.

Mensink RP, Temme EH, Hornstra G. 1994. Dietary saturated and trans fatty acids and lipoprotein metabolism. *Ann Med* 26:461–464.

Meyer KA, Kushi LH, Jacobs DR, Slavin J, Sellers TA, Folsom AR. 2000. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930.

Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. 2001. Physical activity, obesity, height, and the risk of pancreatic cancer. *J Am Med Assoc* 286:921–929.

Miller AB, Kelly A, Choi NW, Matthews V, Morgan RW, Munan L, Burch JD, Feather J, Howe GR, Jain M. 1978. A study of diet and breast cancer. *Am J Epidemiol* 107:499–509.

Miller WC, Lindeman AK, Wallace J, Niederpruem M. 1990. Diet composition, energy intake, and exercise in relation to body fat in men and women. *Am J Clin Nutr* 52:426–430.

Morris MC, Sacks F, Rosner B. 1993. Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation* 88:523–533.

Must A, Lipman RD. 1999. Childhood energy intake and cancer mortality in adulthood. *Nutr Rev* 57:21–24.

Neaton JD, Wentworth D. 1992. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. *Arch Intern Med* 152:56–64.

Neugut AI, Garbowski GC, Lee WC, Murray T, Nieves JW, Forde KA, Treat MR, Waye JD, Fenoglio-Preiser C. 1993. Dietary risk factors for the incidence and recurrence of colorectal adenomatous polyps. A case-control study. *Ann Intern Med* 118:91–95.

NHLBI/NIDDK (National Heart, Lung, and Blood Institute/National Institute of Diabetes and Digestive and Kidney Diseases). 1998. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report.* NIH Publication No. 98-4083. Bethesda, MD: National Institutes of Health.

Nikkilä EA, Taskinen M-R, Rehunen S, Härkönen M. 1978. Lipoprotein lipase activity in adipose tissue and skeletal muscle of runners: Relation to serum lipoproteins. *Metabolism* 27:1661–1671.

Obarzanek E, Velletri PA, Cutler JA. 1996. Dietary protein and blood pressure. *J Am Med Assoc* 275:1598–1603.

Paffenbarger RS, Hyde RT, Jung DL, Wing AL. 1984. Epidemiology of exercise and coronary heart disease. *Clin Sports Med* 3:297–318.

Parker DR, Weiss ST, Troisi R, Cassano PA, Vokonas PS, Landsberg L. 1993. Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations: The Normative Aging Study. *Am J Clin Nutr* 58:129–136.

Parks EJ, Hellerstein MK. 2000. Carbohydrate-induced hypertriacylglycerolemia: Historical perspective and review of biological mechanisms. *Am J Clin Nutr* 71:412–433.

Parmley WW. 1997. Nonlipoprotein risk factors for coronary heart disease: Evaluation and management. *Am J Med* 102:7–14.

Pietinen P, Rimm EB, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. 1996. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation* 94:2720–2727.

Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. 1997. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol* 145:876–887.

Pi-Sunyer FX, Woo R. 1985. Effect of exercise on food intake in human subjects. *Am J Clin Nutr* 42:983–990.

Platz EA, Giovannucci E, Rimm EB, Rickett HRH, Stampfer MJ, Colditz GA, Willett WC. 1997. Dietary fiber and distal colorectal adenoma in men. *Cancer Epidemiol Biomarkers Prev* 6:661–670.

Purnell JQ, Kahn SE, Albers JJ, Nevin DN, Brunzell JD, Schwartz RS. 2000. Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism in older men. *J Clin Endocrinol Metab* 85:977–982.

Ramon JM, Bou R, Romea S, Alkiza ME, Jacas M, Ribes J, Oromi J. 2000. Dietary fat intake and prostate cancer risk: A case-control study in Spain. *Cancer Causes Control* 11:679–685.

Rath R, Masˇek J, Kujalová V, Slabochová Z. 1974. Effect of a high sugar intake on some metabolic and regulatory indicators in young men. *Nahrung* 18:343–353.

Reiser S, Hallfrisch J. 1987. Lipogenesis and blood lipids. In: *Metabolic Effects of Dietary Fructose.* Boca Raton, FL: CRC Press. Pp. 83–111.

Reiser S, Hallfrisch J, Michaelis OE, Lazar FL, Martin RE, Prather ES. 1979. Isocaloric exchange of dietary starch and sucrose in humans. I. Effects on levels of fasting blood lipids. *Am J Clin Nutr* 32:1659–1669.

Richter EA, Ruderman NB, Schneider SH. 1981. Diabetes and exercise. *Am J Med* 70:201–209.

Rigaud D, Ryttig KR, Angel LA, Apfelbaum M. 1990. Overweight treated with energy restriction and a dietary fibre supplement: A 6-month randomized, double-blind, placebo-controlled trial. *Int J Obes* 14:763–769.

Risch HA, Jain M, Marrett LD, Howe GR. 1994. Dietary fat intake and risk of epithelial ovarian cancer. *J Natl Cancer Inst* 86:1409–1415.

Rivellese A, Riccardi G, Giacco A, Pacioni D, Genovese S, Mattioli PL, Mancini M. 1980. Effect of dietary fibre on glucose control and serum lipoproteins in diabetic patients. *Lancet* 2:447–450.

Roberfroid M. 1993. Dietary fiber, inulin, and oligofructose: A review comparing their physiological effects. *Crit Rev Food Sci Nutr* 33:103–148.

Roche HM, Zampelas A, Jackson KG, Williams CM, Gibney MJ. 1998. The effect of test meal monounsaturated fatty acid:saturated fatty acid ratio on postprandial lipid metabolism. *Br J Nutr* 79:419–424.

Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. 1993. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: A cohort study. *Cancer Causes Control* 4:29–37.

Rose DP. 1997. Dietary fatty acids and cancer. *Am J Clin Nutr* 66:998S–1003S.

Rose DP, Connolly JM. 2000. Regulation of tumor angiogenesis by dietary fatty acids and eicosanoids. *Nutr Cancer* 37:119–127.

Rose DP, Boyar AP, Wynder EL. 1986. International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. *Cancer* 58:2363–2371.

Rose DP, Goldman M, Connolly JM, Strong LE. 1991. High-fiber diet reduces serum estrogen concentrations in premenopausal women. *Am J Clin Nutr* 54:520–525.

Rössner S, von Zweigbergk D, Öhlin A, Ryttig K. 1987. Weight reduction with dietary fibre supplements. Results of two double-blind randomized studies. *Acta Med Scand* 222:83–88.

Ryttig KR, Tellnes G, Haegh L, Boe E, Fagerthun H. 1989. A dietary fibre supplement and weight maintenance after weight reduction: A randomized, double-blind, placebo-controlled long-term trial. *Int J Obes* 13:165–171.

Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. 1997a. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550.

Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. 1997b. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *J Am Med Assoc* 277:472–477.

Saltzman E, Dallal GE, Roberts SB. 1997. Effect of high-fat and low-fat diets on voluntary energy intake and substrate oxidation: Studies in identical twins consuming diets matched for energy density, fiber, and palatability. *Am J Clin Nutr* 66:1332–1339.

Sasaki S, Horacsek M, Kesteloot H. 1993. An ecological study of the relationship between dietary fat intake and breast cancer mortality. *Prev Med* 22:187–202.

Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, Cahill J. 2000. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 342:1149–1155.

Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB. 1984. Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 26:355–360.

Schuurman AG, van den Brandt PA, Dorant E, Brants HAM, Goldbohm RA. 1999. Association of energy and fat intake with prostate carcinoma risk. Results from the Netherlands Cohort Study. *Cancer* 86:1019–1027.

Shephard RJ. 1990. Physical activity and cancer. *Int J Sports Med* 11:413–420.

Shephard RJ. 1996. Exercise and cancer: Linkages with obesity? *Crit Rev Food Sci Nutr* 36:321–339.

Sonnenberg LM, Quatromoni PA, Gagnon DR, Cupples LA, Franz MM, Ordovas JM, Wilson PWF, Schaefer EJ, Millen BE. 1996. Diet and plasma lipids in women. II. Macronutrients and plasma triglycerides, high-density lipoprotein, and the ratio of total to high-density lipoprotein cholesterol in women: The Framingham Nutrition Studies. *J Clin Epidemiol* 49:665–672.

Sorkin JD, Andres R, Muller DC, Baldwin HL, Fleg JL. 1992. Cholesterol as a risk factor for coronary heart disease in elderly men. The Baltimore Longitudinal Study of Aging. *Ann Epidemiol* 2:59–67.

Stacpoole PW, Alig J, Ammon L, Crockett SE. 1989. Dose–response effects of dietary marine oil on carbohydrate and lipid metabolism in normal subjects and patients with hypertriglyceridemia. *Metabolism* 38:946–956.

Stamler J. 1979. Population studies. In: Levy R, Rifkind B, Dennis B, Ernst N, eds. *Nutrition, Lipids, and Coronary Heart Disease.* New York: Raven Press. Pp. 25–88.

Stamler J, Wentworth D, Neaton JD. 1986. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *J Am Med Assoc* 256:2823–2828.

Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks FM, Hennekens CH. 1996. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *J Am Med Assoc* 276:882–888.

Stemmermann GN, Nomura AM, Heilbrun LK. 1985. Cancer risk in relation to fat and energy intake among Hawaii Japanese: A prospective study. *Princess Takamatsu Symp* 16:265–274.

Straznicky NE, O'Callaghan CJ, Barrington VE, Louis WJ. 1999. Hypotensive effect of low-fat, high-carbohydrate diet can be independent of changes in plasma insulin concentrations. *Hypertension* 34:580–585.

Stubbs RJ, Ritz P, Coward WA, Prentice AM. 1995. Covert manipulation of the ratio of dietary fat to carbohydrate and energy density: Effect on food intake and energy balance in free-living men eating ad libitum. *Am J Clin Nutr* 62:330–337.

Stubbs RJ, Harbron CG, Prentice AM. 1996. Covert manipulation of the dietary fat to carbohydrate ratio of isoenergetically dense diets: Effect on food intake in feeding men ad libitum. *Int J Obes Relat Metab Disord* 20:651–660.

Swinburn BA, Boyce VL, Bergman RN, Howard BV, Bogardus C. 1991. Deterioration in carbohydrate metabolism and lipoprotein changes induced by modern, high fat diet in Pima Indians and Caucasians. *J Clin Endocrinol Metab* 73:156–165.

Takahashi M, Przetakiewicz M, Ong A, Borek C, Lowenstein JM. 1992. Effect of omega 3 and omega 6 fatty acids on transformation of cultured cells by irradiation and transfection. *Cancer Res* 52:154–162.

Tannenbaum A. 1942. The genesis and growth of tumors. II. Effects of caloric restriction per se. *Cancer Res* 2:460–467.

Tannenbaum A, Silverstone H. 1957. Nutrition and the genesis of tumours. In: Raven RW, ed. *Cancer,* Vol. 1. London: Butterworth. Pp. 306–334.

Taylor RJ, Bennett PH, LeGonidec G, Lacoste J, Combe D, Joffres M, Uili R, Charpin M, Zimmet PZ. 1983. The prevalence of diabetes mellitus in a traditional-living Polynesian population: The Wallis Island Survey. *Diabetes Care* 6:334–340.

Thomsen C, Rasmussen O, Christiansen C, Pedersen E, Vesterlund M, Storm H, Ingerslev J, Hermansen K. 1999. Comparison of the effects of a monounsaturated fat diet and a high carbohydrate diet on cardiovascular risk factors in first degree relatives to type-2 diabetic subjects. *Eur J Clin Nutr* 52:818–823.

Trichopoulou A, Katsouyanni K, Stuver S, Tzala L, Gnardellis C, Rimm E, Trichopoulos D. 1995. Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *J Natl Cancer Inst* 87:110–116.

Trock B, Lanza E, Greenwald P. 1990. Dietary fiber, vegetables, and colon cancer: Critical review and meta-analyses of the epidemiologic evidence. *J Natl Cancer Inst* 82:650–661.

Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350.

Tuyns AJ, Kaaks R, Haelterman M. 1988. Colorectal cancer and the consumption of foods: A case-control study in Belgium. *Nutr Cancer* 11:189–204.

Tzonou A, Hsieh C-C, Polychronopoulou A, Kaprinis G, Toupadaki N, Trichopoulou A, Karakatsani A, Trichopoulos D. 1993. Diet and ovarian cancer: A case-control study in Greece. *Int J Cancer* 55:411–414.

Vainio H, Bianchini F. 2001. Physical activity and cancer prevention—Is 'no pain, no gain' passé? *Eur J Cancer Prev* 10:301–302.

van den Brandt PA, van't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJJ, Sturmans F. 1993. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. *Cancer Res* 53:75–82.

Van Munster IP, Nagengast FM. 1993. The role of carbohydrate fermentation in colon cancer prevention. *Scand J Gastroenterol* 200:80–86.

van Raaij JMA, Katan MB, West CE, Hautvast JGAJ. 1982. Influence of diets containing casein, soy isolate, and soy concentrate on serum cholesterol and lipoproteins in middle-aged volunteers. *Am J Clin Nutr* 35:925–934.

van Stratum P, Lussenburg RN, van Wezel LA, Vergroesen AJ, Cremer HD. 1978. The effect of dietary carbohydrate:fat ratio on energy intake by adult women. *Am J Clin Nutr* 31:206–212.

van't Veer P, Kok FJ, Brants HAM, Ockhuizen T, Sturmans F, Hermus RJJ. 1990. Dietary fat and the risk of breast cancer. *Int J Epidemiol* 19:12–18.

Veierød MB, Laake P, Thelle DS. 1997a. Dietary fat intake and risk of lung cancer: A prospective study of 51,452 Norwegian men and women. *Eur J Cancer Prev* 6:540–549.

Veierød MB, Laake P, Thelle DS. 1997b. Dietary fat intake and risk of prostate cancer: A prospective study of 25,708 Norwegian men. *Int J Cancer* 73:634–638.

Velie E, Kulldorff M, Schairer C, Block G, Albanes D, Schatzkin A. 2000. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: A prospective cohort study. *J Natl Cancer Inst* 92:833–839.

Vessby B. 2000. Dietary fat and insulin action in humans. *Br J Nutr* 83:S91–S96.

Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nälsén C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson I-B, Storlien LH. 2001. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. *Diabetologia* 44:312–319.

Visek WJ. 1978. Diet and cell growth modulation by ammonia. *Am J Clin Nutr* 31:S216–S220.

von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. 1999. The effect of dietary ω-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 130:554–562.

Walker ARP, Cleaton-Jones PE. 1992. Sugar intake and dental caries. *Br Dent J* 172:7.

Wang G-S, Olsson JM, Eriksson LC, Stål P. 2000. Diet restriction increases ubiquinone contents and inhibits progression of hepatocellular carcinoma in the rat. *Scand J Gastroenterol* 35:83–89.

West CE, Sullivan DR, Katan MB, Halferkamps IL, van der Torre HW. 1990. Boys from populations with high-carbohydrate intake have higher fasting triglyceride levels than boys from populations with high-fat intake. *Am J Epidemiol* 131:271–282.

West DB, York B. 1998. Dietary fat, genetic predisposition, and obesity: Lessons from animal models. *Am J Clin Nutr* 67:505S–512S.

White E, Jacobs EJ, Daling JR. 1996. Physical activity in relation to colon cancer in middle-aged men and women. *Am J Epidemiol* 144:42–50.

Willett WC. 1997. Specific fatty acids and risks of breast and prostate cancer: Dietary intake. *Am J Clin Nutr* 66:1557S–1563S.

Willett WC. 1998. Is dietary fat a major determinant of body fat? *Am J Clin Nutr* 67:556S–562S.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. 1987. Dietary fat and the risk of breast cancer. *N Engl J Med* 316:22–28.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. 1990. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 323:1664–1672.

Willett WC, Hunter DJ, Stampfer MJ, Colditz G, Manson JE, Spiegelman D, Rosner B, Hennekens CH, Speizer FE. 1992. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. *J Am Med Assoc* 268:2037–2044.

Willett WC, Stampfer MJ, Mason JE, Colditz GA, Speizer FE, Rosner BA, Sampson LA, Hennekens CH. 1993. Intake of *trans* fatty acids and risk of coronary heart disease among women. *Lancet* 341:581–585.

Williams PT. 1997. Relationship of distance run per week to coronary heart disease risk factors in 8283 male runners. The National Runners' Health Study. *Arch Intern Med* 157:191–198.

Williams PT, Wood PD, Krauss RM, Haskell WL, Vranizan KM, Blair SN, Terry R, Farquhar JW. 1983. Does weight loss cause the exercise-induced increase in plasma high density lipoproteins? *Atherosclerosis* 47:173–185.

Williams PT, Krauss RM, Wood PD, Lindgren FT, Giotas C, Vranizan KM. 1986. Lipoprotein subfractions of runners and sedentary men. *Metabolism* 35:45–52.

Williams PT, Krauss RM, Vranizan KM, Wood PDS. 1990. Changes in lipoprotein subfractions during diet-induced and exercise-induced weight loss in moderately overweight men. *Circulation* 81:1293–1304.

Williams PT, Krauss RM, Vranizan KM, Albers JJ, Wood PDS. 1992. Effects of weight-loss by exercise and by diet on apolipoproteins A-I and A-II and the particle-size distribution of high-density lipoproteins in men. *Metabolism* 41:441–449.

Williams PT, Stefanick ML, Vranizan KM, Wood PD. 1994. The effects of weight loss by exercise or by dieting on plasma high-density lipoprotein (HDL) levels in men with low, intermediate, and normal-to-high HDL at baseline. *Metabolism* 43:917–924.

Williamson DF, Madans J, Anda RF, Kleinman JC, Kahn HS, Byers T. 1993. Recreational physical activity and ten-year weight change in a US national cohort. *Int J Obes Relat Metab Disord* 17:279–286.

Wolever TMS, Jenkins DJA. 1993. Effect of dietary fiber and foods on carbohydrate metabolism. In: Spiller G, ed. *CRC Handbook of Dietary Fiber in Human Nutrition.* Boca Raton, FL: CRC Press. Pp. 111–162.

Wolever TMS, Jenkins DJA, Ocana AM, Rao VA, Collier GR. 1988. Second-meal effect: Low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. *Am J Clin Nutr* 48:1041–1047.

Wolfe BMJ, Piché LA. 1999. Replacement of carbohydrate by protein in a conventional-fat diet reduces cholesterol and triglyceride concentrations in healthy normolipidemic subjects. *Clin Invest Med* 22:140–148.

Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM, Ellsworth NM, Terry RB, Haskell WL. 1988. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 319:1173–1179.

Wood PJ, Braaten JT, Scott FW, Riedel KD, Wolynetz MS, Collins MW. 1994. Effect of dose and modification of viscous properties of oat gum on plasma glucose and insulin following an oral glucose load. *Br J Nutr* 72:731–743.

Wu Y, Zheng W, Sellars TA, Kushi LH, Bostick RM, Potter JD. 1994. Dietary cholesterol, fat, and lung cancer incidence among older women: The Iowa Women's Health Study (United States). *Cancer Causes Control* 5:395–400.

Yost TJ, Jensen DR, Haugen BR, Eckel RH. 1998. Effect of dietary macronutrient composition on tissue-specific lipoprotein lipase activity and insulin action in normal-weight subjects. *Am J Clin Nutr* 68:296–302.

Yu S, Derr J, Etherton TD, Kris-Etherton PM. 1995. Plasma cholesterol-predictive equations demonstrate that stearic acid is neutral and monounsaturated fatty acids are hypocholesterolemic. *Am J Clin Nutr* 61:1129–1139.

Yudkin J, Eisa O, Kang SS, Meraji S, Bruckdorfer KR. 1986. Dietary sucrose affects plasma HDL cholesterol concentration in young men. *Ann Nutr Metab* 30: 261–266.

Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM. 1999. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: A meta-analysis. *Am J Clin Nutr* 69:632–646.

Zambon S, Friday KE, Childs MT, Fujimoto WY, Bierman EL, Ensinck JW. 1992. Effect of glyburide and ω3 fatty acid dietary supplements on glucose and lipid metabolism in patients with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 56:447–454.

Zhu Z, Jiang W, Thompson HJ. 1999. Effect of energy restriction on tissue size regulation during chemically induced mammary carcinogenesis. *Carcinogenesis* 20:1721–1726.

4

A Model for the Development of Tolerable Upper Intake Levels

BACKGROUND

The *Tolerable Upper Intake Level* (UL) refers to the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases. The term *tolerable* is chosen because it connotes a level of intake that can, with high probability, be tolerated biologically by individuals; it does not imply acceptability of that level in any other sense. The setting of a UL does not indicate that nutrient intakes greater than the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) are recommended as being beneficial to an individual. Many individuals are self-medicating with nutrients for curative or treatment purposes. It is beyond the scope of this report to address the possible therapeutic benefits of higher nutrient intakes that may offset the risk of adverse effects. The UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient. This chapter describes a model for developing ULs.

The term *adverse effect* is defined as any significant alteration in the structure or function of the human organism (Klaassen et al., 1986) or any impairment of a physiologically important function that could lead to a health effect that is adverse, in accordance with the definition set by the joint World Health Organization, Food and Agriculture Organization of the United Nations, and International Atomic Energy Agency Expert Consultation in Trace Elements in Human Nutrition and Health (WHO, 1996). In the case of nutrients, it is exceedingly important to consider the possi-

bility that the intake of one nutrient may alter, in detrimental ways, the health benefits conferred by another nutrient. Any such alteration (referred to as an adverse nutrient–nutrient interaction) is considered an adverse health effect. When evidence for such adverse interactions is available, it is considered in establishing a nutrient's UL.

ULs are useful because of the increased interest in, and availability of, fortified foods, the increased use of dietary supplements, and the growing recognition of the health consequences of excesses, as well as inadequacies of nutrient intakes. ULs are based on total intake of a nutrient from food, water, and supplements if adverse effects have been associated with total intake. However, if adverse effects have been associated with intake from supplements or food fortificants only, the UL is based on a nutrient intake from those sources only, not on total intake. The UL applies to chronic daily use.

For many nutrients, there are insufficient data on which to develop a UL. This does not mean that there is no potential for adverse effects resulting from high intake. When data about adverse effects are extremely limited, extra caution may be warranted.

Like all chemical agents, nutrients can produce adverse health effects if their intake from a combination of food, water, nutrient supplements, and pharmacological agents is excessive. Some lower level of nutrient intake will ordinarily pose no likelihood (or risk) of adverse health effects in normal individuals even if the level is above that associated with any benefit. It is not possible to identify a single risk-free intake level for a nutrient that can be applied with certainty to all members of a population. However, it is possible to develop intake levels that are unlikely to pose risk of adverse health effects for most members of the general population, including sensitive individuals. For some nutrients, these intake levels may pose a risk to subpopulations with extreme or distinct vulnerabilities.

Whether routine, long-term intake above the UL is safe is not well documented. Although members of the general population should not routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity, and as long as these trials employ appropriate safety monitoring of trial subjects.

A MODEL FOR THE DERIVATION OF TOLERABLE UPPER INTAKE LEVELS

The possibility that the methodology used to derive Tolerable Upper Intake Levels (ULs) might be reduced to a mathematical model that could

be generically applied to all nutrients was considered. Such a model might have several potential advantages, including ease of application and assurance of consistent treatment of all nutrients. It was concluded, however, that the current state of scientific understanding of toxic phenomena in general, and nutrient toxicity in particular, is insufficient to support the development of such a model. Scientific information about various adverse effects and their relationships to intake levels varies greatly among nutrients and depends on the nature, comprehensiveness, and quality of available data. The uncertainties associated with the unavoidable problem of extrapolating from the circumstances under which data are developed (e.g., in the laboratory or clinic) to other circumstances (e.g., to the healthy population) add to the complexity.

Given the current state of knowledge, any attempt to capture, in a mathematical model, all of the information and scientific judgments that must be made to reach conclusions about ULs would not be consistent with contemporary risk assessment practices. Instead, the model for the derivation of ULs consists of a set of scientific factors that always should be considered explicitly. The framework by which these factors are organized is called *risk assessment*. Risk assessment (NRC, 1983, 1994) is a systematic means of evaluating the probability of occurrence of adverse health effects in humans from excess exposure to an environmental agent (in this case, a nutrient) (FAO/WHO, 1995; Health Canada, 1993). The hallmark of risk assessment is the requirement to be explicit in all of the evaluations and judgments that must be made to document conclusions.

RISK ASSESSMENT AND FOOD SAFETY

Basic Concepts

Risk assessment is a scientific undertaking having as its objective a characterization of the nature and likelihood of harm resulting from human exposure to agents in the environment. The characterization of risk typically contains both qualitative and quantitative information and includes a discussion of the scientific uncertainties in that information. In the present context, the agents of interest are nutrients, and the environmental media are food, water, and nonfood sources such as nutrient supplements and pharmacological preparations.

Performing a risk assessment results in a characterization of the relationships between exposure to an agent and the likelihood that adverse health effects will occur in members of exposed populations. Scientific uncertainties are an inherent part of the risk assessment process and are discussed below. Deciding whether the magnitude of exposure is *acceptable*

or *tolerable* in specific circumstances is not a component of risk assessment; this activity falls within the domain of *risk management*. Risk management decisions depend on the results of risk assessments, but may also involve the public health significance of the risk, the technical feasibility of achieving various degrees of risk control, and the economic and social costs of this control. Because there is no single, scientifically definable distinction between safe and unsafe exposures, risk management necessarily incorporates components of sound, practical decision making that are not addressed by the risk assessment process (NRC, 1983, 1994).

Risk assessment requires that information be organized in rather specific ways, but it does not require any specific scientific evaluation methods. Rather, risk assessors must evaluate scientific information using what they judge to be appropriate methods and must make explicit the basis for their judgments, the uncertainties in risk estimates, and, when appropriate, alternative scientifically plausible interpretations of the available data (NRC, 1994; OTA, 1993).

Risk assessment is subject to two types of scientific uncertainties: those related to data and those associated with inferences that are required when directly applicable data are not available (NRC, 1994). Data uncertainties arise during the evaluation of information obtained from the epidemiological and toxicological studies of nutrient intake levels that are the basis for risk assessments. Examples of inferences include the use of data from experimental animals to estimate responses in humans and the selection of uncertainty factors to estimate inter- and intraspecies variabilities in response to toxic substances. Uncertainties arise whenever estimates of adverse health effects in humans are based on extrapolations of data obtained under dissimilar conditions (e.g., from experimental animal studies). Options for dealing with uncertainties are discussed below and in detail in Appendix L.

Steps in the Risk Assessment Process

The organization of risk assessment is based on a model proposed by the National Research Council (NRC, 1983, 1994) that is widely used in public health and regulatory decision making. The steps of risk assessment as applied to nutrients follow (see also Figure 4-1).

- Step 1. Hazard identification involves the collection, organization, and evaluation of all information pertaining to the adverse effects of a given nutrient. It concludes with a summary of the evidence concerning the capacity of the nutrient to cause one or more types of toxicity in humans.
- Step 2. Dose–response assessment determines the relationship between nutrient intake (dose) and adverse effect (in terms of incidence

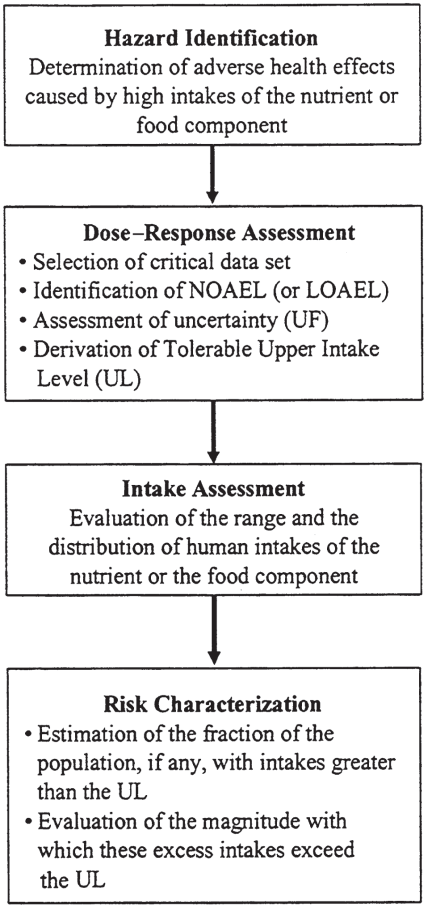

FIGURE 4-1 Risk assessment model for nutrient toxicity. NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level; UF = uncertainty factor.

and severity). This step concludes with an estimate of the Tolerable Upper Intake Level (UL)—it identifies the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. Different ULs may be developed for various life stage groups.

- Step 3. Intake assessment evaluates the distribution of usual total daily nutrient intakes for members of the general population. In cases where the UL pertains only to supplement use and does not pertain to

usual food intakes of the nutrient, the assessment is directed at supplement intakes only. It does not depend on Step 1 or 2.

- Step 4. Risk characterization summarizes the conclusions from Steps 1 and 2 with Step 3 to determine the risk. The risk is generally expressed as the fraction of the exposed population, if any, having nutrient intakes (Step 3) in excess of the estimated UL (Steps 1 and 2). If possible, characterization also covers the magnitude of any such excesses. Scientific uncertainties associated with both the UL and the intake estimates are described so that risk managers understand the degree of scientific confidence they can place in the risk assessment.

The risk assessment contains no discussion of recommendations for reducing risk; these are the focus of risk management.

Thresholds

A principal feature of the risk assessment process for noncarcinogens is the long-standing acceptance that no risk of adverse effects is expected unless a threshold dose (or intake) is exceeded. The adverse effects that may be caused by a nutrient almost certainly occur only when the threshold dose is exceeded (NRC, 1994; WHO, 1996). The critical issue concerns the methods used to identify the approximate threshold of toxicity for a large and diverse human population. Because most nutrients are not considered to be carcinogenic in humans, approaches used for carcinogenic risk assessment are not discussed here.

Thresholds vary among members of the general population (NRC, 1994). For any given adverse effect, if the distribution of thresholds in the population could be quantitatively identified, it would be possible to establish ULs by defining some point in the lower tail of the distribution of thresholds that would protect some specified fraction of the population. The method described here for identifying thresholds for a general population is designed to ensure that almost all members of the population will be protected, but it is not based on an analysis of the theoretical (but practically unattainable) distribution of thresholds. By using the model to derive the threshold, however, there is considerable confidence that the threshold, which becomes the UL for nutrients or food components, lies very near the low end of the theoretical distribution and is the end representing the most sensitive members of the population. For some nutrients there may be subpopulations that are not included in the general distribution because of extreme or distinct vulnerabilities to toxicity. Data relating to the effects observed in these groups are not used to derive ULs. Such distinct groups, whose conditions warrant medical supervision, may not be protected by the UL.

The Joint FAO/WHO Expert Committee on Food Additives and various national regulatory bodies have identified factors (called *uncertainty factors* [UFs]) that account for interspecies and intraspecies differences in response to the hazardous effects of substances and for other uncertainties (WHO, 1987). UFs are used to make inferences about the threshold dose of substances for members of a large and diverse human population from data on adverse effects obtained in epidemiological or experimental studies. These factors are applied consistently when data of specific types and quality are available. They are typically used to derive acceptable daily intakes for food additives and other substances for which data on adverse effects are considered sufficient to meet minimum standards of quality and completeness (FAO/WHO, 1982). These adopted or recognized UFs have sometimes been coupled with other factors to compensate for deficiencies in the available data and other uncertainties regarding data.

When possible, the UL is based on a no-observed-adverse-effect level (NOAEL), which is the highest intake (or experimental oral dose) of a nutrient at which no adverse effects have been observed in the individuals studied. This is identified for a specific circumstance in the hazard identification and dose–response assessment steps of the risk. If there are no adequate data demonstrating a NOAEL, then a lowest-observed-adverse-effect level (LOAEL) may be used. A LOAEL is the lowest intake (or experimental oral dose) at which an adverse effect has been identified. The derivation of a UL from a NOAEL (or LOAEL) involves a series of choices about which factors should be used to deal with uncertainties. Uncertainty factors are applied in an attempt to deal both with gaps in data and with incomplete knowledge about the inferences required (e.g., the expected variability in response within the human population). The problems of both data and inference uncertainties arise in all steps of the risk assessment. A discussion of options available for dealing with these uncertainties is presented below and in greater detail in Appendix L.

A UL is not, in itself, a description or estimate of human risk. It is derived by application of the hazard identification and dose–response evaluation steps (Steps 1 and 2) of the risk assessment model. To determine whether populations are at risk requires an intake or exposure assessment (Step 3, evaluation of intakes of the nutrient by the population) and a determination of the fractions of these populations, if any, whose intakes exceed the UL. In the intake assessment and risk characterization steps (Steps 3 and 4), the distribution of usual intakes for the population is used as a basis for determining whether, and to what extent, the population is at risk (Figure 4-1). A discussion of other aspects of the risk characterization that may be useful in judging the public health significance of the risk and in risk management decisions is provided in the final section of this chapter "Risk Characterization."

APPLICATION OF THE RISK ASSESSMENT MODEL TO NUTRIENTS

This section provides guidance for applying the risk assessment framework (the model) to the derivation of Tolerable Upper Intake Levels (ULs) for nutrients.

Special Problems Associated with Substances Required for Human Nutrition

Although the risk assessment model outlined above can be applied to nutrients to derive ULs, it must be recognized that nutrients possess some properties that distinguish them from the types of agents for which the risk assessment model was originally developed (NRC, 1983). In the application of accepted standards for risk assessment of environmental chemicals to risk assessment of nutrients, a fundamental difference between the two categories must be recognized: within a certain range of intakes, nutrients are essential for human well-being and usually for life itself. Nonetheless, they may share with other chemicals the production of adverse effects at excessive exposures. Because the consumption of balanced diets is consistent with the development and survival of humankind over many millennia, there is less need for the large uncertainty factors that have been used for the risk assessment of nonessential chemicals. In addition, if data on the adverse effects of nutrients are available primarily from studies in human populations, there will be less uncertainty than is associated with the types of data available on nonessential chemicals.

There is no evidence to suggest that nutrients consumed at the recommended intake (the Recommended Dietary Allowance or Adequate Intake) present a risk of adverse effects to the general population.[1] It is clear, however, that the addition of nutrients to a diet through the ingestion of large amounts of highly fortified food, nonfood sources such as supplements, or both, may (at some level) pose a risk of adverse health effects. The UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases.

If adverse effects have been associated with total intake, ULs are based on total intake of a nutrient from food, water, and supplements. For cases in which adverse effects have been associated with intake only from supple-

[1]It is recognized that possible exceptions to this generalization relate to specific geochemical areas with excessive environmental exposures to certain trace elements (e.g., selenium) and to rare case reports of adverse effects associated with highly eccentric consumption of specific foods. Data from such findings are generally not useful for setting ULs for the general North American population.

ments and food fortificants, the UL is based on intake from these sources only, rather than on total intake. The effects of nutrients from fortified foods or supplements may differ from those of naturally occurring constituents of foods because of the chemical form of the nutrient, the timing of the intake and amount consumed in a single bolus dose, the matrix supplied by the food, and the relation of the nutrient to the other constituents of the diet. Nutrient requirements and food intake are related to the metabolizing body mass, which is also at least an indirect measure of the space in which the nutrients are distributed. This relation between food intake and space of distribution supports homeostasis, which maintains nutrient concentrations in that space within a range compatible with health. However, excessive intake of a single nutrient from supplements or fortificants may compromise this homeostatic mechanism. Such elevations alone may pose risks of adverse effects; imbalances among the nutrients may also be possible. These reasons and those discussed previously support the need to include the form and pattern of consumption in the assessment of risk from high nutrient or food component intake.

Consideration of Variability in Sensitivity

The risk assessment model outlined in this chapter is consistent with classical risk assessment approaches in that it must consider variability in the sensitivity of individuals to adverse effects of nutrients or food components. A discussion of how variability is dealt with in the context of nutritional risk assessment follows.

Physiological changes and common conditions associated with growth and maturation that occur during an individual's lifespan may influence sensitivity to nutrient toxicity. For example, sensitivity increases with declines in lean body mass and with the declines in renal and liver function that occur with aging; sensitivity changes in direct relation to intestinal absorption or intestinal synthesis of nutrients; sensitivity increases in the newborn infant because of rapid brain growth and limited ability to secrete or biotransform toxicants; and sensitivity increases with decreases in the rate of metabolism of nutrients. During pregnancy, the increase in total body water and glomerular filtration results in lower blood levels of water-soluble vitamins dose for dose, and therefore results in reduced susceptibility to potential adverse effects. However, in the unborn fetus this may be offset by active placental transfer, accumulation of certain nutrients in the amniotic fluid, and rapid development of the brain. Examples of life stage groups that may differ in terms of nutritional needs and toxicological sensitivity include infants and children, the elderly, and women during pregnancy and lactation.

Even within relatively homogeneous life stage groups, there is a range

of sensitivities to toxic effects. The model described below accounts for the normal expected variability in sensitivity, but it excludes subpopulations with extreme and distinct vulnerabilities. Such subpopulations consist of individuals needing medical supervision; they are better served through the use of public health screening, product labeling, or other individualized health care strategies. Such populations may not be at *negligible risk* when their intakes reach the UL developed for the healthy population. The decision to treat identifiable vulnerable subgroups as distinct (not protected by the UL) is a matter of judgment and is discussed in the individual nutrient chapters, as applicable.

Bioavailability

In the context of toxicity, the bioavailability of an ingested nutrient can be defined as its accessibility to normal metabolic and physiological processes. Bioavailability influences a nutrient's beneficial effects at physiological levels of intake and also may affect the nature and severity of toxicity due to excessive intakes. The concentration and chemical form of the nutrient, the nutrition and health of the individual, and excretory losses all affect bioavailability. Bioavailability data for specific nutrients must be considered and incorporated into the risk assessment process.

Some nutrients may be less readily absorbed when part of a meal than when consumed separately. Supplemental forms of some nutrients may require special consideration if they have higher bioavailability since they may present a greater risk of producing adverse effects than equivalent amounts from the natural form found in food.

Nutrient–Nutrient Interactions

A diverse array of adverse health effects can occur as a result of the interaction of nutrients. The potential risks of adverse nutrient–nutrient interactions increase when there is an imbalance in the intake of two or more nutrients. Excessive intake of one nutrient may interfere with absorption, excretion, transport, storage, function, or metabolism of a second nutrient. Possible adverse nutrient–nutrient interactions are considered as a part of setting a UL. Nutrient–nutrient interactions may be considered either as a critical endpoint on which to base a UL, or as supportive evidence for a UL based on another endpoint.

Other Relevant Factors That Affect the Bioavailability of Nutrients

In addition to nutrient interactions, other considerations have the potential to influence nutrient bioavailability, such as the nutritional status

of an individual and the form of intake. These issues are considered in the risk assessment. With regard to the form of intake, fat-soluble vitamins, such as vitamin A, are more readily absorbed when they are part of a meal that is high in fat. ULs must therefore be based on nutrients as part of the total diet, including the contribution from water. Nutrient supplements that are taken separately from food require special consideration because they are likely to have different bioavailabilities and therefore may represent a greater risk of producing adverse effects.

STEPS IN THE DEVELOPMENT OF THE TOLERABLE UPPER INTAKE LEVEL

Hazard Identification

Based on a thorough review of the scientific literature, the hazard identification step outlines the adverse health effects that have been demonstrated to be caused by the nutrient. The primary types of data used as background for identifying nutrient hazards in humans are:

- *Human studies.* Human data provide the most relevant kind of information for hazard identification and, when they are of sufficient quality and extent, are given the greatest weight. However, the number of controlled human toxicity studies conducted in a clinical setting is very limited because of ethical reasons. Such studies are generally most useful for identifying very mild (and ordinarily reversible) adverse effects. Observational studies that focus on well-defined populations with clear exposures to a range of nutrient intake levels are useful for establishing a relationship between exposure and effect. Observational data in the form of case reports or anecdotal evidence are used for developing hypotheses that can lead to knowledge of causal associations. Sometimes a series of case reports, if it shows a clear and distinct pattern of effects, may be reasonably convincing on the question of causality.
- *Animal data.* Most of the available data used in regulatory risk assessments come from controlled laboratory experiments in animals, usually mammalian species other than humans (e.g., rodents). Such data are used in part because human data on nonessential chemicals are generally very limited. Moreover, there is a long-standing history of the use of animal studies to identify the toxic properties of chemical substances, and there is no inherent reason why animal data should not be relevant to the evaluation of nutrient toxicity. Animal studies offer several advantages over human studies. They can, for example, be readily controlled so that causal relationships can be recognized. It is possible to identify the full range of toxic effects produced by a chemical, over a wide range of exposures, and

BOX 4-1
Development of Tolerable Upper Intake Levels (ULs)

COMPONENTS OF HAZARD IDENTIFICATION

- Evidence of adverse effects in humans
- Causality
- Relevance of experimental data
- Pharmacokinetic and metabolic data
- Mechanisms of toxic action
- Quality and completeness of the database
- Identification of distinct and highly sensitive subpopulations

COMPONENTS OF DOSE–RESPONSE ASSESSMENT

- Data selection and identification of critical endpoints
- Identification of no-observed-adverse-effect level (NOAEL) (or lowest-observed-adverse-effect level [LOAEL]) and critical endpoint
- Assessment of uncertainty and data on variability in response
- Derivation of a UL
- Characterization of the estimate and special considerations

to establish dose–response relationships. The effects of chronic exposures can be identified in far less time than they can with the use of epidemiological methods. All these advantages of animal data, however, may not always overcome the fact that species differences in response to chemical substances can sometimes be profound, and any extrapolation of animal data to predict human response needs to take this possibility into account.

Key issues that are addressed in the data evaluation of human and animal studies are described below (see Box 4-1).

Evidence of Adverse Effects in Humans

The hazard identification step involves the examination of human, animal, and in vitro published evidence that addresses the likelihood of a nutrient eliciting an adverse effect in humans. Decisions about which observed effects are adverse are based on scientific judgment. Although toxicologists generally regard any demonstrable structural or functional alteration as representing an adverse effect, some alterations may be considered to be of little or self-limiting biological importance. As noted earlier, adverse nutrient–nutrient interactions are considered in the definition of an adverse effect.

Causality

The identification of a hazard is strengthened by evidence of causality. As explained in Chapter 2, the criteria of Hill (1971) are considered in judging the causal significance of an exposure–effect association indicated by epidemiological studies.

Relevance of Experimental Data

Consideration of the following issues can be useful in assessing the relevance of experimental data.

Animal Data. Some animal data may be of limited utility in judging the toxicity of nutrients because of highly variable interspecies differences in nutrient requirements. Nevertheless, relevant animal data are considered in the hazard identification and dose–response assessment steps where applicable, and, in general, they are used for hazard identification unless there are data demonstrating they are not relevant to humans, or it is clear that the available human data are sufficient.

Route of Exposure.[2] Data derived from studies involving oral exposure (rather than parenteral, inhalation, or dermal exposure) are most useful for the evaluation of nutrients. Data derived from studies involving parenteral, inhalation, or dermal routes of exposure may be considered relevant if the adverse effects are systemic and data are available to permit interroute extrapolation.

Duration of Exposure. Because the magnitude, duration, and frequency of exposure can vary considerably in different situations, consideration needs to be given to the relevance of the exposure scenario (e.g., chronic daily dietary exposure versus short-term bolus doses) to dietary intakes by human populations.

Pharmacokinetic and Metabolic Data

When available, data regarding the rates of nutrient absorption, distribution, metabolism, and excretion may be important in derivation of Tolerable Upper Intake Levels (ULs). Such data may provide significant information regarding the interspecies differences and similarities in

[2]The terms *route of exposure* and *route of intake* refer to how a substance enters the body (e.g., by ingestion, injection, or dermal absorption). These terms should not be confused with *form of intake*, which refers to the medium or vehicle used (e.g., supplements, food, or drinking water).

nutrient behavior, and so may assist in identifying relevant animal data. They may also assist in identifying life stage differences in response to nutrient toxicity.

In some cases, there may be limited or even no significant data relating to nutrient toxicity. It is conceivable that in such cases pharmacokinetic and metabolic data may provide valuable insights into the magnitude of the UL. Thus, if there are significant pharmacokinetic and metabolic data over the range of intakes that meet nutrient requirements, and if it is shown that this pattern of pharmacokinetic and metabolic data does not change in the range of intakes greater than those required for nutrition, it may be possible to infer the absence of toxic risk in this range. In contrast, an alteration of pharmacokinetics or metabolism may suggest the potential for adverse effects. There has been no case encountered thus far in which sufficient pharmacokinetic and metabolic data are available for establishing ULs in this fashion, but it is possible such situations may arise in the future.

Mechanisms of Toxic Action

Knowledge of molecular and cellular events underlying the production of toxicity can assist in dealing with the problems of extrapolation between species and from high to low doses. It may also aid in understanding whether the mechanisms associated with toxicity are those associated with deficiency. In most cases, however, because knowledge of the biochemical sequence of events resulting from toxicity and deficiency is still incomplete, it is not yet possible to state with certainty whether these sequences share a common pathway.

Quality and Completeness of the Database

The scientific quality and quantity of the database are evaluated. Human or animal data are reviewed for suggestions that the nutrient has the potential to produce additional adverse health effects. If suggestions are found, additional studies may be recommended.

Identification of Distinct and Highly Sensitive Subpopulations

The ULs are based on protecting the most sensitive members of the general population from adverse effects of high nutrient intake. Some highly sensitive subpopulations have responses (in terms of incidence, severity, or both) to the agent of interest that are clearly distinct from the responses expected for the healthy population. The risk assessment process recognizes that there may be individuals within any life stage group who

are more biologically sensitive than others, and thus their extreme sensitivities do not fall within the range of sensitivities expected for the general population. The UL for the general population may not be protective for these subgroups. As indicated earlier, the extent to which a distinct subpopulation will be included in the derivation of a UL for the general population is an area of judgment to be addressed on a case-by-case basis.

Dose–Response Assessment

The process for deriving the UL is described in this section and outlined in Box 4-1. It includes selection of the critical data set, identification of a critical endpoint with its no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL), and assessment of uncertainty.

Data Selection and Identification of Critical Endpoints

The data evaluation process results in the selection of the most appropriate or critical data sets for deriving the UL. Selecting the critical data set includes the following considerations:

- Human data, when adequate to evaluate adverse effects, are preferable to animal data, although the latter may provide useful supportive information.
- In the absence of appropriate human data, information from an animal species with biological responses most like those of humans is most valuable. Pharmacokinetic, metabolic, and mechanistic data may be available to assist in the identification of relevant animal species.
- If it is not possible to identify such a species or to select such data, data from the most sensitive animal species, strain, and gender combination are given the greatest emphasis.
- The route of exposure that most resembles the route of expected human intake is preferable. This consideration includes the digestive state (e.g., fed or fasted) of the subjects or experimental animals. When this is not possible, the differences in route of exposure are noted as a source of uncertainty.
- The critical data set defines a dose–response relationship between intake and the extent of the toxic response known to be most relevant to humans. Data on bioavailability are considered and adjustments in expressions of dose–response are made to determine whether any apparent differences in response can be explained.
- The critical data set documents the route of exposure and the magnitude and duration of the intake. Furthermore, the critical data set documents the NOAEL (or LOAEL).

Identification of a NOAEL (or LOAEL)

A nutrient can produce more than one toxic effect (or endpoint), even within the same species or in studies using the same or different exposure durations. The NOAELs and LOAELs for these effects will ordinarily differ. The critical endpoint used to establish a UL is the adverse biological effect exhibiting the lowest NOAEL (e.g., the most sensitive indicator of a nutrient's toxicity). Because the selection of uncertainty factors (UFs) depends in part upon the seriousness of the adverse effect, it is possible that lower ULs may result from the use of the most *serious* (rather than most *sensitive*) endpoint. Thus, it is often necessary to evaluate several endpoints independently to determine which leads to the lowest UL.

For some nutrients, there may be inadequate data on which to develop a UL. The lack of reports of adverse effects following excess intake of a nutrient does not mean that adverse effects do not occur. As the intake of any nutrient increases, a point (see Figure 4-2) is reached at which intake begins to pose a risk. Above this point, increased intake increases the risk of adverse effects. For some nutrients and for various reasons, there are inadequate data to identify this point, or even to estimate its location.

Because adverse effects are almost certain to occur for any nutrient at some level of intake, it should be assumed that such effects may occur for nutrients for which a scientifically documentable UL cannot now be derived. Until a UL is set or an alternative approach to identifying protec-

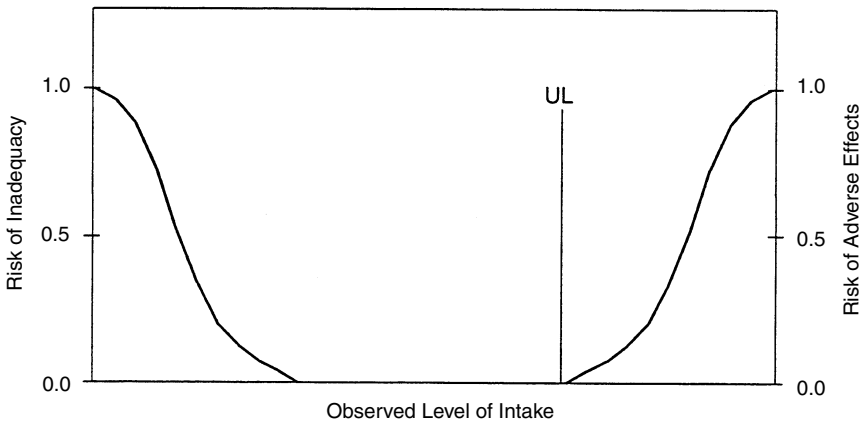

FIGURE 4-2 Theoretical description of health effects of a nutrient as a function of level of intake. The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. At intakes above the UL, the risk of adverse effects increases.

tive limits is developed, intakes greater than the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) should be viewed with caution.

The absence of sufficient data to establish a UL points to the need for studies suitable for developing ULs.

Uncertainty Assessment

Several judgments must be made regarding the uncertainties and thus the uncertainty factor (UF) associated with extrapolating from the observed data to the general population (see Appendix L). Applying a UF to a NOAEL (or LOAEL) results in a value for the derived UL that is less than the experimentally derived NOAEL unless the UF is 1. The greater the uncertainty, the larger the UF and the smaller the resulting UL. This is consistent with the ultimate goal of the risk assessment: to provide an estimate of a level of intake that will protect the health of virtually all members of the healthy population (Mertz et al., 1994).

Although several reports describe the underlying basis for UFs (Dourson and Stara, 1983; Zielhuis and van der Kreek, 1979), the strength of the evidence supporting the use of a specific UF will vary. Because the imprecision of these UFs is a major limitation of risk assessment approaches, considerable leeway must be allowed for the application of scientific judgment in making the final determination. Because data are generally available regarding intakes of nutrients in human populations, the data on nutrient toxicity may not be subject to the same uncertainties as are data on nonessential chemical agents. The resulting UFs for nutrients and food components are typically less than the factors of 10 often applied to nonessential toxic substances. The UFs are lower with higher quality data and when the adverse effects are extremely mild and reversible.

In general, when determining a UF, the following potential sources of uncertainty are considered and combined in the final UF:

- *Interindividual variation in sensitivity.* Small UFs (close to 1) are used to represent this source of uncertainty if it is judged that little population variability is expected for the adverse effect, and larger factors (close to 10) are used if variability is expected to be great (NRC, 1994).
- *Extrapolation from experimental animals to humans.* A UF to account for the uncertainty in extrapolating animal data to humans is generally applied to the NOAEL when animal data are the primary data available. While a default UF of 10 is often used to extrapolate animal data to humans for nonessential chemicals, a lower UF may be used because of data showing some similarities between the animal and human responses (NRC, 1994).
- *LOAEL instead of NOAEL.* If a NOAEL is not available, a UF may be applied to account for the uncertainty in deriving a UL from the LOAEL.

The size of the UF involves scientific judgment based on the severity and incidence of the observed effect at the LOAEL and the steepness (slope) of the dose–response.

- *Subchronic NOAEL to predict chronic NOAEL.* When data are lacking on chronic exposures, scientific judgment is necessary to determine whether chronic exposures are likely to lead to adverse effects at lower intakes than those producing effects after subchronic exposures (exposures of shorter duration).

Derivation of a UL

The UL is derived by dividing the NOAEL (or LOAEL) by a single UF that incorporates all relevant uncertainties. ULs, expressed as amount per day, are derived for various life stage groups using relevant databases, NOAELs, LOAELs, and UFs. In cases where no data exist with regard to NOAELs or LOAELs for the group under consideration, extrapolations from data in other age groups or animal data are made on the basis of known differences in body size, physiology, metabolism, absorption, and excretion of the nutrient.

Generally, any age group adjustments are made based solely on differences in body weight, unless there are data demonstrating age-related differences in nutrient pharmacokinetics, metabolism, or mechanism of action.

The derivation of the UL involves the use of scientific judgment to select the appropriate NOAEL (or LOAEL) and UF. As shown in Figure 4-3, when using the same critical endpoint there is a greater level of uncertainty in setting the UL based on a LOAEL compared with a NOAEL. The risk assessment requires explicit consideration and discussion of all choices made regarding both the data used and the uncertainties accounted for. These considerations are discussed in the nutrient chapters.

Characterization of the Estimate and Special Considerations

If the data review reveals the existence of subpopulations having distinct and exceptional sensitivities to a nutrient's toxicity, these subpopulations are explicitly discussed and concerns related to adverse effects are noted; however, the use of the data is not included in the identification of the NOAEL or LOAEL, upon which the UL for the general population is based.

Circumstances in Which No UL Is Established

There are two general conditions under which ULs are not established. In some cases, the availability of insufficient evidence regarding a

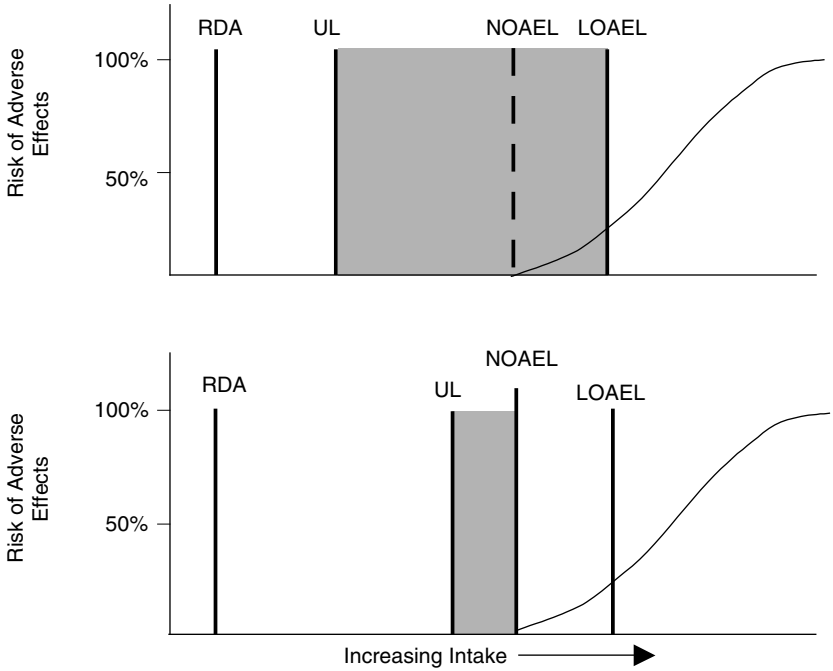

FIGURE 4-3 Effect of uncertainty assessment on the Tolerable Upper Intake Level (UL). Dashed line represents a hypothetical no-observed-adverse-effect level (NOAEL). Solid lines represent available data used to set the UL. Area containing diagonal lines represents theoretical range of uncertainty. LOAEL = lowest-observed-adverse-effect level; RDA = Recommended Dietary Allowance.

nutrient's capacity to cause adverse effects prohibits the application of the UL model. In other cases, the evidence is available, but meeting the UL derived from such evidence will necessarily result in the introduction of undesirable health effects because of the required adjustments in dietary patterns.

Insufficient Evidence of Adverse Effects

The scientific evidence relating to adverse effects of nutrient excess varies greatly among nutrients. The type of data and evidence of causation used to derive ULs have been described earlier in this chapter, but such data and evidence are simply unavailable for some nutrients. In some cases (e.g., the individual amino acids), some data relating to adverse effects may be available, but are of such uncertain relevance to human health that

their use in deriving ULs is scientifically insupportable. In every instance in which ULs are not derived because of lack of adequate evidence, the specific limitations in the database are described.

Offsetting Benefits Reduction

In the case of macronutrients, particularly, problems arise because of the adjustments in dietary patterns that would be required to meet a derived UL. For saturated and *trans* fatty acids and dietary cholesterol, for example, there is evidence that any intake greater than zero will increase serum levels of low density lipoprotein cholesterol, an established risk for cardiovascular disease. In such cases, the UL model calls for the establishment of a UL of 0. But it is clear that, because saturated fat and cholesterol are both unavoidable in ordinary diets, achieving such a UL will require extraordinary changes in patterns of dietary intake. Such extraordinary adjustments may introduce other undesirable health effects (e.g., elimination of foods containing saturated fats may result in a large excess intake of carbohydrate and insufficient intake of micronutrients). In addition, unknown and unquantifiable health risks may also be introduced. For these reasons, no UL will be proposed in circumstances in which implementation of measures to achieve the UL may lead to undesirable dietary adjustments. In all such cases, the basis for failing to propose a UL will be described.

Lack of ULs for Macronutrients and Implications

ULs were not set for macronutrients because (1) there was insufficient evidence for identifying an adverse effect, and therefore a LOAEL, upon which to determine a UL (e.g., protein), (2) data relating to adverse effects were available (e.g., amino acids), but were of uncertain relevance to human health because their use in deriving ULs was not scientifically supportable, (3) macronutrients are interrelated in providing energy and therefore it is not known whether the adverse effect is due to a high intake of one macronutrient (e.g., fat), due to a low intake of another macronutrient (e.g., carbohydrate, which is usually low in a high fat diet), or both (high fat, low carbohydrate diet), and (4) adjustments of dietary patterns to prevent exceeding a UL of near 0 g/d (e.g., *trans* and saturated fatty acids and cholesterol), resulting in inadequate intakes of certain micronutrients (e.g., iron and zinc). In addition, the UL method is not applicable to energy since any intake above the requirement would be expected to result in weight gain and an increased risk of premature mortality.

The failure to establish a UL for any nutrient should not be interpreted as a lack of concern for adverse health effects (i.e., it is not equiva-

lent to a recommendation that the nutrient can be consumed without limit). Lack of data regarding adverse effects is not evidence of safety. Indeed, in some cases (the previous example of saturated fat) there is clearly evidence of adverse health effects, but a UL is not established to avoid the need for drastic changes that may introduce undesirable health effects.

In every instance in which a UL is not established, it is necessary to offer specific advice regarding the need to avoid deficiency, or in some cases, to reduce intakes, consistent with the need to maintain healthy dietary patterns.

INTAKE ASSESSMENT

In order to assess the risk of adverse effects, information on the range of nutrient intakes in the general population is required. As noted earlier, in cases where the Tolerable Upper Intake Level (UL) pertains only to supplement use and not to usual food intakes of the nutrient, the assessment is directed at supplement intake only.

RISK CHARACTERIZATION

As described earlier, the question of whether nutrient intakes create a risk of toxicity requires a comparison of the range of nutrient intakes (from food, supplements, and other sources, or from supplements alone, depending upon the basis for the Tolerable Upper Intake Level [UL]) with the UL.

Figure 4-4 illustrates a distribution of chronic nutrient intakes in a population; the fraction of the population experiencing chronic intakes above the UL represents the potential at-risk group. A policy decision is needed to determine whether efforts should be made to reduce risk. No precedents are available for such policy decisions, although in the areas of food additives or pesticide regulations, federal regulatory agencies have generally sought to ensure that the 90th or 95th percentile of intake falls below the UL (or its approximate equivalent measure of risk). If this goal is achieved, the fraction of the population remaining above the UL is likely to experience intakes only slightly greater than the UL and is likely to be at little or no risk.

For risk management decisions, it is useful to evaluate the public health significance of the risk, and information contained in the risk characterization is critical for this purpose.

Thus, the significance of the risk to a population consuming a nutrient in excess of the UL is determined by the following:

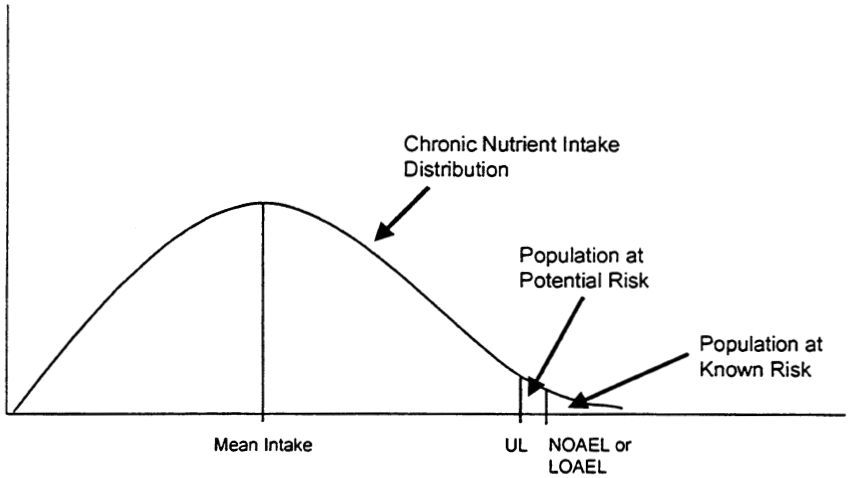

FIGURE 4-4 Illustration of the population at risk from excessive nutrient intakes. The fraction of the population consistently consuming a nutrient at intake levels in excess of the Tolerable Upper Intake Level (UL) is potentially at risk of adverse health effects. See text for a discussion of additional factors necessary to judge the significance of the risk. NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level.

1. the fraction of the population consistently consuming the nutrient at intake levels in excess of the UL,
2. the seriousness of the adverse effects associated with the nutrient,
3. the extent to which the effect is reversible when intakes are reduced to levels less than the UL, and
4. the fraction of the population with consistent intakes above the no-observed-adverse-effect level or even the lowest-observed-adverse-effect level.

Thus, the significance of the risk of excessive nutrient intake cannot be judged only by reference to Figure 4-4, but requires careful consideration of all of the above factors. Information on these factors is contained in sections of the nutrient chapters that describe the bases for each of the ULs.

REFERENCES

Dourson ML, Stara JF. 1983. Regulatory history and experimental support of uncertainty (safety) factors. *Regul Toxicol Pharmacol* 3:224–238.

FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization). 1982. *Evaluation of Certain Food Additives and Contaminants.* Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 683. Geneva: WHO.

FAO/WHO. 1995. *The Application of Risk Analysis to Food Standard Issues.* Recommendations to the Codex Alimentarius Commission (ALINORM 95/9, Appendix 5). Geneva: WHO.

Health Canada. 1993. *Health Risk Determination—The Challenge of Health Protection.* Ottawa: Health Canada, Health Protection Branch.

Hill AB. 1971. *Principles of Medical Statistics,* 9th ed. New York: Oxford University Press.

Klaassen CD, Amdur MO, Doull J. 1986. *Casarett and Doull's Toxicology: The Basic Science of Poisons,* 3rd ed. New York: Macmillan.

Mertz W, Abernathy CO, Olin SS. 1994. *Risk Assessment of Essential Elements.* Washington, DC: ILSI Press.

NRC (National Research Council). 1983. *Risk Assessment in the Federal Government: Managing the Process.* Washington, DC: National Academy Press.

NRC. 1994. *Science and Judgment in Risk Assessment.* Washington, DC: National Academy Press.

OTA (Office of Technology Assessment). 1993. *Researching Health Risks.* Washington, DC: OTA.

WHO (World Health Organization). 1987. *Principles for the Safety Assessment of Food Additives and Contaminants in Food.* Environmental Health Criteria 70. Geneva: WHO.

WHO. 1996. *Trace Elements in Human Nutrition and Health.* Geneva: WHO.

Zielhuis RL, van der Kreek FW. 1979. The use of a safety factor in setting health-based permissible levels for occupational exposure. *Int Arch Occup Environ Health* 42:191–201.

5
Energy

SUMMARY

Energy is required to sustain the body's various functions, including respiration, circulation, physical work, and maintenance of core body temperature. The energy in foods is released in the body by oxidation, yielding the chemical energy needed to sustain metabolism, nerve transmission, respiration, circulation, and physical work. The heat produced during these processes is used to maintain body temperature. Energy balance in an individual depends on his or her dietary energy intake and energy expenditure. Imbalances between intake and expenditure result in gains or losses of body components, mainly in the form of fat, and these determine changes in body weight.

The Estimated Energy Requirement (EER) is defined as the average dietary energy intake that is predicted to maintain energy balance in a healthy, adult of a defined age, gender, weight, height, and level of physical activity consistent with good health. To calculate the EER, prediction equations for normal weight individuals were developed from data on total daily energy expenditure measured by the doubly labeled water technique. In children and pregnant or lactating women, the EER includes the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health. While the expected between-individual variability is calculated for the EER, there is no Recommended Dietary Allowance (RDA) for energy because energy intakes above the EER would be expected to result in weight gain. Similarly, the Tolerable Upper Intake Level (UL) concept does not apply to

energy, because any intake above an individual's energy requirement would lead to undesirable (and potentially hazardous) weight gain.

BACKGROUND INFORMATION

Humans and other mammals constantly need to expend energy to perform physical work; to maintain body temperature and concentration gradients; and to transport, synthesize, degrade, and replace small and large molecules that make up body tissue. This energy is generated by the oxidation of various organic substances, primarily carbohydrates, fats, and amino acids. In 1780, Lavoisier and LaPlace measured the heat production of mammals by calorimetry (Kleiber, 1975). They demonstrated that it was equal to the heat released when organic substances were burned, and that the same quantities of oxygen were consumed by animal metabolism as were used during the combustion of the same organic substrates (Holmes, 1985). Indeed, it has been verified by numerous experiments on animals and humans since then that the energy produced by oxidation of carbohydrates and fats in the body is the same as the heat of combustion of these substances (Kleiber, 1975). The crucial difference is that in organisms oxidation proceeds through many steps, allowing capture of some of the energy in an intermediate chemical form—the high energy pyrophosphate bond of adenosine triphosphate (ATP). Hydrolysis of these high-energy bonds can then be coupled to various chemical reactions, thereby driving them to completion, even if by themselves they would not proceed (Lipmann, 1941). Typically, the rates of energy expenditure in adults at rest are slightly less than 1 kcal/min in women (i.e., 0.8 to 1.0 kcal/min or 1,150 to 1,440 kcal/d), and slightly more than 1 kcal/min in men (i.e., 1.1 to 1.3 kcal/min or 1,580 to 1,870 kcal/d) (Owen et al., 1986, 1987). One kcal/min corresponds approximately to the heat released by a burning candle or by a 75-watt light bulb (i.e., 1 kcal/min corresponds to 70 J/sec or 70 W).

Energy Yields from Substrates

Carbohydrate, fat, protein, and alcohol provide all of the energy supplied by foods and are generally referred to as macronutrients (in contrast to vitamins and elements, usually referred to as micronutrients). The amount of energy released by the oxidation of carbohydrate, fat, protein, and alcohol (also known as Heat of Combustion, or ΔH) is shown in Table 5-1.

When alcohol (ethanol or ethyl alcohol) is consumed, it promptly appears in the circulation and is oxidized at a rate determined largely by its concentration and by the activity of liver alcohol dehydrogenase. Oxi-

TABLE 5-1 Heat of Combustion of Various Macronutrients

Macronutrient	Heat of Combustion[a] (kcal/g)	kcal[b]/L O_2	RQ[c] (CO_2/O_2)	Atwater Factor[d] (kcal/g)
Starch	4.18	5.05	1.0	4.0
Sucrose	3.94	5.01	1.0	4.0
Glucose	3.72	4.98	1.0	4.0
Fat	9.44	4.69	0.71	9.0
Protein by combustion[a]	5.6			
Protein through metabolism[a]	4.70	4.66	0.835	4.0
Alcohol[e]	7.09	4.86	0.67	—

[a] The energy derived by protein oxidation in living organisms is less than the heat of combustion of protein, because the nitrogen-containing end product of metabolism in mammals is urea (or uric acid in birds and reptiles), whereas nitrogen is converted into nitrous oxide when protein is combusted. The heat liberated by biological oxidation of proteins was long thought to be 4.3 kcal/g (Merrill and Watt, 1973), but a more recent demonstration showed that the actual value is 4.7 kcal/g (Livesey and Elia, 1988).
[b] One calorie is the amount of energy needed to increase the temperature of 1 g of water from 14.5° to 15.5°C. In the context of foods and nutrition, "large calorie" (i.e., Calories, with a capital C), which is more properly referred to as "kilocalorie" (kcal), has been traditionally used. In the International System of Units, the basic energy unit is the Joule (J). One J = 0.239 calories, so that 1 kcal = to 4.186 kJ. A daily energy expenditure of 2,400 kcal corresponds to the expenditure of 10,000 kJ, or 10 MJ (Mega Joules)/d.
[c] RQ = respiratory quotient, which is defined as the ratio of CO_2 produced divided by O_2 consumed (in terms of mols, or in terms of volumes of CO_2 and O_2).
[d] Atwater, a pioneer in the study and characterization of nutrients and metabolism, proposed to use the values of 4, 9, and 4 kcal/g of carbohydrate, fat, and protein, respectively (Merrill and Watt, 1973). This equivalent is now uniformly used in nutrient labeling and diet formulation. Nutrition Labeling of Food. 21 C.F.R. §101.9 (1991).
[e] Alcohol (ethanol) content of beverages is usually described in terms of percent by volume. The heat of combustion of alcohol is 5.6 kcal/mL. (One mL of alcohol weighs 0.789 g.)

dation of alcohol elicits a prompt reduction in the oxidation of other substrates used for ATP regeneration, demonstrating that ethanol oxidation proceeds in large part via conversion to acetate and oxidative phosphorylation. The phenomenon has been precisely measured by indirect calorimetry in human subjects, in whom ethanol consumption was found to primarily reduce fat oxidation (Suter et al., 1992). About 80 percent of the energy liberated by ethanol oxidation is used to drive ATP regeneration, so that the thermic effect of ethanol comes to about 20 percent (Siler et al., 1999). The thermic effect of food is the increase in energy expendi-

ture as measured by heat produced upon ingestion of that food. The thermic effect of alcohol is about twice the thermic effect of carbohydrate, but less than the thermic effect of protein (see later section, "Thermic Effect of Food").

Reported food intake in individuals consuming alcohol is often similar to that of individuals who do not consume alcohol (de Castro and Orozco, 1990). As a result, it has sometimes been questioned whether alcohol contributes substantially to energy production. However, the biochemical and physiological evidence about the contribution made by ethanol to oxidative phosphorylation is so unambiguous that the apparent discrepancies between energy intake data and body weights must be attributed to inaccuracies in reported food intakes. In fact, in individuals consuming a healthy diet, the additional energy provided by alcoholic beverages can be a risk factor for weight gain (Suter et al., 1997), as opposed to alcoholics in whom the pharmacological impact of excessive amounts of ethanol tends to inhibit normal eating and may cause emaciation.

Energy Requirements Versus Nutrient Requirements

Recommendations for nutrient intakes are generally set to provide an ample supply of the various nutrients needed (i.e., enough to meet or exceed the requirements of almost all healthy individuals in a given life stage and gender group). For most nutrients, recommended intakes are thus set to correspond to the median amounts sufficient to meet a specific criterion of adequacy plus two standard deviations to meet the needs of nearly all healthy individuals (see Chapter 1). However, this is not the case with energy because excess energy cannot be eliminated, and is eventually deposited in the form of body fat. This reserve provides a means to maintain metabolism during periods of limited food intake, but it can also result in obesity.

The first alternate criterion that may be considered as the basis for a recommendation for energy is that energy intake should be commensurate with energy expenditure, so as to achieve energy balance. Although frequently applied in the past, this is not appropriate as a sole criterion, as described by the FAO/WHO/UNU publication, *Energy and Protein Requirements* (1985):

> The energy requirement of an individual is a level of energy intake from food that will balance energy expenditure when the individual has a body size and composition, and level of physical activity, consistent with long-term good health; and that would allow for the maintenance of economically necessary and socially desirable physical activity. In children and pregnant or lactating women the energy requirement includes the energy needs associated with

> the deposition of tissues or the secretion of milk at rates consistent with good health (p. 12).

This definition indicates that desirable energy intakes for obese individuals are less than their current energy expenditure, as weight loss and establishment of a steady state at a lower body weight is desirable for them. In underweight individuals, on the other hand, desirable energy intakes are greater than their current energy expenditure to permit weight gain and maintenance of a higher body weight. Thus, it seems logical to base estimated values for energy intake on the amounts of energy that need to be consumed to maintain energy balance in adult men and women who are maintaining desirable body weights, taking into account the increments in energy expenditure elicited by their habitual level of activity.

There is another fundamental difference between the requirements for energy and those for other nutrients. Body weight provides each individual with a readily monitored indicator of the adequacy or inadequacy of habitual energy intake, whereas a comparably obvious and individualized indicator of inadequate or excessive intake of other nutrients is not usually evident.

Energy Balance

Because of the effectiveness in regulating the distribution and use of metabolic fuels, man and animals can survive on foods providing widely varying proportions of carbohydrates, fats, and proteins. The ability to shift from carbohydrate to fat as the main source of energy, coupled with the presence of substantial reserves of body fat, makes it possible to accommodate large variations in macronutrient intake, energy intake, and energy expenditure. The amount of fat stored in an adult of normal weight commonly ranges from 6 to 20 kg. Since one gram of fat provides 9.4 kcal, body fat energy reserves thus range typically from approximately 50,000 to 200,000 kcal, providing a large buffer capacity as well as the ability to provide energy to survive for extended periods (i.e., several months) of severe food deprivation. Large daily deviations from energy balance are thus readily tolerated, and accommodated primarily by gains or losses of body fat (Abbott et al., 1988; Stubbs et al., 1995). Coefficients of variation for intra-individual variability in daily energy intake average ± 23 percent (Bingham et al., 1994); variations in physical activity are not closely synchronized with adjustments in food intake (Edholm et al., 1970). Thus, substantial positive as well as negative energy balances of several hundred kcal/d occur as a matter of course under free-living conditions among normal and overweight subjects. Yet over the long term, energy balance is maintained with remarkable accuracy. Indeed, during long periods in the

life of most individuals, gains or losses of adipose tissue are less than 1 to 2 kg over a year (McCargar et al., 1993), implying that the cumulative error in adjusting energy intake to expenditure amounts to less than 2 percent of energy expenditure.

Components of Energy Expenditure

Basal and Resting Metabolism

The basal metabolic rate (BMR) describes the rate of energy expenditure that occurs in the postabsorptive state, defined as the particular condition that prevails after an overnight fast, the subject having not consumed food for 12 to 14 hours and resting comfortably, supine, awake, and motionless in a thermoneutral environment. This standardized metabolic state corresponds to the situation in which food and physical activity have minimal influence on metabolism. The BMR thus reflects the energy needed to sustain the metabolic activities of cells and tissues, plus the energy needed to maintain blood circulation, respiration, and gastrointestinal and renal processing (i.e., the basal cost of living). BMR thus includes the energy expenditure associated with remaining awake (the cost of arousal), reflecting the fact that the sleeping metabolic rate (SMR) during the morning is some 5 to 10 percent lower than BMR during the morning hours (Garby et al., 1987).

BMR is commonly extrapolated to 24 hours to be more meaningful, and it is then referred to as basal energy expenditure (BEE), expressed as kcal/24 h. Resting metabolic rate (RMR), energy expenditure under resting conditions, tends to be somewhat higher (10 to 20 percent) than under basal conditions due to increases in energy expenditure caused by recent food intake (i.e., by the "thermic effect of food") or by the delayed effect of recently completed physical activity (see Chapter 12). Thus, it is important to distinguish between BMR and RMR and between BEE and resting energy expenditure (REE) (RMR extrapolated to 24 hours).

Basal, resting, and sleeping energy expenditures are related to body size, being most closely correlated with the size of the fat-free mass (FFM), which is the weight of the body less the weight of its fat mass. The size of the FFM generally explains about 70 to 80 percent of the variance in RMR (Nelson et al., 1992; Ravussin et al., 1986). However, RMR is also affected by age, gender, nutritional state, inherited variations, and by differences in the endocrine state, notably (but rarely) by hypo- or hyperthyroidism. The relationships among RMR, body weight, and FFM are illustrated in Figures 5-1 and 5-2 (Owen, 1988), which show that differences in RMR relative to body weight among diverse individuals such as men, women, and athletes mostly disappear when RMR is considered relative to FFM.

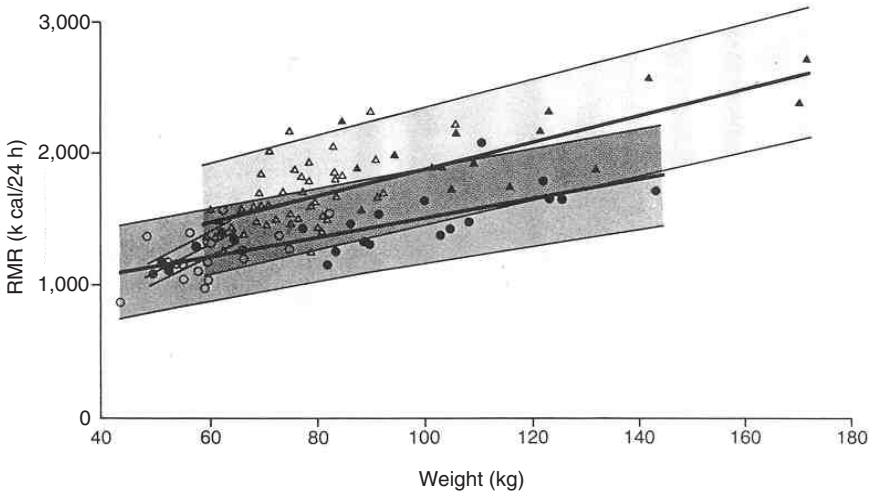

FIGURE 5-1 Resting metabolic rates (RMR) are contrasted against the weights of 44 lean (○) and obese (●) healthy women, 8 of whom were athletes (⊕), and 60 lean (Δ) and obese (▲) healthy men. Reprinted, with permission, from Owen (1988). Copyright 1988 by W.B. Saunders.

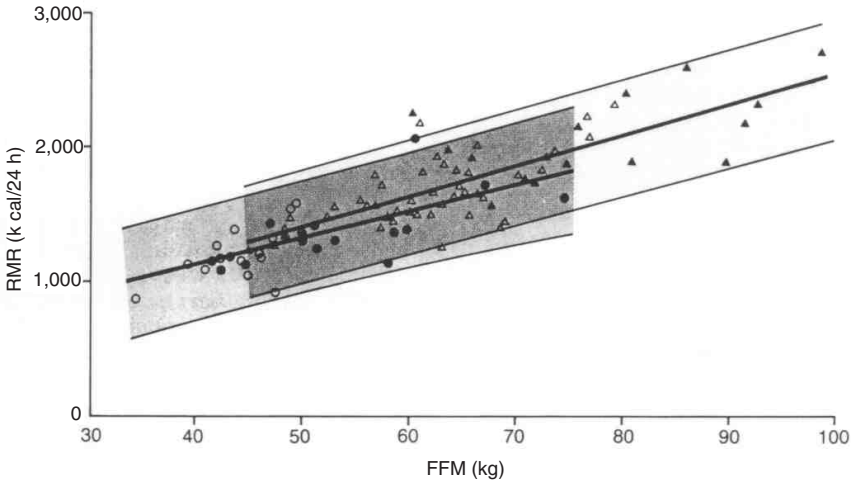

FIGURE 5-2 Resting metabolic rates (RMR) are contrasted against the fat-free masses (FFM) of 44 lean (○) and obese (●) healthy women, 8 of whom were athletes (⊕), and 60 lean (Δ) and obese (▲) healthy men. Reprinted, with permission, from Owen (1988). Copyright 1988 by W.B. Saunders.

BEE has been predicted from age, gender, and body size. Prediction equations were developed for each gender (WN Schofield, 1985) by pooling and analyzing reported measurements made in 7,393 individuals. A recent re-evaluation of all available data performed by Henry (2000) has led to a new set of predicting equations.

Thermic Effect of Food

It has long been known that food consumption elicits an increase in energy expenditure (Kleiber, 1975). Originally referred to as the Specific Dynamic Action (SDA) of food, this phenomenon is now more commonly referred to as the thermic effect of food (TEF). The intensity and duration of meal-induced TEF is determined primarily by the amount and composition of the foods consumed, mainly due to the metabolic costs incurred in handling and storing ingested nutrients (Flatt, 1978). Activation of the sympathetic nervous system elicited by dietary carbohydrate and by sensory stimulation causes an additional, but modest, increase in energy expenditure (Acheson et al., 1983). The increments in energy expenditure during digestion above baseline rates, divided by the energy content of the food consumed, vary from 5 to 10 percent for carbohydrate, 0 to 5 percent for fat, and 20 to 30 percent for protein. The high TEF for protein reflects the relatively high metabolic cost involved in processing the amino acids yielded by absorption of dietary protein, for protein synthesis, or for the synthesis of urea and glucose (Flatt, 1978; Nair et al., 1983). Consumption of the usual mixture of nutrients is generally considered to elicit increases in energy expenditure equivalent to 10 percent of the food's energy content (Kleiber, 1975). Since TEF occurs during a limited part of the day only, it can result in noticeable increases in REE if energy expenditure is measured during the hours following meals.

Thermoregulation

Birds and mammals, including humans, regulate their body temperature within narrow limits. This process, termed *thermoregulation*, can elicit increases in energy expenditure that are greater when ambient temperatures are below the zone of thermoneutrality. The environmental temperature at which oxygen consumption and metabolic rate are lowest is described as the critical temperature or thermoneutral zone (Hill, 1964). Because most people adjust their clothing and environment to maintain comfort, and thus thermoneutrality, the additional energy cost of thermoregulation rarely affects total energy expenditure to an appreciable extent. However, there does appear to be a small influence of ambient temperature on energy expenditure as described in more detail below.

Physical Activity

The energy expended for physical activity varies greatly among individuals as well as from day to day. In sedentary individuals, about two-thirds of total energy expenditure goes to sustain basal metabolism over 24 hours (the BEE), while one-third is used for physical activity. In very active individuals, 24-hour total energy expenditure can rise to twice as much as basal energy expenditure (Grund et al., 2001), while even higher total expenditures occur among heavy laborers and some athletes.

The efficiency with which energy from food is converted into physical work is remarkably constant when measured under conditions where body weight and athletic skill are not a factor, such as on bicycle ergometers (Kleiber, 1975; Nickleberry and Brooks, 1996; Pahud et al., 1980). For weight-bearing physical activities, the cost is roughly proportional to body weight. In the life of most persons, walking represents the most significant form of physical activity, and many studies have been performed to determine the energy expenditures induced by walking or running at various speeds (Margaria et al., 1963; Pandolf et al., 1977; Passmore and Durnin, 1955). Walking at a speed of 2 mph is considered to correspond to a mild degree of exertion, walking speeds of 3 to 4 mph correspond to moderate degrees of exertion, and a walking speed of 5 mph to vigorous exertion (Table 12-1, Fletcher et al., 2001). Over this range of speeds, the increment in energy expenditure amounts to some 60 kcal/mi walked for a 70-kg individual, or 50 kcal/mi walked for a 57-kg individual (see Chapter 12, Figure 12-4). The exertion caused by walking/jogging increases progressively at speeds of 4.5 mph and beyond, reaching 130 kcal/mi at 5 mph for a 70-kg individual.

The increase in daily energy expenditure is somewhat greater, however, because exercise induces an additional small increase in expenditure for some time after the exertion itself has been completed. This excess post-exercise oxygen consumption (EPOC) depends on exercise intensity and duration and has been estimated at some 15 percent of the increment in expenditure that occurs during exertions of the type described above (Bahr et al., 1987). This raises the cost of walking at 3 mph to 69 kcal/mi (60 kcal/mi × 1.15) for a 70-kg individual and to 58 kcal/mi (50 kcal/mi × 1.15) for a 57-kg individual. Taking into account the dissipation of 10 percent of the energy consumed on account of the thermic effect of food to cover the expenditure associated with walking, then walking 1 mile raises daily energy expenditure to 76 kcal/mi (69 kcal/mi × 1.1) in individuals weighing 70 kg, or 64 kcal/mi (58 kcal/mi × 1.1) for individuals weighing 57 kg. Since the cost of walking is proportional to body weight, it is convenient to consider that the overall cost of walking at moderate speeds is approximately 1.1 kcal/mi/kg body weight (75 kcal/mi/70 kg or 64 kcal/mi/57 kg). The effects of varia-

tions in body weights and the impact of various physical activities on energy expenditure are considered in more detail in Chapter 12.

Physical Activity Level

The level of physical activity is commonly described as the ratio of total to basal daily energy expenditure (TEE/BEE). This ratio is known as the Physical Activity Level (PAL), or the Physical Activity Index. Describing physical activity habits in terms of PAL is not entirely satisfactory because the increments above basal needs in energy expenditure, brought about by most physical activities where body weight is supported against gravity (e.g., walking, but not cycling on a stationary cycle ergometer), are directly proportional to body weight, whereas BEE is more nearly proportional to body weight$^{0.75}$. However, PAL is a convenient comparison and is used in this report to describe and account for physical activity habits. The effect of variations in activities on PAL is described in Chapter 12.

Total Energy Expenditure

Total Energy Expenditure (TEE) is the sum of BEE (which includes a small component associated with arousal, as compared to sleeping), TEF, physical activity, thermoregulation, and the energy expended in depositing new tissues and in producing milk. With the emergence of information on TEE by the doubly labeled water (DLW) method (Schoeller, 1995), it has become possible to determine energy expenditure of infants, children, and adults under free-living conditions. TEE from doubly labeled water does not include the energy content of the tissue constituents laid down during normal growth and pregnancy or the milk produced during lactation, as it refers to energy expended during oxidation of energy-yielding nutrients to water and carbon dioxide.

It should be noted that direct measurements of TEE represent a distinct advantage over previous TEE evaluations, which had to rely on the factorial approach and on food intake data, which have limited accuracy due to the inability to reliably determine average physical activity cost and nutrient intakes.

Estimated Energy Requirement

Information on energy expenditure obtained by DLW studies conducted by a number of research units (see Appendix I) are used in this report to estimate energy requirements, taking into account estimates of the energy content of new body constituents during growth and preg-

nancy and of the milk produced during lactation. Energy expenditure depends on age and varies primarily as a function of body size and physical activity, both of which vary greatly among individuals. Recommendations about energy intake vary accordingly, and are also subject to the criterion that an individual adult's body weight should remain stable and within the healthy range.

SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR ENERGY

Reported Energy Intake

The reported energy intakes of weight-stable subjects (i.e., those in energy balance) could, in principle, be used to predict energy requirements for weight maintenance. However, it is now widely recognized that reported energy intakes in dietary surveys underestimate usual energy intake (Black et al., 1993).

The most compelling evidence about underreporting has come from measurements of total energy expenditure (TEE) by the doubly labeled water (DLW) method (Schoeller, 1995). The use of a measure or estimate of TEE to validate instruments that measure food intake is dependent on the principle of energy balance. That is, in weight-stable adults, energy intake must equal TEE. By comparing reported energy intake to TEE, the accuracy of food intake reporting can be assessed (Goldberg et al., 1991a).

A large body of literature documents the underreporting of food intake, which can range from 10 to 45 percent depending on the age, gender, and body composition of individuals in the sample population (Johnson, 2000). Underreporting tends to increase as children grow older (Livingstone et al., 1992b), is worse among women than in men (Johnson et al., 1994), and is more pronounced among overweight and obese than among lean individuals (Bandini et al., 1990a; Lichtman et al., 1992; Prentice et al., 1986). Low socioeconomic status, characterized by low income, low educational attainment, and low literacy levels increase the tendency to underreport energy intakes (Briefel et al., 1997; Johnson et al., 1998; Price et al., 1997; Pryer et al., 1997). Ethnic differences affecting sensitivities and psychological perceptions relating to eating and body weight can also affect the accuracy of reported food intakes (Tomoyasu et al., 2000). Finally, individuals with infrequent symptoms of hunger underreport to a greater degree than those who experience frequent hunger (Bathalon et al., 2000).

There is some evidence suggesting that underreporters often fail to report foods perceived to be bad or sinful, such as cakes/pies, savory

snacks, cheese, fried potatoes, meat mixtures, soft drinks, spreads, condiments, and generally foods known to be high in fat (Bingham and Day, 1997; Krebs-Smith et al., 2000). Reported intakes of added sugars are also significantly lower than that consumed, due in part to the frequent omission of snack foods from 24-hour food recording (Poppitt et al., 1998).

Finally, there is no objective evidence for the existence of "small eaters," individuals who can survive long term on the low energy intakes that they report in dietary surveys (Black, 1999; Lichtman et al., 1992; Prentice et al., 1986). Clearly, it is no longer tenable to base energy requirements on self-reported food consumption data.

Factorial Approach

Previous Recommended Dietary Allowances for energy (NRC, 1989) used the factorial method to estimate TEE. This method calculates TEE using information on the amount of time devoted to different activities and the energy costs of each activity throughout a theoretical 24-hour period. The factorial method allowed theoretical estimation of TEE for a defined activity pattern (using measured average costs of standard activities and theoretical activity duration). Thus, mean expected energy requirements for different levels of physical activity were defined.

However, there are recognized problems with the factorial method and doubts about the validity of energy requirement predictions based on it (Roberts et al., 1991). The first problem is that there are a wide range of activities and physical efforts performed during normal life, and it is not feasible to measure the energy cost of each. Another concern with the factorial method is that the measurement of the energy costs of specific activities imposes constraints (due to mechanical impediments associated with performing an activity while wearing unfamiliar equipment) that may alter the measured energy costs of different activities. Although generalizations are essential in trying to account for the energy costs of daily activities, substantial errors may be introduced. In addition, energy expenditure during sleep, once considered to be equivalent to basal metabolic rate (BMR), is generally somewhat lower (–5 to –10 percent) than BMR (Garby et al., 1987).

Also, and perhaps most importantly, the factorial method only takes into account activities that can be specifically accounted for (e.g., sleeping, walking, household work, occupational activity, and so on). However, 24-hour room calorimeter studies have shown that a significant amount of energy is expended in spontaneous physical activities, some of which are part of a sedentary lifestyle (Ravussin et al., 1986; Zurlo et al., 1992). In addition, some individuals manifest a substantial amount of fidgeting. Together these were reported to average about 350 kcal/d, ranging from

140 to 700 kcal/d (Ravussin et al., 1986). Thus, the factorial method is bound to underestimate usual energy needs (Durnin, 1990; Roberts et al., 1991).

Most comparisons of the factorial approach with DLW determinations of TEE have shown significantly higher measured values for TEE than predicted by the factorial method (Haggarty et al., 1994; Jones et al., 1997; Roberts et al., 1991; Sawaya et al., 1995). In two direct comparisons of factorial energy requirement estimates with DLW, one confirmed that the factorial method underestimated energy needs (Leonard et al., 1997), while the other found no difference between the methods in an elderly population with a mean age of 70 years (Morio et al., 1997).

Measurement of Energy Expenditure by Doubly Labeled Water

The DLW method is a relatively new technique that measures TEE in free-living individuals. It was originally proposed and developed by Lifson for use in small animals (Lifson and McClintock, 1966; Lifson et al., 1955), but has been adapted for human studies and extensively used (Schoeller et al., 1986). Two stable isotopic forms of water ($H_2{}^{18}O$ and ${}^2H_2O$) are administered, and their disappearance rates from a body fluid (i.e., urine or blood) are monitored for a period of time, optimally equivalent to 1 to 3 half lives for these isotopes (7 to 21 days in most human subjects). The disappearance rate of ${}^2H_2O$ relates to water flux, while that of $H_2{}^{18}O$ reflects water flux plus carbon dioxide (CO_2) production rate, because of the rapid equilibration of the body water and bicarbonate pools by carbonic anhydrase (Lifson et al., 1949). The difference between the two disappearance rates can therefore be used to calculate the CO_2 production rate, and with knowledge of the composition of the diet, TEE can be calculated.

To predict TEE from a measurement of CO_2 production, it is necessary to have an estimate of the average respiratory quotient (RQ = ratio of CO_2 produced to the O_2 consumed) of the subject during the period of measurement. This is because the energy released per liter of CO_2 varies with the RQ and hence with the substrate mix oxidized by the body (Elia, 1991). The ratio of the CO_2 produced to the O_2 consumed by the biological oxidation of a representative sample of the diet is commonly referred to as the food quotient, or FQ (Flatt, 1978).

Short-term measurements of RQ by indirect calorimetry are not useful for the DLW technique because RQ varies markedly during the day, particularly after meals. It is therefore more accurate to estimate the average RQ from information on the subjects' dietary intake. When energy balance prevails, the average RQ is equal to the FQ. If substantial gains or losses of body constituents are known to occur during the period of measurement,

appropriate adjustments can be made in estimating the average RQ. Although food reports are inaccurate for measuring total energy intake, FQ calculations from food records can be used because FQ has a relatively small effect on DLW measurements of TEE.

Several validations of the DLW study have been conducted in which DLW-derived estimates of TEE were compared with measurements of TEE in whole-body calorimeters (Table 5-2). Although studies in whole-body calorimeters do not mimic normal life conditions, they do allow for an exact comparison of the DLW method with classic calorimetry, which is considered the most reliable measurement of energy expenditure. As shown in Table 5-2, there is a close agreement between means for the CO_2 production rate determined by the two methods in all the validation studies. The precision of DLW measurements, as assessed by the variability of individual DLW measurements from the calorimetry assessments, ranged from –2.5 to 5.9 percent in the different studies. These validation studies show that the DLW method can provide an accurate assessment of the CO_2 production rate and hence TEE in a wide range of human subjects.

One particular advantage of the DLW method is that it provides an index of TEE over a period of several days. Because 1 to 3 half-lives of isotope disappearance are needed for changes in isotopic abundance to be measured accurately by mass spectrometry, optimal time periods for DLW measurements of TEE range from 1 to 3 weeks in most groups of individuals (Schoeller, 1983). Thus, in contrast to other techniques, DLW can provide TEE estimates over biologically meaningful periods of time that can reduce the impact of spontaneous daily variations in physical activity. Moreover, because DLW is noninvasive (requiring only that the subject drink the stable isotopes and provide at least three urine samples over the study period), measurements can be made in subjects leading their normal daily lives. A critical mass of DLW data has now accumulated on a wide range of age groups and body sizes, so that the estimated energy requirements provided in this report could be based on DLW measurements of TEE.

The available DLW data (Appendix I) are not from randomly selected individuals, except in the recent study of Bratteby and coworkers (1997), and they do not constitute a sample representative of the population of the United States and Canada. However, the measurements were obtained in men, women, and children whose ages, body weights, heights, and physical activities varied over wide ranges. At the present time, a few age groups are underrepresented and interpolations had to be performed in these cases. Thus, while the available DLW data do not yet provide an entirely satisfactory set of data, they nevertheless offer the best currently available information.

A second potential criticism of using DLW-derived estimates of TEE as a basis for estimating energy requirements is that the approach assumes that TEE is relatively unaffected by fluctuations in energy balance. Although there is some capacity for TEE to increase or decrease spontaneously when energy intakes increase or decrease, these changes are small and attenuate the effect of energy imbalances only modestly (Levine et al., 1999; Roberts et al., 1990). Indeed, overfeeding studies show that overeating is inevitably accompanied by substantial weight gain, and that reduced energy intake induces weight loss (Saltzman and Roberts, 1995). Thus, although there may be some adaptive capacity to alter TEE in response to changes in dietary energy intake, the DLW-based evaluation of TEE at approximate weight maintenance provides an appropriate estimate of energy expenditure from which energy requirements for maintaining energy balance can be derived.

Body Mass Index

Adults

A growing literature supports the use of the body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) as a predictor of the impact of body weight on morbidity and mortality risks (Seidell et al., 1996; Troiano et al., 1996). As an index of healthy weight and as a predictor of morbidity and mortality risk, it has supplanted weight-for-height tables, which were derived primarily from white populations and relied on questionable estimates of frame size (NHLBI/NIDDK, 1998). BMI, although only an indirect indicator of body composition, is now used to classify underweight and overweight individuals.

While sophisticated techniques are available to precisely measure fat-free mass (FFM) and fat mass (FM) of individuals, these techniques are used mainly in research protocols. For most clinical and epidemiological applications, body size is judged on the basis of the BMI, which is easy to determine, accurate, and reproducible. The main disadvantages of relying on BMI are that (1) it does not reliably reflect body fat content, which is an independent predictor of health risk, and (2) very muscular individuals may be misclassified as overweight (Willett et al., 1999).

The National Institutes of Health (NIH) clinical guidelines on the identification, evaluation, and treatment of normal, overweight and obese adults and the World Health Organization have defined BMI cutoffs for adults over 19 years of age, regardless of age or gender (NHLBI/NIDDK, 1998; WHO, 1998). Underweight is defined as a BMI of less than 18.5 kg/m^2, overweight as a BMI from 25 up to 30 kg/m^2, and obese as a BMI of 30 kg/m^2 or higher. A healthy or desirable BMI is considered to be from 18.5 up to

TABLE 5-2 Comparison of Carbon Dioxide Production Rates Measured by the Doubly Labeled Water Method and Indirect Calorimetry in Humans

Reference	Subjects	*n*	Time (d)
Coward et al., 1984	Adults, in energy balance[d]	4	12
Klein et al., 1984	Adults, in energy balance	1	5
Schoeller and Webb, 1984	Adults, in energy balance	5	5
Roberts et al., 1986	Preterm infants, growing	4	5
Schoeller et al., 1986	Adults, in energy balance		
	"Low" dose	6	4
	"High" dose	3	4
Jones et al., 1987	Infants, after surgery	9	5–6
Westerterp et al., 1988	Adults, in energy balance		
	Sedentary	5	6
	Active	4	3.5
Riumallo et al., 1989	Adults	6	7
Seale et al., 1990	Adults, in energy balance	4	13
Ravussin et al., 1991	Obese adults, in energy balance	12	7
Schulz et al., 1992	Adults, in energy balance	9	7
Seale and Rumpler, 1997	Adults, in energy balance	19	10

[a] Calculations for pool: I = 2-pool model using measured pool sizes as proposed by Coward et al. (1984) and detailed by Roberts et al. (1986), S = single-pool model as described by Lifson et al. (1955) and Lifson and McClintock (1966), F = 2-pool model with fixed ratio of 1.03 between pool sizes as described by Schoeller et al. (1986).
[b] Calculations for fractionated water loss: 50 = assumed to be 50 percent of total water output, 25 = assumed to be 25 percent of total water output, M = measured or calcu-

$T_{1/2}$ (d)	Calculations			CO_2 % Error
	Pool[a]	Fractionated[b]	Growth[c]	
	I	50	L	1.9
10.1	S	25	L	1.8
6.3–9.5	S	50	L	5.9 ± 7.6
2.5–3.6	I	M	E	–1.4 ± 4.8
6.7–9.8	F	P	L	5.0 ± 9.5
8.6–9.9	F	P	L	1.7 ± 4.5
2.9–4.5	F	P	L	–0.9 ± 6.2
5.7–9.0	F	P	L	1.4 ± 3.9
4.0–4.9	F	P	L	–1.0 ± 7.0
	F	P	L	
	F	P	L	–1.04 ± 0.63
	I	P	L	–2.5 ± 5.8
	I	P	L	
	F	P	L	

lated from data on water balance, P = assumed to be proportional to carbon dioxide output (Jones et al., 1987; Schoeller et al., 1986).

[c] Growth correction: L = no change or linear change in pool sizes, E = exponential change in pool sizes.

[d] Energy balance indicates that induction of positive or negative energy balance was not part of study protocol.

25 kg/m^2, a view adopted in this report. Although the healthy BMI range is the result of a consensus, there are reasons to suggest that slightly different mortality-based BMI ranges may be appropriate for different populations (NHLBI/NIDDK, 1998).

In establishing the 2000 Dietary Guidelines, the U.S. Departments of Agriculture and of Health and Human Services set the "healthy weight" upper limit at a BMI of 24.99 kg/m^2 for adult men and women because mortality increases significantly beyond this point (USDA/HHS, 2000). Although the incidence of diabetes, hypertension, and coronary heart disease begins to increase even below this cutoff, a BMI of 24.99 kg/m^2 is considered a reasonable upper limit of healthy weight. The lower BMI limit of 18.5 kg/m^2 is not as well substantiated. The point at which low BMI poses a health risk is poorly defined. The ability to identify persons with low BMIs who are at increased risk for morbidity and mortality is highly nonspecific.

Reference Weights. Weights corresponding to BMIs from 18.5 up to 25 kg/m^2 are tabulated for adult men and women with heights ranging from 1.47 to 1.98 m in Table 5-3 (men) and Table 5-4 (women). Reference weights used in this report correspond to a BMI of 22.5 kg/m^2 for men and a BMI of 21.5 kg/m^2 for women, which match the 50th percentile among 19-year-old individuals (Kuczmarski et al., 2000).

Relationship Between BMI and Body Fat Content. The Third National Health and Nutrition Examination Survey (NHANES III) data that provide the major anthropometric parameters, including waist circumference, skin-fold measurements, and bioimpedance data for some 15,000 women and men were examined to evaluate the body fat content typical for all BMI values (Appendix Table H-1) and among the 5,700 women and men whose BMIs were from 18.5 up to 25 kg/m^2 (Appendix Table H-2). Bioimpedance data were used to calculate percent body fat using equations developed by Sun and coworkers (2003).

The regressions of percent body fat versus BMI (Appendix Table H-3) were used to define the percent body fat ranges given in Table 5-5. The multiple regressions of percent body fat versus BMI and waist circumference (Appendix Table H-4) and of percent body fat versus BMI and triceps skinfold (Appendix Table H-5) were used to construct Figures 5-3 and 5-4.

One of the most commonly cited problems encountered in using BMI as a criterion for assessing the presence of excess body fat is that muscular subjects may have a BMI greater than 25 kg/m^2 without carrying excess body fat. In such cases, it is helpful to consider waist circumference in addition to BMI. As shown in Figure 5-3, a man with a BMI of 30 kg/m^2

TABLE 5-3 Reference Heights and Weights for Men Based on a Body Mass Index (BMI) Range from 18.5 up to 25 kg/m^2

Height (m[in])	Weight at BMI of 18.5 kg/m^2 (kg [lb])	Weight at BMI of 22.5 kg/m^2[a] (kg [lb])	Weight at BMI of 25 kg/m^2 (kg [lb])
1.47 (58)	40 (88)	49 (108)	54 (119)
1.50 (59)	42 (93)	51 (112)	56 (123)
1.52 (60)	43 (95)	52 (115)	58 (128)
1.55 (61)	44 (97)	54 (119)	60 (132)
1.57 (62)	46 (101)	55 (121)	62 (137)
1.60 (63)	47 (104)	58 (128)	64 (141)
1.63 (64)	49 (108)	60 (132)	66 (146)
1.65 (65)	50 (110)	61 (134)	68 (150)
1.68 (66)	52 (115)	64 (141)	70 (154)
1.70 (67)	53 (117)	65 (143)	72 (159)
1.73 (68)	55 (121)	67 (148)	75 (165)
1.75 (69)	57 (126)	69 (152)	76 (168)
1.77 (70)	58 (128)	70 (154)	78 (172)
1.78 (70)	59 (130)	71 (156)	79 (174)
1.80 (71)	60 (132)	73 (161)	81 (178)
1.83 (72)	62 (137)	75 (165)	84 (185)
1.85 (73)	63 (139)	77 (170)	86 (190)
1.88 (74)	65 (143)	80 (176)	88 (194)
1.91 (75)	67 (148)	82 (181)	91 (201)
1.93 (76)	69 (152)	84 (185)	93 (205)
1.96 (77)	71 (156)	86 (190)	96 (212)
1.98 (78)	72 (159)	88 (194)	98 (216)

[a] Weights for men at a BMI of 22.5 kg/m^2, equivalent to the 50th percentile for BMI at 19 years of age (Kuczmarski et al., 2000).

and a waist circumference of 85 cm (33.5 in) would still be expected to have less than 21 percent body fat. In women ($R^2 = 0.77$), BMI is a better predictor of differences in percentage of body fat than in men ($R^2 = 0.55$, Appendix Table H-3), and in women, triceps skinfold data ($R^2 = 0.82$, Appendix Table H-5) provide a better parameter than waist circumference ($R^2 = 0.79$, Appendix Table H-4) in complementing the indication of body fat percentage provided by BMI. In contrast, in men, waist circumference ($R^2 = 0.61$, Appendix Table H-4) provides a better parameter than triceps skinfold data ($R^2 = 0.58$, Appendix Table H-5) in complementing the indication of body fat percentage provided by BMI.

Relationship Between Height and Body Fat Content. The NHANES III data allowed examination of the impact of height on FFM, and hence on FM and on adiposity (as estimated by percent body fat). The impact of height

TABLE 5-4 Reference Heights and Weights for Women Based on a Body Mass Index (BMI) Range from 18.5 up to 25 kg/m^2

Height (m[in])	Weight at BMI of 18.5 kg/m^2 (kg [lb])	Weight at BMI of 21.5 kg/m^2[a] (kg [lb])	Weight at BMI of 25 kg/m^2 (kg [lb])
1.47 (58)	40 (88)	46 (101)	54 (119)
1.50 (59)	42 (93)	48 (106)	56 (123)
1.52 (60)	43 (95)	50 (110)	58 (128)
1.55 (61)	44 (97)	52 (115)	60 (132)
1.57 (62)	46 (101)	53 (117)	62 (137)
1.60 (63)	47 (104)	55 (121)	64 (141)
1.63 (64)	49 (108)	57 (126)	66 (146)
1.65 (65)	50 (110)	59 (130)	68 (150)
1.68 (66)	52 (115)	61 (134)	70 (154)
1.70 (67)	53 (117)	62 (137)	72 (159)
1.73 (68)	55 (121)	64 (141)	75 (165)
1.75 (69)	57 (126)	66 (146)	76 (168)
1.77 (70)	58 (128)	67 (148)	78 (172)
1.78 (70)	59 (130)	68 (150)	79 (174)
1.80 (71)	60 (132)	70 (154)	81 (178)
1.83 (72)	62 (137)	72 (159)	84 (185)
1.85 (73)	63 (139)	74 (163)	86 (190)
1.88 (74)	65 (143)	76 (168)	88 (194)
1.91 (75)	67 (148)	78 (172)	91 (201)
1.93 (76)	69 (152)	80 (176)	93 (205)
1.96 (77)	71 (156)	82 (181)	96 (212)
1.98 (78)	72 (159)	84 (185)	98 (216)

[a] Weights for women at a BMI of 21.5 kg/m^2, equivalent to the 50th percentile for BMI at 19 years of age (Kuczmarski et al., 2000).

TABLE 5-5 Body Weight Classification by Body Mass Index (BMI) and Body Fat Content[a]

BMI Range (kg/m^2)	Classification	Body Fat (%)[b]	
		Men	Women
From 18.5 up to 25	Normal	13–21	23–31
From 25 up to 30	Overweight	21–25	31–37
From 30 up to 35	Obese	25–31	37–42
35 or higher	Clinically obese	> 31	> 42

[a] Developed from regression of percent body fat versus BMI (kg/m^2) (Appendix H) using equations by Sun et al. (2003).
[b] Estimated from equations derived from bioimpedence data (Sun et al., 2003).

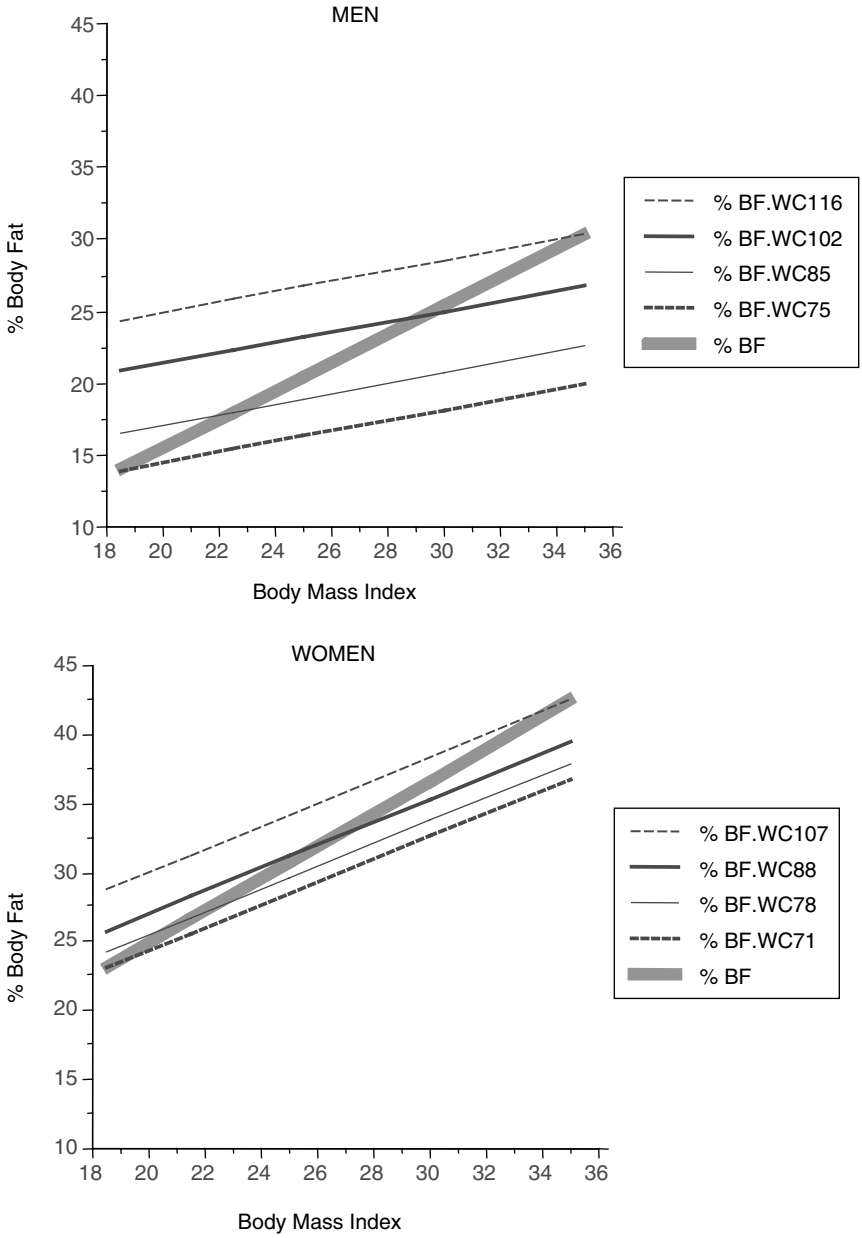

FIGURE 5-3 Regressions of percent body fat (% BF) vs. body mass index (BMI) (heavy lines), and vs. BMI relationships (thin lines) for adult men and women with BMI of 18.5 kg/m^2 and higher and with a specified waist circumference (WC) in men (WC = 116, 102, 85, or 75 cm) and women (WC = 107, 88, 78, or 71 cm).

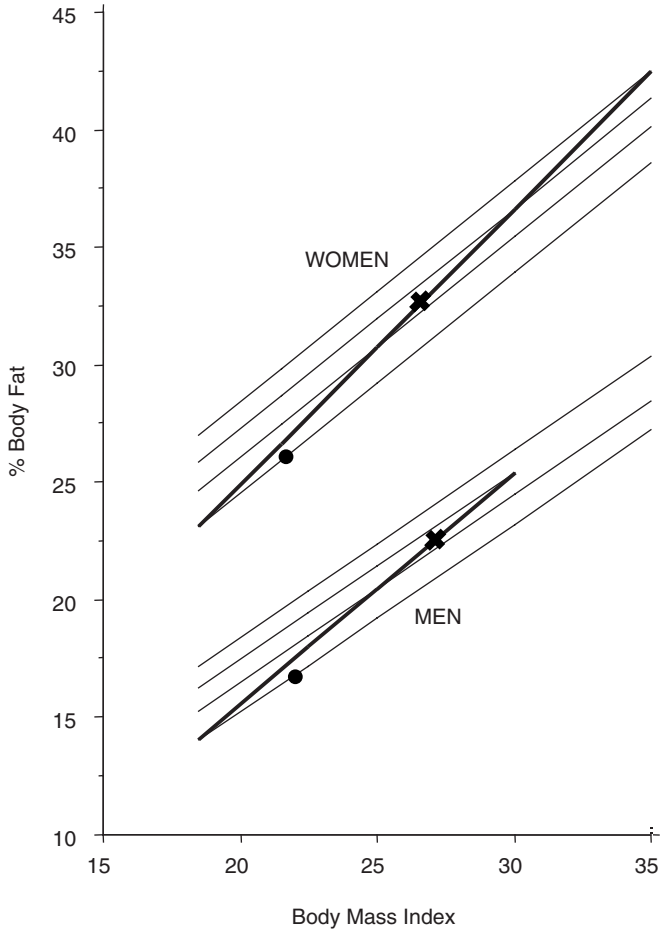

FIGURE 5-4 Regressions of percent body fat (% BF) versus body mass index (BMI) (heavy lines) and the % BF versus BMI relationships (thin lines) for adult men and women 19 years and older with BMI 18.5 kg/m^2 and higher and with specified triceps skinfold (TSF) thickness in men (TSF = 19.6, 15.8, 11.9, and 6.9 mm) and women (TSF = 30.7, 26.4, 22.2, and 16.7 mm). The • indicates the mean BMI and % BF for men and women with BMIs from 18.5 up to 25 kg/m^2 and the × indicates the mean BMI and % BF values for all men and women estimated in Appendix Table H-4.

on FFM for various BMI values is shown in Figure 5-5. BEE and REE are correlated with FFM. Yet no correlation can be detected between height and percent body fat in men, whereas in women a negative correlation exists, but with a very small R^2 value (0.0026) (Appendix Table H-6). Thus

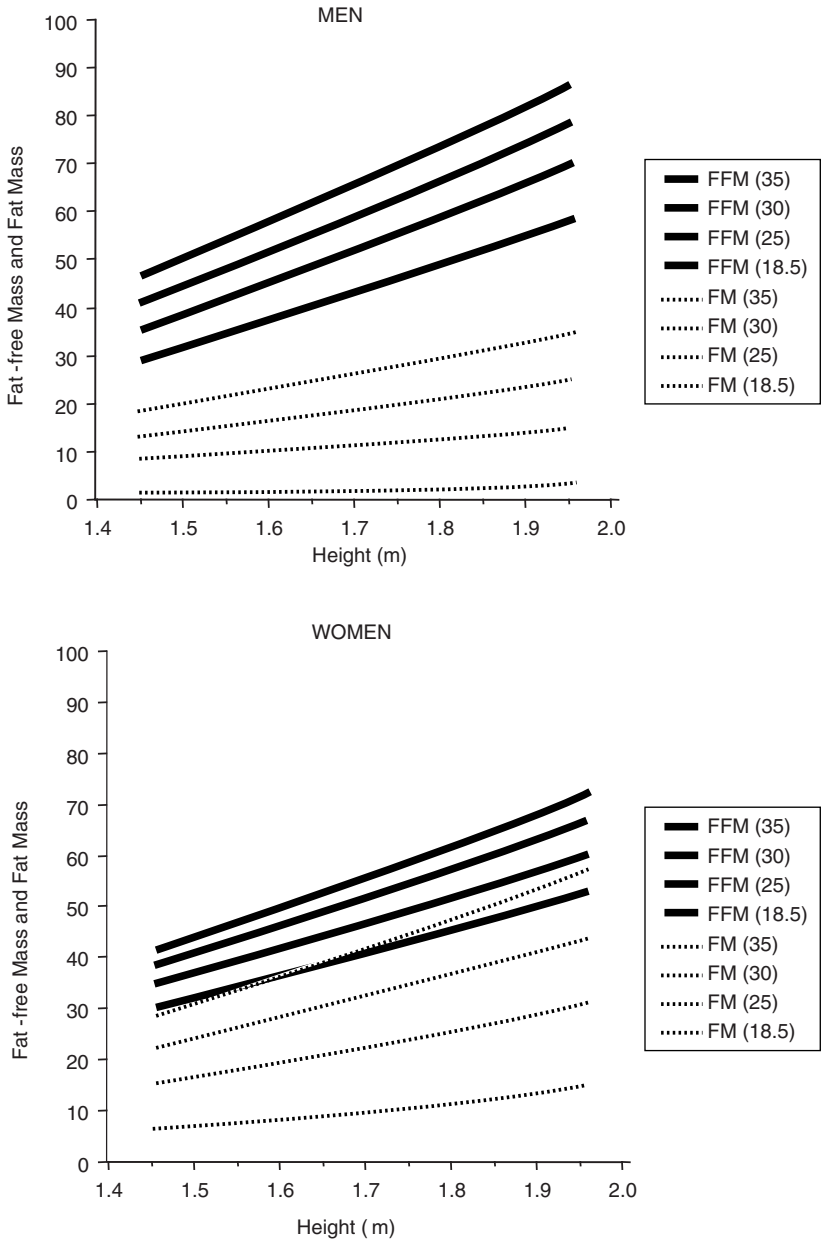

FIGURE 5-5 Regression of fat-free mass (FFM) and fat mass (FM) as a function of height in adult men and women with body mass indexes of 18.5, 25, 30, and 35 kg/m^2 (from Appendix H).

in women, as in men, differences in height have very little, if any, impact on adiposity.

Children

As children grow and develop, linear and ponderal growth do not occur at exactly commensurate rates; consequently, BMI is not constant throughout childhood. In U.S. children, BMI declines and reaches a minimum around 4 to 6 years, and then gradually increases through adolescence (Kuczmarski et al., 2000). Therefore, cutoff points to define underweight and overweight must be age- and gender-specific. The revised growth charts for the United States were derived from five national health examination surveys collected from 1963 to 1994 (Kuczmarski et al., 2000). Smoothed curves were developed for infants from birth to 36 months and for children 2 to 20 years, and BMI charts were developed for boys and girls greater than 2 years of age. Based on these data, the Centers for Disease Control and Prevention (CDC) defined underweight in children as a BMI of less than the 5th percentile. Children are considered to be at risk of overweight when their BMI is greater than the 85th percentile, and overweight when their BMI is greater than the 95th percentile (Kuczmarski et al., 2000).

Data from NHANES III on children 6 years of age and older were not used in the CDC analysis because of the recent rise in obesity among American youth. The most recent data from the NHANES III survey (1988–1994) (Troiano et al., 1995) show that substantially more than 22 percent of children in the United States now fall into the at-risk-for-overweight category (from the 85th BMI percentile) and more than 10 percent are in the overweight category (from the 95th BMI percentile). Childhood overweight is associated with several risk factors for later heart disease and other chronic diseases including hyperlipidemia, hyperinsulinemia, hypertension, and early arteriosclerosis (Must and Strauss, 1999).

Generally, an abnormal anthropometric measure is statistically defined as a value below –2 standard deviations (SD) or Z-scores (less than the 2.3 percentile) or above +2 SD or Z-scores (greater than the 97.7 percentile) relative to the reference mean (WHO Working Group, 1986). Undernutrition is defined as below the 3rd percentile for weight-for-length. Similarly, overweight has been defined as above the 97th percentile for weight-for-length. For lengths between the 3rd and 97th percentiles, the median and range of weights defined by the 3rd and 97th weight-for-length percentiles for children 0 to 3 years of age are presented in Tables 5-6 (boys) and 5-7 (girls) (Kuczmarski et al., 2000).

Reference heights and weights for boys and girls 3 to 18 years of age are given in Tables 5-8 (boys) and 5-9 (girls). Median and range of weights corresponding to the 5th and 85th BMI percentiles are designated for the 3rd and 97th height percentiles.

FACTORS AFFECTING ENERGY EXPENDITURE AND REQUIREMENTS

Body Composition and Body Size

While body size and body weight exert marked effects on energy expenditure, it is still disputed whether differences in body composition quantitatively affect energy expenditure. In adult men and women with moderate levels of body fat (20 to 35 percent), it has been suggested that the relative proportions of fat-free mass (FFM) and of fat mass are unlikely to influence energy metabolism at rest or while physically active in ways other than through their impact on body weight (Durnin, 1996). It is unlikely that body composition to any important extent affects energy expenditure at rest or the energy costs of physical activities among adults with body mass indexes from 18.5 up to 25 kg/m^2 (Heymsfield et al., 2002). In adults with higher percentages of body fat composition, mechanical hindrances can increase the energy expenditure associated with certain types of activity.

Effects on Basal and Resting Metabolic Rate

FFM includes the metabolically active compartments of the body, and the size of the FFM is the major parameter in determining the rate of energy expenditure under fasting basal metabolic rate (BMR) and resting metabolic rate (RMR) conditions. The contribution of FFM and FM to the variability in RMR was examined in a meta-analysis of seven published studies (Nelson et al., 1992). FFM was the single best predictor of RMR, accounting for 73 percent of the variability; FM accounted for only an additional 2 percent. Adjusted for FFM, RMR did not differ between genders, but it did between lean and obese individuals. In another compilation of studies, the relationship of RMR to FFM was found to be nonlinear across a wide range of individuals, from infants to adults (Weinsier et al., 1992). RMR/kg of weight or RMR/kg of FFM falls as mass increases because the relative contributions made by the most metabolically active tissues (brain, liver, and heart) decline as body size increases. The decline in BMR with increasing age is to some extent also the consequence of changes in the relative size of organs and tissues (Henry, 2000).

TABLE 5-6 Reference Lengths and Weights for Boys 1 Through 35 Months of Age Based on Median Length and Median Weight for Age

Age (mo)	Median Length (cm [in])	Length Range 3rd–97th Percentile (cm [in])
1	54.7 (21.5)	50.2–59.6 (19.8–23.5)
2	58.1 (22.9)	53.8–63.1 (21.2–24.8)
3	60.8 (23.9)	56.6–65.9 (22.3–25.9)
4	63.1 (24.8)	58.8–68.3 (23.1–26.9)
5	65.2 (25.7)	60.8–70.4 (23.9–27.7)
6	67.0 (26.4)	62.5–72.3 (24.6–28.5)
7	68.7 (27.0)	64.1–74.1 (25.2–29.2)
8	70.2 (27.6)	65.6–75.7 (25.8–29.8)
9	71.6 (28.2)	66.9–77.2 (26.3–30.4)
10	73.0 (28.7)	68.1–78.7 (26.8–31.0)
11	74.3 (29.3)	69.3–80.0 (27.3–31.5)
12	75.5 (29.7)	70.4–81.3 (27.7–32.0)
15	78.9 (31.1)	73.4–84.9 (28.9–33.4)
18	81.9 (32.2)	76.1–88.1 (30.0–34.7)
21	84.7 (33.3)	78.5–91.1 (30.9–35.9)
24	87.2 (34.3)	80.7–93.8 (31.8–36.9)
27	89.6 (35.3)	82.9–96.5 (32.6–38.0)
30	91.8 (36.1)	85.0–99.0 (33.5–39.0)
33	93.8 (36.9)	87.0–101.3 (34.3–39.9)
35	95.1 (37.4)	88.2–102.7 (34.7–40.4)

SOURCE: Kuczmarski et al. (2000).

Effects on Total Energy Expenditure

Factors affecting total energy expenditure (TEE) were examined in a meta-analysis of 13 adult studies (n = 162) (Carpenter et al., 1995). The relationships between weight and TEE were highly variable across studies (z = 0.68; r = 0.18–1.0). Differences in RMR accounted for less than 50 percent of the variance in TEE (z = 0.66; r = 0.42–0.89). Adjusted for RMR, TEE was not affected by FM and was lower in women than men. In a separate study, Roberts and Dallal (1998) reported a negative relationship between FM and TEE consistent with the general perception that low physical activity and fat accumulation are correlated.

Obesity

Another question relevant to the effect of body composition on energy requirements is whether obese individuals taken as a group have altered energy requirements, either prior to the development of obesity (in

Median Weight (kg [lb])	Weight Range 3rd–97th Percentile (kg [lb])
4.4 (9.7)	3.2–5.6 (7.0–12.3)
5.3 (11.7)	4.0–6.6 (8.8–14.5)
6.0 (13.2)	4.7–7.6 (10.4–16.7)
6.7 (14.8)	5.3–8.4 (11.7–18.5)
7.3 (16.1)	5.8–9.2 (12.8–20.3)
7.9 (17.4)	6.3–9.8 (13.9–21.6)
8.4 (18.5)	6.8–10.5 (15.0–23.1)
8.9 (19.6)	7.2–11.0 (15.9–24.2)
9.3 (20.5)	7.5–11.5 (16.5–25.3)
9.7 (21.4)	7.8–12.0 (17.2–26.4)
10.0 (22.0)	8.1–12.4 (17.8–27.3)
10.3 (22.7)	8.4–12.7 (18.5–28.0)
11.1 (24.4)	9.1–13.7 (20.0–30.2)
11.7 (25.8)	9.6–14.4 (21.1–31.7)
12.2 (26.9)	10.0–15.0 (22.0–33.0)
12.7 (28.0)	10.4–15.6 (22.9–34.4)
13.1 (28.9)	10.7–16.1 (23.6–35.5)
13.5 (29.7)	11.1–16.7 (24.4–36.8)
13.9 (30.6)	11.4–17.3 (25.1–38.1)
14.2 (31.3)	11.6–17.7 (25.6–39.0)

which case they could potentially contribute to weight gain) or following weight stabilization at a high level. The information relating to the former issue is conflicting, as cross-sectional studies consistently show that overweight and obese individuals have higher absolute values for TEE than nonobese adults, as the effect of high RMR values associated with increased body size generally outweighs the influence of low energy expenditure of physical activity (EEPA) (Platte et al., 1995; Prentice et al., 1996a; Schoeller and Fjeld, 1991). In extremely obese adults, TEE can be as high as 4,500 kcal/d even when the physical activity level is low (where TEE is only 1.5 × BEE) (Prentice et al., 1996a).

Cross-sectionally, Goran and coworkers (1995a) and Griffiths and Payne (1976) reported significantly lower resting energy expenditure in children born to one or both overweight parents when the children were not themselves overweight. However, others (Davies et al., 1995; Goran et al., 1994b; Treuth et al., 2000), but not all (Roberts et al., 1988), reported no mean difference in energy expenditure between children of lean and overweight parents. While the thermic effect of food (TEF) has not been

TABLE 5-7 Reference Lengths and Weights for Girls 1 Through 35 Months of Age Based on Median Length and Median Weight for Age

Age (mo)	Median Length (cm [in])	Length Range 3rd–97th Percentile (cm [in])
1	53.5 (21.1)	49.3–58.2 (19.4–22.9)
2	56.7 (22.3)	52.4–61.3 (20.6–24.1)
3	59.3 (23.3)	54.8–63.9 (21.6–25.2)
4	61.5 (24.2)	56.9–66.1 (22.4–26.0)
5	63.5 (25.0)	58.7–68.1 (23.1–26.8)
6	65.3 (25.7)	60.4–70.0 (23.8–27.6)
7	66.9 (26.3)	61.9–71.7 (24.4–28.2)
8	68.4 (26.9)	63.4–73.4 (25.0–28.9)
9	69.9 (27.5)	64.7–74.9 (25.5–29.5)
10	71.3 (28.1)	65.9–76.4 (25.9–30.1)
11	72.6 (28.6)	67.1–77.8 (26.4–30.6)
12	73.8 (29.1)	68.3–79.1 (26.9–31.1)
15	77.2 (30.4)	71.4–82.8 (28.1–32.6)
18	80.3 (31.6)	74.3–86.2 (29.3–33.9)
21	83.1 (32.7)	76.8–89.3 (30.2–35.2)
24	85.8 (33.8)	79.2–92.3 (31.2–36.3)
27	88.4 (34.8)	81.6–95.2 (32.1–37.5)
30	90.8 (35.7)	83.7–97.9 (33.0–38.5)
33	92.9 (36.6)	85.7–100.2 (33.7–39.4)
35	94.1 (37.0)	86.9–101.6 (34.2–40.0)

SOURCE: Kuczmarski et al. (2000).

widely studied in obese children, Tounian and colleagues (1993) reported no difference in TEF values among obese or overweight and normal-weight prepubertal children in contrast to the widespread finding of low TEF in obese adults (Segal et al., 1987, 1990a, 1990b, 1992).

In longitudinal studies of preobese adults and children, low RMR in apparently susceptible populations (Pima Indians and those infants of overweight mothers who themselves gained weight), 24-hour sedentary energy expenditure or TEE predicted excess weight gain over time in some studies (Ravussin et al., 1988; Roberts et al., 1988), but not in one other (Goran et al., 1998c).

There are also some studies that investigated apparently susceptible children (i.e., born to overweight parents) in whom weight gain was normal (Davies et al., 1995; Stunkard et al., 1999). In those studies, there was no relationship between TEE and growth rate, further suggesting that TEE is within the normal range in individuals who are apparently susceptible to excess weight gain but maintain a normal weight. The combina-

Median Weight (kg [lb])	Weight Range 3rd–97th Percentile (kg [lb])
4.2 (9.3)	3.1–5.2 (6.8–11.5)
4.9 (10.8)	3.7–6.1 (8.1–13.4)
5.5 (12.1)	4.3–6.9 (9.5–15.2)
6.1 (13.4)	4.8–7.6 (10.6–16.7)
6.7 (14.8)	5.3–8.3 (11.7–18.3)
7.2 (15.9)	5.7–8.9 (12.6–19.6)
7.7 (17.0)	6.2–9.5 (13.7–20.9)
8.1 (17.8)	6.5–10.0 (14.3–22.0)
8.5 (18.7)	6.9–10.4 (15.2–22.9)
8.9 (19.6)	7.2–10.9 (15.9–24.0)
9.2 (20.3)	7.5–11.3 (16.5–24.9)
9.5 (20.9)	7.8–11.7 (17.2–25.8)
10.3 (22.7)	8.5–12.7 (18.7–28.0)
11.0 (24.2)	9.1–13.5 (20.0–29.7)
11.6 (25.6)	9.6–14.3 (21.1–31.5)
12.1 (26.7)	10.0–15.0 (22.0–33.0)
12.5 (27.5)	10.3–15.5 (22.7–34.1)
13.0 (28.6)	10.7–16.4 (23.6–36.1)
13.4 (29.5)	11.0–17.1 (24.2–37.7)
13.7 (30.2)	11.2–17.6 (24.7–38.8)

tion of these findings from different studies suggests that low energy expenditure is a risk factor for weight gain in a subgroup of individuals susceptible to excess weight gain, but not in all susceptible individuals and not in individuals with a normal level of risk. As such, these data are consistent with the general view that obesity is a multifactor problem.

The question of whether obese individuals may have decreased energy requirements after weight loss, a factor that would help explain the common phenomenon of weight regain following weight loss, has also been investigated. As reviewed by Saltzman and Roberts (1995), RMR is consistently depressed during active weight loss out of proportion to the loss of FFM, but controversy exists over whether RMR remains depressed after weight has stabilized at a lower level. Most of the cross-sectional studies comparing post-obese with never-obese individuals have reported no difference between groups, suggesting no long-term effect of weight loss or susceptibility to depressed RMR in individuals who have been obese (Larson et al., 1995; Saltzman and Roberts, 1995; Weinsier et al., 2000). In

TABLE 5-8 Reference Heights and Weights for Boys 3 Through 18 Years of Age Based on Median Height and Median Weight for Age

Age (y)	Median Height (m [in])	Height Range 3rd–97th Percentile (m [in])
3	0.95 (37.4)	0.88–1.03 (34.6–40.6)
4	1.02 (40.2)	0.94–1.10 (37.0–43.3)
5	1.09 (42.9)	1.00–1.18 (39.4–46.5)
6	1.15 (45.3)	1.06–1.25 (41.7–49.2)
7	1.22 (48.0)	1.12–1.32 (44.1–52.0)
8	1.28 (50.4)	1.17–1.39 (46.1–54.7)
9	1.34 (52.8)	1.22–1.45 (48.0–57.1)
10	1.39 (54.7)	1.26–1.51 (49.6–59.4)
11	1.44 (56.7)	1.31–1.57 (51.6–61.8)
12	1.49 (58.7)	1.35–1.63 (53.1–64.2)
13	1.56 (61.4)	1.41–1.71 (55.5–67.3)
14	1.64 (64.6)	1.48–1.79 (58.3–70.5)
15	1.70 (66.9)	1.54–1.84 (60.6–72.4)
16	1.74 (68.5)	1.59–1.87 (62.6–73.6)
17	1.75 (68.9)	1.61–1.89 (63.4–74.4)
18	1.76 (69.3)	1.62–1.89 (63.8–74.4)

SOURCE: Kuczmarski et al. (2000).

TABLE 5-9 Reference Heights and Weights for Girls 3 Through 18 Years of Age Based on Median Height and Median Weight for Age

Age (y)	Median Height (m [in])	Height Range 3rd–97th Percentile (m [in])
3	0.94 (37.0)	0.87–1.01 (34.3–39.8)
4	1.01 (39.8)	0.93–1.09 (36.6–42.9)
5	1.08 (42.5)	0.99–1.17 (39.0–46.1)
6	1.15 (45.3)	1.06–1.25 (41.7–49.2)
7	1.21 (47.6)	1.12–1.32 (44.1–52.0)
8	1.28 (50.4)	1.17–1.39 (46.1–54.7)
9	1.33 (52.4)	1.22–1.45 (48.0–57.1)
10	1.38 (54.3)	1.26–1.51 (49.6–59.4)
11	1.44 (56.7)	1.30–1.58 (51.2–62.2)
12	1.51 (59.4)	1.37–1.65 (53.9–65.0)
13	1.57 (61.8)	1.44–1.70 (56.7–66.9)
14	1.60 (63.0)	1.48–1.73 (58.3–68.1)
15	1.62 (63.8)	1.50–1.74 (59.1–68.5)
16	1.63 (64.2)	1.50–1.75 (59.1–68.9)
17	1.63 (64.2)	1.51–1.75 (59.4–68.9)
18	1.63 (64.2)	1.51–1.75 (59.4–68.9)

SOURCE: Kuczmarski et al. (2000).

Median Weight (kg [lb])	Weight Range 3rd–97th Percentile (kg [lb])
14.3 (31.5)	11.8–17.9 (26.0–39.4)
16.2 (35.7)	13.2–20.9 (29.1–46.0)
18.4 (40.5)	14.8–24.3 (32.6–53.5)
20.7 (45.6)	16.4–28.1 (36.1–61.9)
23.1 (50.9)	18.2–32.3 (37.9–67.2)
25.6 (56.4)	20.0–37.2 (44.1–81.9)
28.6 (63.0)	22.0–42.8 (48.5–94.3)
31.9 (70.3)	24.1–49.1 (53.1–108.1)
35.9 (79.1)	26.5–56.0 (58.4–123.3)
40.5 (89.2)	29.3–63.0 (64.5–138.8)
45.6 (100.4)	32.8–70.0 (72.2–154.2)
51.0 (112.3)	36.9–76.7 (81.3–168.9)
56.3 (124.0)	41.3–83.0 (91.0–182.8)
60.9 (134.1)	45.6–88.7 (100.4–195.4)
64.6 (142.3)	49.2–93.6 (108.4–206.2)
67.2 (148.0)	51.6–97.1 (113.7–213.9)

Median Weight (kg [lb])	Weight Range 3rd–97th Percentile (kg [lb])
13.9 (30.6)	11.3–17.9 (24.9–39.4)
15.8 (34.8)	12.7–21.1 (28.0–46.5)
17.9 (39.4)	14.3–24.8 (31.5–54.6)
20.2 (44.5)	15.9–28.7 (35.0–63.2)
22.8 (50.2)	17.7–33.2 (39.0–73.1)
25.6 (56.4)	19.5–38.3 (43.0–84.4)
29.0 (63.9)	21.5–44.3 (47.4–97.6)
32.9 (72.5)	23.9–51.1 (52.6–112.6)
37.2 (81.9)	26.7–58.4 (58.8–128.6)
41.6 (91.6)	29.9–65.6 (65.9–144.5)
45.8 (100.9)	33.3–72.1 (73.3–158.8)
49.4 (108.8)	36.6–77.5 (80.6–170.7)
52.0 (114.5)	39.5–81.5 (87.0–179.5)
53.9 (118.7)	41.7–84.3 (91.9–185.7)
55.1 (121.4)	43.3–86.1 (95.4–189.6)
56.2 (123.8)	44.2–87.4 (97.4–192.5)

contrast, most longitudinal studies following individuals over the course of weight loss and subsequent weight stabilization have observed low RMR after adjusting for body composition change (Saltzman and Roberts, 1995). Notable exceptions to the latter conclusion are from studies of Amatruda and colleagues (1993) and Weinsier and colleagues (2000), which compared individuals longitudinally over the course of weight loss with a cross-sectional, never-obese control group. In these studies, there was no significant difference in TEE among the groups after adjusting for body composition. The combination of these data from different types of studies does not permit any general conclusion at the current time, and further studies in this area are needed.

Physical Activity

The impact of physical activity on energy expenditure is discussed briefly here and in more detail in Chapter 12. EEPA is the most variable component of TEE (Schoeller, 2001). Given that the basal oxygen (O_2) consumption rate of adults is approximately 250 mL/min, and that athletes such as elite marathon runners can sustain O_2 consumption rates of 5,000 mL/min, the scale of metabolic responses to exercise varies over a 20-fold range. The increase in energy expenditure elicited while physical activities take place accounts for the largest part of the effect of physical activity on overall energy expenditure, which is the product of the cost of particular activities and their duration (see Table 12-1 for examples of the energy cost of typical activities).

Recent studies have focused on using doubly labeled water to quantify the effects of physical activity on TEE. In cross-sectional studies, there is a substantial difference in physical activity level (PAL) between long-term exercising women and sedentary women. For example, Withers and coworkers (1998) observed a mean PAL value of 2.48 in long-term active women reporting a mean of 8.6 h/wk of aerobic exercise compared with a mean PAL value of 1.87 in nonexercisers. Intensive exercise programs such as those undertaken by subjects training to run a half-marathon and requiring 8 to 10 h/wk of strenuous exercise can also effect a substantial 15 to 50 percent increase in TEE in both adults and children (Eliakim et al., 1996; Goran et al., 1994a; Westerterp et al., 1992). However, more moderate exercise programs are reported to have a much smaller effect, with two studies (one in children and one in elderly individuals) reporting no significant increase in TEE (Goran and Poehlman, 1992; Treuth et al., 1998b). This lack of effect of a moderate increase in planned physical activity on TEE emphasizes the fact that intentional and spontaneous energy expenditures are interrelated. In some circumstances an increase in

one component may be balanced by a decrease in another, so that TEE remains relatively unaffected.

Effect of Exercise on Postexercise Energy Expenditure

In addition to the immediate energy cost of individual activities, physical activity also affects energy expenditure in the post-exercise period. Excess postexercise O_2 consumption depends on exercise intensity and duration as well as other factors, such as environmental temperatures, state of hydration, and degree of trauma, demonstrable sometimes up to 24 hours after exercise (Bahr et al., 1987; Benedict and Cathcart, 1913; Bielinski et al., 1985; Gaesser and Brooks, 1984). In one study, residual effects of exercise could be seen following 15 hours of exercise, but not after 30 hours (Herring et al., 1992). However, a significant decrease in RMR over 3 days following cessation of training in athletes has been observed (Tremblay et al., 1988).

There may also be chronic changes in energy expenditure associated with regular physical activity as a result of changes in body composition and alterations in the metabolic rate of muscle tissue, neuroendocrine status, and changes in spontaneous physical activity associated with altered levels of fitness (van Baak, 1999; Webber and Macdonald, 2000). However, the magnitude and direction of change in energy expenditure associated with these factors remain controversial due to the variable effects of exercise on the coupling of oxidative phosphorylation in mitochondria, on ion shifts, on substrates, and on other factors (Gaesser and Brooks, 1984).

Since FFM is the major predictor of BMR and RMR, increases in FFM due to increased physical activity would be expected to increase BMR or RMR. However, three studies reported no measurable increase in BMR or RMR with increased physical activity (Bingham et al., 1989; Tremblay et al., 1990; Treuth et al., 1998b). This may be explained by the fact that energy expenditure in resting muscle is relatively low, accounting for only 20 to 25 percent of RMR even though muscle constitutes some 75 percent of the body cell mass (Moore, 1963).

Spontaneous Nonexercise Activity

Spontaneous nonexercise activity has been reported to be quantitatively important, accounting for 100 to 700 kcal/d, even in subjects residing in a whole-body calorimeter chamber (Ravussin et al., 1986). Sitting without or with fidgeting raises energy expenditure by 4 or 54 percent respectively, compared to lying supine (Levine et al., 2000), whereas standing motionless or while fidgeting raised energy expenditure by 13 or 94 percent, respectively. The impact of fidgeting was positively correlated with

body weight while standing, but not while sitting. (For comparison, walking at speeds of 2 or 3 mph increases energy expenditure by 150 or 230 percent, respectively.) It is not known to what extent spontaneous nonexercise activity is affected by intentional physical activity and by its intensity.

Shah and coworkers (1988) reported a 5 percent mean increase in 24-hour TEE with a program of moderate exercise (walking) compared with a 3 percent increase with an equivalent amount of strenuous aerobic training. This suggests that the subjects had lower levels of spontaneous movement after strenuous exercise because they were more tired. In contrast, Schulz and coworkers (1991) reported no difference in sedentary 24-hour TEE between aerobically fit and sedentary individuals, and Pacy and coworkers (1996) showed no differential effect of moderate versus strenuous activity on 24-hour TEE after accounting for the energy costs of the exercise itself. On the other hand, Van Etten and colleagues (1997) showed no significant increase in 24-hour TEE with a standardized exercise program beyond that immediately associated with the exercise program. Similarly, Blaak and coworkers (1992) reported no measurable change in spontaneous physical activity in obese boys enrolled in an exercise-training program.

The combination of these different results indicates that the effects of planned physical activity on activity at other times are highly variable (ranging from overall positive to negative effects on overall energy expenditure). This most likely depends on a number of factors, including the nature of the exercise (strenuous versus moderate), the initial fitness of the subjects, body composition, and gender.

Gender

There are substantial data on the effects of gender on energy expenditure throughout the lifespan. In adult premenopausal women, the majority of studies show that RMR, BMR, or sleeping metabolic rate (SMR) is slightly increased in the luteal phase of the menstrual cycle compared to the follicular phase (Bisdee et al., 1989; Hessemer and Bruck, 1985; Meijer et al., 1992; Melanson et al., 1996; Solomon et al., 1982), but two studies reported no increase in the luteal phase compared to the follicular phase (Howe et al., 1993; Piers et al., 1995a). However, Howe and colleagues (1993) reported that both sleeping metabolic rate and sedentary 24-hour TEE were significantly increased. Twenty-four hour sedentary TEE (measured in a whole-body calorimeter) was increased in the luteal phase compared to the follicular phase in two studies (Ferraro et al., 1992; Howe et al., 1993), whereas Bisdee and colleagues (1989) found no significant change.

Because of the weight of evidence indicating cyclical changes in BMR and perhaps also sedentary 24-hour TEE in premenopausal adult women, studies of 24-hour TEE have necessarily adjusted or averaged for stage of the menstrual cycle when comparing men and women. In such adjusted studies, two studies reported lower 24-hour sedentary TEE in women compared to men after adjusting for FFM and FM (Dionne et al., 1999; Ferraro et al., 1992), while one study reported no significant gender effect in adjusted data (Klausen et al., 1997).

DLW data show a 16 percent lower TEE in women than men after controlling for FFM (Carpenter et al., 1998). This was partly accounted for by lower RMR and partly by other factors (presumably lower EEPA). Finally, menopause has also been associated with decreased RMR and EEPA and increased FM in women receiving no hormone replacement therapy (Poehlman et al., 1995).

Thus, the question of whether the hormonal differences between premenopausal women and men are responsible for the observed differences in TEE, or whether they are a secondary consequence of differences in body composition remain uncertain. Although most of the above studies adjusted data for gender differences in FFM and FM, it was not possible to adjust for differences in the *make-up* of FFM (the contribution made by different tissues and organs). It is recognized that different body tissues have different metabolic rates, with brain and organ tissues having the highest values and muscle and adipose tissues having the lowest values (FAO/WHO/UNU, 1985). Therefore, it is possible that the lower RMR in women compared to men is due to a different balance of organ and brain tissue and skeletal muscle, rather than lower energy expenditure per unit of individual tissues. Further studies are needed to address this issue.

Two of three studies investigating differences in prepubertal children reported that girls have lower values for REE than boys when adjusted for differences in body composition (Goran et al., 1994b, 1995b). The one study that reported no gender effect on REE in prepubertal children (Grund et al., 2000) used imprecise methods for assessing body composition. A separate longitudinal study (Goran et al., 1998a) reported a fall-off in TEE prior to puberty in girls but not boys.

Because commonly used BMR equations are based on body weight (Henry, 2000; WN Schofield, 1985), differences in BMR between genders are due both to the greater level of body fatness in women and to differences in the RMR–FFM relationship. These differences are ultimately reflected by lower numerical coefficients for height and weight in women compared with men in various equations to predict basal energy expenditure (BEE), or for weight and height when both variables are considered to predict BEE and TEE.

Growth

In infants and children, the energy requirement includes the energy associated with the deposition of tissues at rates consistent with good health. Although the energy requirement for growth relative to maintenance is low, except for the first months of life, satisfactory growth is a sensitive indicator of whether energy needs are being met. The energy cost of growth as a percentage of total energy requirements decreases from around 35 percent at 1 month to 3 percent at 12 months of age, and remains low until the pubertal growth spurt, at which time it increases to about 4 percent (Butte, 2000).

Growth is most impressive during infancy. Infants double their birth weight by 6 months of age, and triple it by 12 months (Butte et al., 2000a). At birth, the newborn is about 11 percent body fat. Progressive fat deposition in the early months results in a peak in the percentage body weight that is fat at 3 to 6 months (about 31 percent) and body fatness subsequently declines to an average of 27 percent at 12 months (Butte et al., 2000a). During infancy and childhood, girls grow slightly slower than boys, and girls have slightly more body fat (Butte et al., 2000a). During adolescence the gender differences in body composition are accentuated (Ellis, 1997; Ellis et al., 1997; Forbes, 1987; Tanner, 1955). Adolescence in boys is characterized by rapid acquisition of FFM and a modest increase in FM in early puberty, followed by a decline. FFM accretion coincides with the rapid spurt in height, though height gain may also continue until 20 to 25 years of age. Adolescence in girls is characterized by a modest increase in FFM and a continual accumulation of FM. The pubertal increase in FFM ceases at about 18 years, following the decrease in the rate of height gain after menarche (Forbes, 1987; Tanner, 1955).

Growth velocity is a sensitive indicator of energy status and use of growth velocity charts will detect growth faltering earlier than detected using attained growth charts. There is a wide range of variation in the growth rate of infants and children. Growth occurs in spurts, even in healthy children. Problems with measurement precision and high variability in individual growth rates over short time periods complicate the interpretation of growth velocity data. The timing of the adolescent growth spurt, which typically lasts 2 to 3 years, is also very variable, with the onset typically between 10 and 13 years of age in the majority of children (Forbes, 1987; Tanner, 1955). In general, weight velocity reflects acute episodes of dietary intake, whereas length velocity is affected by chronic factors.

Older Age

All three major components of energy expenditure decrease with aging: RMR, TEF, and EEPA. There is an average decline in BMR of 1 to 2 percent per decade in men who maintain constant weight (Keys et al., 1973). The suggested breakpoint for a more rapid decline apparently occurs around 40 years of age in men and 50 years of age in women (Poehlman, 1992, 1993). For women, this may be due to an accelerated loss of FFM during menopause (Svendsen et al., 1995).

In addition to the loss of FFM being a cause of age-associated decline in RMR, several (Fukagawa et al., 1990; Klausen et al., 1997; Pannemans and Westerterp, 1995; Poehlman et al., 1991; Roberts et al., 1995; Vaughan et al., 1991; Visser et al., 1995), though not all (Tzankoff and Norris, 1977), studies suggest that RMR adjusted for the change in FFM is decreased by about 5 percent in older adults compared to younger adults. However, in individuals who gain significant amounts of weight as they get older, RMR may actually increase due to gains of FM and FFM.

There is evidence suggesting that the RMR response to changes in energy balance may be attenuated in old versus young adults (Roberts and Dallal, 1998). The primary connection between RMR changes with age and FFM is also emphasized by research showing that endurance training (which increases FFM) increases RMR in elders (Poehlman and Danforth, 1991).

Concerning TEF, some studies report a decrease with aging (Golay et al., 1982; Morgan and York, 1983; Schutz et al., 1984; Schwartz et al., 1990; Thorne and Wahren, 1990), while other studies report no change or a nonsignificant increase (Bloesch et al., 1988; Fukagawa et al., 1991; Melanson et al., 1998; Poehlman et al., 1991; Tuttle et al., 1953; Visser et al., 1995). Although this controversy cannot currently be resolved, a suggested explanation is that TEF does not decline with aging per se, but that some studies may have included subjects with factors that decrease TEF independent of aging, such as obesity and digestive problems that limit nutrient absorption (Melanson et al., 1998).

PAL has been shown to decrease progressively with age and is lower in elderly adults compared to young adults (Roberts et al., 1992). Twenty-four-hour sedentary TEE measured in a whole-body calorimeter is also lower in elderly subjects compared with young adults (Vaughan et al., 1991). However, in whole body calorimeter protocols in which sedentary activity protocols were standardized, TEE did not differ between young and old adults (Pannemans et al., 1995).

The apparent decline in EEPA is consistent with the reported decreased frequency of strenuous physical activities in elderly men (Roberts, 1996). In addition, the decrease in TEE with age closely parallels the increase in

FM (Roberts and Dallal, 1998). However, the extent to which the increase in FM with age is a consequence or a cause of the age-related decrease in EEPA is not known. In relation to this observation, it should be noted that some elderly individuals clearly are able to maintain very high levels of TEE; Withers and coworkers (1998) report PAL values of 2.48 among older women with routine exercise habits compared to 1.87 in nonexercising women. However, mean maximal oxygen consumption declines 0.70 to 1 percent/y after age 35 in both sedentary adults and active adults (Suominen et al., 1977). Further studies are needed to determine the extent to which EEPA can be maintained in older adults in the general population.

Genetics

Energy requirements vary substantially between individuals due to combinations of differences in body size and composition, differences in RMR independent of body composition, differences in TEF, and differences in physical activity and in EEPA. All of these determinants of energy requirements are potentially influenced by genetic inheritance, with transmissible and nontransmissible cultural factors contributing to variability as well. Currently there is insufficient research data to predict differences in energy requirements among specific genetic groups, but as data accumulate this may become possible.

The effects of genetic inheritance on body composition are well known, with most studies reporting that 25 to 50 percent of interindividual variability in body composition can be attributed to genetic factors (Bouchard and Perusse, 1993). Because FFM and FM are major determinants of both RMR and TEE (Roberts and Dallal, 1998), these genetic influences on FFM and FM must be expected to influence energy requirements.

In addition to genetic influences on energy requirements mediated by genetic influences on body composition, there also appear to be genetic influences on TEE independent of body composition. Bogardus and coworkers (1986) reported a significant familial (intra-family) influence on RMR independent of FFM, age, and gender. Although the origin of this familial association is not currently known, it may potentially be due to differences in the relative sizes of FFM components (e.g., muscle, brain, organs) because recent work has suggested that organ size determined by magnetic resonance imaging strongly predicts RMR (Illner et al., 2000). In addition, Bouchard and coworkers (1989) reported that about 40 percent or more of the variances in RMR, TEF, and the energy costs of low-to-moderate intensity exercise are explained by inherited characteristics. The same group also reported that there is a genetic component to the weight-gain response to 1,000 kcal/d of overfeeding (Bouchard et al., 1990).

The question of which specific genes underlie genetic differences in TEE components is starting to be addressed, but few data are yet available. Valve and coworkers (1998) reported that polymorphisms within the UCP1 gene had no effect on BMR, but a combination of polymorphisms in the UCP1 and β_3-adrenergic receptor genes were associated with a significant 79 kcal/d decrease in BEE. Klannemark and coworkers (1998) reported no association between polymorphisms in the UCP2 gene and BMR, while Astrup and coworkers (1999) reported significant associations of these polymorphisms with TEE determined in a whole-body calorimeter and adjusted for FFM.

The study of Astrup and coworkers (1999) suggesting an association of specific gene polymorphisms with sedentary TEE is also consistent with the work of Heitmann and coworkers (1997) suggesting genetic influences on voluntary physical activity. Since EEPA is the major variable component of TEE, it is likely that genetic influences on EEPA may contribute substantially to intra-individual variability in TEE. Further work in this area is needed.

Ethnicity

African Americans and Caucasians

Most (Albu et al., 1997; Carpenter et al., 1998; Forman et al., 1998; Foster et al., 1997, 1999; Jakicic and Wing, 1998; Weyer et al., 1999a), but not all (Kushner et al., 1995; Nicklas et al., 1997), studies comparing RMR, BMR, or SMR between African-American and Caucasian adults have reported that RMR or SMR, adjusted for differences in body composition, are significantly lower in African Americans by about 10 percent. Foster and colleagues (1999) reported that the decrease in RMR with weight loss (adjusted for body composition change) is greater in African-American women than in Caucasian women, with weight loss of the African-American women in that study less than that of the Caucasian women. Similarly, the majority of studies reported lower RMR or BMR adjusted for body composition in African-American children than in Caucasian children (Kaplan et al., 1996; Morrison et al., 1996; Treuth et al., 2000; Wong et al., 1999; Yanovski et al., 1997); only one study found no difference between groups (Sun et al., 1998).

In addition, free-living EEPA, measured using the DLW method, appears to be lower in African-American compared to Caucasian individuals by about 10 to 20 percent (Carpenter et al., 1998; Kushner et al., 1995). These studies are consistent with the reports of lower levels of reported physical activity in African-American versus Caucasian adults (Washburn et al., 1992) and also lower maximal oxygen consumption (Vo_2max)

(Hunter et al., 2000). However, 24-hour sedentary TEE measured by whole-body calorimetry was not significantly different between African-American and Caucasian groups (Weyer et al., 1999a).

In children, EEPA adjusted for body composition was reported to be lower in African Americans than Caucasians (Wong et al., 1999). This finding is consistent with another study (Trowbridge et al., 1997) showing a 15 percent lower Vo_2max in African-American compared with Caucasian children. However, another DLW study observed no significant difference in TEE or EEPA between African-American and Caucasian children (Sun et al., 1998). Further studies in this area are needed.

The combination of data from these studies in adults and children indicate that BMR is usually lower in African Americans compared to Caucasians. Currently, insufficient data exist to create prediction equations for BMRs in African-American adults that would be accurate for both males and females throughout the life stages. In this report, therefore, the general prediction equations are used for all races, recognizing their potential to overestimate BMR in some groups such as African Americans.

Other Ethnic Groups

In addition to African Americans and Caucasians, other ethnic groups have been investigated for potential differences in energy requirements. In Pima Indians, an ethnic group widely considered to have a form of genetic obesity, RMR or SMR is not different from RMR or SMR in Caucasians after adjustment for body composition (Fontvieille et al., 1992; Weyer et al., 1999b). Similarly, physical activity levels were not different between Pima Indian and Caucasian children (Salbe et al., 1997), although the same group observed that spontaneous physical activity is a familial trait (Zurlo et al., 1992). Mohawk Indian children were reported to have higher values for TEE than Caucasian children, due to high levels of EEPA (Goran et al., 1995b). Thus, there are currently insufficient data to define specific differences in energy requirements between different racial groups and more research is needed in this area.

Environment

Climate

In the United States and Canada, indoor temperatures are typically controlled to remain within the 20°C to 25°C (68°F to 77°F) range during winter, and are frequently maintained to within a similar range in summer (EPA, 1991). In addition, most individuals intentionally create a relatively consistent temperature microenvironment for themselves by using more

insulating clothing in cold weather and cooler clothes in hot weather. The question of whether normal variations in ambient temperature influence energy requirements is therefore complex.

Potential effects of ambient temperature on energy requirements include the postprandial and postabsorptive metabolic rate (which would also include energy expenditure for shivering and nonshivering thermogenesis), the amount and types of voluntary and required physical activity, and EEPA. Ambient temperature effects are probably only significant when there is prolonged exposure to substantial cold or heat. The energy cost of work was judged to be 5 percent greater in a cold environment as compared to a warm environment (Consolazio et al., 1963). There can also be an additional energy cost (2 to 5 percent) of both the increased weight of clothing worn and the hobbling effect of that clothing in cold weather compared with clothing worn in warm weather (Consolazio et al., 1963). In addition, temperatures low enough to induce shivering or increased muscular activity will increase energy needs because of the increase in mechanical work (Timmons et al., 1985). More recent work also suggests that the recognized increase in energy expenditure in markedly cold climates may be greater in physically active individuals than in sedentary ones (Armstrong, 1998).

High ambient temperatures may also increase energy requirements. There is an increase in the energy expenditure of standard tasks when ambient temperatures are very high (Consolazio et al., 1963). However, this increase in energy expenditure may be attenuated by continued exposure. Garby and colleagues (1990) reported that the extra energy expenditure for 2 hours of light activity at 34°C fell progressively a total of 3 to 8 percent with acclimatization over 8 days of the study compared with activity at 20°C to 24°C.

Relative to high-normal ambient temperatures (26°C to 28°C), low-normal ambient temperatures (20°C to 22°C) were associated with increased sedentary TEE values in lean female subjects (Blaza and Garrow, 1983; Dauncey, 1981). More recent studies have reported a significant effect of variations in ambient temperature within the usual range on energy requirements. Lean and colleagues (1988) reported a 4 percent increase in the sleeping metabolic rate of women at an ambient temperature of 22°C compared with 28°C. Warwick and Busby (1990) reported a 5 percent increase in sedentary TEE at 20°C in men and women wearing clothing of their own choice and performing a standardized pattern of physical activity compared with similar activity at 28°C. Buemann and coworkers (1992) reported a significant 2 percent increase in TEE at 16°C compared with 24°C (with no difference in response seen between postobese and normal women). Men showed a significant increase in sedentary TEE at the lowest (20°C) and highest (30°C) temperatures studied com-

pared to temperatures in the middle range (23°C and 26°C) (Valencia et al., 1992). This study also confirmed earlier findings (Nielsen, 1987) that humidity did not significantly affect RMR. These data consistently suggest that low-normal temperatures (20°C to 22°C) and high-normal temperatures (28°C to 30°C) are associated with an increase in sedentary TEE of 2 to 5 percent compared to temperatures of 24°C to 27°C. This conclusion is also consistent with the report of Lanzola and colleagues (1990) that skin temperature closely predicts BMR in normal individuals.

A summary of changes in BMR among individuals migrating between the tropic and temperate climates has demonstrated that changes in ambient temperature do not produce a long-term change in metabolic rate (Hayter and Henry, 1993). Instead, the effect of ambient temperature appears to be confined to the period of time during which the ambient temperature is altered. Nevertheless, the energy expenditure response to cold temperatures may be enhanced with previous acclimatization by prolonged exposure to a cool environment (Kashiwazaki et al., 1990).

The question of whether there are gender differences in the apparent increase in sedentary TEE at low-normal ambient temperatures compared to high-normal temperatures remains uncertain. In a re-analysis of the data of Warwick and Busby (1990), Murgatroyd and coworkers (1990) reported that the increase in sedentary TEE was only statistically significant in women, raising the question of whether women may be more responsive to low-normal ambient temperatures than men. Since most of the recent data has been collected in women, further research in this area is needed.

In addition to the effects of normal variations in ambient temperature on sedentary TEE, there may also be season-related influences on the amount of voluntary physical activity and EEPA, but these potential effects are less well defined. Burstein and coworkers (1996) reported a nonsignificant increase in TEE in soldiers participating in an intense exercise regimen in winter compared to summer. There was also no significant difference in season-related values for physical activity in free-living adult Dutch women, but in contrast to the values reported above for soldiers, the values tended to be higher in summer than in winter (van Staveren et al., 1986). However, unlike these nonsignificant effects of season and temperature on TEE in adults, children were reported to have significantly greater TEE in the spring than in the fall (Bitar et al., 1999; Goran et al. 1998b).

The combination of these results indicates that there is a modest 2 to 5 percent increase in sedentary TEE at low-normal ambient temperatures compared to high-normal ambient temperatures. However, it is not possible to generalize these results to seasonal effects on TEE because of the potentially important and variable impact of seasonal changes in physical activity that are likely dependent on local temperature fluctuations and

cultural factors. For this reason, no specific allowance is made for ambient temperature in the requirements for energy. It should also be noted that the TEE values used to predict the energy requirements of different groups were made throughout the year, and can be considered values averaged for the ambient temperatures of the different seasons.

Altitude

Hypoxia increases glucose utilization whether measurements are made on isolated muscle tissue (Cartee et al., 1991), tissues in situ (Zinker et al., 1995), or intact functioning individuals (Brooks et al., 1991, 1992). The hypobaric hypoxia of high altitude increases BMR and TEE but it is unclear at which heights the effect becomes prominent. A study on men at 4,300 m (14,100 ft) found an increase in BMR of about 200 to 500 kcal/d when energy intakes were maintained (Butterfield et al., 1992). However, in a subsequent study on women, the effect of altitude on raising BMR and TEE was less prominent (Mawson et al., 2000).

Adaptation and Accommodation

There are two key differences between nutritional adaptation and accommodation (Waterlow, 1999). First, while adaptation implies maintenance of essentially unchanged functional capacity in spite of some alteration in steady-state conditions, accommodation allows maintenance of adequate functional capacity under altered steady-state conditions. Second, whereas accommodation involves relatively short-term adjustments, such as the responses needed to maintain homeostasis, adaptation involves changes in body composition that occur over a more extended period of time.

Adaptation

The term adaptation describes the normal physiological responses of humans to different environmental conditions. A good example of adaptation is the increase in hemoglobin concentration that occurs when individuals live at high altitudes (Leon-Velarde et al., 2000).

Energy balance is regulated by a complex set of feedback mechanisms. Changes in energy intake or in energy expenditure trigger metabolic and behavioral responses aimed at restoring energy balance in adults. These responses involve the endocrine system, the central nervous system, and the body energy stores. When effective, these regulatory mechanisms result in the maintenance of a stable body weight (Jequier and Tappy, 1999).

The estimation of energy requirements from energy expenditure implicitly assumes that the efficiency of energy utilization is more or less

uniform across all individuals. Otherwise, individuals with higher efficiency would require less energy for equal energy expenditure than persons with lower efficiency. The experimental data supports the notion that differences in efficiency of energy utilization among healthy individuals living under similar conditions fluctuate within a narrow range (James et al., 1990; Waterlow et al., 1989).

Body weight can be remarkably stable in many healthy adults, demonstrating the human potential for maintaining energy balance and stable body composition in spite of conditions that have promoted the recent secular trends in increasing body weights. Maintenance of stable body weight and composition are affected by genetic factors, energy intake, and diet composition, as well as by other environmental factors (Hill and Peters, 1998). Environmental conditions favoring high energy consumption and low physical activity can overwhelm these mechanisms and lead to positive energy balance, resulting in body fat accumulation and weight gain until another state of weight maintenance becomes established. Thus, weight gain and obesity can be seen as a form of adaptation that brings about a new steady state (Astrup et al., 1994).

Adaptation has been defined as "a process by which a new or different steady state is reached in response to a change or difference in the intake of food and nutrients" (FAO/WHO/UNU, 1985). A more practical definition, applied to the study of energy requirements, would be the ability to compensate for changes in energy (energy intake, expenditure, or balance) without any discernible detriment to health.

Although the concept applies both to increases and decreases in energy intake or energy expenditure, a focus of controversy has been its application to the definition of energy needs in poor areas of the world. In studies that specifically attempted to assess whether some adaptive mechanism may permit those populations to subsist with lower than predicted energy intakes, no reduction in weight-adjusted basal metabolic rates could be detected (Soares et al., 1991).

Studies by numerous investigators (Minghelli et al., 1990; Ravussin et al., 1988; Weinsier et al., 1998; Weyer et al., 1999a, 1999b) tend to confirm the limited capacity of homeostasis to prevent or attenuate the impact of changes in energy intake on weight gain or weight loss without discernible impact on activity. Thus, a reduction in BEE or REE is generally associated with reduced body weight (Minghelli et al., 1990). Reports on the ethnic and gender differences in energy efficiency have yielded conflicting results, but the overall contributions such differences can make toward the maintenance of energy balance appears to be small (Soares et al., 1998; Weyer et al., 1999a, 1999b). The TEF component of the energy balance equation accounts for only a small fraction of TEE and does not appear to vary adaptively in relationship to changes in energy balance. Thus, mainte-

nance of energy balance is largely dependent on adjustments in food intake and physical activity.

Some studies suggest a capacity for TEE to increase or decrease spontaneously when energy intake increases or decreases (Levine et al., 1999; Roberts et al., 1990). However, most overfeeding studies show that overeating is accompanied by substantial weight gain, and likewise reduced energy intake induces weight loss (Saltzman and Roberts, 1995). Thus, although there is some adaptive capacity of TEE to adjust to changes in dietary energy intake, the extent of this adjustment (other than what can be attributed to change in body size) is much too small to offset the impact observed by changes in energy intake. Body weight is a direct indicator of the relationship between food intake or availability and TEE.

Accommodation

The term accommodation was proposed to characterize an adaptive response that allows survival but results in some more or less serious consequences on health or physiological function. The most common example is a decrease in growth velocity in children. By reducing growth rate, children are able to save energy and may subsist for prolonged periods of time on marginal energy intakes, though at the cost of eventually becoming stunted. Another common example of accommodation is a reduction in physical activity. This can result in reduced productivity of physical work or in decreased leisure physical activity, which in children is important for behavioral and mental development (Twisk, 2001).

APPROACH USED TO DETERMINE TOTAL ENERGY EXPENDITURE

Based on the preceding review of possible approaches to estimating energy requirements, direct measurement of total energy expenditure (TEE) by the doubly labeled water (DLW) method represents a distinct advantage over previous TEE evaluations that had to rely on the factorial approach and/or on food intake data, both of which have limited reliability.

Description of the Doubly Labeled Water Database

Total energy expenditure data obtained by the DLW method were solicited for this report from investigators identified in the literature. Over 20 investigators responded and submitted individual TEE and ancillary data including age, gender, height, weight, basal energy expenditure (BEE) (observed or estimated), and descriptors for each individual in the data set (see Appendix I; also available at www.iom.edu/fnb). A normative

DLW database was created based on the inclusion/exclusion criteria described below.

Since the DLW data were not obtained in randomly selected individuals (except in the recent study of Bratteby and coworkers [1997]), they do not therefore constitute a representative sample of the populations of the United States and Canada. However, the measurements were obtained from men, women, and children whose ages, body weight, height, and physical activities varied over wide ranges, so they provide an appropriate base to estimate energy expenditures and requirements at different life stages in relation to gender, body weight, height, age, and for different activity estimations. A few age groups are underrepresented in the data set and interpolations had to be performed in these cases. Thus, while the available DLW data set used is not entirely satisfactory, it nevertheless offers the best currently available information. This data set, used to estimate the current energy recommendations, can be used to refine other existing communicated recommendations or guidelines developed by other organizations and agencies.

Inclusion/Exclusion Criteria

Normative Database. To arrive at estimates of TEE, the normative DLW database, as summarized in Table 5-10, included infants and very young children (0 through 2 years of age) within the 3rd to 97th percentile for weight-for-height (Kuczmarski et al., 2000) (Appendix Table I-1), children (3 through 18 years of age) within the 5th to 85th percentile for body mass index (BMI) (Kuczmarski et al., 2000) (Appendix Table I-2), and adults (19 years of age and older) with BMI from 18.5 up to 25 kg/m^2 (Appendix Table I-3). Subjects were required to be healthy, free-living, maintaining their body weight, and with measured heights and weights. Exclusion criteria included undernutrition, acute and chronic diseases, underfeeding and overfeeding protocols, and lifestyles involving uncommonly high levels of physical activity (e.g., elite athletes, astronauts, military trainees, and those with a physical activity level [PAL] greater than 2.5). A subset of DLW data was formulated for pregnant (Appendix Table I-4) and lactating (Appendix Table I-5) women meeting the inclusion/exclusion criteria prior to pregnancy.

There are 407 adults in the normative database (Appendix Table I-3), 169 men and 238 women. Among the men whose ethnicity was reported, there are 33 Caucasians, 7 African Americans, and 2 Asians, and among the women there are 94 Caucasians, 13 African Americans, 3 Asians, and 3 Hispanics. The majority of the adult data come from studies that were

conducted in the United States or the Netherlands, with the remainder from studies done in the United Kingdom, Australia, and Sweden. For the 100 adults for whom data were provided on occupation, the most commonly reported types of occupations were offices workers, followed by teachers and students, scientists, medical workers, active occupations (e.g., aerobics instructor, police officer, physical therapist, dog trainer), homemakers, artists, and the unemployed.

The database for normal-weight children (n = 525) (Appendix Table I-2) includes 167 boys (73 Caucasians, 13 African Americans, 4 Hispanics, and 62 American Indians) and 358 girls (197 Caucasians 58 African Americans, 20 Hispanics, 10 Asians, and 60 American Indians); ethnicity was not provided for 15 boys and 13 girls. All data on children were collected in the United States.

Overweight and Obese Database. DLW databases of overweight and obese children and adults were also developed and are summarized in Table 5-11. Children (3 through 18 years of age) above the 85th percentile for BMI (Kuczmarski et al., 2000) (Appendix Table I-6) and adults (19 years of age and older) with BMIs from 25 kg/m^2 and higher (Appendix Table I-7) were included in the database. Subjects were required to be free-living. Diet and exercise intervention studies were excluded. There were insufficient data to address pregnancy and lactation in overweight and obese women.

The database for overweight and obese adults contains information on 360 individuals—165 men and 195 women (Appendix Table I-7). Among the men whose ethnicity was reported, there are 22 Caucasians and 21 African Americans; among the women there are 51 Caucasians, 34 African Americans, and 5 Hispanics. The majority of the data come from studies conducted in the United States and the Netherlands; the rest are from studies conducted in the United Kingdom, Sweden, and Australia. Occupations were not provided for 326 individuals. For those 34 individuals for whom an occupation was given, the most common types were office workers, followed by medical personnel, homemakers, active occupations (e.g., firefighter, fitness instructors), teachers and students, researchers, and artists.

The database for overweight and obese children (n = 319) (Appendix Table I-6) includes 127 boys (33 Caucasian, 20 African-American, 2 Hispanic, and 71 American Indian) and 192 girls (63 Caucasian, 48 African-American, 6 Hispanic, 68 American Indian, and 1 Asian; ethnicity was not provided for 1 boy and 6 girls. All data were collected in the United States.

TABLE 5-10 Doubly Labeled Water Databases for All Individuals with a Body Mass Index (BMI) in the Range from 18.5 up to 25 kg/m^2[a]

Age (y)	*n*	Mean Weight (kg [lb])	Mean Height (m [in])
0–0.5	116	6.9 (15)	0.64 (25)
0.6–1.0	72	9.0 (20)	0.72 (28)
1–2	132	11.0 (24)	0.82 (32)
Males			
3–8	129	20.4 (45)	1.15 (45)
9–13	28	35.8 (79)	1.44 (57)
14–18	10	58.8 (130)	1.70 (67)
19–30	48	71.0 (156)	1.80 (71)
31–50	59	71.4 (157)	1.78 (70)
51–70	24	70.0 (154)	1.74 (69)
71+	38	68.9 (152)	1.74 (69)
Females			
3–8	227	22.9 (50)	1.20 (47)
9–13	89	36.4 (80)	1.44 (57)
14–18	42	54.1 (119)	1.63 (64)
19–30	82	59.3 (131)	1.66 (65)
31–50	61	58.6 (129)	1.64 (65)
51–70	71	59.1 (130)	1.63 (63)
71+	24	54.8 (121)	1.58 (62)

[a] Summary of data in Appendix Tables I-1 through I-5.
[b] For adults (19 years of age and over), the observed BEE was used to calculate the mean BEE. BEE and physical activity level were not used for infants. For children, BEE

Data Analysis and Assumptions Made for the Total Energy Expenditure Equations

For the normative DLW database, prediction equations of TEE from age, gender, height, and weight were developed. The validity of these equations to predict TEE rest on three general assumptions: that the database represents the phenomena of interest, that the model describes the physiological phenomena of the data, and that the fitted equations accurately describe the data. As in any realistic statistical modeling activity, the balance is between fitting the data and fitting the phenomena, while making optimal use of the available data.

The available data were reviewed and analyzed and it is assumed that they are representative of the phenomena of interest—the energy metabo-

Mean Body Mass Index (kg/m^2)	Mean Basal Energy Expenditure (BEE) (kcal/d)[b]	Mean Total Energy Expenditure (TEE) (kcal/d)	Mean Physical Activity Level (TEE/BEE)
16.9	—	501	—
17.2	—	713	—
16.2	—	869	—
15.4	1,035	1,441	1.39
17.2	1,320	2,079	1.56
20.4	1,729	3,116	1.80
22.0	1,769	3,081	1.74
22.6	1,675	3,021	1.81
23.0	1,524	2,469	1.63
22.8	1,480	2,238	1.52
15.6	1,004	1,487	1.48
17.4	1,186	1,907	1.60
20.4	1,361	2,302	1.69
21.4	1,361	2,436	1.80
21.6	1,322	2,404	1.83
22.2	1,226	2,066	1.70
21.8	1,183	1,564	1.33

was predicted based on the following equations (see "TEE Equations for Normal-Weight Children"):

Boys: BEE (kcal/d) = 68 – 43.3 × age (y) + 712 × height (m) + 19.2 × weight (kg).

Girls: BEE (kcal/d) = 189 – 17.6 × age (y) + 625 × height (m) + 7.9 × weight (kg).

lism of healthy individuals over the normal range of age, height, weight, and energy expenditure. The analyses were restricted to include individuals within the specific ranges of body sizes and excluded individuals who were identified as being full-time in physical training.

An additive model was chosen as the default, with the relative contributions of height and weight kept constant for each gender. Because of the difficulty of estimating physical activity in the field, a four-level ordinal variable was generated, estimated from PAL data and used in the model to modify the total height and weight contribution to TEE. Various transformations of the data and the inclusion of multiplicative terms were explored, but none significantly improved how well the model described the data.

TABLE 5-11 Doubly Labeled Water Database for Overweight and Obese Males and Females[a]

Age (y)	*n*	Mean Weight (kg [lb])	Mean Height (m [in])
Males			
3–8	91	28.6 (63)	1.19 (46)
9–13	36	54.7 (120)	1.46 (57)
14–18	—	—	—
19–30	11	98.5 (217)	1.82 (72)
31–50	68	98.3 (217)	1.78 (70)
51–70	54	90.4 (199)	1.75 (69)
71+	32	82.3 (181)	1.72 (68)
Females			
3–8	123	30.5 (67)	1.22 (48)
9–13	56	55.8 (123)	1.50 (59)
14–18	13	73.9 (163)	1.64 (65)
19–30	37	82.3 (181)	1.66 (65)
31–50	51	88.3 (194)	1.66 (65)
51–70	79	79.7 (176)	1.62 (64)
71+	28	69.0 (152)	1.58 (62)

[a] Summary of data in Appendix Tables I-6 and I-7.
[b] For adults (ages 19 and over), the observed BEE was used to calculate the mean BEE. For children, BEE was predicted based on the following equations (see "Estimation of Energy Expenditure in Overweight Children Ages 3 through 18 Years"):

Finally, although the equations are essentially linear (within each PAL), a nonlinear regression procedure was used, with a least squares loss function. During the exploratory phase, evaluations of alternative models were based on the magnitude of residual error and examination of residual plots. These residual plots showed that while errors are not constant over the whole range of the variables, there is no simple pattern. As noted above, various transformations of the dependent variable (TEE) were explored, and in light of these results it was decided that assuming a least squares loss function did not lead to serious bias in the fitted models, and that the effect on error estimates was not important given the large amount of unexplained variability in the data. Since nonlinear regression is an iterative approach, the influence of varying the starting point was investigated and was found not to be a problem. The standard errors of the coefficients were estimated asymptotically; for a sample of the fits estimates were determined by jackknife techniques; these were found not to change the conclusions.

Mean Body Mass Index (kg/m^2)	Mean Basal Energy Expenditure (BEE) (kcal/d)[b]	Mean Total Energy Expenditure (TEE) (kcal/d)	Mean Physical Activity Level (TEE/BEE)
19.8	1,210	1,728	1.42
25.4	1,612	2,451	1.52
—	—	—	—
29.6	1,970	3,599	1.85
30.8	1,955	3,598	1.85
29.6	1,722	2,946	1.72
27.8	1,667	2,510	1.52
20.3	1,149	1,669	1.45
24.7	1,443	2,346	1.63
27.6	1,596	2,798	1.75
29.8	1,524	2,677	1.77
31.9	1,629	2,895	1.79
30.4	1,380	2,176	1.59
27.6	1,258	1,763	1.40

Boys: BEE (kcal/d) = 419.9 – 33.5 × age (y) + 418.9 × height (m) + 16.7 × weight (kg).
Girls: BEE (kcal/d) = 515.8 – 26.8 × age (y) + 347 × height (m) + 12.4 × weight (kg).

Examination of the normative DLW database showed an initial increase of TEE with age until a plateau from age 20 to 45 in women, followed by a decline (Figure 5-6). Men peaked around 35 years of age, and then declined (Figure 5-6). Increased TEE is related to greater heights (Figure 5-7) and weights (Figure 5-8). For adults, TEE was independent of BMI when the analysis was adjusted for height. Analyses indicated that the best predictions for TEE were obtained by fitting all the data separately for adults (ages 19 years and older), children and adolescents (ages 3 through 18 years), and young children (ages 0 through 2 years).

Gender-specific equations were found to be unnecessary in children less than 3 years of age. All data were entered into and analyzed with SPSS, version 10.0.

Physical Activity Level Categories

The PAL categories were defined as sedentary (PAL ≥ 1.0 < 1.4), low active (PAL ≥ 1.4 < 1.6), active (PAL ≥ 1.6 < 1.9), and very active (PAL ≥

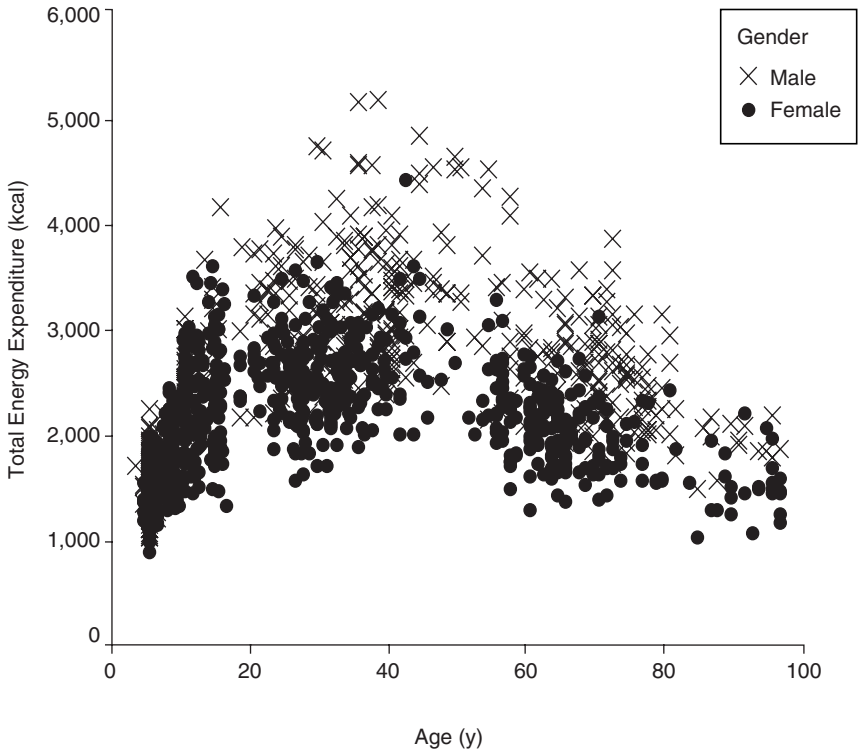

FIGURE 5-6 Total energy expenditure and age in all individuals (excluding infants and pregnant or lactating women) in the doubly labeled water database (Appendix I).

1.9 < 2.5) (Table 5-12). The mean PALs for the four categories are shown in Table 5-13. The energy expenditure in sedentary individuals is set to reflect their BEE, the thermic effect of food, and the physical activities that are required for independent living. A low-active lifestyle (PAL = 1.5) for an adult weighing 70 kg is set to include an exertion *equivalent to* walking 2.2 mi/d at a rate of 3 to 4 mph or the equivalent energy expenditure in other activities, in addition to the activities that are part of independent living (Table 5-12). The active lifestyle was set at a PAL of 1.6 to 1.89. The physical activities performed by active, mid-weight individuals with a PAL of 1.75 (midpoint in this PAL category) would on average to be equivalent to walking 7 mi/d at the rate of 3 to 4 mph, while walking ~17 mi/d would be equivalent to the sum of the activities above independent living carried out by a very active, mid-weight individual with a PAL of 2.2 (Table 5-12). The PAL range set for a "very active" lifestyle is 1.9 to 2.49. As shown in

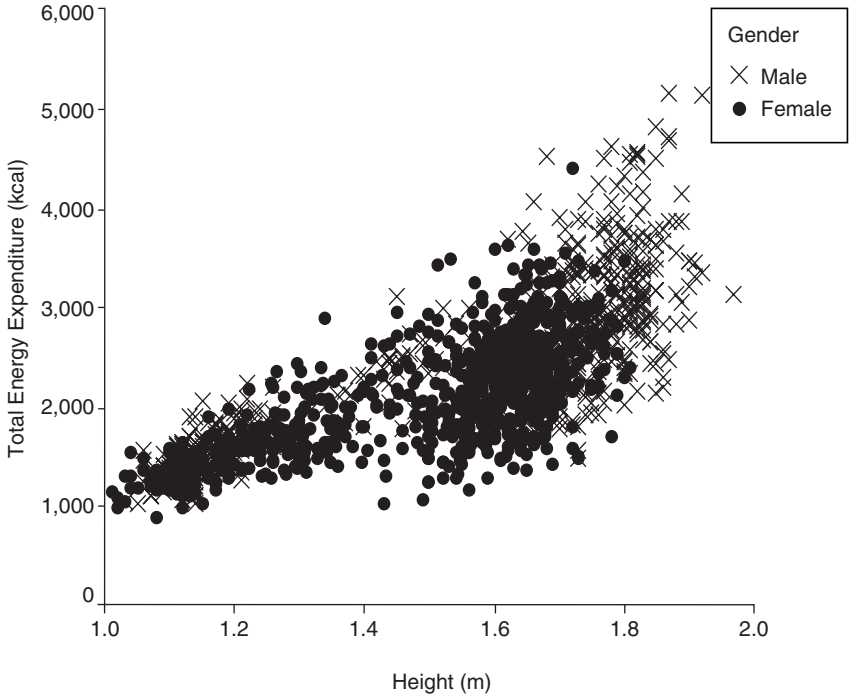

FIGURE 5-7 Total energy expenditure and height in all individuals (excluding infants and pregnant and lactating women) in the doubly labeled water database (Appendix I).

Table 5-12, these distances vary with the actual PAL value as well as with body weights. Tables are included in Chapter 12 that indicate how an individual can estimate his or her PAL on a daily (Table 12-2) or weekly (Table 12-3) basis.

Regression of Total Energy Expenditure on Age, Height, Weight, and Physical Activity Level Category

While stepwise multiple linear regressions were used to identify gender, age, height, and weight as the important variables for predicting TEE, physiological considerations determined that the form of the best predictive equation was nonlinear:

$$\text{TEE} = \text{A} + \text{B} \times \text{age} + \text{PA} \times (\text{D} \times \text{weight} + \text{E} \times \text{height})$$

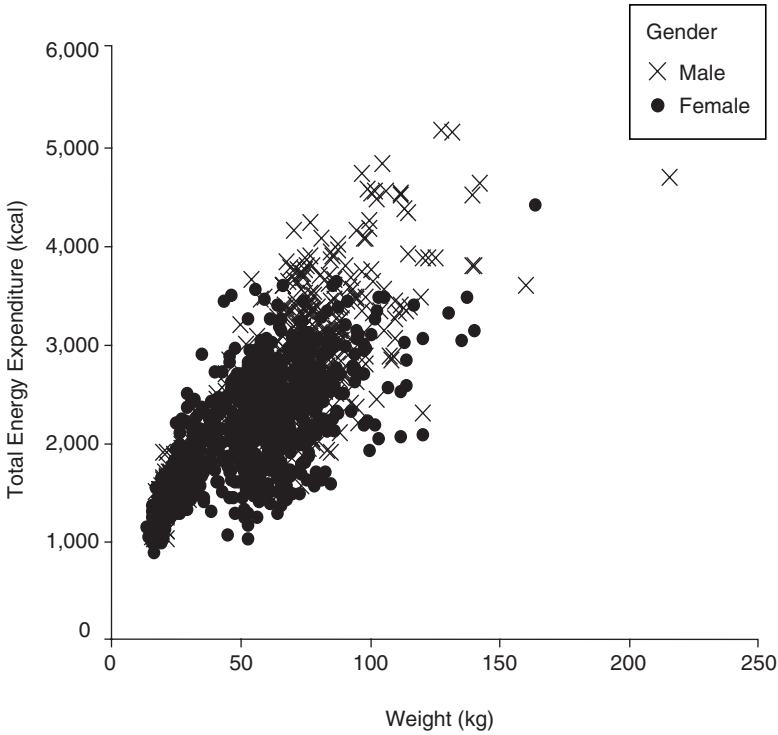

FIGURE 5-8 Total energy expenditure and weight in all individuals (excluding infants and pregnant and lactating women in the doubly labeled water database (Appendix I).

where TEE is in kcal/d, age is in years, weight is in kilograms, and height is in meters. In this equation, A is the constant term; B is the age coefficient; PA is the physical activity coefficient, which depends on whether the individual is estimated to be in the sedentary, low-active, active, or very active PAL categories; D is the weight coefficient; and E is the height coefficient. It should be noted that this approach is equivalent to fitting the individuals in each PAL category separately but keeping their equations parallel.

In the above equation the relative importance of height and weight is constant for different activity levels but the magnitude of their combined contribution changes for different PAL levels. Because of the mathematical interdependencies between the physical activity coefficients and the height and weight coefficients, the physical activity coefficient for the sedentary PAL category is set to 1.0.

The standard error of fit (the standard deviation of the residuals) represents how variable the measurements of the energy requirements of

TABLE 5-12 Physical Activity Level (PAL) Categories and Walking Equivalence

PAL Category	PAL Range	PAL	Walking Equivalence (mi/d at 3–4 mph)[a] Light-Weight Individual (44 kg)	Middle-Weight Individual (70 kg)	Heavy-Weight Individual (120 kg)
Sedentary	1.0-1.39	1.25	~ 0	~ 0	~ 0
Low active	1.4-1.59				
Mean		1.5	2.9	2.2	1.5
Active	1.6-1.89				
Minimum		1.6	5.8	4.4	3.0
Mean		1.75	9.9	7.3	5.3
Very active	1.9-2.49				
Minimum		1.9	14.0	10.3	17.5
Mean		2.2	22.5	16.7	12.3
Maximum		2.5	31.0	23.0	17.0

[a] In addition to energy spent for the generally unscheduled activities that are part of a normal daily life.
SOURCE: Chapter 12.

individuals with similar characteristics might be. In order to estimate the true between-individual variability, it was necessary to partition this observed variability into biological and experimental; in the light of limited data, and following the suggestion of the 1981 FAO/WHO/UNU Expert Consultation, it is assumed that the biological and the experimental variance are equal. Therefore, values for individual standard deviations are recommended as 70 percent of the observed standard error of fit (Table 5-14).

The data were fitted to this equation using nonlinear regression and the Levenberg-Marquardt method for searching for convergence based on minimizing the sum of residuals squared. For each fit an R-squared was calculated as the ratio of the explained sum of squared error to the total sum of squared error, and asymptotic standard errors of the coefficients were calculated.

TEE Equations for Normal-Weight Children

Separate TEE predictive equations were developed for normal-weight boys and girls from age, height, weight, and PAL category using the same definitions as that for adults (see Table 5-12) using nonlinear regression techniques. In order to utilize all the TEE data, PAL categorization was determined using predicted rather than observed BEE, since only 71 percent (256/358) of the girls and 66 percent (111/167) of the boys had

TABLE 5-13 Sample Size, Mean Total Energy Expenditure (TEE), Body Mass Index (BMI), and Physical Activity Level (PAL) for each of the PAL Categories in Adults Included in the DLW Database[a]

BMI (kg/m^2)	Gender	PAL Category	*n*
18.5 to 25	Women	Sedentary	35
		Low active	45
		Active	87
		Very active	71
		Total	238
	Men	Sedentary	22
		Low active	36
		Active	76
		Very active	35
		Total	169
25 and higher	Women	Sedentary	39
		Low active	43
		Active	78
		Very active	35
		Total	195
	Men	Sedentary	20
		Low active	35
		Active	58
		Very active	52
		Total	165

[a] From Appendix I.
[b] Mean ± standard deviation.

observed BEE (Appendix Table I-2). The following predictive equations for BEE were derived from the observed BEE provided in the DLW database.

For boys:
BEE (kcal/d) = 68 − (43.3 × age [y]) + 712 × height (m) + 19.2 × weight (kg) [standard error = 88; $R^2 = 0.89$]

For girls:
BEE (kcal/d) = 189 − (17.6 × age [y]) + 625 × height (m) + 7.9 × weight (kg) [standard error = 95; $R^2 = 0.75$]

TEE Measured (kcal/d)[b]	BMI Measured (kg/m^2)[b]	PAL Measured[b]
1,567 ± 261	22.1 ± 1.7	1.23 ± 0.11
2,036 ± 252	22.1 ± 1.8	1.52 ± 0.05
2,303 ± 288	21.8 ± 1.7	1.74 ± 0.09
2,588 ± 348	21.2 ± 1.6	2.09 ± 0.16
2,229 ± 447	21.7 ± 1.7	1.73 ± 0.31
1,992 ± 263	23.0 ± 1.5	1.29 ± 0.10
2,500 ± 381	22.4 ± 1.5	1.51 ± 0.05
2,892 ± 402	22.5 ± 1.5	1.74 ± 0.08
3,338 ± 419	22.4 ± 1.6	2.06 ± 0.01
2,784 ± 561	22.5 ± 1.5	1.70 ± 0.25
1,788 ± 373	30.3 ± 5.0	1.25 ± 0.10
2,205 ± 344	30.2 ± 4.3	1.52 ± 0.06
2,594 ± 452	31.0 ± 6.6	1.74 ± 0.08
2,888 ± 347	28.9 ± 3.3	2.04 ± 0.11
2,400 ± 545	30.3 ± 5.3	1.65 ± 0.27
2,378 ± 546	30.3 ± 6.3	1.27 ± 0.09
2,719 ± 544	29.7 ± 6.5	1.50 ± 0.06
3,142 ± 425	29.4 ± 4.1	1.73 ± 0.09
3,821 ± 608	29.9 ± 4.2	2.10 ± 0.14
3,174 ± 727	29.7 ± 5.0	1.74 ± 0.30

Prediction equations of TEE for normal-weight boys and girls ages 3 through 18 years were then developed using age, height, weight, and PAL category as predicted from the above BEE equations. Data were not used in the derivation of the TEE equations if the PAL value was less than 1.0 or greater than 2.5.

Plots of the residuals (predicted versus observed TEE) for each PAL category did not differ from zero and showed no evidence of nonlinear patterns of bias. Standard deviation (SD) of the residuals ranged from 56 to 167, with the highest SD for the very active PAL category. The residuals were not correlated with weight, height, BMI, or age.

TABLE 5-14 Estimated Standard Deviation of Estimated Energy Requirements (kcal/d) Derived from Regression Equations for Individuals of a Specific Age, Height, Weight, and Physical Activity Level Category[a]

Age (y)	Body Mass Index	Males	Females
3–18	≥ 3rd < 85th percentile	58	68
3–18	≥ 85th percentile	69	75
3–18	≥ 3rd percentile	67	70
≥ 19	≥ 18.5 < 25 kg/m^2	199	162
≥ 19	≥ 25 kg/m^2	208	160
≥ 19	≥ 18.5 kg/m^2	202	160

[a] Observed variance = biological variance + experimental variance, for the square root of biological variance = biological standard deviation, assuming biological variance = experimental variance.

The coefficients and standard error for the prediction of TEE in boys and girls ages 3 through 18 years of age in the normative database are described in Appendix Table I-8.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants and Children Ages 0 Through 2 Years

Evidence Considered in Determining the Estimated Energy Requirement

Energy Expenditure and Energy Deposition. The energy requirements of infants and young children should balance energy expenditure at a level of physical activity consistent with normal development and allow for deposition of tissues at a rate consistent with health. This approach requires knowledge of what constitutes developmentally appropriate levels of physical activity, normal growth, and body composition. Although the energy requirement for growth relative to maintenance is small, except during the first months of life, satisfactory growth is a sensitive indicator of whether energy needs are being met. To determine the energy cost of growth, the energy content of the newly synthesized tissues must be estimated, preferably from the separate costs of protein and fat deposition.

Basal Metabolism. The brain, liver, heart, and kidney account for most of the basal metabolism of infants. Holliday (1971) analyzed basal meta-

bolic rate (BMR) in relation to body and organ weight, and noted that oxygen (O_2) consumption increased at a rate greater than that of organ or body weight during the intrauterine and postnatal periods. There is also an increase in O_2 consumption during the transition to extrauterine life. After birth, the O_2 consumption of these vital organs increases in proportion to increases in organ weight. The contribution of the brain to BMR is exceptionally high in the newborn period (70 percent) and throughout the first years of life (60 to 65 percent).

Basal metabolism of term infants has been investigated extensively. Karlberg (1952) and Benedict and Talbot (1921) reported BMR ranges from 43 to 60 kcal/kg/d. The high variability is attributable to biological differences in body composition and technical differences in experimental conditions and methods. (In most studies of infants, BMR is measured while they are either asleep or sedated, which may lead to an underestimate of BEE.) Nevertheless, it should be appreciated that energy expenditure per kg is approximately two times greater in infants than in adults (Denne and Kalhan, 1987).

The basal metabolism of infants is dependent on gender, age, and feeding mode. Significant differences between breast-fed and formula-fed infants have been reported at 3 and 6 months (Butte, 1990; Butte et al., 2000b; Wells and Davies, 1995). BMR predicted from Schofield equations (WN Schofield, 1985) was equal to 0.88 measured BMR at 3–12 months (Butte et al., 2000b). Schofield compiled approximately 300 measurements from Benedict and Talbot (1914, 1921), Clagett and Hathaway (1941), Harris and Benedict (1919), and Karlberg (1952) to develop predictive models based on weight and length (C Schofield, 1985). Experimental conditions varied across studies in which indirect calorimetry was used to measure SMR or resting metabolic rate (RMR) rather than BMR. In the older studies, the influence of neonatal age, sedation, or experimental techniques in some of the older studies may explain the lower values predicted by the Schofield equation compared to measured BMR.

Thermic Effect of Feeding. Since infants normally are fed frequently and not subjected to prolonged fasting, the thermic effect of food (TEF) will exert a continual, albeit variable, influence on energy expenditure. The TEF in preterm infants (Reichman et al., 1982) and in infants recovering from malnutrition (Ashworth, 1969) has been shown to be proportional to the rate of weight gain. These observations support the view that some of the observed energy expenditure is due to the metabolic costs of tissue synthesis.

Thermoregulation. In the first 24 hours after birth, thermoneu-trality is reported to be at 34°C to 36°C for the naked infant and falls to 30°C to

32°C by 7 to 10 days of age (Sinclair, 1978). The amount of energy required to maintain normal body temperature is greater at lower than at higher temperatures (Sinclair, 1978). Basal oxygen consumption rates increase from 4.8 ml O_2/kg/min at 0 to 6 hours postpartum to 7.0 ml O_2/kg/min at 6 to 10 days of life and remain fairly constant thereafter throughout the first year of life (Widdowson, 1974). The neonate responds to mild cold exposure with an increase in nonshivering thermogenesis, which increases metabolic rate and may be mediated by increased sympathetic tone (Penn and Schmidt-Sommerfeld, 1989). Increased oxidation of fatty acids in brown adipose tissue located between the scapulae and around major vessels and organs of the mediastinum and abdomen is thought to make the most important contribution to nonshivering thermogenesis in infants (Penn and Schmidt-Sommerfeld, 1989). Shivering thermogenesis occurs at lower ambient temperatures when nonshivering thermogenesis is insufficient to maintain body temperature.

Physical Activity. Physical activity represents an increasingly larger component of the total energy expenditure (TEE) as the young child grows and develops. In a longitudinal study of 76 developmentally normal infants, PAL (TEE/BEE) increased significantly from 1.2 at 3 months of age to 1.4 at 24 months of age (Butte et al., 2000b).

Total Energy Expenditure (TEE). While application of the doubly labeled water (DLW) method is subject to errors in infants and small children, the method has been validated in term and preterm infants (Jensen et al., 1992; Jones et al., 1987; Roberts et al., 1986; Westerterp et al., 1991). Mean discrepancies between the DLW method and respiration calorimetry were 0.3 ± 2.6 percent (Roberts et al., 1986), –0.9 ± 6.2 percent (Jones et al., 1987), –4.5 ± 6.0 percent (Westerterp et al., 1991), and –0.4 ± 11.5 percent (Jensen et al., 1992).

TEE is influenced by age, gender, and feeding mode (Butte et al., 2000b). In a longitudinal study of children from 3 to 24 months of age, absolute TEE differed by age (older greater than younger), gender (boys greater than girls), and feeding mode (human milk-fed less than formula-fed infants). Adjusted for body weight, TEE still differed by age and feeding mode, but not by gender. Adjusted for fat-free mass (FFM) and fat mass (FM), TEE differed by feeding mode, but not by age or gender (Butte et al., 2000b). TEE has been shown to be lower in breast-fed than formula-fed infants in a number of other studies (Butte et al., 1990; Davies et al., 1990; Jiang et al., 1998).

Growth. Body composition data may be used to compute the energy cost of growth. The energy content of the newly synthesized tissues is theo-

retically more accurate when the separate costs of protein and fat deposition are taken into account since the composition of weight gain varies with age. Much understanding of the energy cost of growth has been derived from preterm infants or children recovering from malnutrition (Butte et al., 1989; Roberts and Young, 1988). Typically, the energy cost of growth in these studies ranges from 2.4 to 6.0 kcal/g (10 to 25 kJ/g). In practicality, the energy cost of growth is an issue only during the first half of infancy when energy deposition contributes significantly to energy requirements.

In this report, the energy content of tissue deposition was computed from rates of protein and fat deposition observed in a longitudinal study of infants from 0.5 to 24 months of age (Butte et al., 2000b). The energy content of tissue deposition (kcal/g) derived from the above study was applied to the 50th percentile of weight gain published by Guo and colleagues (1991) as shown in Table 5-15 for infants and children 0 through 24 months of age. The estimated energy cost of tissue deposition averaged approximately 175 kcal/d for the age interval 0 to 3 months, 60 kcal/d for

TABLE 5-15 Weight Gain and Energy Deposition of Boys and Girls 0 Through 2 Years of Age

Age Interval (mo)	Protein Gain (g/d)[a]	Fat Mass Gain (g/d)[a]	Energy Cost of Tissue Deposition (kcal/g)	Weight Gain (g/d)[b]	Energy Deposition (kcal/d)
Boys					
0–3	2.6	19.6	6.0	31	186
4–6	2.3	3.9	2.8	18	50
7–9	2.3	0.5	1.5	12	18
10–12	1.6	1.7	2.7	10	27
13–15	1.3	1.0	2.2	9	20
16–18	1.3	1.0	2.2	8	17
19–24	1.1	2.1	4.7	7	33
Girls					
0–3	2.2	19.7	6.3	26	163
4–6	1.9	5.8	3.7	17	63
7–9	2.0	0.8	1.8	12	21
10–12	1.8	1.1	2.3	10	23
13–15	1.3	1.4	2.5	9	23
16–18	1.3	1.4	2.5	8	20
19–24	1.0	0.8	2.2	7	15

[a] Body composition (Butte et al., 2000a).
[b] Increments in weight at the 50th percentile (Guo et al., 1991).

4 to 6 months, 22 kcal/d for 7 to 12 months, and 20 kcal for 13 to 35 months.

Estimated Energy Requirements (EER). Total energy requirements of infants and young children have thus been shown to vary by age, gender, and feeding mode. Total energy requirements increase as children grow and are higher in boys than girls. Weight or FFM and FM accounted for the differences in energy requirements between ages and genders. The effect of feeding mode on energy requirements was apparent throughout the first year, primarily due to the higher TEE in formula-fed than human milk-fed infants (Butte et al., 2000b). Energy requirements (kcal/kg/d) were 7, 8, 9, and 3 percent higher in formula-fed than human milk-fed infants at 3, 6, 9, 12 months, respectively. The differences in energy requirements between feeding groups appeared to diminish beyond the first year of life.

Based upon analysis of the DLW data for infants and very young children (Appendix Table I-1), a single equation to predict total energy expenditure involving only weight was found to fit all of the individuals (n = 320 measurements) regardless of gender. Because the data included repeated measurements of individuals, dummy variables were used to link those individual data. While age, height, and weight were all independently correlated with TEE, weight was the best predictor. TEE values, adjusted for weight, were not correlated with age or height. Gender was not a statistically significant predictor of TEE, once body weight was accounted for. Because of the small sample size and limited range of estimated physical activity, the physical activity level (PAL) category was not included in the TEE equation. Examination of the residuals revealed no bias and including the squares of age, height, and weight added nothing to the prediction of TEE. Additionally, the inclusion of mean published data (Butte et al., 1990; Davies et al., 1989, 1991, 1997; de Bruin et al., 1998; Lucas et al., 1987; Stunkard et al., 1999; Wells et al., 1996), weighted for sample size, did not change the predictive equations.

Because of the lack of gender differences, it was decided to use a single equation for individuals 0 through 2 years of age:

$$\text{TEE (kcal/d)} = 89\ (\pm 3\ [\text{standard error}]) \times \text{weight of the child (kg)} - 100\ (\pm 56\ [\text{standard error}])$$

EER Summary, Ages 0 Through 2 Years

Since infants and very young children are growing, an allowance for energy deposition (estimated in Table 5-15) must be added to the TEE to

derive the EER. This energy deposition allowance is the average of energy deposition for boys and girls of similar ages. The EER is equal to the sum of TEE from the equation above plus energy deposition. Specific EERs are given in Tables 5-16 (boys) and 5-17 (girls) and are summarized for each age group below. The estimated energy deposition is the average of boys and girls taken from Table 5-15.

EER for Ages 0 Through 36 Months

EER = TEE + energy deposition

0–3 months	**(89 × weight [kg] – 100) + 175 kcal**
4–6 months	**(89 × weight [kg] – 100) + 56 kcal**
7–12 months	**(89 × weight [kg] – 100) + 22 kcal**
13–36 months	**(89 × weight [kg] – 100) + 20 kcal**

TABLE 5-16 Estimated Energy Requirement (EER) for Boys 0 Through 2 Years of Age

Age (mo)	Reference Weight (kg [lb])[a]	Total Energy Expenditure[b] (TEE) (kcal/d)	Energy Deposition[c] (ED) (kcal/d)	EER (kcal/d) (TEE + ED)
1	4.4 (9.7)	292	180	472
2	5.3 (11.7)	372	195	567
3	6.0 (13.2)	434	138	572
4	6.7 (14.8)	496	52	548
5	7.3 (16.1)	550	46	596
6	7.9 (17.4)	603	42	645
7	8.4 (18.5)	648	20	668
8	8.9 (19.6)	692	18	710
9	9.3 (20.5)	728	18	746
10	9.7 (21.4)	763	30	793
11	10.0 (22.0)	790	27	817
12	10.3 (22.7)	817	27	844
15	11.1 (24.4)	888	20	908
18	11.7 (25.8)	941	20	961
21	12.2 (26.9)	986	20	1,006
24	12.7 (28.0)	1,030	20	1,050
27	13.1 (28.9)	1,066	20	1,086
30	13.5 (29.7)	1,101	20	1,121
33	13.9 (30.6)	1,137	20	1,157
35	14.2 (31.3)	1,164	20	1,184

[a] From Table 5-6.
[b] Estimated from TEE = 89 × weight (kg) – 100 derived from DLW data (Appendix I).
[c] From Table 5-15.

TABLE 5-17 Estimated Energy Requirement (EER) for Girls 0 Through 2 Years of Age

Age (mo)	Reference Weight (kg [lb])[a]	Total Energy Expenditure[b] (TEE) (kcal/d)	Energy Deposition[c] (ED) (kcal/d)	EER (kcal/d) (TEE + ED)
1	4.2 (9.3)	274	164	438
2	4.9 (10.8)	336	164	500
3	5.5 (12.1)	389	132	521
4	6.1 (13.4)	443	65	508
5	6.7 (14.8)	496	57	553
6	7.2 (15.9)	541	52	593
7	7.7 (17.0)	585	23	608
8	8.1 (17.8)	621	22	643
9	8.5 (18.7)	656	22	678
10	8.9 (19.6)	692	25	717
11	9.2 (20.3)	719	23	742
12	9.5 (20.9)	745	23	768
15	10.3 (22.7)	817	20	837
18	11.0 (24.2)	879	20	899
21	11.6 (25.6)	932	20	952
24	12.1 (26.7)	977	20	997
27	12.5 (27.5)	1,013	20	1,033
30	13.0 (28.6)	1,057	20	1,077
33	13.4 (29.5)	1,093	20	1,113
35	13.7 (30.2)	1,119	20	1,139

[a] From Table 5-6.
[b] Estimated from TEE = 89 × weight (kg) − 100 derived from DLW data (Appendix I).
[c] From Table 5-15.

EERs for energy calculated by these equations are slightly lower than those estimated by Prentice and colleagues (1988). Their estimates were 95, 85, 83, and 83 kcal/kg/d at 3, 6, 9, and 12 months, respectively. These estimates of total energy expenditures are approximately 80 percent of the 1985 FAO/WHO/UNU recommendations for energy intake of infants and toddlers (FAO/WHO/UNU, 1985), which were based upon observed energy intakes of infants compiled by Whitehead and colleagues (1981) from the literature predating 1940 and up to 1980.

More recent intake data are 2 to 15 percent lower than those on which the 1985 FAO/WHO/UNU recommendations were based (Davies et al., 1997; Prentice et al., 1988). In addition, an extra 5 percent allowance was factored into the FAO/WHO/UNU recommendations to correct for a presumed underestimation of energy intake (FAO/WHO/UNU, 1985).

Human Milk

Human milk is recognized as the optimal milk source for infants throughout at least the first year of life and is recommended as the sole nutritional milk source for infants through the first 4 to 6 months of life (IOM, 1991). Infants receiving human milk for this period would have an energy intake of some 500 kcal/d based on an average volume of milk intake of 0.78 L/d (Heinig et al., 1993; Neville et al., 1988) and an average caloric density of human milk of 650 kcal/L (Anderson et al., 1983; Butte and Calloway, 1981; Butte et al., 1984a; Dewey et al., 1984; Nommsen et al., 1991) (Table 5-18). The EERs derived in this report are thus more consistent with energy intakes of human milk-fed infants than the recommendations in the 1985 FAO/WHO/UNU report; it should be noted that the EERs based on the equations given *do* exceed the calculated 500 kcal/d from human milk for some infant boys and girls (Tables 5-16 and 5-17), which is in agreement with studies that have shown that infants fed human milk as a sole source of nutrients have lower TEE values than formula-fed infants.

Children Ages 3 Through 8 Years

Evidence Considered in Determining the Estimated Energy Requirement

Basal Metabolism. BMR may be measured by indirect calorimetry or estimated from weight using the Schofield equations (WN Schofield, 1985). Validation of the Schofield equations has been undertaken by comparing predicted values with measured values (Torun et al., 1996) in British 7- to 10-year-old children (Livingstone et al., 1992a) and Dutch 8- to 10-year-old children (Saris et al., 1989). Mean differences between the measured and calculated BMR ranged from 7.6 to 9.9 percent, suggesting that the Schoefield equations are adequate for use in this population.

In this report, predictive equations for basal energy expenditure (BEE) (BMR extrapolated to 24 hours) were derived from observed BEE measured in the children in the DLW database and are described in the earlier section "TEE Equations for Normal-Weight Children."

Thermic Effect of Food. The TEF was studied in prepubertal children for 3 hours after ingestion of a mixed meal in liquid form (Maffeis et al., 1993). In normal-weight children, the rise in energy expenditure was equivalent to 14 percent RMR or to 5.9 percent of the energy ingested.

Physical Activity. Energy needs per unit body weight for maintenance and growth decrease in relation to the increased energy needed for physi-

TABLE 5-18 Human Milk Intake and Composition

Study	Country	*n*	Stage of Lactation	Energy Intake from Milk (As Reported in Study)[a]
Anderson et al., 1981	Canada	10 women	3–5 d 8–11 d 15–18 d 26–29 d	Not reported
Anderson et al., 1983	United States	9 women	3 d 7 d 14 d	Not reported
Butte and Calloway, 1981	United States	23	1 mo	Not reported
Butte et al., 1984a, 1984b	United States	37 infants 40 infants 37 infants 41 infants	1 mo 2 mo 3 mo 4 mo	520 ± 131 kcal/d 468 ± 115 kcal/d 458 ± 124 kcal/d 477 ± 111 kcal/d
Dewey et al., 1984	United States	12 women	7–20 mo	610 kcal/d at 7 mo 735 kcal/d at 11–16 mo
Ferris et al., 1998	United States	12 women	2 wk 6 wk 12 wk 16 wk	Not reported
Lammi-Keefe et al., 1990	United States	6 women	8 wk	Not reported
Nommsen et al., 1991	United States	58 infants 45 infants 28 infants 21 infants	3 mo 6 mo 9 mo 12 mo	Not reported
Heinig et al., 1993	United States	38 F, 33 M 30 F, 26 M 22 F, 24 M 21 F, 19 M	3 mo 6 mo 9 mo 12 mo	535.37 ± 81.26 kcal/d 518.64 ± 114.72 kcal/d 439.77 ± 143.40 kcal/d 303.54 ± 172.08 kcal/d

[a] Mean ± SD, unless otherwise noted.

Energy Content of Milk[a]	Maternal Intake[a]	Comments
50 kcal/dL 60 kcal/dL 60 kcal/dL 60 kcal/dL	Not reported	Full-term infants Milk energy content was approximated from study figure
51 ± 9 kcal/dL 63 ± 9 kcal/dL 67 ± 10 kcal/dL	Not reported	Full-term pregnancies
66 ± 12 kcal/dL	Not reported	Navajo women
0.68 ± 0.08 kcal/g 0.64 ± 0.08 kcal/g 0.62 ± 0.09 kcal/g 0.64 ± 0.10 kcal/g	2,334 ± 536 kcal/d 2,125 ± 582 kcal/d 2,170 ± 629 kcal/d 2,092 ± 498 kcal/d	Healthy term infants, exclusively breast-fed
65 kcal/dL	Not reported	Breast-feeding mothers
78.1 ± 12.5 kcal/dL 75.3 ± 7.7 kcal/dL 79.2 ± 9.3 kcal/dL 82.9 ± 12.2 kcal/dL	2,315 ± 658 kcal/d 2,439 ± 806 kcal/d 2,384 ± 845 kcal/d 2,337 ± 724 kcal/d	Full-term pregnancies, healthy nonsmokers, exclusively breast-feeding Energy content measured by bomb calorimetry
66.5 kcal/dL ± 7.74 (range 51.9–81.2 kcal/dL)	2,531 ± 442 kcal/d	Exclusively breast-feeding Full-term pregnancies
69.7 ± 6.7 kcal/dL 70.7 ± 9.2 kcal/dL 70.9 ± 7.4 kcal/dL 70.6 ± 11.0 kcal/dL	2,340 kcal/d (range: 1,477–3,201 kcal/d)	Healthy, exclusively breast-feeding mothers
66.9 kcal/dL 69.3 kcal/dL 71.7 kcal/dL 71.7 kcal/dL	Not reported	Healthy, full-term, exclusively breast-fed No additional solid foods consumed before 4 mo of age

cal activity in healthy, active children. An index of physical activity, PAL, defined as the ratio of TEE:BEE, reflects differences in lifestyle, geographic habitat, and socioeconomic conditions. Torun and coworkers (1996) reviewed PALs estimated by DLW, heart rate monitoring, and time-motion/activity diary techniques in children. Mean PALs were between 1.4 and 1.5 for children less than 5 years of age and between 1.5 and 1.8 for children 6 to 18 years of age living in urban settings in industrialized countries.

Total Energy Expenditure. TEE has been measured by the DLW method in a number of studies of children. Black and coworkers (1996) compiled DLW studies on 2- to 6-year-old children from around the world. In their analysis of cross sectional data on 196 children they found the mean TEE per kg of body weight was significantly higher in boys ($p < 0.05$) than in girls, but not for BMR or PAL.

Growth. The energy cost of growth for children (Table 5-19) was computed based on rates of weight gain of children enrolled in the FELS Longitudinal Study (Baumgartner et al., 1986) and estimated rates of protein and fat deposition for children (Fomon et al., 1982). It is recognized that the energy content of newly synthesized tissues varies in childhood, particularly during the childhood adiposity rebound (Rolland-Cachera, 2001; Rolland-Cachera et al., 1984), but these variations are assumed to minimally impact total energy requirements of children, as only from 8 to 32 kcal/d are estimated to be required for tissue deposition.

EER Summary, Ages 3 Through 8 Years

Marked variability exists for boys and girls in the EER because of variations in growth rate and physical activity (Zlotkin, 1996). To derive total energy requirements, the DLW data (Appendix Table I-2) were utilized to develop equations to predict TEE based on a child's gender, age, height, weight and PAL category (Appendix Table I-8 gives the constants and standard errors of the predictive equations). The calculated TEE is increased by an average of 20 kcal/d for estimated energy deposition (Table 5-19) to get the EER. EER predictions for children with reference weights for ages 3 through 8 years are given below and values are summarized at yearly intervals for reference-weight children in Tables 5-20 (boys) and 5-21 (girls).

EER for Boys 3 Through 8 years

$$\mathbf{EER = TEE + energy\ deposition}$$

$$\mathbf{EER = 88.5 - (61.9 \times age\ [y]) + PA \times (26.7 \times weight\ [kg] + 903 \times height\ [m]) + 20\ kcal}$$

TABLE 5-19 Weight Gain and Energy Deposition of Boys and Girls 3 Through 18 Years of Age

Age at End of Interval (y)	Weight Gain (kg/6 mo)[a]	Weight Gain (g/d)[a]	Energy Deposition (kcal/g)[b]	Energy Deposition (kcal/d)[b]
Boys				
3.5	1.0	5	1.5	8.1
4.5	1.1	6	1.5	8.7
5.5	1.2	6	1.5	9.5
6.5	1.2	6	1.7	10.8
7.5	1.4	8	2.4	18.2
8.5	1.4	8	2.4	18.8
9.5	1.5	8	2.6	22.0
10.5	1.6	9	2.9	25.6
11.5	1.9	10	3.1	32.6
12.5	2.5	13	1.8	24.1
13.5	3.1	17	1.3	22.1
14.5	3.7	20	1.5	29.3
15.5	2.6	14	1.7	24.3
16.5	1.7	9	1.9	18.0
17.5	1.1	6	2.0	12.2
Girls				
3.5	1.0	5	1.7	9.3
4.5	0.9	5	2.0	10.3
5.5	1.0	5	2.2	11.7
6.5	1.2	7	2.6	17.0
7.5	1.3	7	2.9	21.0
8.5	1.5	8	3.1	25.2
9.5	1.5	8	3.3	27.7
10.5	2.0	11	2.8	30.1
11.5	2.5	14	2.3	31.8
12.5	2.8	15	1.9	28.3
13.5	2.3	13	3.0	37.9
14.5	1.5	8	4.1	33.7
15.5	0.9	5	5.1	25.7
16.5	0.8	4	4.9	20.3
17.5	0.4	2	4.0	8.8

[a] Increments in weight at the 50th percentile (Baumgartner et al., 1986).
[b] Rates of protein and fat deposition (Fomon et al., 1982; Haschke, 1989).

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.13 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.26 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.42 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

TABLE 5-20 Estimated Energy Requirement (EER) for Boys 3 Through 18 Years of Age

Age (y)	Reference Weight (kg [lb])[a]	Reference Height (m [in])	Total Energy Expenditure[b] (TEE) (kcal/d) Sedentary PAL	Low Active PAL	Active PAL	Very Active PAL
3	14.3 (31.5)	0.95 (37.4)	1,142	1,304	1,465	1,663
4	16.2 (35.7)	1.02 (40.2)	1,195	1,370	1,546	1,763
5	18.4 (40.5)	1.09 (42.9)	1,255	1,446	1,638	1,874
6	20.7 (45.6)	1.15 (45.3)	1,308	1,515	1,722	1,977
7	23.1 (50.9)	1.22 (48.0)	1,373	1,597	1,820	2,095
8	25.6 (56.4)	1.28 (50.4)	1,433	1,672	1,911	2,205
9	28.6 (63.0)	1.34 (52.8)	1,505	1,762	2,018	2,334
10	31.9 (70.3)	1.39 (54.7)	1,576	1,850	2,124	2,461
11	35.9 (79.1)	1.44 (56.7)	1,666	1,960	2,254	2,615
12	40.5 (89.2)	1.49 (58.7)	1,773	2,088	2,403	2,792
13	45.6 (100.4)	1.56 (61.4)	1,910	2,251	2,593	3,013
14	51.0 (112.3)	1.64 (64.6)	2,065	2,434	2,804	3,258
15	56.3 (124.0)	1.70 (66.9)	2,198	2,593	2,988	3,474
16	60.9 (134.1)	1.74 (68.5)	2,295	2,711	3,127	3,638
17	64.6 (142.3)	1.75 (68.9)	2,341	2,771	3,201	3,729
18	67.2 (148.0)	1.76 (69.3)	2,358	2,798	3,238	3,779

[a] From Table 5-8.
[b] Based on equations given in Appendix Table I-8. PAL = physical activity level.
[c] EER = TEE + 20 kcal/d – estimate of energy deposition during childhood.

EER for Girls 3 Through 8 Years

EER = TEE + energy deposition

EER = 135.3 – (30.8 × age [y]) + PA × (10.0 × weight [kg] + 934 × height [m]) + 20 kcal

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.16 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.31 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.56 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

EER[c] (kcal/d)			
Sedentary PAL	Low Active PAL	Active PAL	Very Active PAL
1,162	1,324	1,485	1,683
1,215	1,390	1,566	1,783
1,275	1,466	1,658	1,894
1,328	1,535	1,742	1,997
1,393	1,617	1,840	2,115
1,453	1,692	1,931	2,225
1,530	1,787	2,043	2,359
1,601	1,875	2,149	2,486
1,691	1,985	2,279	2,640
1,798	2,113	2,428	2,817
1,935	2,276	2,618	3,038
2,090	2,459	2,829	3,283
2,223	2,618	3,013	3,499
2,320	2,736	3,152	3,663
2,366	2,796	3,226	3,754
2,383	2,823	3,263	3,804

Children Ages 9 Through 18 Years

Evidence Considered in Determining the Estimated Energy Requirement

Energy requirements of adolescents are defined to maintain health, promote optimal growth and maturation, and support a desirable level of physical activity. Growth refers to increases in height and weight and changes in physique, body composition, and organ systems. Maturation refers to the rate and timing of progress toward the mature biological state. Developmental changes occur in the reproductive organs, and lead to the development of secondary gender characteristics and to changes in the cardiorespiratory and muscular systems leading to an increases in strength and endurance. As a result of these changes, energy requirements of adolescents increase. In adolescents, changes in occupational and recreational activities further alter energy requirements.

TABLE 5-21 Estimated Energy Requirement (EER) for Girls 3 Through 18 Years of Age

Age (y)	Reference Weight (kg [lb])[a]	Reference Height (m [in])	Total Energy Expenditure[b] (TEE) (kcal/d)			
			Sedentary PAL[b]	Low Active PAL	Active PAL	Very Active PAL
3	13.9 (30.6)	0.94 (37.0)	1,060	1,223	1,375	1,629
4	15.8 (34.8)	1.01 (39.8)	1,113	1,290	1,455	1,730
5	17.9 (39.4)	1.08 (42.5)	1,169	1,359	1,537	1,834
6	20.2 (44.5)	1.15 (45.3)	1,227	1,431	1,622	1,941
7	22.8 (50.2)	1.21 (47.6)	1,278	1,495	1,699	2,038
8	25.6 (56.4)	1.28 (50.4)	1,340	1,573	1,790	2,153
9	29.0 (63.9)	1.33 (52.4)	1,390	1,635	1,865	2,248
10	32.9 (72.5)	1.38 (54.3)	1,445	1,704	1,947	2,351
11	37.2 (81.9)	1.44 (56.7)	1,513	1,788	2,046	2,475
12	41.6 (91.6)	1.51 (59.4)	1,592	1,884	2,158	2,615
13	45.8 (100.9)	1.57 (61.8)	1,659	1,967	2,256	2,737
14	49.4 (108.8)	1.60 (63.0)	1,693	2,011	2,309	2,806
15	52.0 (114.5)	1.62 (63.8)	1,706	2,032	2,337	2,845
16	53.9 (118.7)	1.63 (64.2)	1,704	2,034	2,343	2,858
17	55.1 (121.4)	1.63 (64.2)	1,685	2,017	2,328	2,846
18	56.2 (123.8)	1.63 (64.2)	1,665	1,999	2,311	2,833

[a] From Table 5-9.
[b] Based on equations given in Appendix Table I-8. PAL = physical activity level.
[c] EER = TEE + 20 kcal/d – estimate of energy deposition during childhood.

Basal Metabolism. The effect of age on basal metabolism is a function of changes in body composition through adolescence. FFM comprises the bulk of the active metabolic tissue, and energy expenditure is strongly correlated with FFM (Webb, 1981). Marked gender differences in intensity and duration of the adolescent growth spurt in FFM dictates higher energy and nutrient needs in boys than girls (Butte, 2000).

The accuracy of the Schofield equations (WN Schofield, 1985) for the prediction of BEE has been evaluated by comparing predicted BEE values with measured BEE values from several studies of adolescents (Torun et al., 1996). Predicted BEE values were within –4.9, and –0.2 percent of measured values in American adolescents (Bandini et al., 1990b) and were within –4.8, –2.9, –7.2, and +16.8 percent of measured values in British adolescents (Livingstone et al., 1992a); however, the sample size was small in some of the age and gender categories.

In a large-scale study of 5- to 16-year-old children, predicted BEE agreed within ± 8 percent of measured values (Firouzbakhsh et al., 1993),

EER[c] (kcal/d)			
Sedentary PAL	Low Active PAL	Active PAL	Very Active PAL
1,080	1,243	1,395	1,649
1,133	1,310	1,475	1,750
1,189	1,379	1,557	1,854
1,247	1,451	1,642	1,961
1,298	1,515	1,719	2,058
1,360	1,593	1,810	2,173
1,415	1,660	1,890	2,273
1,470	1,729	1,972	2,376
1,538	1,813	2,071	2,500
1,617	1,909	2,183	2,640
1,684	1,992	2,281	2,762
1,718	2,036	2,334	2,831
1,731	2,057	2,362	2,870
1,729	2,059	2,368	2,883
1,710	2,042	2,353	2,871
1,690	2,024	2,336	2,858

while in another study, the Schofield equations overestimated the BEE of African-American girls in the United States by 8 percent compared to measured values (Wong et al., 1999). The tendency for the equations to overestimate BEE of some adolescents will require further research to determine if universal equations or specific equations for different ethnic groups are warranted.

In this report, predictive equations for BEE were derived from the observed BEE provided in the DLW database as described in the earlier section "TEE Equations for Normal-Weight Children."

Thermic Effect of Food. No publications describing TEF in this age group were available.

Physical Activity. Physical activity reflects the energy expended in activities beyond basal processes for survival and for the attainment of physical, intellectual, and social well-being. Physical fitness entails muscular,

motor, and cardiorespiratory fitness. Dietary energy recommendations include recommendations for physical activity compatible with health, prevention of obesity, and appropriate social and psychological development.

The assessment of habitual physical activity and its impact on the energy needs of adolescents is difficult because of the wide variability in lifestyles. PALs of 1.60 to 1.73 at 11 to 14 years of age and 1.50 to 1.65 at 15 to 18 years of age were designated as typical for adolescent boys and girls, respectively, in the 1985 FAO/WHO/UNU report. A detailed categorization of adolescent lifestyles was also provided that allowed for individualization of energy requirements (FAO/WHO/UNU, 1985).

Physical activity in adolescents has been estimated by the DLW method, heart rate monitoring, and activity–time allocation studies. Although heart rate monitors, calibrated against indirect calorimetry, can be used to predict TEE of individuals (Treuth et al., 1998a), the DLW method shows closer agreement when validated against calorimetry than heart rate monitoring or activity–time allocation studies. Torun and coworkers (1996) extensively reviewed PALs as estimated by DLW, heart rate monitoring, and activity–time allocation studies conducted in urban and rural areas of industrialized and developing countries. Mean PALs were between 1.45 and 2.05 for children 6 to 18 years of age engaged in light, moderate, or heavy levels of physical activity.

Physical activity is generally viewed as having a favorable influence on the growth and physical fitness of youth, but longitudinal data addressing these relationships are limited. Regular physical activity has no apparent effect on statural growth and biological maturation (i.e., skeletal age, age at peak height velocity, and age at menarche) (Malina, 1994; Geithner et al. 1998; Beunen et al., 1992). Data suggesting later menarche in female athletes are associational and retrospective, and do not control for other factors that influence the age at menarche (e.g., genotype, physique, and dietary practices). Regular physical activity is often associated with decreased body fat in both genders and, sometimes, increased FFM, at least in males (Parizkova, 1974; Sunnegardh et al., 1986; Deheeger et al., 1997). It is also associated with greater skeletal mineralization, bone density, and bone mass (Bailey and McCulloch, 1990). However, excessive training associated with, or causing, sustained weight loss and maintenance of excessively low body weights may contribute to bone loss and increased susceptibility to stress fractures (Dhuper et al., 1990; Warren et al., 1986).

Information is scant on the relationship between children's physical activity and fitness and present and future health status (Malina, 1994; Twisk, 2001). Most evidence is limited to cross-sectional comparisons of active and nonactive children. Active children tend to have lower skinfold thickness than inactive children (Raitakari et al., 1994; Moore et al., 1995). Short-term training does not seem to alter high blood pressure, low HDL

cholesterol, and triacylglycerols in otherwise healthy children (Gilliam and Freedson, 1980; Hunt and White, 1980; Linder et al., 1983; Savage et al., 1986). Exercise training has been shown to slightly reduce the percentage body fat and improve lipoprotein profile in obese children (Gutin et al., 2002; Owens et al., 1999; Sasaki et al., 1987). The tracking of body fatness, blood pressure, and lipoprotein profile appears to be moderate from adolescence into adulthood (Clarke et al., 1978; Webber et al., 1983; Newman et al., 1986).

Total Energy Expenditure. A number of investigators have measured the TEE of adolescents using the DLW method (Davies et al., 1991; Livingstone et al., 1992a; Wong, 1994). While absolute energy expenditure increases with age, energy expenditure per unit body weight decreases across adolescence, primarily due to the decrease in BEE.

Growth. The energy cost of growth comprises the energy deposited in newly accrued tissues and the energy expended for tissue synthesis. It is recognized that the energy deposited in newly synthesized tissues varies in childhood, particularly around the adolescent growth spurt, but these variations minimally impact total energy requirements. Longitudinal data on the body composition of normally growing adolescents are not available. However, Haschke (1989) estimated the typical body composition of male and female adolescents from literature values of total body water, potassium, and calcium. FFM increased dramatically from approximately 28 kg at 10.5 years of age to 61 kg at 18.5 years of age in boys of median height and weight, with peak deposition coinciding with peak rates of height gains. The FFM:height ratio was higher in boys than girls, while FM deposition was greater in girls, increasing from 8 kg at 10.5 years of age to 14 kg at 18.5 years of age. As a percentage of body weight, FM increased during this period from 23.5 to 25 percent in girls, and actually declined in boys from 16 to 13 percent by 18.5 years.

In this report, the energy cost of growth was computed based on rates of weight gain of children enrolled in the FELS Longitudinal Study (Baumgartner et al., 1986) and rates of protein and fat deposition for children (Fomon et al., 1982) and adolescents (Haschke, 1989) (Table 5-19). The energy cost of tissue deposition was approximately 20 kcal/d, increasing to 30 kcal/d at peak growth velocity.

EER Summary, Ages 9 Through 18 Years

EERs for adolescents have been based on estimates of energy expenditure and requirements for growth based on tissue deposition. Energy requirements of adolescents must take into account habitual physical

activity level and lifestyle consistent with the maintenance of health, optimal growth and maturation, and social and economic demands.

Marked variability exists in the energy requirements of adolescents due to varying rates of growth and physical activity levels (Zlotkin, 1996). In adolescents, growth is relatively slow except around the adolescent growth spurt, which varies considerably in timing and magnitude between individuals. Occupational and recreational activities also variably affect energy requirements.

To derive the EER for children, the DLW data (Appendix Table I-2) were utilized to develop equations (Appendix Table I-8) to predict TEE based on a child's gender, age, height, weight, and PAL category and added to 25 kcal/d as an estimate of energy deposition (Table 5-19). The TEE equations allow for four levels of activity as shown in Table 5-12. EERs for children with reference heights and weights (Tables 5-8 and 5-9) for ages 9 through 18 are given below and values are summarized in yearly intervals for children with reference weights in Tables 5-20 (boys) and 5-21 (girls). The equations below are the same as those used for children ages 3 to 8 years, but the additional amount added to cover energy deposition resulting from growth is somewhat larger (25 kcal/d compared with 20 kcal/d).

EER for Boys 9 Through 18 Years

EER = TEE + energy deposition

EER = 88.5 – (61.9 × age [y]) + PA × (26.7 × weight [kg] + 903 × height [m]) + 25 kcal

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.13 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.26 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.42 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

EER for Girls 9 Through 18 Years

EER = TEE + energy deposition

EER = 135.3 – (30.8 × age [y]) + PA × (10.0 × weight [kg] + 934 × height [m]) + 25 kcal

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.16 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.31 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.56 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Adults Ages 19 Years and Older

Evidence Considered in Determining the Estimated Energy Requirement

Weight and Height. In adults, BEE predictions are not generally or significantly improved by considering weight and height, as compared to weight alone (WN Schofield, 1985). In the present approach for evaluating TEE in adults with body weights in the desirable range, however, height becomes a significant factor because desirable body weights (i.e., those corresponding to BMIs in the range from 18.5 up to 25 kg/m^2) depend on an individual's height. The impact of height and weight on TEE are shown quantitatively in Figures 5-7 and 5-8.

Age. Age comes out as a significant parameter in the multiple regression analysis performed on the DLW database for subjects with BMIs from 18.5 up to 25 kg/m^2 (Appendix Table I-3). The age-related decline in TEE was found to amount to approximately 10 and 7 kcal/y for adult men and women, respectively.

Physical Activity. The physical activities carried out by free-living individuals vary greatly in intensity as well as duration, and assessment of physical activity-induced increments in TEE in individuals is fraught with considerable uncertainties. For this reason, individuals in the DLW database are classified as sedentary, low active, active, or very active (Table 5-12). Currently available reliable data on PAL can be obtained only by the DLW technique. The 407 individuals studied in this manner have been included in the DLW database shown in Appendix Table I-3. Other techniques involving heart rate monitors and accelerometers have also been used to estimate TEE, but their accuracy depends on careful individual calibration of these instruments for each subject studied.

In spite of concerns about obtaining accurate estimates, it is important to be able to evaluate PAL and TEE in individuals for whom such data are not available or for whom these approaches are not practical. One way to do this is to evaluate physical efforts by estimating how many miles an individual would have to walk in one day to induce a comparable level of exertion (in terms of kcal expended). For example, individuals who have 30 minutes of moderately intense activity (equivalent to walking 2 miles in 30 minutes or an equivalent amount of physical exertion in addition to the activities involved in maintaining a sedentary lifestyle) have a PAL of about 1.5 (see Table 12-2), and they are classified as "low active" in this report. To raise a PAL from 1.5 to 1.75, in addition to activity equivalent to

walking 2 miles in 30 minutes, each day one would to need increase activity to the equivalent of walking an additional 1 hour at 4.5 mph (an equivalent activity would be to bicycle for 1 hour at 10 to 12 mph, use a stair-treadmill for 1 hour, or run for 30 minutes at 6 mph while maintaining the habitual daily routine of other activities).

The change in PAL induced by various types of physical activities can be estimated with the help of Table 12-1, which contains a list of the physical activities typically performed and the impact on PAL when they are performed for 10 minutes or 1 hour. Unlike food intake, which is generally underreported, physical activities tend to be overestimated, and activities of one kind may cause a reduction in activities of another. Thus, subjective determination of PAL has errors similar to using dietary intake to obtain EERs.

Body Weight and PAL. PAL describes the ratio of TEE divided by BEE extrapolated to one day. Whereas the energy cost of weight-bearing physical activities is approximately proportional to body weight, BEE is not proportional to body weight, as the contribution of FFM to basal metabolism is much greater than FM (resulting in a substantial intercept in the equations relating BEE to body weight). The relationship between miles walked per day (or between other weight bearing activities) and PAL is thus not linear, and it will take fewer miles at a given walking speed to raise PAL in a heavy compared to a light-weight individual (see Table 5-12).

EER Summary, Ages 19 Years and Older

Separate TEE predictive equations for EER were developed for adult men and women from age, height, weight, and PAL category, which were determined using the observed BEE for individuals in the DLW database (Appendix Table I-3). Individual data were not used in the derivation of the TEE equations if the PAL value was less than 1.0 or greater than 2.5.

Plots of the residuals showed no evidence of nonlinear patterns of bias (although there was a general increased magnitude of residuals with increasing values of each variable). The additional predictive value of BMI and the squares of age, height, and weight were explored for the linear predictions and none of these significantly reduced the standard error of the fit. The coefficients and standard error for the prediction of TEE of adults, ages 19 years and older, are described in Appendix Table I-9 and are summarized below. EERs for 30-year-old adult women and men of various heights with BMIs from 18.5 up to 25 kg/m^2 are shown in Table 5-22.

EER for Men Ages 19 Years and Older

$$\mathbf{EER = 662 - (9.53 \times age\ [y]) + PA \times (15.91 \times weight\ [kg] + 539.6 \times height\ [m])}$$

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.11 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.25 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.48 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

EER for Women Ages 19 Years and Older

$$\mathbf{EER = 354 - (6.91 \times age\ [y]) + PA \times (9.36 \times weight\ [kg] + 726 \times height\ [m])}$$

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.12 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.27 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.45 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Pregnancy

Evidence Considered to Determine the Estimated Energy Requirement

Basal Metabolism. Basal metabolism increases during pregnancy due to the metabolic contribution of the uterus and fetus and increased work of the heart and lungs. The increase in basal metabolism is one of the major components of the increased energy requirements during pregnancy (Hytten, 1991a). Variation in energy expenditure between individuals is largely due to differences in FFM, which in pregnancy is comprised of low energy-requiring expanded blood volume, high energy-requiring fetal and uterine tissues, and moderate energy-requiring skeletal muscle mass (Hytten, 1991a). In late pregnancy, approximately one-half the increment in energy expenditure can be attributed to the fetus (Hytten, 1991a). The fetus uses about 8 ml O_2/kg body weight/min or 56 kcal/kg body weight/d; for a 3-kg fetus, this would be equivalent to 168 kcal/d (Sparks et al., 1980). FM, a low energy-requiring tissue, contributes to the variation in energy expenditure, but to a much lesser extent than FFM, which has been found to be the strongest predictor of BEE (Butte et al., 1999).

The basal metabolism of pregnant women has been estimated longitudinally in a number of studies using a Douglas bag, ventilated hood, or whole-body respiration calorimeter (Durnin et al., 1987; Forsum et al.,

TABLE 5-22 Estimated Energy Requirements (EER) for Men and Women 30 Years of Age[a]

Height (m [in])	PAL[b]	Weight for BMI of 18.5 kg/m^2 (kg [lb])	Weight for BMI of 24.99 kg/m^2 (kg [lb])
1.45 (57)	Sedentary	38.9 (86)	52.5 (116)
	Low active		
	Active		
	Very active		
1.50 (59)	Sedentary	41.6 (92)	56.2 (124)
	Low active		
	Active		
	Very active		
1.55 (61)	Sedentary	44.4 (98)	60.0 (132)
	Low active		
	Active		
	Very active		
1.60 (63)	Sedentary	47.4 (104)	64.0 (141)
	Low active		
	Active		
	Very active		
1.65 (65)	Sedentary	50.4 (111)	68.0 (150)
	Low active		
	Active		
	Very active		
1.70 (67)	Sedentary	53.5 (118)	72.2 (159)
	Low active		
	Active		
	Very active		
1.75 (69)	Sedentary	56.7 (125)	76.5 (168)
	Low active		
	Active		
	Very active		
1.80 (71)	Sedentary	59.9 (132)	81.0 (178)
	Low active		
	Active		
	Very active		
1.85 (73)	Sedentary	63.3 (139)	85.5 (188)
	Low active		
	Active		
	Very active		

EER, Men (kcal/d)[c]		EER, Women (kcal/d)[d]	
BMI of 18.5 kg/m^2	BMI of 24.99 kg/m^2	BMI of 18.5 kg/m^2	BMI of 24.99 kg/m^2
1,777	1,994	1,563	1,691
1,931	2,172	1,733	1,877
2,128	2,399	1,946	2,108
2,450	2,771	2,201	2,386
1,848	2,080	1,625	1,762
2,010	2,268	1,803	1,956
2,216	2,506	2,025	2,198
2,554	2,898	2,291	2,489
1,919	2,168	1,688	1,834
2,089	2,365	1,873	2,036
2,305	2,616	2,104	2,290
2,661	3,028	2,382	2,593
1,993	2,257	1,752	1,907
2,171	2,464	1,944	2,118
2,397	2,728	2,185	2,383
2,769	3,160	2,474	2,699
2,068	2,349	1,816	1,981
2,254	2,566	2,016	2,202
2,490	2,842	2,267	2,477
2,880	3,296	2,567	2,807
2,144	2,442	1,881	2,057
2,339	2,670	2,090	2,286
2,586	2,959	2,350	2,573
2,993	3,434	2,662	2,916
2,222	2,538	1,948	2,134
2,425	2,776	2,164	2,372
2,683	3,078	2,434	2,670
3,108	3,576	2,758	3,028
2,301	2,636	2,015	2,211
2,513	2,884	2,239	2,459
2,782	3,200	2,519	2,769
3,225	3,720	2,855	3,140
2,382	2,735	2,082	2,290
2,602	2,995	2,315	2,548
2,883	3,325	2,605	2,869
3,344	3,867	2,954	3,255

continued

TABLE 5-22 Continued

Height (m [in])	PAL[b]	Weight for BMI of 18.5 kg/m^2 (kg [lb])	Weight for BMI of 24.99 kg/m^2 (kg [lb])
1.90 (75)	Sedentary	66.8 (147)	90.2 (198)
	Low active		
	Active		
	Very active		
1.95 (77)	Sedentary	70.3 (155)	95.0 (209)
	Low active		
	Active		
	Very active		

[a] For each year below 30, add 7 kcal/d for women and 10 kcal/d for men. For each year above 30, subtract 7 kcal/d for women and 10 kcal/d for men.
[b] PAL = physical activity level.
[c] EER for men calculated as: EER = 662 – (9.53 × age [y]) + PA × (15.91 × weight [kg] + 539.6 × height [m]), where PA is the physical activity coefficient of 1.00 for sedentary

1988; Goldberg et al., 1993; van Raaij et al., 1990). Cumulative changes in BEE throughout pregnancy ranged from 29,636 to 50,300 kcal or 106 to 180 kcal/d (Table 5-23). Marked variation in the basal metabolic response to pregnancy was seen in 12 British women measured before and throughout pregnancy (Goldberg et al., 1993; Prentice et al., 1989). By 36 weeks of gestation, the increment in absolute BEE ranged from 8.6 to 35.4 percent, or –9.2 to 18.6 percent/kg FFM. Energy-sparing or energy-profligate responses to pregnancy were dependent on prepregnancy body fatness. In 12 Dutch women, the late-pregnancy increment in absolute TEE varied from 9.5 to 26 percent (de Groot et al., 1994). Mean increments in BEE over prepregnancy values were 48, 96, and 263 kcal/d, or 4, 7, and 19 percent in the first, second, and third trimesters in healthy women with positive pregnancy outcomes (Prentice et al., 1996b). The cumulative increase in BEE was positively correlated with weight gain and body fatness.

Prediction equations for the BEE of pregnant women have not been published. Nonpregnant prediction equations based on weight are not accurate during pregnancy since metabolic rate increases disproportionately to the increase in total body weight. Prentice and colleagues (1996b) suggested that BEE could be predicted from weight using the Schofield equations, plus an additional 48, 96, and 263 kcal/d during the first, second, and third trimesters.

EER, Men (kcal/d)[c]		EER, Women (kcal/d)[d]	
BMI of 18.5 kg/m^2	BMI of 24.99 kg/m^2	BMI of 18.5 kg/m^2	BMI of 24.99 kg/m^2
2,464	2,837	2,151	2,371
2,694	3,107	2,392	2,637
2,986	3,452	2,692	2,971
3,466	4,018	3,053	3,371
2,548	2,940	2,221	2,452
2,786	3,222	2,470	2,728
3,090	3,581	2,781	3,074
3,590	4,171	3,154	3,489

PAL (≥ 1.0 < 1.4), 1.11 for low active PAL (≥ 1.4 < 1.6), 1.25 for active PAL (≥ 1.6 < 1.9), and 1.48 for very active PAL (≥ 1.9 < 2.5).

[d] EER for women calculated as: EER = 354 – (6.91 × age [y]) + PA × (9.36 × weight [kg] + 726 × height [m]), where PA is the physical activity coefficient of 1.00 for sedentary PAL, 1.12 for low active PAL, 1.27 for active PAL, and 1.45 for very active PAL.

In late gestation, the anti-insulinogenic and lipolytic effects of human chorionic somatomammotropin, prolactin, cortisol, and glucagon contribute to glucose intolerance, insulin resistance, decreased hepatic glycogen, and mobilization of adipose tissue (Kalkhoff et al., 1978). Although levels of serum prolactin, cortisol, glucagon, and fatty acids were elevated and serum glucose levels were lower in one study, a greater utilization of fatty acids was not observed during late pregnancy (Butte et al., 1999). On the contrary, higher mean respiratory quotients (RQs) were observed for BEE and TEE compared with the postpartum period. Higher basal RQs have been observed in pregnancy by several (Bronstein et al., 1995; Denne et al., 1991; Knuttgen and Emerson, 1974; van Raaij et al., 1989), but not all (Spaaij et al., 1994b) investigators. These observations are consistent with persistent glucose production in fasted pregnant women, despite lower fasting plasma glucose concentrations. After fasting, the total rates of glucose production and total gluconeogenesis were increased, even though the fraction of glucose oxidized and the fractional contribution of gluconeogenesis to glucose production remained unchanged (Assel et al., 1993; Kalhan et al., 1997). In pregnant women, the sustained energy expenditure and higher RQ may reflect the obligatory oxygen consumption of the fetus and the contribution of glucose as the primary oxidative substrate of the fetus. In late gestation, the fetus is estimated to use 17 to 26 g/d of

TABLE 5-23 Cumulative Changes in Basal Energy Expenditure (BEE) Throughout Pregnancy

Reference	*n*	Pregravid Weight (kg [lb])	Gestation Interval
Durnin et al., 1987	88	57.3±7.5 (126.1±16.5)	Prepregnancy to 40 wk
van Raaij et al., 1987	57	62.5±8.1 (137.5±17.8)	3 wk to term
Forsum et al., 1988	22	61.0± 9.9 (134.2±21.8)	Prepregnancy to 40 wk
Goldberg et al., 1993	12	61.7±8.8 (135.7±19.3)	Prepregnancy to 40 wk
Kopp-Hoolihan et al., 1999	10	NA	Prepregnancy to 35 wk

[a] The Douglas bag technique of indirect calorimetry was used to estimate BEE.

glucose (Hay, 1994), well within the increment of carbohydrate oxidation observed in pregnancy.

Thermic Effect of Food. In studies of pregnant women, TEF has been shown to be unchanged (Bronstein et al., 1995; Nagy and King, 1984; Spaaij et al., 1994b) or lower (Schutz et al., 1988) than values of nonpregnant women.

Physical Activity. Until late gestation, the gross energy cost of standardized nonweight-bearing activity does not significantly change. In the last month of pregnancy, the energy expended while cycling was increased on the order of 10 percent. However, when corrected for increased BMR the increased energy expenditure due to the activity of cycling was 6 percent (Prentice et al., 1996b). The energy cost of standardized weight-bearing activities such as treadmill walking was unchanged until 25 weeks of gestation, after which it increased by 19 percent (Prentice et al., 1996b). Standardized protocols, however, do not allow for behavioral changes in pace and intensity of physical activity, which may occur and conserve energy during pregnancy.

Growth of Maternal and Fetal Tissues. Gestational weight gain includes the products of conception (fetus, placenta, and amniotic fluid) and accretion of maternal tissues (uterus, breasts, blood, extracellular fluid, and adipose). The energy cost of deposition can be calculated from the amount of protein and fat deposited. Hytten (1991b) made theoretical

Cumulative Increase in BEE (kcal)	Cumulative Increase in BEE (kcal/d)	Method Used to Estimate BEE
30,114	108	Indirect calorimetry[a]
34,416	133	Indirect calorimetry[a]
50,300	180	DLW
29,636	106	DLW
36,089	147	DLW

calculations based on a weight gain of 12.5 kg and birth weight of 3.4 kg. The energy equivalents for protein and fat deposition were assumed to be 5.6 kcal/g and 9.5 kcal/g, respectively. The energy cost of tissue deposition was equivalent to 3.32 kcal/g gained (Table 5-24).

Current recommendations for weight gain during pregnancy are specified for a woman's prepregnancy BMI (IOM, 1990). Total weight gain during pregnancy varies widely among women. For normal-weight women, the mean rate of weight gain is 1.6 kg in the first trimester and 0.44 kg/wk in the second and third trimesters (IOM, 1990). For underweight women, the mean rate of weight gain is 2.3 kg in the first trimester and 0.49 kg/wk in the second and third trimesters. For overweight women, the mean rate of weight gain is 0.9 kg in the first trimester and 0.30 kg/wk in the second and third trimesters.

Fat gains associated with gestational weight gains within the IOM recommended ranges were measured in 200 women with varying prepregnancy BMIs using a four-component body composition model (Lederman et al., 1997). The total energy deposition between 14 and 37+ weeks of gestation was calculated based on an assumed protein deposition of 925 g of protein, and energy equivalences of 5.65 kcal/g of protein and 9.25 kcal/g of fat (Table 5-25).

Empirical data on the longitudinal changes in the body composition of well-nourished, normal weight (prepregnancy BMI from 18.5 up to 25 kg/m^2) pregnant women were used to estimate the energy deposition during pregnancy. Studies in which a prepregnancy baseline or first trimester value was available and methodology was appropriately corrected

TABLE 5-24 Theoretical Energy Cost of Tissue Deposition During Pregnancy

	Protein Gain (g)	Fat Gain (g)	Protein Gain (kcal)	Fat Gain (kcal)	Total Energy Deposition[a] (kcal)
Fetus	440	440	2,464	4,180	6,644
Placenta	100	4	560	38	598
Amniotic fluid	3	0	17	0	17
Uterus	166	4	930	38	968
Breasts	81	12	454	114	568
Blood	135	20	756	190	946
Maternal stores		3,345		31,778	31,778
Total	925	3,825	5,180	36,338	41,518

[a] Based on 5.6 kcal/g for protein gained and 9.5 kcal/g for fat gained.
SOURCE: Adapted from Hytten (1991b).

TABLE 5-25 Estimated Energy Deposition During Pregnancy

Prepregnancy Body Mass Index (BMI) (kg/m^2)	Recommended Gestational Weight Gain[a] (GWG) (kg [lb])	Actual GWG (kg [lb])	Fat Gain (kg)	Estimated Energy Deposition[b] (kcal)
Low (BMI < 19.8)	12.5–18.0 (28–40)	12.6±2.4 (28±5.3)	6.0±2.6	60,726
Normal (BMI = 19.8–26.0)	11.5–16.0 (25–35)	12.1±3.4 (27±7.5)	3.8±3.5	40,376
High (BMI > 26.0–29.0)	7.0–11.5 (15–25)	9.1±3.1 (20±6.8)	2.8±4.1	31,126
Obese (BMI > 29.0)	At least 6.8 (15)[c]	6.9±4.4 (15±9.7)	–0.6±4.6	–324

[a] As recommended by IOM (1990).
[b] Calculated based on assumed 5.65 kcal/g of protein gained and 9.25 kcal/g of fat gained.
[c] Lederman et al. (1997), used 7–9.2 kg (15–20 lb).
SOURCE: Adapted from Lederman et al. (1997).

for pregnancy-induced changes in the hydration or density of FFM were used (Table 5-26). Total energy deposition during pregnancy was estimated from the mean fat gain of 3.7 kg from these studies, plus an assumed deposition of 925 g of protein, applying energy equivalencies of 5.65 kcal/g of protein and 9.25 kcal/g of fat. Mean total energy deposition was equal to 39,862 kcal or 180 kcal/d (Table 5-26).

Total Energy Expenditure. The DLW method has been employed in four studies of well-nourished, pregnant women to measure free-living TEE (Forsum et al., 1992; Goldberg et al., 1991b, 1993; Kopp-Hoolihan et al., 1999) (Table 5-27). There appeared to be a steady decrease in PAL as pregnancy advanced, primarily due to the increase in the denominator, BEE. In the British (Goldberg et al., 1993) and Swedish women (Forsum et al., 1992) studied, the energy expenditure for activity (TEE – BEE) decreased in the 36th week of gestation; this decrease was not observed in the American women (Kopp-Hoolihan et al., 1999).

EER Summary, Pregnancy

The DLW database on pregnant women with prepregnancy BMIs from 18.5 up to 25 kg/m^2 (Appendix Table I-4) consists of longitudinal measurements of TEE throughout pregnancy, and in most cases includes a TEE measurement prior to pregnancy. Therefore, the average TEE change/gestational week was computed for each woman, and the median value of these data were assumed to represent the general trend. The median change in TEE was 8 kcal per week of gestation with a range of –57 to 107 kcal/wk. There was great variability in the average TEE change/week between women and studies; however, few predictive factors were identified. The change in TEE was not related to maternal age, prepregnancy weight, prepregnancy BMI, or weight gain or loss during pregnancy. The change in TEE, however, is negatively correlated to the baseline PAL.

The EER for energy during pregnancy is derived from the sum of the TEE of the woman in the nonpregnant state plus a median change in TEE of 8 kcal/wk plus the energy deposition during pregnancy of 180 kcal/d (Table 5-26). Since TEE changes little and weight gain is minor during the first trimester, no increase in energy intake during the first trimester is recommended.

EER for Pregnancy

14–18 years

$$\mathbf{EER_{pregnant} = \text{adolescent } EER_{nonpregnant} + \text{additional energy expended during pregnancy} + \text{energy deposition}}$$

1st trimester = adolescent EER + 0 + 0

2nd trimester = adolescent EER + 160 kcal (8 kcal/wk × 20 wk) + 180 kcal

3rd trimester = adolescent EER + 272 kcal (8 kcal/wk × 24 wk) + 180 kcal

TABLE 5-26 Energy Deposition During Pregnancy

Reference	*n*	Gestation Interval (wk)	Observed Gestational Weight Gain (kg [lb])	Body Composition Method[a]
Pipe et al., 1979	27	12–37	10.40 (23)	TBW TBK
Forsum et al., 1988	22	0–36	13.60 (30)	TBW TBK
van Raaij et al., 1988	42	11–35	9.15 (20) 11.60 (26)	UWW
Goldberg et al., 1993	12	0–36	11.91 (26)	TBW
de Groot et al., 1994	12	0–34	11.70 (26)	UWW
Lederman et al., 1997	46	14–37	12.10 (27)	TBW UWW BMC
Lindsay et al., 1997	27	0–33/36	12.61 (28)	UWW
Sohlstrom and Forsum, 1997	16	0–5/10 d postpartum	15.80 (35)	MRI
Kopp-Hoolihan et al., 1999	10	0–34	11.60 (26)	TBW UWW BMC
Mean				

[a] TBW = total body water, TBK = total body potassium, UWW = underwater weighing, BMC = bone mineral content, MRI = magnetic resonance imaging.

19–50 years

$$\mathbf{EER_{pregnant} = EER_{nonpregnant} + \text{additional energy expended during pregnancy} + \text{energy deposition}}$$

1st trimester = adult EER + 0 + 0

2nd trimester = adult EER + 160 kcal (8 kcal/wk × 20 wk) + 180 kcal

3rd trimester = adult EER + 272 kcal (8 kcal/wk × 34 wk) + 180 kcal

Theoretical Protein Gain[b] (kg)	Measured Fat Gain (kg)	Energy Deposition (kcal)	Energy Deposition[c] (kcal/d)	Energy Deposition (kcal/g)
0.925	2.40	27,426	157	2.64
0.925	5.8	58,876	234	4.33
0.925	1.9	22,801	136	2.49
0.925	2.8	31,126	124	2.61
0.925	3.4	36,676	154	3.13
0.925	3.8	40,376	251	3.34
0.925	5.9	59,801	247	4.74
0.925	3.6	38,526	138	2.44
0.925	4.5	43,151	176	3.85
	3.7	38,862	180	

[b] From Hytten (1991b) (see Table 5-24).
[c] Based on 5.65 kcak/g of protein gained and 9.25 kcal/g of fat gained.

Lactation

Evidence Considered in Determining the Estimated Energy Requirement

Basal Metabolism. Increased RMRs and SMRs have been observed in lactating women on the order of 4 to 5 percent (Butte et al., 1999; Forsum et al., 1992; Sadurskis et al., 1988; Spaaij et al., 1994a). The increased energy expenditure is consistent with the additional energy cost of milk synthesis. Others have reported lower (Guillermo-Tuazon et al., 1992) or

TABLE 5-27 Doubly Labeled Water Pregnancy Studies

Reference	*n*	Gestation Week	Pregravid Weight (kg)	Gestational Weight Gain (kg)
Goldberg et al., 1991b	10	36	—	—
Forsum et al., 1992	22	0	60.8	13.5
	22	16–18		
	22	30		
	19	36		
Goldberg et al., 1993	12	0	61.7	11.91
		6		
		12		
		18		
		24		
		30		
		36		
Kopp-Hoolihan et al., 1999	10	0	—	11.6
		8–10		
		24–26		
		34–36		

[a] Physical activity level = total energy expenditure/basal energy expenditure.

similar BEE or RMR in lactating women compared to the nonlactating state (Frigerio et al., 1991; Goldberg et al., 1991b; Illingworth et al., 1986; Motil et al., 1990; Piers et al., 1995b; van Raaij et al., 1991). Interpretation of these studies is difficult because BEE or RMR was not always adjusted for differences in body weight or body composition between comparison groups. In general, it would appear that BEE or RMR is unchanged or slightly elevated during lactation; there is little evidence of energy conservation.

Higher RQs and rates of carbohydrate utilization have been reported in lactating compared with nonlactating women, consistent with the preferential use of glucose by the mammary gland (Butte et al., 1999). Conflicting results of lower fasting RQ (0.82 versus 0.85) (Spaaij et al., 1994a), as well as no significant differences in RQ during lactation, have been reported (Frigerio et al., 1991; Piers et al., 1995b; van Raaij et al., 1991).

Thermic Effect of Food. TEF was reported to be 30 percent lower during than after lactation in one study (Illingworth et al., 1986), but unchanged

Total Energy Expenditure (kcal/d)	Physical Activity Level[a]	Activity Energy Expenditure (kcal/d)
2,470	1.42	731
2,484	1.87	1,147
2,293	1.65	860
2,986	1.82	1,338
2,914	1.66	1,171
2,274	1.58	835
2,322	1.54	818
2,426	1.64	939
2,456	1.65	964
2,621	1.66	1,042
2,675	1.62	1,026
2,688	1.50	885
2,205	1.68	892
2,047	1.57	743
2,410	1.56	867
2,728	1.61	1,038

in another (Spaaij et al., 1994a). Although results are conflicting, it is unlikely that TEF contributes significantly to the energetic economy of lactating women.

Physical Activity. Theoretically, the energy cost of lactation could be met by a reduction in the time spent in physical activity or an increase in the efficiency of performing routine tasks. The energetic cost of nonweight-bearing and weight-bearing activities has been measured in lactating women (Spaaij et al., 1994a; van Raaij et al., 1990). Adaptations in the level of physical activity are not always seen in lactating women. Reductions in physical activity have been reported in early lactation (4 to 5 weeks postpartum) in the Netherlands (van Raaij et al., 1991), the United States (Butte et al., 2001), and Great Britain (Goldberg et al., 1991b). Physical activity increased in the lactating Dutch women from 5 to 27 weeks postpartum (van Raaij et al., 1991). By 3 months postpartum, the American women (Butte et al., 2001) had resumed their prepregnancy occupational and recreational lifestyles in addition to their child-rearing responsibilities

TABLE 5-28 Doubly Labeled Water Lactation Studies

Reference	*n*	Stage of Lactation (mo)	Total Energy Expenditure (kcal/d)	Total Energy Expenditure (kcal/kg/d)	Basal Estimation (kcal/d)
Goldberg et al., 1991b	10	1	2,109	35.8	1,406
		2	2,171	36.9	1,397
		3	2,138	36.5	1,345
Forsum et al., 1992	23	2	2,532	39.3	1,409
		6	2,580	41.0	1,433
Lovelady et al., 1993	9[e]	3–6	2,413	37.2	1,376
Kopp-Hoolihan et al., 1999	10	1	2,146	—	1,328
Butte et al., 2001[f]	24	3	2,391	38.1	1,331

[a] Unless otherwise noted AEE includes TEF.
[b] Estimated to be 0.67 kcal/g (Butte et al., 1984a, 1984b; Neville, 1995).
[c] Observed change in body composition during lactation.

and their physical activity had returned to prepregnancy levels. While a decrease in moderate and discretionary activities appears to occur in most lactating women in the early postpartum period, activity patterns beyond this period are highly variable.

Total Energy Expenditure. TEEs of lactating women have been measured by the DLW method in five studies (Butte et al., 2001; Forsum et al., 1992; Goldberg et al., 1991b; Kopp-Hoolihan et al., 1999; Lovelady et al., 1993) as shown in Table 5-28. There are several potential sources of error in using the DLW method in lactation studies. These sources of error may be attributed to isotope exchange and sequestration that occurs during the de novo synthesis of milk fat and lactose, and to increased water flux into milk (Butte et al., 2001). Underestimation of carbon dioxide by 1.0 to 1.3 percent may theoretically occur due to the export of exchangeable hydrogen bound to solids in milk (IDECG, 1990). This underestimation may increase to 1.5 to 3.4 percent due to ^{2}H sequestration.

As shown in Table 5-28, mean TEE values of 2,391 kcal/d (PAL = 1.79) (Butte et al., 2001) and 2,413 kcal/d (PAL = 1.76) (Lovelady et al., 1993) in American women were higher than average values reported for British women (2,139 kcal/d; PAL = 1.55) (Goldberg et al., 1991b), and lower than average values in Swedish women (2,556 kcal/d, PAL = 1.80) (Forsum et al., 1992) during lactation. The energy expended in activity (TEE –

Activity Energy Expenditure[a] (kcal/d)	Physical Activity Level	Milk Energy Output[b] (kcal/d)	Energy Mobilization[c] (kcal/d)	Energy Requirement[d] (kcal/d)
703	1.50	536	Gained fat	2,645
774	1.55	532	mass	2,703
793	1.59	530		2,668
1,123	1.82	502	72	2,962
1,123	1.79			
1,037	1.75	538	287	2,664
816	1.62	—	—	—
1,061	1.79	483	155	2,719

[d] Energy requirement = measured TEE_{DLW} + energy of milk output – energy mobilized from tissues.
[e] All subjects breast-fed, except one.
[f] TEF only for Butte et al. (2001). TEF was 239.

BEE) ranged from 700 to 1,100 kcal/d in American, British, and Swedish lactating women.

Milk Energy Output. Milk energy output is computed from milk production and the energy density of human milk. Milk production rates increase during the first 6 months of full lactation. Beyond 6 months postpartum, typical milk production rates are variable and depend on weaning practices. Mean milk production rates of American women were 0.78 L/d in term infants from birth through 6 months of age (Allen et al., 1991; Heinig et al., 1993), and 0.6 L/d in term infants from 7 through 12 months of age (Dewey et al., 1984).

The energy density of human milk has been measured by bomb calorimetry or proximate macronutrient analysis of representative 24-hour pooled milk samples. The mean energy density of human milk ranged from 0.64 to 0.74 kcal/g (Butte et al., 1984a, 1984b; Neville, 1995). The value of 0.67 kcal/g is used in this report.

Energy Mobilization. The changes in weight and therefore energy mobilization from tissues occur in some, but not all, lactating women (Butte and Hopkinson, 1998; Butte et al., 2001; IOM, 1991). In general, during the first 6 months postpartum, well-nourished lactating women experience a mild, gradual weight loss, averaging –0.8 kg/mo (Butte et al.,

2001). In some women, the energy costs of lactation may be met by an increase in energy intake or a decrease in physical activity, with no change or even an increase in weight or FM.

After monitoring FM in 23 Swedish women, Sadurskis and colleagues (1988) found that FM decreased from 34.3 to 32.4 percent from 2 to 6 months postpartum by ^{18}O dilution and total body potassium counting. Consistent with a minor weight loss and sedentary lifestyle, British women ($n = 10$) displayed a nonsignificant increase in percent of FM (30.3 to 31.4 percent between 1 to 3 months postpartum) estimated by ^{2}H and ^{18}O dilution (Goldberg et al., 1991b). In American women, FM decreased from 28.0 percent at 1 month to 26.3 percent at 4 months postpartum, measured by underwater weighing (Butte et al., 1984b). Changes in adipose tissue volume in 15 Swedish women were measured by magnetic resonance imaging (Sohlstrom and Forsum, 1995). In the first 6 months postpartum, the subcutaneous region accounted for the entire reduction in adipose tissue volume, which decreased from 23.2 L to 20.0 L; nonsubcutaneous adipose tissue volume actually increased. Mobilization of tissue reserves is a general, but not obligatory, feature of lactation.

Total Energy Requirements. The energy requirements of lactating women were estimated from measurements of TEE, milk energy output, and energy mobilization from tissue stores in the following studies in which DLW was used (Butte et al., 2001; Forsum et al., 1992; Goldberg et al., 1991b; Lovelady et al., 1993) (Table 5-28). In the 10 lactating British women, the total energy requirements (and net energy requirements, since there was no fat mobilization) were 2,646, 2,702, and 2,667 kcal/d (11.1, 11.3, and 11.2 MJ/d) at 1, 2, and 3 months postpartum, respectively. Milk energy output averaged 533 kcal/d (2.2 MJ/d) (Goldberg et al., 1991b). In 23 lactating Swedish women, the total energy requirement at 2 months postpartum was 3,034 kcal/d (12.7 MJ/d), offset by 72 kcal/d (0.3 MJ/d) from tissue stores to yield a net requirement of 2,962 kcal/d (12.4 MJ/d) (Forsum et al., 1992). In nine lactating American women, the total energy requirement was 2,413 kcal/d (10.1 MJ/d), with 538 kcal/d (2.3 MJ/d) exported into milk and 287 kcal/d (1.2 MJ/d) mobilized from tissues, yielding a net requirement of 2,663 kcal/d (11.1 MJ/d) (Lovelady et al., 1993). Data from other lactating American women (Butte et al., 2001) give similar results. The women in the above studies were fully breastfeeding their infants, who were less than 6 months of age. In these studies, mean milk energy outputs during full lactation were similar (483 to 538 kcal/d or 2.0 to 2.3 MJ/d). The energetic inefficiency of milk synthesis is encompassed in the measurement of TEE.

The stage and extent of breastfeeding affect the incremental energy requirements for lactation. During the first 6 months of lactation, milk production rates are increased (Butte et al., 2001). Customary milk production rates beyond 6 months postpartum typically vary and depend on weaning practices (Butte et al., 2001).

EER Summary, Lactation

The DLW database provided TEE values for lactating women with prepregnancy BMIs from 18.5 up to 25 kg/m^2 at 1, 2, 3, 4, and 6 months postpartum (Appendix Table I-5). Analysis of the DLW database showed a small but significant change in TEE over these postpartum time periods (ANOVA, $P = 0.05$). A comparison was made between observed TEE of lactating women and TEE calculated from age, height, weight, and PAL using the prediction equation for adult women (see earlier section, "Adults Ages 19 Years and Older"). At 1 month postpartum, observed TEE was about 200 kcal less than predicted, while no differences were apparent at later months. For derivation of the EER for lactation, the TEE is based on the EER for normal-weight adult women using current age, weight, and PAL.

The EERs to be used during lactation are estimated from TEE, milk energy output, and energy mobilization from tissue stores. Because adaptations in basal metabolism and physical activity are not evident in well-nourished women, energy requirements of lactating women are met partially by mobilization of tissue stores, but primarily from the diet. In the first 6 months postpartum, well-nourished lactating women experience an average weight loss of 0.8 kg/mo, which is equivalent to 170 kcal/d (6,500 kcal/kg) (Butte and Hopkinson, 1998). Weight stability is assumed after 6 months postpartum. Milk production rates average 0.78 L/d from birth through 6 months of age and 0.6 L/d from 7 through 12 months of age. At 0.67 kcal/g of milk (Table 5-18), the milk energy output would be 523 kcal/d, which is rounded to 500 kcal/d, in the first 6 months and 402 kcal/d, which is rounded to 400 kcal/d, in the second 6 months of lactation.

EER for Lactation

14–18 Years

$$\mathbf{EER_{lactation} = adolescent\ EER_{prepregnancy} + milk\ energy\ output - weight\ loss}$$

1st 6 mo **adolescent EER + 500 – 170**

2nd 6 mo **adolescent EER + 400 – 0**

19–50 Years

$EER_{lactation}$ = adult $EER_{prepregnancy}$ + milk energy output – weight loss

1st 6 mo adult EER + 500 – 170

2nd 6 mo adult EER + 400 – 0

Special Considerations

Method Used to Estimate Weight Maintenance in Overweight and Obese Adults

Since Dietary Reference Intakes are designed to apply to apparently health individuals, the EERs are defined as values appropriate for maintenance of long-term good health. Overweight and obese individuals have greater weight than is consistent with long-term good health, thus EER values given in previous sections are not intended for overweight or obese individuals or for those who desire to lose weight. Instead, weight maintenance TEE values are discussed, along with information on the relationship between reduction in energy intake and change in body composition.

Equations to predict TEE for all adults from age, height, weight, gender, and activity level were generated from the combined DLW database of normal, overweight, and obese individuals (Appendix Tables I-3 and I-7). In addition, the DLW database of overweight and obese individuals (Appendix Table I-7) was used to generate equations to predict TEE in overweight and obese adult men and women (BMI 25 kg/m^2 and higher) from age, height, weight, and physical activity category using nonlinear regression. PAL categorization was determined using the adults' observed BEE. Data were not used in the derivation of the TEE equations if the PAL value was less than 1.0 or greater than 2.5.

The coefficients and standard error derived for only overweight and obese men and women are provided in Appendix Table I-10. For the overweight and obese equations, the standard deviations of the residuals ranged from 190 to 331, with the highest value in the very active PAL category. The equations are shown below (see Table I-10 for coefficients used).

Overweight and Obese Men Ages 19 Years and Older

$$\mathbf{TEE = 1086 - (10.1 \times age\ [y]) + PA \times (13.7 \times weight\ [kg] + 416 \times height\ [m])}$$

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be $\geq 1.0 < 1.4$ (sedentary)

PA = 1.12 if PAL is estimated to be $\geq 1.4 < 1.6$ (low active)

PA = 1.29 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.59 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Overweight and Obese Women Ages 19 Years and Older

$$\mathbf{TEE = 448 - (7.95 \times age\ [y]) + PA \times (11.4 \times weight\ [kg] + 619 \times height\ [m])}$$

Where PA is the physical activity coefficient:
PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.16 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.27 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.44 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Method Used to Estimate Weight Maintenance in Normal-weight, Overweight, and Obese Adults

TEE predictive equations were also developed combining normal-weight, overweight, and obese adults (BMI 18.5 kg/m^2 and higher) as mentioned earlier; the coefficients and standard errors are shown in Appendix Table I-11. Mean of the residuals did not differ from zero. For the combined data sets, the standard deviations of the residuals ranged from 182 to 321.

The adult predictive equations for TEE were subjected to statistical testing of their estimated coefficients and asymptotic standard deviations using a chi-square distribution (Hotelling T-squared test). The specific equations for the overweight and obese men and women (BMI from 25 kg/m^2 and higher) given above were not statistically different from the equations derived solely from normal-weight individuals given in the previous section (BMI from 18.5 up to 25 kg/m^2; $P > 0.99$) or normal plus overweight and obese individuals shown below (BMI from 18.5 kg/m^2 and higher; $P = 0.96$–0.99).

In addition, the equations generated to predict TEE from the combined data set of normal plus overweight and obese individuals had a larger sample size, thus reducing the standard error of the coefficients, and improved the continuity of predicted TEEs at the BMI junction between normal-weight and overweight individuals. For these reasons, the combined data from normal-weight and overweight and obese individuals were used to develop equations to predict TEE in overweight and obese adults. The resulting equations, described in the following sections, are accurate for use in both normal-weight and overweight and obese adults, and are thus suitable for prediction of energy requirements both in overweight and obese groups and in mixed groups containing normal-weight

and overweight adults. The equations are shown below (see Table I-11 for coefficients used).

Normal-weight, Overweight, and Obese Men Ages 19 Years and Older

$$\mathbf{TEE = 864 - (9.72 \times age\ [y]) + PA \times (14.2 \times weight\ [kg] + 503 \times height\ [m])}$$

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.12 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.27 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.54 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Normal-weight, Overweight, and Obese Women Ages 19 Years and Older

$$\mathbf{TEE = 387 - (7.31 \times age\ [y]) + PA \times (10.9 \times weight\ [kg] + 660.7 \times height\ [m])}$$

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.14 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.27 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.45 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Current consensus guidelines for the management of obesity in adults (BMI 30 kg/m^2 and higher) recommend weight loss of around 10 percent of initial weight over a 6-month period (NIH, 2000). For overweight individuals (BMI from 25 up to 30 kg/m^2) who have no other risk factors, a motivation and desire to lose weight is an important consideration for recommending weight loss. Persons who do not wish to lose weight should receive advice and monitoring aimed at weight maintenance and risk reduction. Nevertheless, there is consensus that BMIs of 25 kg/m^2 and higher increase risk of premature morbidity and mortality (Chan et al., 1994; Colditz GA et al., 1995; Rimm et al., 1995; Stevens et al., 1998; Willett et al., 1999), and that relatively modest weight loss can improve blood pressure (Huang Z et al., 1998; Kannel et al., 1967; Reisin et al., 1978; Schotte and Stunkard, 1990), serum lipid (Grundy et al., 1979; Kesaniemi and Grundy, 1983; Osterman et al., 1992; Wood et al., 1988, 1991), and glucose tolerance (Amatruda et al., 1988; Doar et al., 1975; Hadden et al., 1975; Wing et al., 1991).

Rationale for Recommending Use of Equations Based on Combined Database for Overweight and Obese Individuals

Tables 5-29 and 5-30 show 24-h BEE and TEE values for 30-year-old men and women of different BMIs. The tables illustrate that obese men and women have consistently higher TEE than normal-weight men and women of comparable height and PAL, which implies that, on average, overweight and obese individuals need to consume more dietary energy to maintain weight than individuals within the healthy weight range to maintain their larger body weights.

The following predictive equations for BEE were derived from the observed BEE values in the DLW database (Appendix Tables I-3 and I-7):

For normal-weight men:

$$\text{BEE (kcal/d)} = 204 - (4 \times \text{age [y]}) + 450.5 \times \text{height (m)} + 11.69 \times \text{weight (kg)}$$

$$\text{residual} = 0 \pm 149,\ R^2 = 0.46.$$

For normal-weight, overweight, and obese men:

$$\text{BEE (kcal/d)} = 293 - (3.8 \times \text{age [y]}) + 456.4 \times \text{height (m)} + 10.12 \times \text{weight (kg)}$$

$$\text{residual} = 0 \pm 156,\ R^2 = 0.64.$$

For normal-weight women:

$$\text{BEE (kcal/d)} = 255 - 2.35 \times \text{age (y)} + 361.6 \times \text{height (m)} + 9.39 \times \text{weight (kg)}$$

$$\text{residual} = \pm 125,\ R^2 = 0.39.$$

For normal-weight, overweight, and obese women:

$$\text{BEE (kcal/d)} = 247 - (2.67 \times \text{age [y]}) + 401.5 \times \text{height (m)} + 8.60 \times \text{weight (kg)}$$

$$\text{residual} = \pm 156,\ R^2 = 0.62.$$

The residuals (differences between the observed and predicted BEE) can be compared with the differences between the BEE values calculated for the adults in the DLW database using the BEE predictive equations by Henry (2000) and WN Schofield (1985) based on body weight, and the predictive BEE equation of WN Schofield (1985) based on body weight and height and the observed BEE in the DLW database. These differences (averages ± standard deviation [SD]) are: –35 ± 168, –9 ± 169, and –34 ± 184 in men, and –33 ± 134, 8 ± 137, and 16 ± 135 in women, respectively.

For the normal-weight adults with BMIs from 18.5 up to 25 kg/m^2 in Tables 5-29 and 5-30, BEE was calculated using the above BEE prediction

TABLE 5-29 Basal and Total Daily Energy Expenditure in Men 30 Years of Age as Calculated from Total Energy Expenditure (TEE) Equations for Normal-weight, Overweight, and Obese Men[a]

Height (m [in])	PAL[b]	Weight (kg [lb]) for a Body Mass Index (kg/m^2) of: 18.5	22.5	24.99	25	30	35	40
1.45 (57)	BEE	38.9 (86)	47.3 (104)	52.5 (116)	52.6 (116)	63.1 (139)	73.6 (162)	84.1 (185)
	Sedentary							
	Low active							
	Active							
	Very active							
1.50 (59)	BEE	41.6 (92)	50.6 (111)	56.2 (124)	56.3 (124)	67.5 (149)	78.8 (173)	90.0 (198)
	Sedentary							
	Low active							
	Active							
	Very active							
1.55 (61)	BEE	44.4 (98)	54.1 (119)	60.0 (132)	60.1 (132)	72.1 (159)	84.1 (185)	96.1 (211)
	Sedentary							
	Low active							
	Active							
	Very active							
1.60 (63)	BEE	47.4 (104)	57.6 (127)	64.0 (141)	64.0 (141)	76.8 (169)	89.6 (197)	102.4 (225)
	Sedentary							
	Low active							
	Active							
	Very active							
1.65 (65)	BEE	50.4 (111)	61.3 (135)	68.0 (150)	68.1 (150)	81.7 (180)	95.3 (210)	108.9 (240)
	Sedentary							
	Low active							
	Active							
	Very active							
1.70 (67)	BEE	53.5 (118)	65.0 (143)	72.2 (159)	72.3 (159)	86.7 (191)	101.2 (223)	115.6 (254)
	Sedentary							
	Low active							
	Active							
	Very active							
1.75 (69)	BEE	56.7 (125)	68.9 (152)	76.5 (168)	76.6 (168)	91.9 (202)	107.2 (236)	122.5 (270)
	Sedentary							
	Low active							
	Active							
	Very active							

TEE[c] (kcal/d) for a Body Mass Index (kg/m^2) of:						
18.5	22.5	24.99	25	30	35	40
1,192	1,290	1,351	1,373	1,479	1,585	1,692
1,777	1,911	1,994	2,048	2,197	2,347	2,496
1,931	2,080	2,172	2,225	2,393	2,560	2,727
2,128	2,295	2,399	2,447	2,636	2,826	3,015
2,450	2,648	2,771	2,845	3,075	3,305	3,535
1,246	1,352	1,417	1,433	1,547	1,661	1,774
1,848	1,991	2,080	2,126	2,285	2,445	2,605
2,010	2,169	2,268	2,312	2,491	2,670	2,849
2,216	2,395	2,506	2,545	2,748	2,951	3,154
2,554	2,766	2,898	2,964	3,210	3,456	3,702
1,302	1,414	1,484	1,494	1,616	1,737	1,859
1,920	2,073	2,168	2,205	2,376	2,546	2,717
2,089	2,259	2,365	2,401	2,592	2,783	2,974
2,305	2,497	2,616	2,646	2,862	3,079	3,296
2,661	2,887	3,028	3,087	3,349	3,612	3,875
1,358	1,478	1,553	1,557	1,686	1,816	1,946
1,993	2,156	2,257	2,286	2,468	2,650	2,831
2,171	2,352	2,464	2,492	2,695	2,899	3,102
2,397	2,601	2,728	2,749	2,980	3,210	3,441
2,769	3,010	3,160	3,211	3,491	3,771	4,051
1,416	1,543	1,623	1,621	1,759	1,896	2,034
2,068	2,241	2,349	2,369	2,562	2,755	2,949
2,254	2,446	2,566	2,584	2,801	3,017	3,234
2,491	2,707	2,842	2,854	3,099	3,345	3,590
2,880	3,136	3,296	3,339	3,637	3,934	4,232
1,475	1,610	1,694	1,686	1,832	1,979	2,125
2,144	2,328	2,442	2,453	2,659	2,864	3,069
2,339	2,542	2,670	2,679	2,909	3,139	3,369
2,586	2,816	2,959	2,961	3,222	3,483	3,743
2,993	3,265	3,434	3,469	3,785	4,101	4,417
1,535	1,678	1,767	1,753	1,907	2,062	2,217
2,222	2,417	2,538	2,540	2,757	2,975	3,192
2,425	2,641	2,776	2,776	3,019	3,263	3,507
2,683	2,927	3,079	3,071	3,347	3,623	3,899
3,108	3,396	3,576	3,602	3,937	4,272	4,607

continued

TABLE 5-29 Continued

Height (m [in])	PAL[b]	Weight (kg [lb]) for a Body Mass Index (kg/m^2) of: 18.5	22.5	24.99	25	30	35	40
1.80 (71)	BEE	59.9 (132)	72.9 (160)	81.0 (178)	81.0 (178)	97.2 (214)	113.4 (249)	129.6 (285)
	Sedentary							
	Low active							
	Active							
	Very active							
1.85 (73)	BEE	63.3 (139)	77.0 (169)	85.5 (188)	85.6 (188)	102.7 (226)	119.8 (264)	136.9 (301)
	Sedentary							
	Low active							
	Active							
	Very active							
1.90 (75)	BEE	66.8 (147)	81.2 (179)	90.2 (198)	90.3 (199)	108.3 (239)	126.4 (278)	144.4 (318)
	Sedentary							
	Low active							
	Active							
	Very active							
1.95 (77)	BEE	70.3 (155)	85.6 (188)	95.0 (209)	95.1 (209)	114.1 (251)	133.1 (293)	152.1 (335)
	Sedentary							
	Low active							
	Active							
	Very active							

[a] For each year below 30, add 4 kcal/d to BEE and 10 kcal/d to TEE. For each year above 30, subtract 4 kcal/d from BEE and 10 kcal/d from TEE. Equations determined from combined DLW databases (Appendix Table I-11).

equations for normal-weight men and women, and TEE was calculated utilizing the EER equations in the section "Adults Ages 19 Years and Older." For overweight and obese adults with BMIs from 25 up to 40 kg/m^2, the above BEE prediction equations for normal, overweight, and obese men and women were utilized to calculate BEE, and the above TEE equations for normal, overweight, and obese individuals were used to predict the TEE. The differences between the predictions made for BMI of 24.99 kg/m^2 and BMI of 25 kg/m^2 in Tables 5-29 and 5-30 show that the discrepancies at the junction of the two prediction ranges are essentially negligible as average differences (± SD) are 0.4 ± 2.1 percent in men, and 0.9 ± 1.1 percent in women, respectively.

TEE[c] (kcal/d) for a Body Mass Index (kg/m^2) of:						
18.5	22.5	24.99	25	30	35	40
1,596	1,747	1,841	1,820	1,984	2,148	2,312
2,301	2,507	2,635	2,628	2,858	3,088	3,318
2,513	2,742	2,884	2,875	3,132	3,390	3,648
2,782	3,040	3,200	3,183	3,475	3,767	4,059
3,225	3,530	3,720	3,738	4,092	4,447	4,801
1,658	1,818	1,917	1,889	2,062	2,236	2,409
2,382	2,600	2,735	2,718	2,961	3,204	3,447
2,602	2,844	2,995	2,975	3,248	3,520	3,792
2,883	3,155	3,325	3,297	3,606	3,915	4,223
3,344	3,667	3,867	3,877	4,251	4,625	4,999
1,721	1,889	1,995	1,959	2,142	2,325	2,507
2,464	2,694	2,837	2,810	3,066	3,322	3,579
2,694	2,949	3,107	3,078	3,365	3,652	3,939
2,986	3,273	3,452	3,414	3,739	4,065	4,390
3,466	3,806	4,018	4,018	4,412	4,807	5,202
1,785	1,963	2,073	2,031	2,223	2,416	2,608
2,548	2,790	2,940	2,903	3,173	3,443	3,713
2,786	3,055	3,222	3,183	3,485	3,788	4,090
3,090	3,393	3,581	3,532	3,875	4,218	4,561
3,590	3,948	4,171	4,162	4,578	4,993	5,409

[b] PAL = physical activity level, BEE = basal energy expenditure.

Weight Reduction in Overweight and Obese Adults

When obese individuals need to lose weight, the necessary negative energy balance can theoretically be achieved by either a reduction in energy intake or an increase in energy expenditure of physical activity (EEPA). Most usually, a combination of both is desirable (NIH, 2000) because it is hard to achieve the high levels of negative energy balance necessary for 1 to 2 lb/wk weight loss with exercise alone. In support of this contention, meta-analyses show very low levels of weight loss in structured exercise programs (Ballor and Keesey, 1991), but at the same time several studies suggest that the combination of dietary change and increased physical activity appears effective for promoting weight loss and successful weight maintenance after weight loss, perhaps by promoting

TABLE 5-30 Basal and Total Daily Energy Expenditure in Women 30 Years of Age as Calculated from Total Energy Expenditure (TEE) Equations for Normal-weight, Overweight, and Obese Women[a]

Height (m [in])	PAL[b]	Weight (kg [lb]) for a Body Mass Index (kg/m^2) of: 18.5	22.5	24.99	25	30	35	40
1.45 (57)	BEE	38.9 (86)	45.2 (100)	52.5 (116)	52.6 (116)	63.1 (139)	73.6 (162)	84.1 (185)
	Sedentary							
	Low active							
	Active							
	Very active							
1.50 (59)	BEE	41.6 (92)	48.4 (107)	56.2 (124)	56.3 (124)	67.5 (149)	78.8 (174)	90.0 (198)
	Sedentary							
	Low active							
	Active							
	Very active							
1.55 (61)	BEE	44.4 (98)	51.7 (114)	60.0 (132)	60.1 (132)	72.1 (159)	84.1 (185)	96.1 (212)
	Sedentary							
	Low active							
	Active							
	Very active							
1.60 (63)	BEE	47.4 (104)	55.0 (121)	64.0 (141)	64.0 (141)	76.8 (169)	89.6 (197)	102.4 (226)
	Sedentary							
	Low active							
	Active							
	Very active							
1.65 (65)	BEE	50.4 (111)	58.5 (129)	68.0 (150)	68.1 (150)	81.7 (180)	95.3 (210)	108.9 (240)
	Sedentary							
	Low active							
	Active							
	Very active							
1.70 (67)	BEE	53.5 (118)	62.1 (137)	72.2 (159)	72.3 (159)	86.7 (191)	101.2 (223)	115.6 (255)
	Sedentary							
	Low active							
	Active							
	Very active							
1.75 (69)	BEE	56.7 (125)	65.8 (145)	76.5 (169)	76.6 (169)	91.9 (202)	107.2 (236)	122.5 (270)
	Sedentary							
	Low active							
	Active							
	Very active							

TEE (kcal/d) for a Body Mass Index (kg/m^2) of:						
18.5	22.5	24.99	25	30	35	40
1,074	1,133	1,202	1,201	1,291	1,382	1,472
1,564	1,623	1,691	1,698	1,813	1,927	2,042
1,734	1,800	1,877	1,912	2,043	2,174	2,304
1,946	2,021	2,108	2,112	2,257	2,403	2,548
2,201	2,287	2,386	2,387	2,553	2,719	2,886
1,118	1,181	1,255	1,253	1,349	1,446	1,543
1,625	1,689	1,762	1,771	1,894	2,017	2,139
1,803	1,874	1,956	1,996	2,136	2,276	2,415
2,025	2,105	2,198	2,205	2,360	2,516	2,672
2,291	2,382	2,489	2,493	2,671	2,849	3,027
1,163	1,230	1,309	1,306	1,409	1,512	1,615
1,688	1,756	1,834	1,846	1,977	2,108	2,239
1,873	1,949	2,037	2,081	2,230	2,380	2,529
2,104	2,190	2,290	2,299	2,466	2,632	2,798
2,382	2,480	2,593	2,601	2,791	2,981	3,171
1,208	1,280	1,364	1,360	1,470	1,580	1,690
1,752	1,824	1,907	1,922	2,061	2,201	2,340
1,944	2,025	2,118	2,168	2,327	2,486	2,645
2,185	2,276	2,383	2,396	2,573	2,750	2,927
2,474	2,578	2,699	2,712	2,914	3,116	3,318
1,254	1,331	1,420	1,415	1,532	1,649	1,766
1,816	1,893	1,982	1,999	2,148	2,296	2,444
2,016	2,102	2,202	2,256	2,425	2,594	2,763
2,267	2,364	2,477	2,494	2,682	2,871	3,059
2,567	2,678	2,807	2,824	3,039	3,254	3,469
1,301	1,383	1,478	1,471	1,595	1,719	1,843
1,881	1,963	2,057	2,078	2,235	2,393	2,550
2,090	2,180	2,286	2,345	2,525	2,705	2,884
2,350	2,453	2,573	2,594	2,794	2,994	3,194
2,662	2,780	2,917	2,938	3,166	3,395	3,623
1,350	1,436	1,536	1,528	1,659	1,791	1,923
1,948	2,034	2,134	2,158	2,325	2,492	2,659
2,164	2,260	2,372	2,437	2,627	2,817	3,007
2,434	2,543	2,670	2,695	2,907	3,119	3,331
2,758	2,883	3,028	3,054	3,296	3,538	3,780

continued

TABLE 5-30 Continued

Height (m [in])	PAL[b]	Weight (kg [lb]) for a Body Mass Index (kg/m^2) of: 18.5	22.5	24.99	25	30	35	40
1.80 (71)	BEE	59.9 (132)	69.7 (154)	81.0 (178)	81.0 (178)	97.2 (214)	113.4 (250)	129.6 (285)
	Sedentary							
	Low active							
	Active							
	Very active							
1.85 (73)	BEE	63.3 (139)	73.6 (162)	85.5 (188)	85.6 (189)	102.7 (226)	119.8 (264)	136.9 (302)
	Sedentary							
	Low active							
	Active							
	Very active							
1.90 (75)	BEE	66.8 (147)	77.6 (171)	90.2 (198)	90.3 (199)	108.3 (239)	126.4 (278)	144.4 (318)
	Sedentary							
	Low active							
	Active							
	Very active							
1.95 (77)	BEE	70.3 (155)	81.8 (180)	95.0 (209)	95.1 (209)	114.1 (251)	133.1 (293)	152.1 (335)
	Sedentary							
	Low active							
	Active							
	Very active							

[a] For each year below 30, add 2.5 kcal/d to BEE and 7 kcal/d to TEE. For each year above 30, subtract 2.5 kcal/d from BEE and 7 kcal/d from TEE. Equations determined from combined DLW databases (Appendix Table I-11).

favorable metabolic changes or improved dietary compliance (DePue et al., 1995; Dunn et al., 1999; Hartman et al., 1993; Holden et al., 1992; Miller et al., 1997).

Several studies indicate that energy expenditure decreases when energy intake is less than TEE, with the result that weight loss is less than anticipated based on the reduction in energy intake. As shown in Figure 5-9, a summary of studies on changes in resting energy expenditure (REE) with negative energy balance in adults have shown that the decline in REE with weight loss is greater than predicted from the loss of FFM that occurs concomitantly during negative energy balance. This suggests that there is a decrease in REE per unit of FFM during active weight loss (underfeeding).

TEE (kcal/d) for a Body Mass Index (kg/m^2) of:						
18.5	22.5	24.99	25	30	35	40
1,398	1,490	1,596	1,586	1,725	1,865	2,004
2,015	2,106	2,211	2,239	2,416	2,593	2,769
2,239	2,341	2,459	2,529	2,731	2,932	3,133
2,519	2,634	2,769	2,799	3,023	3,247	3,472
2,855	2,987	3,141	3,172	3,428	3,684	3,940
1,448	1,545	1,657	1,645	1,792	1,940	2,087
2,083	2,179	2,290	2,322	2,509	2,695	2,882
2,315	2,422	2,548	2,624	2,836	3,049	3,262
2,605	2,727	2,869	2,904	3,141	3,378	3,615
2,954	3,093	3,255	3,292	3,562	3,833	4,103
1,499	1,601	1,719	1,706	1,861	2,016	2,171
2,151	2,253	2,371	2,406	2,603	2,800	2,996
2,392	2,505	2,637	2,720	2,944	3,168	3,393
2,693	2,821	2,971	3,011	3,261	3,511	3,760
3,053	3,200	3,371	3,414	3,699	3,984	4,270
1,550	1,657	1,782	1,767	1,931	2,094	2,258
2,221	2,328	2,452	2,492	2,699	2,906	3,113
2,470	2,589	2,729	2,817	3,053	3,290	3,526
2,781	2,917	3,074	3,119	3,383	3,646	3,909
3,154	3,309	3,489	3,538	3,838	4,139	4,439

[b] PAL = Physical activity level, BEE = basal energy expenditure.

Role of Decreased Food Intake with or Without Increased Physical Activity

There are also four underfeeding studies that have examined changes in TEE with negative energy balance achieved by a reduction in energy intake. As shown in Table 5-31, the reduction in energy intake in these studies ranged from 758 to 1,620 kcal/d and was associated with a reduction in TEE that averaged 36 percent of the reduction in energy intake. It should be noted that there was a period of 3 to 52 weeks of underfeeding between the measurements of TEE made during weight maintenance and negative energy balance. Thus, some of the reduction in TEE was due to reduced energy requirements associated with reduced body weight.

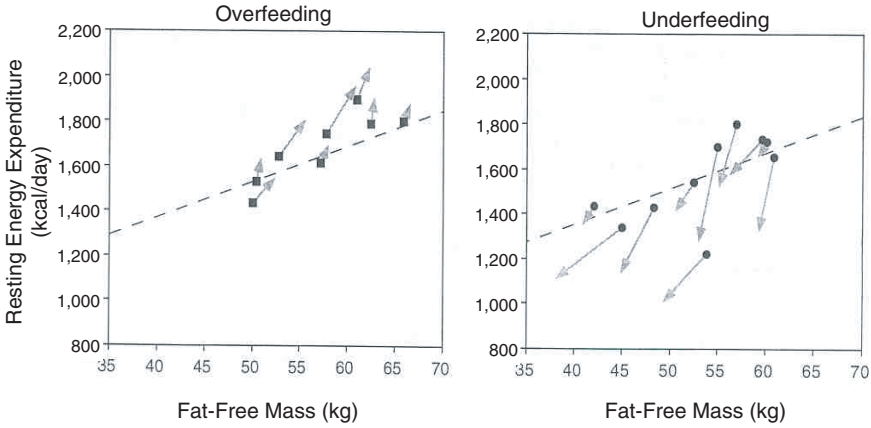

FIGURE 5-9 Relationship between changes in fat-free mass and resting energy expenditure during overfeeding and underfeeding. Reprinted, with permission, from Saltzman and Roberts (1995). Copyright 1995 by International Life Sciences Institute.

In multiple regression analyses using the DLW data of the studies in Table 5-31, weight, age, and gender significantly predicted TEE, and the b-coefficient for the weight term was 16.6 kcal/d. This implies that for weight-stable individuals, differences in body weight of 1 kg are associated with differences in TEE of 16.6 kcal/d. By correcting the changes in TEE that can be attributed to the decrease in body size in the four underfeeding studies described in Table 5-31, 8.4 percent of the reduction in TEE was unaccounted for by weight loss and appears therefore to be associated with a state of negative energy balance. This could be due to a reduction in energy expenditure per kg body weight or to a decrease in physical activity.

These values can be used to estimate the anticipated reduction in metabolizable energy intake necessary to achieve a given level of weight loss, if weight loss is achieved solely by a reduction in energy intake and there is no change in energy expenditure for physical activity. For example, a weight loss of 1 to 2 lb/wk (65 to 130 g/d) is equivalent to a body energy loss of 468 to 936 kcal/d, because the energy content of weight loss averages 7.2 kcal/g (i.e., 75 percent fat containing 9.25 kcal/g and 25 percent FFM containing 1 kcal/g) (Saltzman and Roberts, 1995). Taking into account the decrease in TEE due to weight loss (16.6 kcal/kg) and due to negative energy balance (8.4 percent of initial TEE), the total expected reduction in TEE after 10 weeks of dieting is predicted to be 376 to

TABLE 5-31 Changes (Δ) in Total Energy Expenditure (TEE) During Underfeeding Studies[a]

Reference	ΔTEE (kcal/d)	ΔBE[b] (kcal/d)	ΔEI[c] (kcal/d)	ΔTEE/ΔEI	CoorΔTEE/ΔEI[d]
Heyman et al., 1992	–297	–461	–758	0.392	0.076
Kempen et al., 1995	–359	–765	–1,124	0.319	0.087
Racette et al., 1995	–349	–695	–1,044	0.334	0.079
van Gemert et al., 2000	–645	–975	–1,620	0.398	0.093
Means				0.361	0.084

[a] Where all values are in kcal/d, Δ describes changes in value between weight maintenance and underfeeding.
[b] BE = body energy.
[c] EI = energy intake (calculated as ΔBE + ΔTEE).
[d] CorrΔTEE is change in total energy expenditure after subtracting the estimated change in TEE due to weight loss in the underfeeding period prior to measurement of TEE. This value indicates the change in TEE is due to negative energy balance rather than weight loss. It was estimated as weight loss prior to the underfeeding TEE × 16.6, where 16.6 is the weight coefficient in the relationship, TEE = constant + weight + age + gender in the doubly labeled water data from these studies.

542 kcal/d for an individual with an initial weight maintenance TEE of 2,500 kcal/d. Therefore, to maintain a rate of weight loss of 1 to 2 lb/wk, the reduction in energy intake would need to be 844 (468 + 376) to 1,478 kcal/d (936 + 542) after 10 weeks of weight loss.

This calculation serves both to emphasize the importance of exercise in helping prevent reduced TEE during weight loss, and to illustrate the relatively high level of reduction in energy intake needed when weight loss is to be achieved by dieting alone. It should be noted that the above calculations were based on TEE data derived from studies in adults in which reduction in energy intake was in the range of 758 to 1,620 kcal/d. The impact on energy expenditure of weight loss regimens involving lesser or greater reductions in energy intake need to be assessed before rates of weight reduction can be more precisely predicted. However, it must be appreciated that reduction in resting rates of energy expenditure per kilogram of body weight have a small impact on the prediction of energy deficits imposed by food restriction, and the greatest cause of deviation from projected rates of weight loss lies in the degree of compliance. The coefficient of 16.6 kcal/kg of weight loss calculated from the data in Table 5-31 could be utilized to anticipate the reduction in energy intake required for maintaining lower body weights. Further studies in this area are needed.

Estimation of Energy Expenditure for Weight Maintenance in Overweight Children Ages 3 Through 18 Years

While the Centers for Disease Control and Prevention (CDC) currently defines childhood "risk of overweight" as greater than the 85th percentile for BMI and "overweight" as greater than the 95th percentile of BMI, it gives no definition for obesity in childhood. Several organizations, however, define childhood obesity as a BMI above the 95th age-adjusted percentile (Barlow and Dietz, 1998; Bellizzi and Dietz, 1999). An international standardized approach was also recently proposed, based on identifying the childhood BMI at different ages that would be equivalent to a BMI of 25 kg/m^2 (for overweight) or 30 kg/m^2 (for obese) at age 18 years (Cole et al., 2000). Using this approach, the cutoff for obesity would fall near the 97th percentile of the current CDC growth charts (Figure 5-10). For this report, the CDC definitions of risk of overweight and overweight are accepted for children, namely BMI above the 95th percentile for overweight and above the 85th percentile for risk of overweight.

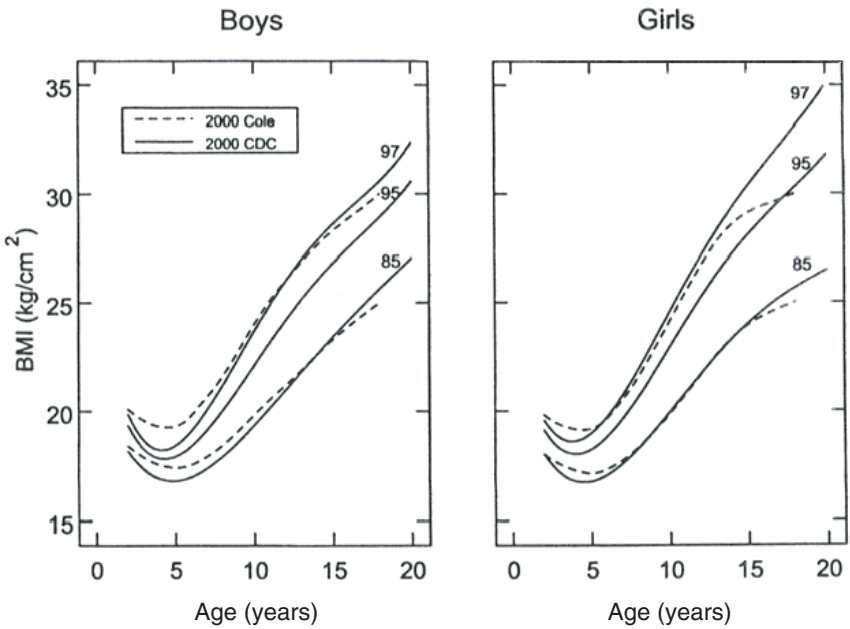

FIGURE 5-10 Comparison of body mass index (BMI) definitions of overweight and obesity during childhood with percentiles for BMI (85th, 95th, 97th). Reprinted, with permission, from Roberts and Dallal (2001). Copyright 2001 by International Life Sciences Institute.

Rapid weight loss is undesirable in children due to the risks of stunting and micronutrient deficiencies. In addition, children under 2 years of age should not be placed on energy-restricted diets out of concern that brain development may inadvertently be compromised by inadequate dietary intake of fatty acids and micronutrients. A recent expert pediatric committee recommended that weight maintenance be the goal for most children over 2 years of age in the 85th to 95th percentiles for BMI (Barlow and Dietz, 1998). In addition, the committee recommended that weight loss be at a rate of 1 lb/mo for children over 7 years of age at or greater than the 95th percentile BMI and for children between the 85th and 95th percentiles who have comorbidities that would be anticipated to be improved by weight loss.

Separate TEE predictive equations were developed from the DLW data for 3- through 18-year-old overweight and obese boys and girls (Appendix Table I-6) from age, height, weight, and PAL categories using nonlinear regression techniques. In order to utilize all the TEE data, PAL categorization was determined using predicted BEE rather than observed BEE, since only 67 percent (85/127) of the boys and 64 percent (123/192) of the girls and had observed BEEs. The following predictive equations for BEE were derived from the observed BEEs provided in the DLW database (Appendix Table I-6).

For overweight and obese boys:

$$\text{BEE (kcal/d)} = 420 - 33.5 \text{ age (y)} + 418.9 \times \text{height (m)} + 16.7 \text{ weight (kg)}$$

$$SE = 89.9,\ R^2 = 0.88.$$

For overweight and obese girls:

$$\text{BEE (kcal/d)} = 516 - (26.8 \times \text{age [y]}) + 347 \text{ height (m)} + 12.4 \text{ weight (kg)}$$

$$SE = 113.4,\ R^2 = 0.79.$$

For normal-weight, overweight, and obese boys:

$$\text{BEE (kcal/d)} = 79 - 934.2 \times \text{age [y]}) + 730 \times \text{height (m)} + 15.3 \text{ weight (kg)}$$

$$SE = 90.6,\ R^2 = 0.89.$$

For normal-weight, overweight, and obese girls:

$$\text{BEE (kcal/d)} = 322 - 926.0 \times \text{age [y]}) + 504 \times \text{height (m)} + 11.6 \text{ weight (kg)}$$

$$SE = 102.1,\ R^2 = 0.80.$$

Prediction equations of TEE for overweight and obese girls and boys were developed using age, height, weight, and PAL category as predicted from the above BEE equations. Data were not used in the derivation of the TEE equations if the PAL value was less than 1.0 or greater than 2.5. In addition, TEE predictive equations were developed combining normal-weight, overweight, and obese children. The coefficients and SE for boys and girls in the overweight and obese database (Appendix Table I-6) are provided in Appendix Table I-12. Mean of the residuals did not differ from zero, and the standard deviation of the residuals ranged from 74 to 213. The coefficients and SE for boys and girls in the combined normal-weight, overweight, and obese database are described in Appendix Table I-13. The mean of the residuals did not differ from zero and the standard deviation of the residuals ranged from 73 to 208.

The children's predictive equations for TEE were subjected to statistical testing of their estimated coefficients and asymptotic standard deviations using a chi-square distribution (Hotelling T-squared test). The specific equation for the overweight and obese boys was statistically different from the equation derived solely from normal-weight boys ($P > 0.032$), and tended to differ from the combined equation derived from normal, overweight, and obese boys ($P = 0.086$). The specific equation for the overweight and obese girls was statistically different from the equation derived solely from normal-weight girls ($P > 0.001$), but not from the combined equation derived from normal, overweight, and obese girls ($P = 0.99$). The equations for the normal-weight boys and girls differed from the combined equation ($P = 0.001$).

Despite the suggestion of differences in the predictive equations for the TEE of boys, and because of the larger sample size, reduced SEs of the coefficients and increased stability, and consistency between the genders, *the prediction equations for TEE based on the combined database are recommended for use in overweight and obese children for weight maintenance—they do not include growth.* (See Table I-13 for coefficients used in the equations.)

Weight Maintenance TEE in Overweight Boys Ages 3 Through 18 Years

$$\mathbf{TEE = 114 - (50.9 \times age\ [y]) + PA \times (19.5 \times weight\ [kg] + 1161.4 \times height\ [m])}$$

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be $\geq 1.0 < 1.4$ (sedentary)
PA = 1.12 if PAL is estimated to be $\geq 1.4 < 1.6$ (low active)
PA = 1.24 if PAL is estimated to be $\geq 1.6 < 1.9$ (active)
PA = 1.45 if PAL is estimated to be $\geq 1.9 < 2.5$ (very active)

Weight Maintenance TEE in Overweight Girls Ages 3 Through 18 Years

$$\text{TEE} = 389 - (41.2 \times \text{age [y]}) + \text{PA} \times (15.0 \times \text{weight [kg]} + 701.6 \times \text{height [m]})$$

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)
PA = 1.18 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)
PA = 1.35 if PAL is estimated to be ≥ 1.6 < 1.9 (active)
PA = 1.60 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

As in adults, these TEE equations do not form the basis of EER values since the weight of the group is considered high (when BMI is greater than the 95th percentile) or at risk of being high (when BMI is greater than the 85th percentile). Nevertheless, TEE values are equivalent to EER values when weight maintenance is the goal. It should be noted that EER values for energy in children of healthy weight also include an amount that will provide sufficient energy for normal rates of growth. When weight maintenance is the goal, as in most children between the 85th and 95th BMI percentiles, it is assumed that linear growth and lean tissue growth can occur at a normal rate when body weight gain is prevented, because over time body fat content gradually decreases in parallel with the increase in FFM.

Weight Reduction in Overweight Children Ages 3 Through 18 Years

Weight reduction at a rate of 1 lb/m (15 g/d) is equivalent to a body energy loss of 108 kcal/d (assuming the energy content of weight loss averages 7.2 kcal/g [Saltzman and Roberts, 1995]), an amount that is small enough to be achievable by either an increase in EEPA, a reduction in energy intake, or a combination of both. There is currently no information on changes in TEE with negative energy balance in children, and no information even from adults on changes in TEE at low levels of negative energy balance. Thus, the extent to which TEE falls when energy intake is reduced with the intention of producing very slow weight loss in children is not known. This lack of data makes it impossible to describe the relationship between change in energy intake and change in body energy for children in whom weight loss is indicated. However, if the negative energy balance is achieved by a reduction in energy intake alone, at least a 108 kcal/d decrease in energy intake (i.e., equivalent to the indicated loss of body energy) would be necessary to result in a slow weight loss, and perhaps more if a reduction in TEE occurs. Small reductions in energy intake of the magnitude required to resolve childhood overweight gradually over time are within the potential for ad libitum changes induced by improvements in dietary composition.

Undernutrition

Undernutrition is still a frequent condition in many parts of the world, particularly in children. When energy intake is unable to match energy needs (due to insufficient dietary intake, excessive intestinal losses, or a combination thereof) several mechanisms of adaptation come into play (see earlier section, "Adaptation and Accommodation"). Reduction in voluntary physical activity is a rapid means of reducing energy needs to match limited energy input. In children, reduction in growth rates is another important mechanism of accommodation to energy deficit. Under conditions of persistent energy deficit, the low growth rate will result in short stature and low weight-for-age, a condition termed *stunting*.

A chronic energy deficit elicits mobilization of energy reserves, progressively depleting its main source: adipose tissue. Thus, an energy deficit of certain duration is associated with changes in body weight and body composition. As body weights decrease, so do energy requirements, although energy turnover may be higher when expressed per kg of body weight due to a predominant loss of fat tissue relative to lean tissue. In healthy, normal-weight individuals who face a sustained energy deficit, several hormonal mechanisms come into play, including a reduction in insulin release by the pancreas, a reduction in the active thyroid hormone T_3, and a decrease in adrenergic tone. These steps are aimed at reducing cellular energy demands by reducing the rates of key energy-consuming metabolic processes. However, there is less evidence that similar mechanisms are available to individuals who already have a chronic energy deficit when they are faced with further reductions in energy input (Shetty et al., 1994).

The effects of chronic undernutrition in children include decreased school performance, delayed bone age, and increased susceptibility to infections. In adults, an abnormally low BMI is associated with decreased work capacity and limited voluntary physical activity.

Additional Energy Requirements to Restore Normal Weight

In an adult with a low BMI (less than 18.5 kg/m^2), the additional energy intake required to normalize body weight will depend on the initial deficit and the desired rate of recovery. Although estimates of energy needs can be made based on the initial deficit, body weight gain will include not only energy stored as fat tissue, but also some amount in the form of skeletal muscle and even visceral tissues. Thus, as recovery of body weight proceeds, the energy requirement will vary not only as a function of body weight but in response to changes in body composition.

Catch-up Growth in Children. The energy needs for catch-up growth for children can be estimated from the energy cost of tissue deposition. The average energy cost of tissue synthesis and deposition was estimated at 5 kcal/g of tissue deposited (FAO/WHO/UNU, 1985). Based on experimental data from DLW studies in infants, Butte and colleagues (1989) estimated this cost as 4.8 kcal/g. Median weight for height has been used in the past as a target for recovery. Using BMI, the 50th BMI percentile for age may be considered as a target. However, in practical terms, the target for recovery depends on the initial deficit and the conditions of nutritional treatment: clinical unit or community. Under the controlled conditions of a clinical setting, undernourished children can exhibit rates of growth of 10 to 15 g/kg body weight/d (Fjeld et al., 1989), which are tenfold higher than normal rates of weight gain at 1 year of age. Under less controlled conditions (e.g., community-dwelling children), the rates of growth are likely to be much lower. The 1985 FAO/WHO/UNU report estimated these rates as twice the normal rate (FAO/WHO/UNU, 1985). Undoubtedly, this figure would be highly dependent on the magnitude and effectiveness of the nutritional intervention.

Dewey and coworkers (1996) estimated the energy needs for recovery growth for children with moderate or severe wasting, assuming that the latter would require a higher proportion of energy relative to protein. These estimates are presented in Table 5-32.

Catch-up Grown Following Stunting. The above estimates apply to children with a weight deficit relative to height. If a child is stunted, however, weight may be adequate for height, and unless an increased energy intake elicits both gains in height and in weight, the child may become overweight without correcting his or her height. In fact, this phenomenon is increasingly documented in urban settings of developing countries. It is a matter of debate whether significant catch-up gains in longitudinal growth are possible beyond about 3 years of age. Clearly, height gain is far more regulated than weight, which is primarily influenced by substrate availability and energy balance. Furthermore, longitudinal growth may also be dependent on the availability of other dietary constituents, such as zinc (Gibson et al., 1989; Walravens et al., 1983).

Athletes

With minor exceptions, dietary recommendations for athletes are not distinguished from the general population. As described in Chapter 12, the amount of dietary energy from the recommended nutrient mix should be adjusted to achieve or maintain optimal body weight for competitive athletes and others engaged in similarly demanding physical activities. As

TABLE 5-32 Energy Needs for Catch-up Growth at Different Rates of Weight Gain

	Normal Composition of Weight Gain[b]		High Rate of Fat Deposition[c]	
	EE[d] = 80	EE = 90	EE = 80	EE = 90
Rate of Gain[a] (g/kg/d)	Energy[e] (kcal/kg/d)	Energy[e] (kcal/kg/d)	Energy[e] (kcal/kg/d)	Energy[e] (kcal/kg/d)
1	83	93	86	96
2	87	97	92	102
5	97	107	110	120
10	113	123	140	150
20	146	156	200	210

[a] In normal children, average rates of weight gain are about 1.3 g/kg/d at 6–12 months, 0.8 g/kg/d at 12–18 months, and 0.5 g/kg/d at 18–24 months.
[b] 17 percent protein, 9 percent fat; assume energy cost of growth = 3.3 kcal/g (based on 5.65 kcal/g protein and 9.25 kcal/g fat, with efficiencies of synthesis of 42 percent and 85 percent, respectively [Roberts and Young, 1988: 0.17 g protein × 5.65 kcal/g/0.42 = 2.3 kcal; 0.09 g fat × 9.25 kcal/g/0.85 = 1.0 kcal]); protein needs for growth = protein need/efficiency = 0.17/0.7 = 0.24 g/kg/d.
[c] 10 percent protein, 43 percent fat; assume energy cost of growth = 6.0 kcal/g (based on 5.65 kcal/g protein and 9.25 kcal/g fat, with efficiencies of synthesis of 42 percent and 85 percent, respectively [Roberts and Young, 1988: 0.10 g protein × 5.65 kcal/g/0.42 = 1.3 kcal; 0.43 g fat × 9.25 kcal/g/0.85 = 4.7 kcal]); protein needs for growth = protein need/efficiency = 0.10/0.7 = 0.14 g/kg/d.
[d] EE = energy expenditure for maintenance and activity expressed as kcal/kg/d. As described by Dewey and colleagues (1996), the lower value is similar to average energy expenditure of preschool children and to energy expenditure for maintenance and activity of recovering malnourished children in Peru. The higher value is typical of normal infants at 9–12 months of age, but may be higher than would be expected of malnourished children if they are less active.
[e] Metabolizable energy intake.
SOURCE: Adapted from Dewey et al. (1996).

in the general population, the need to balance energy intake and expenditure over a wide range of body sizes, body compositions, and forms of exercise means that athletes will, in fact, require vastly different meal sizes and frequencies (e.g., female gymnasts compared to male American football linemen). While some athletes may be able to sustain extremely high power outputs over days or even weeks (such as in the Tour de France bicycle race), such endeavors are episodic and cannot be sustained indefinitely. Further, the recommendation for athletes to select foods in accordance with the same dietary guidelines as the general population is intended

to teach sound dietary practices to men and women whose lifestyles will become more typical when their athletic careers diminish.

Despite the difference in scope of energy flux associated with participation in sports and extremely demanding physical activities such as marathon running and military operations, several advantages are associated with different forms of exercise. For example, resistance exercise promotes muscle hypertrophy and changes in body composition by increasing the ratio of muscle to total body mass (Brooks et al., 2000). Hence, the height-weight values given in Tables 5-4 and 5-5 are of little relevance to lean, but highly muscular individuals such as speed/power athletes who, because of muscle hypertrophy, will have BMIs in excess of 25 kg/m^2. Athletes needing to increase strength will necessarily employ resistance exercises while ensuring that dietary energy is sufficient to increase muscle mass. Total body mass may increase, remain the same, or decrease depending on energy balance. Athletes needing to decrease body mass to obtain biomechanical advantages will necessarily increase total exercise energy output, reduce energy input, or use a combination of the two approaches. As distinct from weight loss by diet alone, having a major exercise component will serve to preserve lean body mass even in the face of negative energy balance.

ADVERSE EFFECTS OF OVERCONSUMPTION OF ENERGY

Hazard Identification

Adverse Effects

Adaptation to High Levels of Energy Intake. The ability of healthy individuals to compensate for increases in energy intake by increasing energy expenditure (either for physical activity or resting metabolism) depends on physiological and behavioral factors. When individuals are given a diet providing a fixed (but limited) amount of energy in excess of the requirements to maintain body weight, they will initially gain weight. However, over a period of several weeks, their energy expenditure will increase, mostly (Durnin, 1990; Ravussin et al., 1991), but perhaps not entirely (Leibel et al., 1995), on account of their increased body size, so that body weight eventually will stabilize at a higher level. A reduction of energy intake will produce the opposite effect. Some reports indicate that the magnitude of the reduction in energy expenditure when energy intake is reduced is greater than the corresponding increase in energy expenditure when energy intake is increased (Saltzman and Roberts, 1995). Nevertheless, weight changes invariably occur under conditions of increased and

decreased energy intake. It is likely that for most individuals the principal mechanism for maintaining body weight is by controlling food intake rather than physical activity (Jequier and Tappy, 1999).

Body Weight Gain and Chronic Disease. Weight gain that causes body mass index (BMI) to reach and exceed 25 kg/m^2 is associated with an increased risk of premature mortality (NHLBI/NIDDK, 1998). As shown in Tables 5-33 through 5-38, cohort studies have shown that morbidity risk for type 2 diabetes, hypertension, coronary heart disease, stroke, gallbladder disease, osteoarthritis, and some types of cancer also increases with increasing BMI of 25 kg/m^2 and higher.

Some data from large cohort studies suggest that disease risk begins to increase at BMI levels lower than those associated with increased risk of mortality (Manson et al., 1990). Thus, some investigators have recommended that individuals should aim at having a BMI of 22 kg/m^2 at the end of adolescence (NHLBI/NIDDK, 1998). This level would also provide some margin for weight gain in mid-life without surpassing the 25 kg/m^2 threshold.

For these reasons, energy intakes associated with adverse risk are defined as those that cause weight gain for individuals with a body weight within the healthy range (BMI from 18.5 up to 25 kg/m^2) and overweight individuals (BMI from 25 up to 30 kg/m^2). In the case of obese individuals who need to lose weight to improve their health, energy intakes that cause adverse risk are those that are higher than those needed to lose weight without causing negative health consequences.

Summary

Because of the direct impact of deviations from energy balance on body weight and of changes in body weight, body-weight data represent critical indicators of the adequacy of energy intake. Energy requirements are defined as the amounts of energy that need to be consumed by individuals to sustain stable body weights in the range desired for good health (BMI from 18.5 up to 25 kg/m^2) while maintaining lifestyles that include adequate levels of physical activity to maintain social, cultural, and economic activity. Since any energy intake above the Estimated Energy Requirement (EER) would be expected to result in weight gain and a likely increased risk of morbidity, the Tolerable Upper Intake Levels are not applicable to energy. If weight gain was identified as the hazard, the lowest-observed-adverse-effect level (LOAEL) would be any intake above the EER for adults. The uncertainty factor would be one as there is no uncertainty in the fact that overconsumption of energy leads to weight gain.

Intake Assessment

Based on distribution data from the 1994–1996, 1998 Continuing Survey of Food Intakes by Individuals, the highest mean intake of energy from diet for any gender and life stage group was estimated to be about 2,840 kcal/d (Appendix Table E-1), the intake of boys ages 14 through 18 years. Men 19 through 30 years of age had the highest reported energy intake with the 99th percentile of intake at 5,378 kcal/d.

RESEARCH RECOMMENDATIONS

- The number of available doubly labeled water studies for the determination of total energy expenditure (TEE) in certain age and gender categories is limited and should be expanded. This is particularly true for young children 3 to 5 years of age, adolescent boys, and adult men and women 40 through 60 years of age.
- Development of reliable methods to track dietary energy intakes in population groups is needed.
- Identification of biological markers of risk of excess weight gain in children and young adults is needed.
- Methods suitable for free-living population-based studies or applications should be developed to measure physical activity levels in order to classify children and adults into sedentary, low active, active, and very active levels of physical activity.
- More studies are necessary to determine whether and which dietary composition patterns facilitate permanent weight loss in adults and children.
- Development of practical, accurate means to assess body composition in populations is needed.
- Physical activity patterns consistent with normal health and development of children should be described that are applicable across age, gender, and ethnic backgrounds.
- Factors affecting the energy intake required to satisfy nutrient requirements should be explored, including diet digestibility, viscosity, and energy and nutrient density.
- Factors affecting the changes in TEE during pregnancy, as well as equations to predict the basal metabolic rate throughout pregnancy, are needed to better predict the energy requirements of nonobese, overweight, and obese pregnant women.
- More information is needed on the energy requirements of overweight and obese adults and children. It would be desirable for this additional TEE information to be collected in studies that also document physical activity patterns, so that the relationship between activity and TEE can be further evaluated.

TABLE 5-33 Body Mass Index (BMI) and Risk of Noninsulin-Dependent Diabetes Mellitus

Reference	Country	Study Population	Length of Follow-Up
Westlund and Nicolaysen, 1972	Sweden	3,751 men, 40–49 y	10 y
Medalie et al., 1974	Israel	10,059 men, 40+ y	5 y
Ohlson et al., 1985	Sweden	792 men, 54 y	13.5 y
Despres et al., 1989	Canada	52 premenopausal obese women	Not applicable
Lundgren et al., 1989	Sweden	1,462 women, 38–60 y	12 y
Colditz et al., 1990	United States	113,861 women, 30–55 y	8 y
Haffner et al., 1991	United States	254 men and 366 women	8 y

Obesity Index	Outcome[a]
Weight-height relationship	Incidence of diabetes (%)
Normal ± 10%	0.6
10–15% overweight	1.8
15–25% overweight	2.5
25–35% overweight	3.7
35–45% overweight	7.1
> 45% overweight	12.6
Weight/height index (kg/cm)	Incidence rate of diabetes
0.24–0.39	26/1,000
0.40–0.45	39/1,000
0.46–0.69	57/1,000
BMI, waist-to-hip ratio	Risk of development of diabetes was significantly associated with BMI ($p = 0.0003$) and waist-to-hip ratio ($p < 0.0001$)
BMI, body fat mass	BMI and body fat mass were significantly associated with plasma glucose and insulin
BMI	Significant correlation between initial BMI and incidence of diabetes during follow-up ($p < 0.001$)
BMI (kg/m^2)	Proportional hazards RR for diabetes (95% CI)
< 22	1.0
22–22.9	2.1 (1.4–3.3)
23–23.9	3.5 (2.3–5.1)
24–24.9	2.9 (1.9–4.5)
25–26.9	5.2 (3.7–7.5)
27–28.9	9.6 (6.8–13.6)
29–30.9	19.0 (13.6–26.4)
31–32.9	28.0 (19.9–39.4)
33–34.9	38.5 (27.0–54.9)
≥ 35	58.2 (42.4–79.9)

	OR for diabetes (95% CI)	
BMI (kg/m^2)	Men	Women
< 24.6	1.00	1.00
24.6–28.2	1.33 (0.25–7.27)	1.38 (0.32–6.08)
> 28.2	2.51 (0.49–12.6)	3.70 (1.03–13.3)

continued

TABLE 5-33 Continued

Reference	Country	Study Population	Length of Follow-Up
Chan et al., 1994	United States	27,983 men, 40–75 y	5 y
Ford et al., 1997	United States	8,545 adults	10 y

[a] RR = relative risk, CI = confidence interval, OR = odds ratio, CVD = cardiovascular disease.

Obesity Index	Outcome[a]
BMI (kg/m^2)	RR for diabetes (95% CI)
< 23	1.0
23–23.9	1.0 (0.5–2.0)
24–24.9	1.5 (0.8–2.9)
25–26.9	2.2 (1.3–3.8)
27–28.9	4.4 (2.6–7.7)
29–30.9	6.7 (3.8–12.0)
31–32.9	11.6 (6.3–21.5)
33–34.9	21.3 (11.4–41.2)
≥ 35	42.1 (22.0–80.6)
Weight gain since age 21	RR for diabetes (95% CI)
0–2 kg	1.0
3–5 kg	0.9 (0.5–1.8)
6–7 kg	1.9 (1.0–3.7)
8–9 kg	3.5 (2.0–6.3)
10–14 kg	3.4 (2.0–5.8)
15+ kg	8.9 (5.5–14.7)
BMI at baseline (kg/m^2)	Hazard ratio for diabetes (95% CI)
< 22	1.00
22–22.9	1.16 (0.48–2.82)
23–23.9	2.39 (1.30–4.40)
24–24.9	2.82 (1.45–5.50)
25–26.9	2.75 (1.55–4.91)
27–28.9	4.63 (2.69–7.96)
29–30.9	4.88 (2.77–8.59)
31–32.9	6.96 (3.79–12.81)
33–34.9	9.28 (4.60–18.72)
≥ 35	11.24 (6.66–18.96)
Weight gain since baseline	Hazard ratio for diabetes (95% CI)
< 5 kg	1.00
5 to < 8 kg	2.11 (1.40–3.18)
8 to < 11 kg	1.19 (0.75–1.89)
11 to < 20 kg	2.66 (1.84–3.85)
≥ 20 kg	3.84 (2.04–7.22)

NOTE: BMI = kg/m^2 unless noted otherwise. Multivariate-adjusted relative risk/hazard risk/odds ratio estimates were used in this table whenever possible.

TABLE 5-34 Body Mass Index (BMI) and Risk of Hypertension and Stroke

Reference	Country	Study Population	Length of Follow-Up
Hypertension			
Ballantyne et al., 1978	UK	637 men and 835 women, mean 45–49 y	Not applicable
Brennan et al., 1980	Australia	600 men and 400 women, 20–49 y	Not applicable
Criqui et al., 1982	United States	2,482 men and 2,298 women, 20+ y	Not applicable
MacMahon et al., 1984	Australia	5,550 men and women, 25–64 y	Not applicable
Brown et al., 2000	United States	16,681 adults, 20+ y	Not applicable
Stroke			
Walker et al., 1996	United States	28,643 men, 40–75 y	5 y
Rexrode et al., 1997	United States	116,759 women, 30–55 y	16 y

[a] RR = relative risk, OR = odds ratio.

Obesity Index	Outcome[a]	
Ponderal Index (height/weight$^{1/3}$)	Ponderal index was significantly associated with blood pressure only in hypertensive, male nonsmokers	
BMI	Significant correlation between BMI and hypertension in men ($p < 0.05$) and women ($p < 0.01$)	
BMI	BMI was significantly associated with diastolic and systolic blood pressure in both men and women	
BMI in men (kg/m^2)	RR for hypertension (95% CI)	
19.5–25.4	1.00	
25.5–30.4	1.72 (1.44–2.05)	
≥ 30.5	2.47 (1.83–3.34)	
BMI in women (kg/m^2)	RR for hypertension (95% CI)	
18.5–24.4	1.00	
24.5–30.4	2.09 (1.72–2.55)	
≥ 30.5	2.96 (2.14–4.10)	
	OR for high blood pressure	
BMI (kg/m^2)	Men	Women
< 25	1.0	1.0
25 to <27	2.4	1.7
27 to <30	3.1	2.3
≥ 30	8.7	9.7
BMI (kg/m^2)	RR for stroke (95% CI)	
< 23	1.00	
23.1–24.4	0.61 (0.32–1.16)	
24.5–25.8	1.00 (0.57–1.75)	
25.9–27.6	1.16 (0.67–2.02)	
≥ 27.7	1.25 (0.72–2.19)	
BMI (kg/m^2)	RR for ischemic stroke (95% CI)	
< 21	1.00	
21 to <23	1.01 (0.70–1.45)	
23 to <25	1.20 (0.83–1.71)	
25 to <27	1.15 (0.78–1.70)	
27 to <29	1.75 (1.17–2.59)	
29 to <32	1.90 (1.28–2.82)	
≥ 32	2.37 (1.60–3.50)	

NOTE: BMI = kg/m^2 unless noted otherwise. Multivariate-adjusted relative risk/hazard risk/odds ratio estimates were used in this table whenever possible.

TABLE 5-35 Body Mass Index (BMI) and Risk of Coronary Heart Disease

Reference	Country	Study Population	Length of Follow-Up
Hubert et al., 1983	United States	2,252 men and 2,818 women, 28–62 y	26 y
Willett et al., 1995	United States	115,818 women, 30–55 y	14 y
Rexrode et al., 2001	United States	16,164 men, 40–84 y	9 y

[a] RR = relative risk, CI = confidence interval.
NOTE: BMI = kg/m^2 unless noted otherwise. Multivariate-adjusted relative risk/hazard risk/odds ratio estimates were used in this table whenever possible.

Obesity Index	Outcome[a]
Metropolitan relative weight (MRW) at baseline (% of desirable weight)	MRW predicted incidence of coronary disease, coronary death, and congestive heart failure in men In women, MRW was positively associated with coronary disease, stroke, congestive failure, and coronary and cardiovascular disease death
BMI at baseline (kg/m^2)	RR for coronary heart disease (95% CI)
< 21	1.00
21–22.9	1.19 (0.98–1.44)
23–24.9	1.46 (1.20–1.77)
25–28.9	2.06 (1.72–2.48)
≥ 29	3.56 (2.96–4.29)
Weight Gain from age 18	RR for coronary heart disease (95% CI)
< 5 kg	1.00
5–7.9 kg	1.25 (1.01–1.55)
8–10.9 kg	1.65 (1.33–2.05)
11–19 kg	1.92 (1.61–2.29)
≥ 20 kg	2.65 (2.17–3.22)
BMI (kg/m^2)	RR for coronary heart disease (95% CI)
< 22.8	1.00
22.8 to < 24.3	1.33 (0.99–1.79)
24.3 to < 25.7	1.28 (0.95–1.73)
25.7 to < 27.6	1.74 (1.31–2.30)
≥ 27.6	1.89 (1.43–2.51)

TABLE 5-36 Body Mass Index (BMI) and Risk of Gallbladder Disease

Reference	Country	Study Population	Length of Follow-Up
Kato et al., 1992	United States	7,831 men, 45+ y	22 y
Stampfer et al., 1992	United States	90,302 women, 34–59 y	8 y
Sahi et al., 1998	United States	16,785 men, 15–24 y	61 y

[a] RR = relative risk, CI = confidence interval.

Obesity Index	Outcome[a]
BMI (kg/m^2)	RR for gallbladder disease (95% CI)
< 21.65	1.0
21.65–23.79	1.1 (0.9–1.5)
23.80–25.80	1.4 (1.1–1.9)
> 25.80	1.8 (1.4–2.3)
BMI (kg/m^2)	RR for cholecystectomy or unremoved gallstones (95% CI)
< 24	1.00
24 to <25	1.36 (1.16–1.60)
25 to <26	1.60 (1.36–1.88)
26 to <27	1.92 (1.60–2.30)
27 to <29	2.32 (2.02–2.66)
29 to <30	2.63 (2.16–3.19)
30 to <35	3.52 (3.11–3.98)
35 to <40	4.64 (3.86–5.57)
40 to <45	5.42 (4.01–7.34)
45+	6.99 (4.48–10.90)
BMI at baseline (kg/m^2)	Rate ratio for gallbladder disease
< 20.0	1.00
20.0–21.9	1.05
22.0–23.9	1.12
≥ 24.0	1.43
BMI change from baseline (kg/m^2)	Rate ratio for gallbladder disease
≤ 0.9	1.00
1.0–2.9	1.01
3.0–5.9	1.74
≥ 6.0	2.16

NOTE: BMI = kg/m^2 unless noted otherwise. Multivariate-adjusted relative risk/hazard risk/odds ratio estimates were used in this table whenever possible.

TABLE 5-37 Body Mass Index (BMI) and Risk of Osteoarthritis

Reference	Country	Study Population	Length of Follow-Up
Felson et al., 1988	United States	1,420 adults, 63–94 at follow-up	~ 36 y
Hart and Spector, 1993	United Kingdom	985 women, 45–64 y	Not applicable
Carman et al., 1994	United States	588 men and 688 women, 50–74 y at follow-up	23 y
Hochberg et al., 1995	United States	465 men and 275 women, 40+ y	Not applicable
Cicuttini et al., 1996	United Kingdom	658 women, twins, 48–69 y	Not applicable

[a] OR = odds ratio.

Obesity Index		Outcome[a]	
Metropolitan relative weight at baseline		Cumulative incidence rate of knee osteoarthritis (n/n [%])	
Men	Women	Men	Women
< 105	< 100	34/110 (30.9)	28/155 (18.1)
105–112	100–108	26/113 (23.0)	42/173 (24.3)
113–120	109–116	38/128 (29.7)	58/170 (34.1)
121–128	117–127	31/112 (27.7)	60/157 (38.2)
≥ 129	≥ 128	53/126 (42.1)	98/176 (55.7)
BMI (kg/m^2)		OR for osteoarthritis of the knee (95% CI)	
< 23.4		1.00	
23.4–26.4		2.86 (1.44–5.68)	
> 26.4		6.17 (3.26–11.71)	
Relative weight index at baseline (% of ideal weight)		Incidence rate for osteoarthritis of the hand and wrist	
< 100		70.0/100	
100–109		74.1/100	
110–119		80.7/100	
120–129		83.7/100	
≥ 130		88.9/100	
		OR for osteoarthritis of the knee (95% CI)	
BMI		Men	Women
Tertile 1		1.00	1.00
Tertile 2		0.94 (0.52–1.70)	2.03 (0.89–4.66)
Tertile 3		2.40 (1.32–4.35)	4.34 (1.89–9.98)
BMI		OR for developing a radiological feature of osteoarthritis per unit of BMI ranged from 1.07 (0.91–1.25) to 1.63 (1.09–2.44) for all twins	

NOTE: BMI = kg/m^2 unless noted otherwise. Multivariate-adjusted relative risk/hazard risk/odds ratio estimates were used in this table whenever possible.

TABLE 5-38 Body Mass Index (BMI) and Risk of Cancer

Reference	Country	Study Population	Length of Follow-Up
Helmrich et al., 1983	United States, Canada, Israel	1,185 women breast cancer cases, median 52 y 3,227 women controls, median 47 y	~ 3 y
Rosenberg et al., 1990	Canada	607 women breast cancer cases, < 70 y 1,214 women controls	4 yr
Chu et al., 1991	United States	4,323 cases and 4,358 controls, women, 20–54 y	Not applicable
Giovannucci et al., 1995	United States	47,723 men, 40–75 y	6 y
Giovannucci et al., 1996	United States	13,057 women, 40–65 y	6 y
Huang et al., 1997	United States	95,256 women, 30–55 y	16 y

[a] RR = relative risk, CI = confidence interval.

Obesity Index	Outcome[a]	
	RR for breast cancer in postmenopausal women	
BMI (kg/m^2)	(95% CI)	
< 21	1.0	
21–24	1.5 (1.1–1.9)	
25–27	1.6 (1.2–2.1)	
≥ 28	1.3 (1.0–1.8)	
	RR for breast cancer (95% CI)	
BMI (kg/m^2)	Premenopausal	Postmenopausal
< 21	1.0	1.0
21–25	0.9 (0.7–1.3)	0.8 (0.5–1.1)
≥ 26	0.8 (0.5–1.2)	1.2 (0.8–1.7)
	RR for breast cancer in menopausal	
BMI (kg/m^2)	women (95% CI)	
< 20.0	1.0	
20.0–21.99	1.1 (0.7–1.5)	
22.0–24.89	1.5 (1.0–2.2)	
24.9–27.29	2.2 (1.4–3.5)	
27.3–32.29	1.8 (1.1–2.8)	
≥ 32.3	2.7 (1.5–5.4)	
BMI (kg/m^2)	RR for colon cancer (95% CI)	
< 22	1.0	
22–24.9	0.87 (0.54–1.39)	
25–26.9	1.31 (0.85–2.02)	
27–28.9	1.48 (0.89–2.56)	
≥ 29	1.48 (0.89–2.46)	
BMI (kg/m^2)	RR for distal colon adenomas (95% CI)	
< 21	1.00	
21–22	0.82 (0.59–1.15)	
23–24	1.18 (0.85–1.63)	
25–28	1.03 (0.72–1.47)	
≥ 29	1.50 (1.02–2.21)	
	RR for breast cancer in postmenopausal women	
Weight gain from age 18	(95% CI)	
≤ 2.0 kg	1.00	
2.1–5.0 kg	1.20 (0.96–1.51)	
5.1–10.0 kg	1.18 (0.96–1.45)	
10.1–20.0 kg	1.20 (0.98–1.47)	
20.1–25.0 kg	1.40 (1.10–1.78)	
> 25.0 kg	1.41 (1.12–1.78)	

NOTE: BMI = kg/m^2 unless noted otherwise. Multivariate-adjusted relative risk/hazard risk/odds ratio estimates were used in this table whenever possible.

- Additional research is needed on the extent to which energy expenditure changes when a hypocaloric diet is consumed, and whether dietary composition affects the extent of change in energy expenditure.
- Independent of energy, identification of dietary components, if any, that could favorably affect body composition is needed.

REFERENCES

Abbott WG, Howard BV, Christin L, Freymond D, Lillioja S, Boyce VL, Anderson TE, Bogardus C, Ravussin E. 1988. Short-term energy balance: Relationship with protein, carbohydrate, and fat balances. *Am J Physiol* 255:E332–E337.

Acheson K, Jéquier E, Wahren J. 1983. Influence of beta-adrenergic blockade on glucose-induced thermogenesis in man. *J Clin Invest* 72:981–986.

Albu J, Shur M, Curi M, Murphy L, Heymsfield SB, Pi-Sunyer FX. 1997. Resting metabolic rate in obese, premenopausal black women. *Am J Clin Nutr* 66:531–538.

Allen JC, Keller RP, Archer P, Neville MC. 1991. Studies in human lactation: Milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutr* 54:69–80.

Amatruda JM, Richeson F, Welle SL, Brodows RG, Lockwood DH. 1988. The safety and efficacy of a controlled low-energy ('very-low-calorie') diet in the treatment of non-insulin-dependent diabetes and obesity. *Arch Intern Med* 148:873–877.

Amatruda JM, Statt MC, Welle SL. 1993. Total and resting energy expenditure in obese women reduced to ideal body weight. *J Clin Invest* 92:1236–1242.

Anderson DM, Williams FH, Merkatz RB, Schulman PK, Kerr DS, Pittard WB. 1983. Length of gestation and nutritional composition of human milk. *Am J Clin Nutr* 37:810–814.

Anderson GH, Atkinson SA, Bryan MH. 1981. Energy and macronutrient content of human milk during early lactation from mothers giving birth prematurely and at term. *Am J Clin Nutr* 34:258–265.

Armstrong DW. 1998. Metabolic and endocrine responses to cold air in women differing in aerobic capacity. *Med Sci Sport Exerc* 30:880–884.

Ashworth A. 1969. Metabolic rates during recovery from protein–calorie malnutrition: The need for a new concept of specific dynamic action. *Nature* 223:407–409.

Assel B, Rossi K, Kalhan S. 1993. Glucose metabolism during fasting through human pregnancy: Comparison of tracer method with respiratory calorimetry. *Am J Physiol* 265:E351–E356.

Astrup A, Buemann B, Western P, Toubro S, Raben A, Christensen NJ. 1994. Obesity as an adaptation to a high-fat diet: Evidence from a cross-sectional study. *Am J Clin Nutr* 59:350–355.

Astrup A, Toubro S, Dalgaard LT, Urhammer SA, Sorensen TI, Pedersen O. 1999. Impact of the v/v 55 polymorphism of the uncoupling protein 2 gene on 24-h energy expenditure and substrate oxidation. *Int J Obes Relat Metab Disord* 23:1030–1034.

Bahr R, Ingnes I, Vaage O, Sejersted OM, Newsholme EA. 1987. Effect of duration of exercise on excess postexercise O_2 consumption. *J Appl Physiol* 62:485–490.

Bailey DA, McCulloch RG. 1990. Bone tissue and physical activity. *Can J Sport Sci* 15:229–239.

Ballantyne D, Devine BL, Fife R. 1978. Interrelation of age, obesity, cigarette smoking, and blood pressure in hypertensive patients. *Br Med J* 1:880–881.

Ballor DL, Keesey RE. 1991. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *Int J Obes* 15:717–726.

Bandini LG, Schoeller DA, Cyr HN, Dietz WH. 1990a. Validity of reported energy intake in obese and nonobese adolescents. *Am J Clin Nutr* 52:421–451.

Bandini LG, Schoeller DA, Dietz WH. 1990b. Energy expenditure in obese and nonobese adolescents. *Pediatr Res* 27:198–203.

Barlow SE, Dietz WH. 1998. Obesity evaluation and treatment: Expert Committee recommendations. *Pediatrics* 102:E29.

Bathalon GP, Tucker KL, Hays NP, Vinken AG, Greenberg AS, McCrory MA, Roberts SB. 2000. Psychological measures of eating behavior and the accuracy of 3 common dietary assessment methods in healthy postmenopausal women. *Am J Clin Nutr* 71:739–745.

Baumgartner RN, Roche AF, Himes JH. 1986. Incremental growth tables: Supplementary to previously published charts. *Am J Clin Nutr* 43:711–722.

Bellizzi MC, Dietz WH. 1999. Workshop on childhood obesity: Summary of the discussion. *Am J Clin Nutr* 70:173S–175S.

Benedict FG, Cathcart EP. 1913. *Muscular Work. A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine.* Washington, DC: Carnegie Institution. Pp. 163–176.

Benedict FG, Talbot FB. 1914. *The Gaseous Metabolism of Infants, with Special Reference to its Relation of Pulse-Rate and Muscular Activity.* Washington, DC: Carnegie Institution.

Benedict FG, Talbot FB. 1921. *Metabolism and Growth from Birth to Puberty.* Washington, DC: Carnegie Institution.

Bielinski R, Schutz Y, Jequier E. 1985. Energy metabolism during the postexercise recovery in man. *Am J Clin Nutr* 42:69–82.

Bingham SA, Day NE. 1997. Using biochemical markers to assess the validity of prospective dietary assessment methods and the effect of energy adjustment. *Am J Clin Nutr* 65:1130S–1137S.

Bingham SA, Goldberg GR, Coward WA, Prentice AM, Cummings JH. 1989. The effect of exercise and improved physical fitness on basal metabolic rate. *Br J Nutr* 61:155–173.

Bingham SA, Gill C, Welch A, Day K, Cassidy A, Khaw KT, Sneyd MJ, Key TJ, Roe L, Day NE. 1994. Comparison of dietary assessment methods in nutritional epidemiology: Weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. *Br J Nutr* 72:619–643.

Bisdee JT, James WP, Shaw MA. 1989. Changes in energy expenditure during the menstrual cycle. *Br J Nutr* 61:187–199.

Bitar A, Fellmann N, Vernet J, Coudert J, Vermorel M. 1999. Variations and determinants of energy expenditure as measured by whole-body indirect calorimetry during puberty and adolescence. *Am J Clin Nutr* 69:1209–1216.

Blaak EE, Westerterp KR, Bar-Or O, Wouters LJ, Saris WH. 1992. Total energy expenditure and spontaneous activity in relation to training in obese boys. *Am J Clin Nutr* 55:777–782.

Black AE. 1999. Small eaters or under-reporters? In: Guy-Grand B, Ailhaud G, eds. *Progress in Obesity Research 8.* London: John Libbey. Pp. 223–228.

Black AE, Prentice AM, Goldberg GR, Jebb SA, Bingham SA, Livingstone MB, Coward WA. 1993. Measurements of total energy expenditure provide insights into the validity of dietary measurements of energy intake. *J Am Diet Assoc* 93:572–579.

Black AE, Coward WA, Prentice AM. 1996. Human energy expenditure in affluent societies: An analysis of 574 doubly-labelled water measurements. *Eur J Clin Nutr* 50:72–92.

Blaza S, Garrow JS. 1983. Thermogenic response to temperature, exercise and food stimuli in lean and obese women, studied by 24 h direct calorimetry. *Br J Nutr* 49:171–180.

Bloesch D, Schutz Y, Breitenstein E, Jequier E, Felber JP. 1988. Thermogenic response to an oral glucose load in man: Comparison between young and elderly subjects. *J Am Coll Nutr* 7:471–483.

Bogardus C, Lillioja S, Ravussin E, Abbott W, Zawadzki JK, Young A, Knowler WC, Jacobowitz R, Moll PP. 1986. Familial dependence of the resting metabolic rate. *N Engl J Med* 315:96–100.

Bouchard C, Perusse L. 1993. Genetics of obesity. *Annu Rev Nutr* 13:337–354.

Bouchard C, Tremblay A, Nadeau A, Despres JP, Theriault G, Boulay MR, Lortie G, Leblanc C, Fournier G. 1989. Genetic effect in resting and exercise metabolic rates. *Metabolism* 38:364–370.

Bouchard C, Tremblay A, Despres JP, Nadeau A, Lupien PJ, Theriault G, Dussault J, Moorjani S, Pinault S, Fournier G. 1990. The response to long-term overfeeding in identical twins. *N Engl J Med* 322:1477–1482.

Bratteby LE, Sandhagen B, Lotborn M, Samuelson G. 1997. Daily energy expenditure and physical activity assessed by an activity diary in 374 randomly selected 15-year-old adolescents. *Eur J Clin Nutr* 51:592–600.

Brennan PJ, Simpson JM, Blacket RB, McGilchrist CA. 1980. The effects of body weight on serum cholesterol, serum triglycerides, serum urate and systolic blood pressure. *Aust N Z J Med* 10:15–20.

Briefel RR, Sempos CT, McDowell MA, Chien S, Alaimo K. 1997. Dietary methods research in the Third National Health and Nutrition Examination Survey: Underreporting of energy intake. *Am J Clin Nutr* 65:1203S–1209S.

Bronstein MN, Mak RP, King JC. 1995. The thermic effect of food in normal-weight and overweight pregnant women. *Br J Nutr* 74:261–275.

Brooks GA, Butterfield GE, Wolfe RR, Groves BM, Mazzeo RS, Sutton JR, Wolfel EE, Reeves JT. 1991. Increased dependence on blood glucose after acclimatization to 4,300 m. *J Appl Physiol* 70:919–927.

Brooks GA, Wolfel EE, Groves BM, Bender PR, Butterfield GE, Cymerman A, Mazzeo RS, Sutton JR, Wolfe RR, Reeves JT. 1992. Muscle accounts for glucose disposal but not lactate appearance during exercise after acclimatization to 4,300 m. *J Appl Physiol* 72:2435–2445.

Brooks GA, Fahey TD, White TP, Baldwin KM. 2000. *Exercise Physiology: Human Bioenergetics and Its Applications*, 3rd ed. Mountain View, CA: Mayfield Publishing.

Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, Ernst ND, Horan M. 2000. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res* 8:605–619.

Buemann B, Astrup A, Christensen NJ, Madsen J. 1992. Effect of moderate cold exposure on 24-h energy expenditure: Similar response in postobese and nonobese women. *Am J Physiol* 263:E1040–1045.

Buenen GP, Malina RM, Renson R, Simons J, Ostyn M, Lefevre J. 1992. Physical activity and growth, maturation and performance: A longitudinal study. *Med Sci Sports Exerc* 24(5):576–585.

Burstein R, Coward AW, Askew WE, Carmel K, Irving C, Shpilberg O, Moran D, Pikarsky A, Ginot G, Sawyer M, Golan R, Epstein Y. 1996. Energy expenditure variations in soldiers performing military activities under cold and hot climate conditions. *Mil Med* 161:750–754.

Butte NF. 1990. Basal metabolism of infants. In: Schürch B, Scrimshaw NS, eds. *Activity, Energy Expenditure and Energy Requirements of Infants and Children.* Switzerland: Nestlé Foundation. Pp. 117–137.

Butte NF. 2000. Fat intake of children in relation to energy requirements. *Am J Clin Nutr* 72:1246S–1252S.

Butte NF, Calloway DH. 1981. Evaluation of lactational performance in Navajo women. *Am J Clin Nutr* 34:2210–2215.

Butte NF, Hopkinson JM. 1998. Body composition changes during lactation are highly variable among women. *J Nutr* 128:381S–385S.

Butte NF, Garza C, O'Brian Smith E, Nichols BL. 1984a. Human milk intake and growth in exclusively breast-fed infants. *J Pediatr* 104:187–195.

Butte NF, Garza C, Stuff JE, Smith EO, Nichols BL. 1984b. Effect of maternal diet and body composition on lactational performance. *Am J Clin Nutr* 39:296–306.

Butte NF, Wong WW, Garza C. 1989. Energy cost of growth during infancy. *Proc Nutr Soc* 48:303–312.

Butte NF, Wong WW, Ferlic L, Smith EO, Klein PD, Garza C. 1990. Energy expenditure and deposition of breast-fed and formula-fed infants during early infancy. *Pediatr Res* 28:631–640.

Butte NF, Hopkinson JM, Mehta N, Moon JK, Smith EO. 1999. Adjustments in energy expenditure and substrate utilization during late pregnancy and lactation. *Am J Clin Nutr* 69:299–307.

Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ. 2000a. Body composition during the first two years of life: An updated reference. *Pediatr Res* 47:578–585.

Butte NF, Wong WW, Hopkinson JM, Heinz CJ, Mehta NR, Smith EO. 2000b. Energy requirements derived from total energy expenditure and energy deposition during the first 2 y of life. *Am J Clin Nutr* 72:1558–1569.

Butte NF, Wong WW, Hopkinson JM. 2001. Energy requirements of lactating women derived from doubly labeled water and milk energy output. *J Nutr* 131:53–58.

Butterfield GE, Gates J, Fleming S, Brooks GA, Sutton JR, Reeves JT. 1992. Increased energy intake minimizes weight loss in men at high altitude. *J Appl Physiol* 72:1741–1748.

Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA. 1994. Obesity as a risk factor for osteoarthritis of the hand and wrist: A prospective study. *Am J Epidemiol* 139:119–129.

Carpenter WH, Poehlman ET, O'Connell M, Goran MI. 1995. Influence of body composition and resting metabolic rate on variation in total energy expenditure: A meta-analysis. *Am J Clin Nutr* 61:4–10.

Carpenter WH, Fonong T, Toth MJ, Ades PA, Calles-Escandon J, Walston JD, Poehlman ET. 1998. Total daily energy expenditure in free-living older African-Americans and Caucasians. *Am J Physiol* 274:E96–E101.

Cartee GD, Douen AG, Ramlal T, Klip A, Holloszy JO. 1991. Stimulation of glucose transport in skeletal muscle by hypoxia. *J Appl Physiol* 70:1593–1600.

Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. 1994. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961–969.

Chu SY, Lee NC, Wingo PA, Senie RT, Greenberg RS, Peterson HB. 1991. The relationship between body mass and breast cancer among women enrolled in the Cancer and Steroid Hormone Study. *J Clin Epidemiol* 44:1197–1206.

Cicuttini FM, Baker JR, Spector TD. 1996. The association of obesity with osteoarthritis of the hand and knee in women: A twin study. *J Rheumatol* 23:1221–1226.

Clagett DD, Hathaway ML. 1941. Basal metabolism of normal infants from three to fifteen months of age. *Am J Dis Child* 62:967–980.

Clarke WR, Schrott HG, Leaverton PE, Connor WE, Lauer RM. 1978. Tracking of blood lipids and blood pressures in school age children: the Muscatine study. *Circulation* 58:626–634.

Colditz GA, Willett SC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE. 1990. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 132:501–513.

Colditz GA, Willett WC, Rotnitzky A, Manson JE. 1995. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122:481–486.

Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. 2000. Establishing a standard definition for child overweight and obesity worldwide: International survey. *Br Med J* 320:1–6.

Consolazio CF, Johnson RE, Pecora LJ. 1963. *Physiological Measurements of Metabolic Functions in Man.* New York: McGraw-Hill. Pp. 414–436.

Coward WA, Prentice AM, Murgatroyd PR, Davies HL, Cole TJ, Sawyer M, Goldberg GR, Halliday D, MacNamara JP. 1984. Measurement of CO_2 and water production rates in man using ^2H, ^{18}O-labelled H_2O: Comparisons between calorimeter and isotope values. In: Van Es AJ, ed. *Human Energy Metabolism: Physical Activity and Energy Expenditure Measurements in Epidemiological Research Based upon Direct and Indirect Calorimetry.* Den Haag: CIP-gegevens Koninklijke Bibliotheek. Pp. 126–128.

Criqui MH, Mebane I, Wallace RB, Heiss G, Holdbrook MJ. 1982. Multivariate correlates of adult blood pressures in nine North American populations: The Lipid Research Clinics Prevalence Study. *Prev Med* 11:391–402.

Dauncey MJ. 1981. Influence of mild cold on 24 h energy expenditure, resting metabolism and diet-induced thermogenesis. *Br J Nutr* 45:257–267.

Davies PS, Ewing G, Lucas A. 1989. Energy expenditure in early infancy. *Br J Nutr* 62:621–629.

Davies PS, Ewing G, Coward WA, Lucas A. 1990. Energy metabolism in breast and formula fed infants. In: Atkinson SA, Hanson LA, Chandra RK, eds. *Breast-Feeding, Nutrition, Infection and Infant Growth in Developed and Emerging Countries.* St. John's, Newfoundland: Arts Biomedical. P. 521.

Davies PS, Day JM, Lucas A. 1991. Energy expenditure in early infancy and later body fatness. *Int J Obes* 15:727–731.

Davies PS, Wells JC, Fieldhouse CA, Day JM, Lucas A. 1995. Parental body composition and infant energy expenditure. *Am J Clin Nutr* 61:1026–1029.

Davies PS, Wells JC, Hinds A, Day JM, Laidlaw A. 1997. Total energy expenditure in 9 month and 12 month infants. *Eur J Clin Nutr* 51:249–252.

de Bruin NC, Degenhart HJ, Gal S, Westerterp KR, Stijnen T, Visser HK. 1998. Energy utilization and growth in breast-fed and formula-fed infants measured prospectively during the first year of life. *Am J Clin Nutr* 67:885–896.

de Castro JM, Orozco S. 1990. Moderate alcohol intake and spontaneous eating patterns of humans: Evidence of unregulated supplementation. *Am J Clin Nutr* 52:246–253.

de Groot LC, Boekholt HA, Spaaij CJ, van Raaij JM, Drijvers JJ, van der Heijden LJ, van der Heide D, Hautvast JG. 1994. Energy balances of healthy Dutch women before and during pregnancy: Limited scope for metabolic adaptations in pregnancy. *Am J Clin Nutr* 59:827–832.

Deheeger M, Rolland-Cachera MF, Fontvieille AM. 1997. Physical activity and body composition in 10 year old French children: linkages with nutritional intake? *Int J Obes Relat Metab Disord* 21:372-379.

Denne SC, Kalhan SC. 1987. Leucine metabolism in human newborns. *Am J Physiol* 253:E608–E615.

Denne SC, Patel D, Kalhan SC. 1991. Leucine kinetics and fuel utilization during a brief fast in human pregnancy. *Metabolism* 40:1249–1256.

DePue JD, Clark MM, Ruggiero L, Medeiros ML, Pera V. 1995. Maintenance of weight loss: A needs assessment. *Obes Res* 3:241–248.

Despres J-P, Nadeau A, Tremblay A, Ferland M, Moorjani S, Lupien PJ, Thériault G, Pinault S, Bouchard C. 1989. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. *Diabetes* 38:304–309.

Dewey KG, Finley DA, Lonnerdal B. 1984. Breast milk volume and composition during late lactation (7–20 months). *J Pediatr Gastroenterol Nutr* 3:713–720.

Dewey KG, Beaton G, Fjeld C, Lonnerdal B, Reeds P. 1996. Protein requirements of infants and children. *Eur J Clin Nutr* 50:S119–S150.

Dhuper S, Warren MP, Brooks-Gunn J, Fox R. 1990. Effects of hormonal status on bone density in adolescent girls. *J Clin Endocrinol Metab* 71:1083–1088.

Dionne I, Despres JP, Bouchard C, Tremblay A. 1999. Gender difference in the effect of body composition on energy metabolism. *Int J Obes Relat Metab Disord* 23:312–319.

Doar JWH, Wilde, Thompson ME, Stewell PFJ. 1975. Influence of treatment with diet alone on oral glucose-tolerance test and plasma sugar and insulin levels in patients with maturity-onset diabetes mellitus. *Lancet* 1:1263–1266.

Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW, Blair SN. 1999. Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: A randomized trial. *J Am Med Assoc* 281:327–334.

Durnin JV. 1990. Low energy expenditures in free-living populations. *Eur J Clin Nutr* 44:95–102.

Durnin JV. 1996. Energy requirements: General principles. *Eur J Clin Nutr* 50: S2–S10.

Durnin JV, McKillop FM, Grant S, Fitzgerald G. 1987. Energy requirements of pregnancy in Scotland. *Lancet* 2:897–900.

Edholm OG, Adam JM, Healey MJ, Wolff HS, Goldsmith R, Best TW. 1970. Food intake and energy expenditure of army recruits. *Br J Nutr* 24:1091–1107.

Elia M. 1991. Energy equivalents of CO_2 and their importance in assessing energy expenditure when using tracer techniques. *Am J Physiol* 260:E75–E88.

Eliakim A, Barstow TJ, Brasel JA, Ajie H, Lee WN, Renslo R, Berman N, Cooper DM. 1996. Effect of exercise training on energy expenditure, muscle volume, and maximal oxygen uptake in female adolescents. *J Pediatr* 129:537–543.

Ellis KJ. 1997. Body composition of a young, multiethnic, male population. *Am J Clin Nutr* 66:1323–1331.

Ellis KJ, Abrams SA, Wong WW. 1997. Body composition of a young, multiethnic female population. *Am J Clin Nutr* 65:724–731.

EPA (Environmental Protection Agency). 1991. *Building Air Quality: A Guide for Building Owners and Facility Managers.* Washington, DC: U.S. Government Printing Office.

FAO/WHO/UNU (Food and Agriculture Organization/World Health Organization/United Nations University). 1985. *Energy and Protein Requirements.* Report of a Joint FAO/WHO/UNU Expert Consultation. Technical Report Series No. 724. Geneva: WHO.

Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. 1988. Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med* 109:18–24.

Ferraro R, Lillioja S, Fontvieille AM, Rising R, Bogardus C, Ravussin E. 1992. Lower sedentary metabolic rate in women compared with men. *J Clin Invest* 90:780–784.

Ferris AM, Dotts MA, Clark RM, Ezrin M, Jensen RG. 1988. Macronutrients in human milk at 2, 12, and 16 weeks postpartum. *J Am Diet Assoc* 88:694–697.

Firouzbakhsh S, Mathis RK, Dorchester WL, Oseas RS, Groncy PK, Grant KE, Finklestein JZ. 1993. Measured resting energy expenditure in children. *J Pediatr Gastroenterol Nutr* 16:136–142.

Fjeld CR, Schoeller DA, Brown KH. 1989. Body composition of children recovering from severe protein-energy malnutrition at two rates of catch-up growth. *Am J Clin Nutr* 50:1266–1275.

Flatt JP. 1978. The biochemistry of energy expenditure. In: Bray GA, ed. *Recent Advances in Obesity Research II.* London: Newman Publishing. Pp. 211–228.

Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R, Simons-Morton DG, Williams MA, Bazzarre T. 2001. Exercise standards for testing and training: A statement for healthcare professionals from the American Heart Association. *Circulation* 104:1694–1740.

Fomon SJ, Haschke F, Ziegler EE, Nelson SE. 1982. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr* 35:1169–1175.

Fontvieille AM, Dwyer J, Ravussin E. 1992. Resting metabolic rate and body composition of Pima Indian and Caucasian children. *Int J Obes Relat Metab Disord* 16:535–542.

Forbes GB. 1987. *Human Body Composition. Growth, Aging, Nutrition, and Activity.* New York: Springer-Verlag.

Ford ES, Williamson DF, Liu S. 1997. Weight change and diabetes incidence: Findings from a national cohort of US adults. *Am J Epidemiol* 146:214–222.

Forman JN, Miller WC, Szymanski LM, Fernhall B. 1998. Differences in resting metabolic rates of inactive obese African-American and Caucasian women. *Int J Obes Relat Metab Disord* 22:215–221.

Forsum E, Sadurskis A, Wager J. 1988. Resting metabolic rate and body composition of healthy Swedish women during pregnancy. *Am J Clin Nutr* 47:942–947.

Forsum E, Kabir N, Sadurskis A, Westerterp K. 1992. Total energy expenditure of healthy Swedish women during pregnancy and lactation. *Am J Clin Nutr* 56:334–342.

Foster GD, Wadden TA, Vogt RA. 1997. Resting energy expenditure in obese African American and Caucasian women. *Obes Res* 5:1–8.

Foster GD, Wadden TA, Swain RM, Anderson DA, Vogt RA. 1999. Changes in resting energy expenditure after weight loss in obese African American and white women. *Am J Clin Nutr* 69:13–17.

Frigerio C, Schutz Y, Whitehead R, Jequier E. 1991. A new procedure to assess the energy requirements of lactation in Gambian women. *Am J Clin Nutr* 54:526–533.

Fukagawa NK, Bandini LG, Young JB. 1990. Effect of age on body composition and resting metabolic rate. *Am J Physiol* 259:E233–E238.

Fukagawa NK, Bandini LG, Lim PH, Roingeard F, Lee MA, Young JB. 1991. Protein-induced changes in energy expenditure in young and old individuals. *Am J Physiol* 260:E345–E352.

Gaesser GA, Brooks GA. 1984. Metabolic bases of excess post-exercise oxygen consumption: A review. *Med Sci Sports Exerc* 16:29–43.

Garby L, Kurzer MS, Lammert O, Nielsen E. 1987. Energy expenditure during sleep in men and women: Evaporative and sensible heat losses. *Hum Nutr Clin Nutr* 41:225–233.

Garby L, Lammert O, Nielsen E. 1990. Changes in energy expenditure of light physical activity during a 10 day period at 34°C environmental temperature. *Eur J Clin Nutr* 44:241–244.

Geithner CA, Woynarowska B, Malina RM. 1998. The adolescent spurt and sexual maturation in girls active and nonactive in sport. *Ann Hum Biol* 25(5):415–423.

Gibson RS, Vanderkooy PD, MacDonald AC, Goldman A, Ryan BA, Berry M. 1989. A growth-limiting, mild zinc-deficiency syndrome in some Southern Ontario boys with low height percentiles. *Am J Clin Nutr* 49:1266–1276.

Gilliam TB, Freedson. 1980. Effects of a 12-week school physical fitness program on peak VO2, body composition and blood lipids in 7 to 9 year old children. *Int J Sports Med* 1:73–78.

Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. 1995. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med* 122:327–334.

Giovannucci E, Colditz GA, Stampfer MJ, Willett WC. 1996. Physical activity, obesity, and risk of colorectal adenoma in women (United States). *Cancer Causes Control* 7:253–263.

Golay A, Schutz Y, Meyer HU, Thiebaud D, Curchod B, Maeder E, Felber JP, Jequier E. 1982. Glucose-induced thermogenesis in nondiabetic and diabetic obese subjects. *Diabetes* 31:1023–1028.

Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, Prentice AM. 1991a. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify underrecording. *Eur J Clin Nutr* 45:569–581.

Goldberg GR, Prentice AM, Coward WA, Davies HL, Murgatroyd PR, Sawyer MB, Ashford J, Black AE. 1991b. Longitudinal assessment of the components of energy balance in well-nourished lactating women. *Am J Clin Nutr* 54:788–798.

Goldberg GR, Prentice AM, Coward WA, Davies HL, Murgatroyd PR, Wensing C, Black AE, Harding M, Sawyer M. 1993. Longitudinal assessment of energy expenditure in pregnancy by the doubly labeled water method. *Am J Clin Nutr* 57:494–505.

Goran MI, Poehlman ET. 1992. Endurance training does not enhance total energy expenditure in healthy elderly persons. *Am J Physiol* 263:E950–E957.

Goran MI, Calles-Escandon J, Poehlman ET, O'Connell M, Danforth E. 1994a. Effects of increased energy intake and/or physical activity on energy expenditure in young healthy men. *J Appl Physiol* 77:366–372.

Goran MI, Kaskoun M, Johnson R. 1994b. Determinants of resting energy expenditure in young children. *J Pediatr* 125:362–367.

Goran MI, Carpenter WH, McGloin A, Johnson R, Hardin JM, Weinsier RL. 1995a. Energy expenditure in children of lean and obese parents. *Am J Physiol* 268:E917–E924.

Goran MI, Kaskoun M, Johnson R, Martinez C, Kelly B, Hood V. 1995b. Energy expenditure and body fat distribution in Mohawk children. *Pediatrics* 95:89–95.

Goran MI, Gower BA, Nagy TR, Johnson RK. 1998a. Developmental changes in energy expenditure and physical activity in children: Evidence for a decline in physical activity in girls before puberty. *Pediatrics* 101:887–891.

Goran MI, Nagy TR, Gower BA, Mazariegos M, Solomons N, Hood V, Johnson R. 1998b. Influence of sex, seasonality, ethnicity, and geographic location on the components of total energy expenditure in young children: Implications for energy requirements. *Am J Clin Nutr* 68:675–682.

Goran MI, Shewchuk R, Gower BA, Nagy TR, Carpenter WH, Johnson RK. 1998c. Longitudinal changes in fatness in white children: No effect of childhood energy expenditure. *Am J Clin Nutr* 67:309–316.

Griffiths M, Payne PR. 1976. Energy expenditure in small children of obese and non-obese parents. *Nature* 260:698–700.

Grund A, Vollbrecht H, Frandsen W, Krause H, Siewers M, Rieckert H, Muller MJ. 2000. No effect of gender on different components of daily energy expenditure in free living prepubertal children. *Int J Obes Relat Metab Disord* 24:299–305.

Grund A, Krause H, Kraus M, Siewers M, Rieckert H, Müller MJ. 2001. Association between different attributes of physical activity and fat mass in untrained, endurance- and resistance-trained men. *Eur J Appl Physiol* 84:310–320.

Grundy SM, Mok HYI, Zech L, Steinberg D, Berman M. 1979. Transport of very low density lipoprotein triglycerides in varying degrees of obesity and hypertriglyceridemia. *J Clin Invest* 63 :1274–1283.

Guillermo-Tuazon MA, Barba CV, van Raaij JM, Hautvast JG. 1992. Energy intake, energy expenditure, and body composition of poor rural Philippine women throughout the first 6 mo of lactation. *Am J Clin Nutr* 56:874–880.

Gutin B, Barbeau P, Owens S, Lemmon CR, Bauman M, Allison J, Kang HS, Litaker MS. 2002. Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents. *Am J Clin Nutr* 75:818–826.

Guo S, Roche AF, Fomon SJ, Nelson SE, Chumlea WC, Rogers RR, Baumgartner RN, Ziegler EE, Siervogel RM. 1991. Reference data on gains in weight and length during the first two years of life. *J Pediatr* 119:355–362.

Hadden DR, Montgomery DAD, Skelly RJ, Trimble ER, Weaver JA, Wilson EA, Buchanan KD. 1975. Maturity onset diabetes mellitus: response to intensive dietary management. *Br Med J* 2:276–278.

Haffner SM, Mitchell BD, Hazuda HP, Stern MP. 1991. Greater influence of central distribution of adipose tissue on incidence of non-insulin-dependent diabetes in women than men. *Am J Clin Nutr* 53:1312–1317.

Haggarty P, McNeill G, Abu Manneh MK, Davidson L, Milne E, Duncan G, Ashton J. 1994. The influence of exercise on the energy requirements of adult males in the UK. *Br J Nutr* 72:799–813.

Harris JA, Benedict FG. 1919. *A Biometric Study of Basal Metabolism in Man.* Washington, DC: Carnegie Institution.

Hart DJ, Spector TD. 1993. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: The Chingford Study. *J Rheumatol* 20:331–335.

Hartman WM, Stroud M, Sweet DM, Saxton J. 1993. Long-term maintenance of weight loss following supplemented fasting. *Int J Eat Disord* 14:87–93.

Haschke F. 1989. Body composition during adolescence. In: *Body Composition Measurements in Infants and Children: Report of the 98th Ross Conference on Pediatric Research.* Columbus, OH: Ross Laboratories. Pp. 76–83.

Hay WW. 1994. Placental supply of energy and protein substrates to the fetus. *Acta Paediatr Suppl* 405:13–19.

Hayter JE, Henry CJ. 1993. Basal metabolic rate in human subjects migrating between tropical and temperate regions: A longitudinal study and review of previous work. *Eur J Clin Nutr* 47:724–734.

Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B, Dewey KG. 1993. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: The DARLING Study. *Am J Clin Nutr* 58:152–161.

Heitmann BL, Kaprio J, Harris JR, Rissanen A, Korkeila M, Koskenvuo M. 1997. Are genetic determinants of weight gain modified by leisure-time physical activity? A prospective study of Finnish twins. *Am J Clin Nutr* 66:672–678.

Helmrich SP, Shapiro S, Rosenberg L, Kaufman DW, Slone D, Bain C, Miettinen OS, Stolley PD, Rosenshein NB, Knapp RC, Leavitt T, Schottenfeld D, Engle RL, Levy M. 1983. Risk factors for breast cancer. *Am J Epidemiol* 117:35–45.

Henry CJ. 2000. Mechanisms of changes in basal metabolism during ageing. *Eur J Clin Nutr* 54:S77–S91.

Herring JL, Mole PA, Meredith CN, Stern JS. 1992. Effect of suspending exercise training on resting metabolic rate in women. *Med Sci Sports Exerc* 24:59–65.

Hessemer V, Bruck K. 1985. Influence of menstrual cycle on thermoregulatory, metabolic, and heart rate responses to exercise at night. *J Appl Physiol* 59:1911–1917.

Heyman MB, Young VR, Fuss P, Tsay R, Joseph L, Roberts SB. 1992. Underfeeding and body weight regulation in normal-weight young men. *Am J Physiol* 263:R250–R257.

Heymsfield SB, Gallagher D, Kotler DP, Wang Z, Allison DB, Heshka S. 2002. Body-size dependence of resting energy expenditure can be attributed to nonenergetic homogeneity of fat-free mass. *Am J Physiol* 282:E132–E138.

Hill JO, Peters JC. 1998. Environmental contributions to the obesity epidemic. *Science* 280:1371–1374.

Hill JR. 1964. The development of thermal stability in the newborn baby. In: Jonxis JH, Visser HK, Troelstra JA, eds. *The Adaptation of the Newborn Infant to Extra-Uterine Life*. Springfield, IL: Charles Thomas. Pp. 223–228.

Hochberg MC, Lethbridge-Cejku M, Scott WW, Reichle R, Plato CC, Tobin JD. 1995. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: Data from the Baltimore Longitudinal Study of Aging. *J Rheumatol* 22:488–493.

Holden JH, Darga LL, Olson SM, Stettner DC, Ardito EA, Lucas CP. 1992. Long-term follow-up of patients attending a combination very-low calorie diet and behaviour therapy weight loss programme. *Int J Obes Relat Metab Disord* 16:605–613.

Holliday MA. 1971. Metabolic rate and organ size during growth from infancy to maturity and during late gestation and early infancy. *Pediatrics* 47:169–179.

Holmes FL. 1985. *Lavoisier and the Chemistry of Life*. Madison, WI: University of Wisconsin Press.

Howe JC, Rumpler WV, Seale JL. 1993. Energy expenditure by indirect calorimetry in premenopausal women: Variation within one menstrual cycle. *J Nutr Biochem* 4:268–273.

Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, Hennekens CH, Rosner B, Speizer FE, Willett WC. 1997. Dual effects of weight and weight gain on breast cancer risk. *J Am Med Assoc* 278:1407–1411.

Huang Z, Willett WC, Manson JE, Rosner B, Stampfer MJ, Speizer FE, Colditz GA. 1998. Body weight, weight change, and risk for hypertension in women. *Ann Intern Med* 128:81–88.

Hubert HB, Feinleib M, McNamara PM, Castelli WP. 1983. Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 67:968–977.

Hunt JF, White JR. 1980. Effect of ten weeks of vigorous daily exercise on serum lipids and lipoproteins in teenage males. *Med Sci Sports Exerc* 12:93.

Hunter GR, Weinsier RL, Darnell BE, Zuckerman PA, Goran MI. 2000. Racial differences in energy expenditure and aerobic fitness in premenopausal women. *Am J Clin Nutr* 71:500–506.

Hytten FE. 1991a. Nutrition. In: Hytten FE, Chamberlain G, eds. *Clinical Physiology in Obstetrics.* Oxford: Blackwell Scientific. Pp. 150–172.

Hytten FE. 1991b. Weight gain in pregnancy. In: Hytten FE, Chamberlain G, eds. *Clinical Physiology in Obstetrics.* Oxford: Blackwell Scientific. Pp. 173–203.

IDECG (International Dietary Energy Consulting Group). 1990. *The Doubly-Labelled Water Method for Measuring Energy Expenditure: A Consensus Report by the IDECG Working Group. Technical Recommendations for Use in Humans.* Vienna, Austria: NAHRES-4, International Atomic Energy Agency.

Illingworth PJ, Jung RT, Howie PW, Leslie P, Isles TE. 1986. Diminution in energy expenditure during lactation. *Br Med J* 292:437–441.

Illner K, Brinkmann G, Heller M, Bosy-Westphal A, Muller MJ. 2000. Metabolically active components of fat free mass and resting energy expenditure in nonobese adults. *Am J Physiol* 278:E308–E315.

IOM (Institute of Medicine). 1990. *Nutrition During Pregnancy.* Washington, DC: National Academy Press.

IOM. 1991. *Nutrition During Lactation.* Washington, DC: National Academy Press.

Jakicic JM, Wing RR. 1998. Differences in resting energy expenditure in African-American vs. Caucasian overweight females. *Int J Obes Relat Metab Disord* 22:236–242.

James WPT, McNeill G, Ralph A. 1990. Metabolism and nutritional adaptation to altered intakes of energy substrates. *Am J Clin Nutr* 51:264–269.

Jensen CL, Butte NF, Wong WW, Moon JK. 1992. Determining energy expenditure in preterm infants: Comparison of $^{2}H_{2}{}^{18}O$ method and indirect calorimetry. *Am J Physiol* 263:R685–R692.

Jequier E, Tappy L. 1999. Regulation of body weight in humans. *Physiol Rev* 79:451–480.

Jiang Z, Yan Q, Su Y, Acheson KJ, Thelin A, Piguet-Welsch C, Ritz P, Ho Z. 1998. Energy expenditure of Chinese infants in Guangdong Province, south China, determined with use of the doubly labeled water method. *Am J Clin Nutr* 67:1256–1264.

Johnson RK. 2000. What are people really eating and why does it matter? *Nutr Today* 35:40–45.

Johnson RK, Goran MI, Poehlman ET. 1994. Correlates of over- and underreporting of energy intake in healthy older men and women. *Am J Clin Nutr* 59:1286–1290.

Johnson RK, Soultanakis RP, Matthews DE. 1998. Literacy and body fatness are associated with underreporting of energy intake in U.S. low-income women using the multiple-pass 24-hour recall: A doubly labeled water study. *J Am Diet Assoc* 98:1136–1140.

Jones PJ, Winthrop AL, Schoeller DA, Swyer PR, Smith J, Filler RM, Heim T. 1987. Validation of doubly labeled water for assessing energy expenditure in infants. *Pediatr Res* 21:242–246.

Jones PJ, Martin LJ, Su W, Boyd NF. 1997. Canadian Recommended Nutrient Intakes underestimate true energy requirements in middle-aged women. *Can J Public Health* 88:314–319.

Kalhan S, Rossi K, Gruca L, Burkett E, O'Brien A. 1997. Glucose turnover and gluconeogenesis in human pregnancy. *J Clin Invest* 100:1775–1781.

Kalkhoff RK, Kissebah AH, Kim H-J. 1978. Carbohydrate and lipid metabolism during normal pregnancy: Relationship to gestational hormone action. *Semin Perinatol* 2:291–307.

Kannel WB, Brand N, Skinner JJ, Dawber TR, McNamara PM. 1967. The relation of adiposity to blood pressure and development of hypertension. *Ann Intern Med* 67:48–59.

Kaplan AS, Zemel BS, Stallings VA. 1996. Differences in resting energy expenditure in prepubertal black children and white children. *J Pediatr* 129:643–647.

Karlberg P. 1952. Determinations of standard energy metabolism (basal metabolism) in normal infants. *Acta Paediatr Scand* 41:11–151.

Kashiwazaki H, Dejima Y, Suzuki T. 1990. Influence of upper and lower thermoneutral room temperatures (20°C and 25°C) on fasting and post-prandial resting metabolism under different outdoor temperatures. *Eur J Clin Nutr* 44:405–413.

Kato I, Nomura A, Stemmermann GN, Chyou P-H. 1992. Prospective study of clinical gallbladder disease and its association with obesity, physical activity, and other factors. *Dig Dis Sci* 37:784–790.

Kempen KP, Saris WH, Westerterp KR. 1995. Energy balance during an 8-wk energy-restricted diet with and without exercise in obese women. *Am J Clin Nutr* 62:722–729.

Kesaniemi YA, Grundy SM. 1983. Increased low density lipoprotein production associated with obesity. *Arteriosclerosis* 3:170–177.

Keys A, Taylor H, Grande F. 1973. Basal metabolism and age of adult man. *Metabolism* 22:579–587.

Klannemark M, Orho M, Groop L. 1998. No relationship between identified variants in the uncoupling protein 2 gene and energy expenditure. *Eur J Endocrinol* 139:217–223.

Klausen B, Toubro S, Astrup A. 1997. Age and sex effects on energy expenditure. *Am J Clin Nutr* 65:895–907.

Kleiber M. 1975. *The Fire of Life. An Introduction to Animal Energetics.* New York: Robert E. Krieger Publishing.

Klein PD, James WP, Wong WW, Irving CS, Murgatroyd PR, Cabrera M, Dallosso HM, Klein ER, Nichols BL. 1984. Calorimetric validation of the doubly-labelled water method for determination of energy expenditure in man. *Hum Nutr Clin Nutr* 38C:95–106.

Knuttgen HG, Emerson K. 1974. Physiological response to pregnancy at rest and during exercise. *J Appl Physiol* 36:549–553.

Kopp-Hoolihan LE, Van Loan MD, Wong WW, King JC. 1999. Longitudinal assessment of energy balance in well-nourished, pregnant women. *Am J Clin Nutr* 69:697–704.

Krebs-Smith SM, Graubard B, Kahle L, Subar A, Cleveland L, Ballard-Barbash R. 2000. Low energy reporters vs. others: A comparison of reported food intakes. *Eur J Clin Nutr* 54:281–287.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. 2000. CDC growth charts: United States. *Adv Data* 314:1–28.

Kushner RF, Racette SB, Neil K, Schoeller DA. 1995. Measurement of physical activity among black and white obese women. *Obes Res* 3:261S–265S.

Lammi-Keefe CJ, Ferris AM, Jensen RG. 1990. Changes in human milk at 0600, 1000, 1400, 1800, and 2200 h. *J Pediatr Gastroenterol Nutr* 11:83–88.

Lanzola E, Tagliabue A, Cena H. 1990. Skin temperature and energy expenditure. *Ann Nutr Metab* 34:311–316.

Larson DE, Ferraro RT, Robertson DS, Ravussin E. 1995. Energy metabolism in weight-stable postobese individuals. *Am J Clin Nutr* 62:735–739.

Lean ME, Murgatroyd PR, Rothnie I, Reid IW, Harvey R. 1988. Metabolic and thyroidal responses to mild cold are abnormal in obese diabetic women. *Clin Endocrinol* 28:665–673.

Lederman SA, Paxton A, Heymsfield SB, Wang J, Thornton J, Pierson RN. 1997. Body fat and water changes during pregnancy in women with different body weight and weight gain. *Obstet Gynecol* 90:483–488.

Leibel RL, Rosenbaum M, Hirsch J. 1995. Changes in energy expenditure resulting from altered body weight. *N Engl J Med* 332:621–628.

Leonard WR, Galloway VA, Ivakine E. 1997. Underestimation of daily energy expenditure with the factorial method: Implications for anthropological research. *Am J Phys Anthropol* 103:443–454.

Leon-Velarde F, Gamboa A, Chuquiza JA, Esteba WA, Rivera-Chira M, Monge CC. 2000. Hematological parameters in high altitude residents living at 4,355, 4,660, and 5,500 meters above sea level. *High Alt Med Biol* 1:97–104.

Levine JA, Eberhardt NL, Jensen MD. 1999. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science* 283:212–214.

Levine JA, Schleusner SJ, Jensen MD. 2000. Energy expenditure of nonexercise activity. *Am J Clin Nutr* 72:1451–1454.

Lichtman SW, Pisarska K, Berman ER, Pestone M, Dowling H, Offenbacher E, Weisel H, Heshka S, Matthews DE, Heymsfield SB. 1992. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med* 327:1893–1898.

Lifson N, McClintock R. 1966. Theory of use of the turnover rates of body water for measuring energy and material balance. *J Theoret Biol* 12:46–74.

Lifson N, Gordon GB, Visscher MB, Nier AO. 1949. The fate of utilized molecular oxygen and the source of the oxygen of respiratory carbon dioxide, studied with the aid of heavy oxygen. *J Biol Chem* 180:803–811.

Lifson N, Gordon GB, McClintock R. 1955. Measurement of total carbon dioxide production by means of D_2O^{18}. *J Appl Physiol* 7:704–710.

Linder CW, Durant RH, Mahoney OM. 1983. The effect of physical conditioning on serum lipids and lipoproteins in white male adolescents. *Med Sci Sports Exerc* 15:232–236.

Lindsay CA, Huston L, Amini SB, Catalano PM. 1997. Longitudinal changes in the relationship between body mass index and percent body fat in pregnancy. *Obstet Gynecol* 89:377–382.

Lipmann F. 1941. Metabolic generation and utilization of phosphate bond energy. *Adv Enzymol* 1:99–162.

Livesey G, Elia M. 1988. Estimation of energy expenditure, net carbohydrate utilization, and net fat oxidation and synthesis by indirect calorimetry: Evaluation of errors with special reference to the detailed composition of fuels. *Am J Clin Nutr* 47:608–628.

Livingstone MB, Coward WA, Prentice AM, Davies PS, Strain JJ, McKenna PG, Mahoney CA, White JA, Stewart CM, Kerr MJ. 1992a. Daily energy expenditure in free-living children: Comparison of heart-rate monitoring with the doubly labeled water ($^2H_2{}^{18}O$) method. *Am J Clin Nutr* 56:343–352.

Livingstone MB, Prentice AM, Coward WA, Strain JJ, Black AE, Davies PS, Stewart CM, McKenna PG, Whitehead RG. 1992b. Validation of estimates of energy intake by weighed dietary record and diet history in children and adolescents. *Am J Clin Nutr* 56:29–35.

Lovelady CA, Meredith CN, McCrory MA, Nommsen LA, Joseph LJ, Dewey KG. 1993. Energy expenditure in lactating women: A comparison of doubly labeled water and heart-rate-monitoring methods. *Am J Clin Nutr* 57:512–518.

Lucas A, Ewing G, Roberts SB, Coward WA. 1987. How much energy does the breast fed infant consume and expend? *Br Med J* 295:75–77.

Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjöström L. 1989. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: Results from a prospective population study in Gothenburg, Sweden. *Int J Obes* 13:413–423.

MacMahon SW, Blacket RB, Macdonald GJ, Hall W. 1984. Obesity, alcohol consumption and blood pressure in Australian men and women. The National Heart Foundation of Australia Risk Factor Prevalence Study. *J Hypertens* 2:85–91.

Maffeis C, Schutz Y, Zoccante L, Micciolo R, Pinelli L. 1993. Meal-induced thermogenesis in lean and obese prepubertal children. *Am J Clin Nutr* 57:481–485.

Malina RM. 1994. Physical activity: Relationship to growth, maturation, and physical fitness. In: Bouchard C, Shephard RJ, Stephens T, eds. *Physical Activity, Fitness, and Health. International Proceedings and Consensus Statement.* Champaign, IL: Human Kinetics. Pp. 918–930.

Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE, Hennekens CH. 1990. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* 322:882–889.

Margaria R, Cerretelli P, Aghemo P, Sassi G. 1963. Energy cost of running *J Appl Physiol* 18:367–370.

Mawson JT, Braun B, Rock PB, Moore LG, Mazzeo R, Butterfield GE. 2000. Women at altitude: Energy requirement at 4,300 m. *J Appl Physiol* 88:272–281.

McCargar L, Taunton J, Birmingham CL, Paré S, Simmons D. 1993. Metabolic and anthropometric changes in female weight cyclers and controls over a 1-year period. *J Am Diet Assoc* 93:1025–1030.

Medalie JH, Papier C, Herman JB, Goldbourt U, Tamir S, Neufeld HN, Riss E. 1974. Diabetes mellitus among 10,000 adult men. I. Five-year incidence and associated variables. *Isr J Med Sci* 10:681–697.

Meijer GA, Westerterp KR, Saris WH, ten Hoor F. 1992. Sleeping metabolic rate in relation to body composition and the menstrual cycle. *Am J Clin Nutr* 55:637–640.

Melanson KJ, Saltzman E, Russell R, Roberts SB. 1996. Postabsorptive and postprandial energy expenditure and substrate oxidation do not change during the menstrual cycle in young women. *J Nutr* 126:2531–2538.

Melanson KJ, Saltzman E, Vinken AG, Russell R, Roberts SB. 1998. The effects of age on postprandial thermogenesis at four graded energetic challenges: Findings in young and older women. *J Gerontol A Biol Sci Med Sci* 53:B409–B414.

Merrill AL, Watt BK. 1973. *Energy Value of Foods, Basis and Derivation.* Agricultural Handbook No.74. Human Nutrition Research Branch, Agricultural Research Service, United States Department of Agriculture. U.S. Government Printing Office, Washington, D.C.

Miller WC, Koceja DM, Hamilton EJ. 1997. A meta-analysis of the past 25 years of weight loss research using diet, exercise or diet plus exercise intervention. *Int J Obes Relat Metab Disord* 21:941–947.

Minghelli G, Schutz Y, Charbonnier A, Whitehead R, Jequier E. 1990. Twenty-four-hour energy expenditure and basal metabolic rate measured in a whole-body indirect calorimeter in Gambian men. *Am J Clin Nutr* 51:563–570.

Moore FS. 1963. *The Body Cell Mass and Its Supporting Environment: Body Composition in Health and Disease.* Philadelphia, PA: Saunders.

Moore LL, Nguyen USDT, Rothman KJ, Cupples LA, Ellison RC. 1995. Preschool physical activity level and change in body fatness in young children. *Am J Epidemiol* 142:982–988.

Morgan JB, York DA. 1983. Thermic effect of feeding in relation to energy balance in elderly men. *Ann Nutr Metab* 27:71–77.

Morio B, Ritz P, Verdier E, Montaurier C, Beaufrere B, Vermorel M. 1997. Critical evaluation of the factorial and heart-rate recording methods for the determination of energy expenditure of free-living elderly people. *Br J Nutr* 78:709–722.

Morrison JA, Alfaro MP, Khoury P, Thornton BB, Daniels SR. 1996. Determinants of resting energy expenditure in young black girls and young white girls. *J Pediatr* 129:637–642.

Motil KJ, Montandon CM, Garza C. 1990. Basal and postprandial metabolic rates in lactating and nonlactating women. *Am J Clin Nutr* 52:610–615.

Murgatroyd PR, Goldberg GR, Diaz E, Prentice AM. 1990. The influence of mild cold on human energy expenditure: Is there a sex difference in the response? *Br J Nutr* 64:777.

Must A, Strauss RS. 1999. Risks and consequences of childhood and adolescent obesity. *Int J Obes Relat Metab Disord* 23:S2–S11.

Nagy LE, King JC. 1984. Postprandial energy expenditure and respiratory quotient during early and late pregnancy. *Am J Clin Nutr* 40:1258–1263.

Nair KS, Halliday D, Garrow JS. 1983. Thermic response to isoenergetic protein, carbohydrate or fat meals in lean and obese subjects. *Clin Sci* 65:307–312.

Nelson KM, Weinsier RL, Long CL, Schutz Y. 1992. Prediction of resting energy expenditure from fat-free mass and fat mass. *Am J Clin Nutr* 56:848–856.

Neville MC. 1995. Determinants of milk volume and composition. In: Jensen RG, ed. *Handbook of Milk Composition.* San Diego, CA: Academic Press. Pp. 87–113.

Neville MC, Keller R, Seacat J, Lutes V, Neifert M, Casey C, Allen J, Archer P. 1988. Studies in human lactation: Milk volumes in lactating women during the onset of lactation and full lactation. *Am J Clin Nutr* 48:1375–1386.

Newman WP 3rd, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL, Williamson GD, Webber LS, Berenson GS. 1986. Relation of serum lipoprotein levels and systolic blood pressure to early artherosclerosis. The Bolgalusa heart study. *N Engl J Med* 314:138–144.

NHLBI/NIDDK (National Heart, Lung, and Blood Institute/National Institute of Diabetes and Digestive and Kidney Diseases). 1998. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report.* NIH Publication No. 98-4083. Bethesda, MD: National Institutes of Health.

Nicklas BJ, Toth MJ, Goldberg AP, Poehlman ET. 1997. Racial differences in plasma leptin concentrations in obese postmenopausal women. *J Clin Endocrinol Metab* 82:315–317.

Nickleberry BL, Brooks GA. 1996. No effect of cycling experience on leg cycle ergometer efficiency. *Med Sci Sports Exerc* 28:1396–1401.

Nielsen E. 1987. Acute modest changes in relative humidity do not affect energy expenditure at rest in human subjects. *Hum Nutr Clin Nutr* 41:485–488.

NIH (National Institutes of Health). 2000. *The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* NIH Publication No. 00-4084. Bethesda, MD: National Institutes of Health.

Nommsen LA, Lovelady CA, Heinig MJ, Lonnerdal B, Dewey KG. 1991. Determinants of energy, protein, lipid, and lactose concentrations in human milk during the first 12 mo of lactation: The DARLING Study. *Am J Clin Nutr* 53:457–465.

NRC (National Research Council). 1989. *Recommended Dietary Allowances,* 10th ed. Washington, DC: National Academy Press.

Ohlson L-O, Larsson B, Svärdsudd K, Welin L, Eriksson H, Wilhelmsen L, Björntorp P, Tibblin G. 1985. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 34:1055–1058.

Osterman J, Lin Tu, Nankin HR, Brown KA, Hornung CA. 1992. Serum cholesterol profiles during treatment of obese outpatients with a very low calorie diet. Effect of initial cholesterol levels. *Int J Obes Relat Metab Disord* 16:49–58.

Owen OE. 1988. Regulation of energy and metabolism. In: MJ Kinney, Jeejeebhoy KN, Hill GH, Owen OE, eds. *Nutrition and Metabolism in Patient Care.* Philadelphia: W.B. Saunders. Pp. 35–59.

Owen OE, Kavle E, Owen RS, Polansky M, Caprio S, Mozzoli MA, Kendrick ZV, Bushman MC, Boden G. 1986. A reappraisal of caloric requirements in healthy women. *Am J Clin Nutr* 44:1–19.

Owen OE, Holup JL, D'Alessio DA, Craig ES, Polansky M, Smalley KJ, Kavle EC, Bushman MC, Owen LR, Mozzoli MA, Kendrick ZV, Boden GH. 1987. A reappraisal of the caloric requirements of men. *Am J Clin Nutr* 46:875–885.

Owens S, Gutin B, Allison J, Riggs S, Ferguson M, Litaker M, Thompson W. 1999. Effect of physical training on total and visceral fat in obese children. *Med Sci Sports Exerc* 31:143–148.

Pacy PJ, Cox M, Khalouha M, Elkins S, Robinson AC, Garrow JS. 1996. Does moderate aerobic activity have a stimulatory effect on 24 h resting energy expenditure: A direct calorimeter study. *Int J Food Sci Nutr* 47:299–305.

Pahud P, Ravussin E, Jequier E. 1980. Energy expended during oxygen deficit period of submaximal exercise in man. *J Appl Physiol* 48:770–775.

Pandolf KB, Givoni B, Goldman RF. 1977. Predicting energy expenditure with loads while standing or walking very slowly. *J Appl Physiol* 43:577–581.

Pannemans DL, Westerterp KR. 1995. Energy expenditure, physical activity and basal metabolic rate of elderly subjects. *Br J Nutr* 73:571–581.

Pannemans DL, Bouten CV, Westerterp KR. 1995. 24 h Energy expenditure during a standardized activity protocol in young and elderly men. *Eur J Clin Nutr* 49:49–56.

Parizkova J. 1974. Particularities of lean body mass and fat development in growing boys as related to their motor activity. *Acta Paediatrica Belgica* 28:233S–243S.

Passmore R, Durnin JV. 1955. Human energy expenditure. *Physiol Rev* 35:801–840.

Penn D, Schmidt-Sommerfeld E. 1989. Lipids as an energy source for the fetus and newborn infant. In: Lebenthal E, ed. *Textbook of Gastroenterology and Nutrition in Infancy*. New York: Raven Press. Pp. 293–310.

Piers LS, Diggavi SN, Rijskamp J, van Raaij JM, Shetty PS, Hautvast JG. 1995a. Resting metabolic rate and thermic effect of a meal in the follicular and luteal phases of the menstrual cycle in well-nourished Indian women. *Am J Clin Nutr* 61:296–302.

Piers LS, Diggavi SN, Thangam S, van Raaij JM, Shetty PS, Hautvast JG. 1995b. Changes in energy expenditure, anthropometry, and energy intake during the course of pregnancy and lactation in well-nourished Indian women. *Am J Clin Nutr* 61:501–513.

Pipe NG, Smith T, Halliday D, Edmonds CJ, Williams C, Coltart TM. 1979. Changes in fat, fat-free mass and body water in human normal pregnancy. *Br J Obstet Gynaecol* 86:929–940.

Platte P, Pirke KM, Wade SE, Trimborn P, Fichter MM. 1995. Physical activity, total energy expenditure, and food intake in grossly obese and normal weight women. *Int J Eating Disord* 17:51–57.

Poehlman ET. 1992. Energy expenditure and requirements in aging humans. *J Nutr* 122:2057–2065.

Poehlman ET. 1993. Regulation of energy expenditure in aging humans. *J Am Geriatr Soc* 41:552–559.

Poehlman ET, Danforth E. 1991. Endurance training increases metabolic rate and norepinephrine appearance rate in older individuals. *Am J Physiol* 261:E233–E239.

Poehlman ET, Melby CL, Badylak SF. 1991. Relation of age and physical exercise status on metabolic rate in younger and older healthy men. *J Gerontol* 46:B54–B58.

Poehlman ET, Toth MJ, Gardner AW. 1995. Changes in energy balance and body composition at menopause: A controlled longitudinal study. *Ann Intern Med* 123:673–675.

Poppitt SD, Swann D, Black AE, Prentice AM. 1998. Assessment of selective under-reporting of food intake by both obese and non-obese women in a metabolic facility. *Int J Obesity Relat Metab Disord* 22:303–311.

Prentice AM, Black AE, Coward WA, Davies HL, Goldberg GR, Murgatroyd PR, Ashford J, Sawyer M, Whitehead RG. 1986. High levels of energy expenditure in obese women. *Br Med J* 292:983–987.

Prentice AM, Lucas A, Vasquez-Velasquez L, Davies PS, Whitehead RG. 1988. Are current dietary guidelines for young children a prescription for overfeeding? *Lancet* 2:1066–1069.

Prentice AM, Goldberg GR, Davies HL, Murgatroyd PR, Scott W. 1989. Energy-sparing adaptations in human pregnancy assessed by whole-body calorimetry. *Br J Nutr* 62:5–22.

Prentice AM, Black AE, Coward WA, Cole TJ. 1996a. Energy expenditure in overweight and obese adults in affluent societies: An analysis of 319 doubly-labelled water measurements. *Eur J Clin Nutr* 50:93–97.

Prentice AM, Spaaij CJ, Goldberg GR, Poppitt SD, van Raaij JM, Totton M, Swann D, Black AE. 1996b. Energy requirements of pregnant and lactating women. *Eur J Clin Nutr* 50:S82–S111.

Price GM, Paul AA, Cole TJ, Wadsworth ME. 1997. Characteristics of the low-energy reporters in a longitudinal national dietary survey. *Br J Nutr* 77:833–851.

Pryer JA, Vrijheid M, Nichols R, Kiggins M, Elliot P. 1997. Who are the 'low energy reporters' in the dietary and nutritional survey of British adults? *Int J Epidemiol* 26:146–154.

Racette SB, Schoeller DA, Kushner RF, Neil KM, Herling-Iaffaldano K. 1995. Effects of aerobic exercise and dietary carbohydrate on energy expenditure and body composition during weight reduction in obese women. *Am J Clin Nutr* 61:486–494.

Raitakari OT, Porkka KVK, Taimela S, Telama R, Rasanen L, Viikari JSA. 1994. Effects of persistent physical activity and inactivity on coronary risk factors in children and young adults. *Am J Epidemiol* 140:195–205.

Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. 1986. Determinants of 24-hour energy expenditure in man: Methods and results using a respiratory chamber. *J Clin Invest* 78:1568–1578.

Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, Boyce V, Howard BV, Bogardus C. 1988. Reduced rate of energy expenditure as a risk factor for body-weight gain. *N Engl J Med* 318:467–472.

Ravussin E, Harper IT, Rising R, Bogardus C. 1991. Energy expenditure by doubly labeled water: Validation in lean and obese subjects. *Am J Physiol* 261:E402–E409.

Reichman BL, Chessex P, Putet G, Verellen GJ, Smith JM, Heim T, Swyer PR. 1982. Partition of energy metabolism and energy cost of growth in the very low-birth-weight infant. *Pediatrics* 69:446–451.

Reisin E, Abel R, Modan M, Silverberg DS, Eliahou HE, Modan B. 1978. Effect of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. *N Engl J Med* 298:1–6.

Rexrode KM, Hennekens CH, Willett WC, Colditz GA, Stampfer MJ, Rich-Edwards JW, Speizer FE, Manson JE. 1997. A prospective study of body mass index, weight change, and risk of stroke in women. *J Am Med Assoc* 277:1539–1545.

Rexrode KM, Buring JE, Manson JE. 2001. Abdominal and total adiposity and risk of coronary heart disease in men. *Int J Obes Relat Metab Disord* 25:1047–1056.

Rimm EB, Stampfer MJ, Giovannucci F, Ascherio A, Spiegelman D, Colditz GA, Willett WC. 1995. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US women. *Am J Epidemiol* 15:1117–1127.

Riumallo JA, Schoeller D, Barrera G, Gattas V, Uauy R. 1989. Energy expenditure in underweight free-living adults: Impact of energy supplementation as determined by doubly labeled water and indirect calorimetry. *Am J Clin Nutr* 49:239–246.

Roberts SB. 1996. Energy requirements of older individuals. *Eur J Clin Nutr* 50:S112–S118.

Roberts SB, Dallal GE. 1998. Effects of age on energy balance. *Am J Clin Nutr* 68:975S–979S.

Roberts SB, Dallal GE. 2001. The new childhood growth charts. *Nutr Rev* 59:31–36.

Roberts SB, Young VR. 1988. Energy costs of fat and protein deposition in the human infant. *Am J Clin Nutr* 48:951–955.

Roberts SB, Coward WA, Schlingenseipen K-H, Nohria V, Lucas A. 1986. Comparison of the doubly labeled water ($^2H_2{}^{18}O$) method with indirect calorimetry and a nutrient-balance study for simultaneous determination of energy expenditure, water intake, and metabolizable energy intake in preterm infants. *Am J Clin Nutr* 44:315–322.

Roberts SB, Savage J, Coward WA, Chew B, Lucas A. 1988. Energy expenditure and intake in infants born to lean and overweight mothers. *N Engl J Med* 318:461–466.

Roberts SB, Young VR, Fuss P, Fiatarone MA, Richard B, Rasmussen H, Wagner D, Joseph L, Holehouse E, Evans WJ. 1990. Energy expenditure and subsequent nutrient intakes in overfed young men. *Am J Physiol* 259:R461–R469.

Roberts SB, Heyman MB, Evans WJ, Fuss P, Tsay R, Young VR. 1991. Dietary energy requirements of young adult men, determined by using the doubly labeled water method. *Am J Clin Nutr* 54:499–505.

Roberts SB, Young VR, Fuss P, Heyman MB, Fiatarone M, Dallal GE, Cortiella J, Evans WJ. 1992. What are the dietary energy needs of elderly adults? *Int J Obes Relat Metab Disord* 16:969–976.

Roberts SB, Fuss P, Heyman MB, Young VR. 1995. Influence of age on energy requirements. *Am J Clin Nutr* 62:1053S–1058S.

Rolland-Cachera MF, Deheeger M, Bellisle F, Sempe M, Guilloud-Bataille M, Patois E. 1984. Adiposity rebound in children: a simple indicator for predicting obesity. *Am J Clin Nutr* 39:129–135.

Rolland-Cachera MF. 2001. Early adiposity rebound is not associated with energy or fat intake in infancy. *Pediatrics* 108:218–219.

Rosenberg L, Palmer JR, Miller DR, Clarke EA, Shapiro S. 1990. A case-control study of alcoholic beverage consumption and breast cancer. *Am J Epidemiol* 131:6–14.

Sadurskis A, Kabir N, Wager J, Forsum E. 1988. Energy metabolism, body composition, and milk production in healthy Swedish women during lactation. *Am J Clin Nutr* 48:44–49.

Sahi T, Paffenbarger RS, Hsieh C-C, Lee I-M. 1998. Body mass index, cigarette smoking, and other characteristics as predictors of self-reported, physician-diagnosed gallbladder disease in male college alumni. *Am J Epidemiol* 147:644–651.

Salbe AD, Fontvieille AM, Harper IT, Ravussin E. 1997. Low levels of physical activity in 5-year-old children. *J Pediatr* 131:423–429.

Saltzman E, Roberts SB. 1995. The role of energy expenditure in energy regulation: Findings from a decade of research. *Nutr Rev* 53:209–220.

Saris WHM, Emons HJG, Groenenboom DC, Westerterp KR. 1989. Discrepancy between FAO/WHO energy requirements and actual energy expenditure in healthy 7-11 year old children. In: Beunen G, Ghesquiere J, Reybrouck T, Claessens AL, eds. *Children and Exercise: 14th International Seminar on Pediatric Work Physiology.* Stuttgart, Germany: Ferdinand Enke Verlag Press.

Sasaki J, Shindo M, Tanaka M, Ando M, Arakawa K. 1987. A long-term aerobic exercise program decreases the obesity index and increases high density lipoprotein cholesterol concentration in obese children. *Int J Obes* 11:339–345.

Savage MP, Petratis MM, Thomson WH, Berg K, Smith JL, Sady SP. 1986. Exercise training effects on serum lipids of prepubescent boys and adult men. *Med Sci Sports Exerc* 18:197–204.

Sawaya AL, Saltzman E, Fuss P, Young VR, Roberts SB. 1995. Dietary energy requirements of young and older women determined by using the doubly labeled water method. *Am J Clin Nutr* 62:338–344.

Schoeller DA. 1983. Energy expenditure from doubly labeled water: Some fundamental considerations in humans. *Am J Clin Nutr* 38:999–1005.

Schoeller DA. 1995. Limitations in the assessment of dietary energy intake by self-report. *Metabolism* 44:18–22.

Schoeller DA. 2001. The importance of clinical research: The role of thermogenesis in human obesity. *Am J Clin Nutr* 73:511–516.

Schoeller DA, Fjeld CR. 1991. Human energy metabolism: What we have learned from the doubly labeled water method? *Annu Rev Nutr* 11:355–373.

Schoeller DA, Webb P. 1984. Five-day comparison of the doubly labeled water method with respiratory gas exchange. *Am J Clin Nutr* 40:153–158.

Schoeller DA, Ravussin E, Schutz Y, Acheson KJ, Baertschi P, Jequier E. 1986. Energy expenditure by doubly labeled water: Validation in humans and proposed calculation. *Am J Physiol* 250:R823–R830.

Schofield C. 1985. An annotated bibliography of source material for basal metabolic rate data. *Hum Nutr Clin Nutr* 39C:42–91.

Schofield WN. 1985. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 39C:5–41.

Schotte DE, Stunkard AJ. 1990. The effects of weight reduction on blood pressure in 301 obese patients. *Ann Intern Med* 150:1701–1704.

Schulz LO, Nyomba BL, Alger S, Anderson TE, Ravussin E. 1991. Effect of endurance training on sedentary energy expenditure measured in a respiratory chamber. *Am J Physiol* 260:E257–E261.

Schulz LO, Alger S, Harper I, Wilmore JH, Ravussin E. 1992. Energy expenditure of elite female runners measured by respiratory chamber and doubly labeled water. *J Appl Physiol* 72:23–28.

Schutz Y, Golay A, Felber JP, Jéquier E. 1984. Decreased glucose-induced thermogenesis after weight loss in obese subjects: A predisposing factor for relapse obesity? *Am J Clin Nutr* 39:380–387.

Schutz Y, Golay A, Jéquier E. 1988. 24 h Energy expenditure (24-EE) in pregnant women with a standardized activity level. *Experentia* 44:A31.

Schwartz RS, Jaeger LF, Veith RC. 1990. The thermic effect of feeding in older men: The importance of the sympathetic nervous system. *Metabolism* 39:733–737.

Seale JL, Rumpler WV. 1997. Comparison of energy expenditure measurements by diet records, energy intake balance, doubly labeled water and room calorimetry. *Eur J Clin Nutr* 51:856–863.

Seale JL, Rumpler WV, Conway JM, Miles CW. 1990. Comparison of doubly labeled water, intake-balance, and direct- and indirect-calorimetry methods for measuring energy expenditure in adult men. *Am J Clin Nutr* 52:66–71.

Segal KR, Gutin B, Albu J, Pi-Sunyer FX. 1987. Thermic effects of food and exercise in lean and obese men of similar lean body mass. *Am J Physiol* 252:E110–E117.

Segal KR, Edano A, Blando L, Pi-Sunyer FX. 1990a. Comparison of thermic effects of constant and relative caloric loads in lean and obese men. *Am J Clin Nutr* 51:14–21.

Segal KR, Edano A, Tomas MB. 1990b. Thermic effect of a meal over 3 and 6 hours in lean and obese men. *Metabolism* 39:985–992.

Segal KR, Chun A, Coronel P, Cruz-Noori A, Santos R. 1992. Reliability of the measurement of postprandial thermogenesis in men of three levels of body fatness. *Metabolism* 41:754–762.

Seidell JC, Verschuren WM, Van Leer EM, Kromhout D. 1996. Overweight, underweight, and mortality: A prospective study of 48,287 men and women. *Arch Intern Med* 156:958–963.

Shah M, Geissler CA, Miller DS. 1988. Metabolic rate during and after aerobic exercise in post-obese and lean women. *Eur J Clin Nutr* 42:455–464.

Shetty PS, Soares MJ, James WPT. 1994. Body mass index: Its relationship to basal metabolic rates and energy requirements. *Eur J Clin Nutr* 48:S28–S38.

Siler SQ, Neese RA, Hellerstein MK. 1999. De novo lipogenesis, lipid kinetics, and whole-body lipid balances in humans after acute alcohol consumption. *Am J Clin Nutr* 70:928–936.

Sinclair JC. 1978. *Temperature Regulation and Energy Metabolism in the Newborn.* New York: Grune and Stratton.

Soares MJ, Piers LS, Shetty PS, Robinson S, Jackson AA, Waterlow CJ. 1991. Basal metabolic rate, body composition and whole-body protein turnover in Indian men with differing nutritional status. *Clin Sci* 81:419–425.

Soares MJ, Piers LS, O'Dea K, Shetty PS. 1998. No evidence for an ethnic influence on basal metabolism: An examination of data from India and Australia. *Br J Nutr* 79:333–341.

Sohlstrom A, Forsum E. 1995. Changes in adipose tissue volume and distribution during reproduction in Swedish women as assessed by magnetic resonance imaging. *Am J Clin Nutr* 61:287–295.

Sohlstrom A, Forsum E. 1997. Changes in total body fat during the human reproductive cycle as assessed by magnetic resonance imaging, body water dilution, and skinfold thickness: A comparison of methods. *Am J Clin Nutr* 66:1315–1322.

Solomon SJ, Kurzer MS, Calloway DH. 1982. Menstrual cycle and basal metabolic rate in women. *Am J Clin Nutr* 36:611–616.

Spaaij CJK, van Raaij JMA, de Groot LC, van der Heijden LJ, Boekholt HA, Hautvast JG. 1994a. Effect of lactation on resting metabolic rate and on diet- and work-induced thermogenesis. *Am J Clin Nutr* 59:42–47.

Spaaij CJK, van Raaij JMA, van der Heijden LJ, Schouten FJM, Drijvers JJ, de Groot LC, Boekholt HA, Hautvast JG. 1994b. No substantial reduction of the thermic effect of a meal during pregnancy in well-nourished Dutch women. *Br J Nutr* 71:335–344.

Sparks JW, Girard JR, Battaglia FC. 1980. An estimate of the caloric requirements of the human fetus. *Biol Neonate* 38:113–119.

Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. 1992. Risk of symptomatic gallstones in women with severe obesity. *Am J Clin Nutr* 55:652–658.

Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. 1998. The effect of age on the association between body-mass index and mortality. *N Engl J Med* 338:1–7.

Stubbs RJ, Harbron CG, Murgatroyd PR, Prentice AM. 1995. Covert manipulation of dietary fat and energy density: Effect on substrate flux and food intake in men eating ad libitum. *Am J Clin Nutr* 62:316–329.

Stunkard AJ, Berkowitz RI, Stallings VA, Schoeller DA. 1999. Energy intake, not energy output, is a determinant of body size in infants. *Am J Clin Nutr* 69:524–530.

Sun M, Gower BA, Nagy TR, Trowbridge CA, Dezenberg C, Goran MI. 1998. Total, resting, and activity-related energy expenditures are similar in Caucasian and African-American children. *Am J Physiol* 274:E232–E237.

Sun SS, Chumlea WC, Heymsfield SB, Lukaski HC, Schoeller D, Friedl K, Kuczmarski RJ, Flegal KM, Johnson CL, Hubbard VS. 2003. Development of bioelectrical impedance analysis prediction equations for body composition with the use of a multicomponent model for use in epidemiologic surveys. *Am J Clin Nutr* 77: 331–340.

Sunnegardh J, Bratteby LE, Hagman U, Samuelson G, Sjolin S. 1986. Physical activity in relation to energy intake and body fat in 8- and 13-year-old children in Sweden. *Acta Paediatr Scand* 75:955–963.

Suominen H, Heikkinen E, Parkatti T, Frosberg S, Kiiskinen A. 1977. Effects of 'lifelong' physical training on functional aging in men. *Scand J Soc Med* 14:225–240.

Suter PM, Schutz Y, Jequier E. 1992. The effect of ethanol on fat storage in healthy subjects. *N Engl J Med* 326:983–987.

Suter PM, Hasler E, Vetter W. 1997. Effects of alcohol on energy metabolism and body weight regulation: Is alcohol a risk factor for obesity? *Nutr Rev* 55:157–171.

Svendsen OL, Hassager C, Christiansen C. 1995. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy x-ray absorptiometry. *Metabolism* 44:369–373.

Tanner JM. 1955. *Growth at Adolescence.* Springfield, IL: Charles C. Thomas.

Thorne A, Wahren J. 1990. Diminished meal-induced thermogenesis in elderly man. *Clin Physiol* 10:427–437.

Timmons BA, Araujo J, Thomas TR. 1985. Fat utilization enhanced by exercise in a cold environment. *Med Sci Sports Exerc* 17:673–678.

Tomoyasu NJ, Toth MJ, Poehlman ET. 2000. Misreporting of total energy intake in older African Americans. *Int J Obes Relat Metab Disord* 24:20–26.

Torun B, Davies PSW, Livingstone MBE, Paolisso M, Sackett R, Spurr GB. 1996. Energy requirements and dietary energy recommendations for children and adolescents 1 to 18 years old. *Eur J Clin Nutr* 50:S37–S81.

Tounian P, Girardet J, Carlier L, Frelut ML, Veinberg F, Fontaine JL. 1993. Resting energy expenditure and food-induced thermogenesis in obese children. *J Pediatr Gastroenterol Nutr* 16:451–457.

Tremblay A, Nadeau A, Fournier G, Bouchard C. 1988. Effect of a three-day interruption of exercise-training on resting metabolic rate and glucose-induced thermogenesis in training individuals. *Int J Obes* 12:163–168.

Tremblay A, Nadeau A, Despres JP, St-Jean L, Theriault G, Bouchard C. 1990. Long-term exercise training with constant energy intake. 2: Effect on glucose metabolism and resting energy expenditure. *Int J Obes* 14:75–84.

Treuth MS, Adolph AL, Butte NF. 1998a. Energy expenditure in children predicted from heart rate and activity calibrated against respiration calorimetry. *Am J Physiol* 275:E12–E18.

Treuth MS, Hunter GR, Pichon C, Figueroa-Colon R, Goran MI. 1998b. Fitness and energy expenditure after strength training in obese prepubertal girls. *Med Sci Sports Exerc* 30:1130–1136.

Treuth MS, Butte NF, Wong W. 2000. Effects of familial predisposition to obesity on energy expenditure in multiethnic prepubertal girls. *Am J Clin Nutr* 71:893–900.

Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. 1995. Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Surveys, 1963 to 1991. *Arch Pediatr Adolesc Med* 149:1085–1091.

Troiano RP, Frongillo EA, Sobal J, Levitsky DA. 1996. The relationship between body weight and mortality: A quantitative analysis of combined information from existing studies. *Int J Obes Relat Metab Disord* 20:63–75.

Trowbridge CA, Gower BA, Nagy TR, Hunter GR, Treuth MS, Goran MI. 1997. Maximal aerobic capacity in African-American and Caucasian prepubertal children. *Am J Physiol* 273:E809–E814.

Tuttle WW, Horvath SM, Presson LF, Daum K. 1953. Specific dynamic action of protein in men past 60 years of age. *J Appl Physiol* 5:631–634.

Twisk JWR. 2001. Physical activity guidelines for children and adolescents. A critical review. *Sports Med* 31:617–627.

Tzankoff SP, Norris AH. 1977. Effect of muscle mass decrease on age-related BMR changes. *J Appl Physiol* 43:1001–1006.

USDA/HHS (U.S. Department of Agriculture/U.S. Department of Health and Human Services). 2000. *Nutrition and Your Health: Dietary Guidelines for Americans.* Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

Valencia ME, McNeill G, Brockway JM, Smith JS. 1992. The effect of environmental temperature and humidity on 24 h energy expenditure in men. *Br J Nutr* 68:319–327.

Valve R, Heikkinen S, Rissanen A, Laakso M, Uusitupa M. 1998. Synergistic effect of polymorphisms in uncoupling protein 1 and β_3-adrenergic receptor genes on basal metabolic rate in obese Finns. *Diabetologia* 41:357–361.

van Baak MA. 1999. Physical activity and energy balance. *Public Health Nutr* 2:335–339.

Van Etten LM, Westerterp KR, Verstappen FT, Boon BJ, Saris WH. 1997. Effect of an 18-wk weight-training program on energy expenditure and physical activity. *J Appl Physiol* 82:298–304.

van Gemert WG, Westerterp KR, van Acker BA, Wagenmakers AJ, Halliday D, Greve JM, Soeters PB. 2000. Energy, substrate and protein metabolism in morbid obesity before, during and after massive weight loss. *Int J Obes Relat Metab Disord* 24:711–718.

van Raaij JMA, Vermaat-Miedema SH, Schonk CM, Peek ME, Hautvast JG. 1987. Energy requirements of pregnancy in the Netherlands. *Lancet* 2:953–955.

van Raaij JMA, Peek ME, Vermaat-Miedema SH, Schonk CM, Hautvast JG. 1988. New equations for estimating body fat mass in pregnancy from body density or total body water. *Am J Clin Nutr* 48:24–29.

van Raaij JMA, Schonk CM, Vermaat-Miedema SH, Peek ME, Hautvast JG. 1989. Body fat mass and basal metabolic rate in Dutch women before, during, and after pregnancy: A reappraisal of energy cost of pregnancy. *Am J Clin Nutr* 49:765–772.

van Raaij JMA, Schonk CM, Vermaat-Miedema SH, Peek ME, Hautvast JG. 1990. Energy cost of physical activity throughout pregnancy and the first year postpartum in Dutch women with sedentary lifestyles. *Am J Clin Nutr* 52:234–239.

van Raaij JMA, Schonk CM, Vermaat-Miedema SH, Peek ME, Hautvast JG. 1991. Energy cost of lactation, and energy balances of well-nourished Dutch lactating women: Reappraisal of the extra energy requirements of lactation. *Am J Clin Nutr* 53:612–619.

van Staveren WA, Deurenberg P, Burema J, de Groot LC, Hautvast JG. 1986. Seasonal variation in food intake, pattern of physical activity and change in body weight in a group of young adult Dutch women consuming self-selected diets. *Int J Obes* 10:133–145.

Vaughan L, Zurlo F, Ravussin E. 1991. Aging and energy expenditure. *Am J Clin Nutr* 53:821–825.

Visser M, Deurenberg P, van Staveren WA, Hautvast JG. 1995. Resting metabolic rate and diet-induced thermogenesis in young and elderly subjects: Relationship with body composition, fat distribution, and physical activity level. *Am J Clin Nutr* 61:772–778.

Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC. 1996. Body size and fat distribution as predictors of stroke among US men. *Am J Epidemiol* 144:1143–1150.

Walravens PA, Krebs NF, Hambidge KM. 1983. Linear growth of low income preschool children receiving a zinc supplement. *Am J Clin Nutr* 38:195–201.

Warren MP, Brooks-Gunn J, Hamilton LH, Warren LF, Hamilton WG. 1986. Scoliosis and fractures in young ballet dancers. Relation to delayed menarche and secondary amenorrhea. *N Engl J Med* 314:1348–1353.

Warwick PM, Busby R. 1990. Influence of mild cold on 24 h energy expenditure in "normally" clothed adults. *Br J Nutr* 63:481–488.

Washburn RA, Kline G, Lackland DT, Wheeler FC. 1992. Leisure time physical activity: Are there black/white differences? *Prev Med* 21:127–135.

Waterlow JC. 1999. The nature and significance of nutritional adaptation. *Eur J Clin Nutr* 53:S2–S5.

Waterlow JC, James WPT, Healy MJR. 1989. Nutritional adaptation and variability. *Eur J Clin Nutr* 43:203–210.

Webb P. 1981. Energy expenditure and fat-free mass in men and women. *Am J Clin Nutr* 34:1816–1826.

Webber J, Macdonald IA. 2000. Signalling in body-weight homeostasis: Neuroendocrine efferent signals. *Proc Nutr Soc* 59:397–404.

Webber LS, Cresanta JL, Voors AW, Berenson GS. 1983. Tracking of cardiovascular disease risk factor variables in school-age children. *J Chron Dis* 36:647–660.

Weinsier RL, Schutz Y, Bracco D. 1992. Reexamination of the relationship of resting metabolic rate to fat-free mass and to the metabolically active components of fat-free mass in humans. *Am J Clin Nutr* 55:790–794.

Weinsier RL, Hunter GR, Heini AF, Goran MI, Sell SM. 1998. The etiology of obesity: Relative contribution of metabolic factors, diet, and physical activity. *Am J Med* 105:145–150.

Weinsier RL, Nagy TR, Hunter GR, Darnell BE, Hensrud DD, Weiss HL. 2000. Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory. *Am J Clin Nutr* 72:1088–1094.

Wells JC, Davies PS. 1995. The effect of diet and sex on sleeping metabolic rate in 12-week old infants. *Eur J Clin Nutr* 49:329–335.

Wells JC, Cole TJ, Davies PS. 1996. Total energy expenditure and body composition in early infancy. *Arch Dis Child* 75:423–426.

Westerterp KR, Brouns F, Saris WHM, ten Hoor F. 1988. Comparison of doubly labeled water with respirometry at low and high activity levels. *J Appl Physiol* 65:53–56.

Westerterp KR, Lafeber HN, Sulkers EJ, Sauer PJ. 1991. Comparison of short term indirect calorimetry and doubly labeled water method for the assessment of energy expenditure in preterm infants. *Biol Neonate* 60:75–82.

Westerterp KR, Meijer GA, Janssen EM, Saris WH, ten Hoor F. 1992. Long-term effect of physical activity on energy balance and body composition. *Br J Nutr* 68:21–30.

Westlund K, Nicolaysen R. 1972. Ten-year mortality and morbidity related to serum cholesterol. A follow-up of 3,751 men aged 40–49. *Scand J Clin Lab Invest* 30:1–24.

Weyer C, Snitker S, Bogardus C, Ravussin E. 1999a. Energy metabolism in African Americans: Potential risk factors for obesity. *Am J Clin Nutr* 70:13–20.

Weyer C, Snitker S, Rising R, Bogardus C, Ravussin E. 1999b. Determinants of energy expenditure and fuel utilization in man: Effects of body composition, age, sex, ethnicity and glucose tolerance in 916 subjects. *Int J Obes Relat Metab Disord* 23:715–722.

Whitehead RG, Paul AA, Cole TJ. 1981. A critical analysis of measured food energy intakes during infancy and early childhood in comparison with current international recommendations. *J Hum Nutr* 35:339–348.

WHO (World Health Organization). 1998. *Obesity: Preventing and Managing the Global Epidemic. Report of a World Health Organization Consultation on Obesity.* Geneva: WHO.

WHO Working Group. 1986. Use and interpretation of anthropometric indicators of nutritional status. *Bull World Health Organ* 64:929–941.

Widdowson EM. 1974. Nutrition. In: Davis JA, Dobbing J, eds. *Scientific Foundations of Paediatrics.* London: William Heinemann Medical Books. Pp. 44–55.

Willett WC, Manson JE, Stampfer MJ, Colditz GA, Rosner B, Speizer FE, Hennekens CH. 1995. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *J Am Med Assoc* 273:461–465.

Willett WC, Dietz WH, Colditz GA. 1999. Guidelines for healthy weight. *N Engl J Med* 341:427–434.

Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Blair EH. 1991. Effects of a very-low-calorie diet on long-term glycemic control in obese Type 2 diabetic subjects. *Arch Intern Med* 151:1334–1340.

Withers RT, Smith DA, Tucker RC, Brinkman M, Clark DG. 1998. Energy metabolism in sedentary and active 49- to 70-yr-old women. *J Appl Physiol* 84:1333–1340.

Wong WW. 1994. Energy expenditure of female adolescents. *J Am Coll Nutr* 13:332–337.

Wong WW, Butte NF, Ellis KJ, Hergenroeder AC, Hill RB, Stuff JE, Smith E. 1999. Pubertal African-American girls expend less energy at rest and during physical activity than Caucasian girls. *J Clin Endocrinol Metab* 84:906–911.

Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, William PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM, et al. 1988. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 319(18):1173-1179.

Wood PD, Stefanick ML, Williams PT, Haskell WL. 1991. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. *N Engl J Med* 325:461–466.

Yanovski SZ, Reynolds JC, Boyle AJ, Yanovski JA. 1997. Resting metabolic rate in African-American and Caucasian girls. *Obes Res* 5:321–325.

Zinker BA, Wilson RD, Wasserman DH. 1995. Interaction of decreased arterial PO_2 and exercise on carbohydrate metabolism in the dog. *Am J Physiol* 269:E409–E417.

Zlotkin SH. 1996. A review of the Canadian "Nutrition Recommendations Update: Dietary Fat and Children." *J Nutr* 126:1022S–1027S.

Zurlo F, Ferraro RT, Fontvieille AM, Rising R, Bogardus C, Ravussin E. 1992. Spontaneous physical activity and obesity: Cross-sectional and longitudinal studies in Pima Indians. *Am J Physiol* 263:E296–E300.

6

Dietary Carbohydrates: Sugars and Starches

SUMMARY

The primary role of carbohydrates (sugars and starches) is to provide energy to cells in the body, particularly the brain, which is the only carbohydrate-dependent organ in the body. The Recommended Dietary Allowance (RDA) for carbohydrate is set at 130 g/d for adults and children based on the average minimum amount of glucose utilized by the brain. This level of intake, however, is typically exceeded to meet energy needs while consuming acceptable intake levels of fat and protein (see Chapter 11). The median intake of carbohydrates is approximately 220 to 330 g/d for men and 180 to 230 g/d for women. Due to a lack of sufficient evidence on the prevention of chronic diseases in generally healthy individuals, no recommendations based on glycemic index are made.

BACKGROUND INFORMATION

Classification of Dietary Carbohydrates

Carbohydrates can be subdivided into several categories based on the number of sugar units present. A *monosaccharide* consists of one sugar unit such as glucose or fructose. A *disaccharide* (e.g., sucrose, lactose, and maltose) consists of two sugar units. *Oligosaccharides*, containing 3 to 10 sugar units, are often breakdown products of *polysaccharides,* which contain more than 10 sugar units. Oligosaccharides such as raffinose and stachyose are found in small amounts in legumes. Examples of polysaccharides include starch and glycogen, which are the storage forms of carbohydrates in plants and

animals, respectively. Finally, *sugar alcohols*, such as sorbitol and mannitol, are alcohol forms of glucose and fructose, respectively.

Definition of Sugars

The term "sugars" is traditionally used to describe mono- and disaccharides (FAO/WHO, 1998). Sugars are used as sweeteners to improve the palatability of foods and beverages and for food preservation (FAO/WHO, 1998). In addition, sugars are used to confer certain functional attributes to foods such as viscosity, texture, body, and browning capacity. The monosaccharides include glucose, galactose, and fructose, while the disaccharides include sucrose, lactose, maltose, and trehalose. Some commonly used sweeteners contain trisaccharides and higher saccharides. Corn syrups contain large amounts of these saccharides; for example, only 33 percent or less of the carbohydrates in some corn syrups are mono- and disaccharides; the remaining 67 percent or more are trisaccharides and higher saccharides (Glinsmann et al., 1986). This may lead to an underestimation of the intake of sugars if the trisaccharides and higher saccharides are not included in an analysis.

Extrinsic and Intrinsic Sugars

The terms extrinsic and intrinsic sugars originate from the United Kingdom Department of Health. Intrinsic sugars are defined as sugars that are present within the cell walls of plants (i.e., naturally occurring), while extrinsic sugars are those that are typically added to foods. An additional phrase, "non-milk extrinsic sugars," was developed due to the lactose in milk also being an extrinsic sugar (FAO/WHO, 1998). The terms were developed to help consumers differentiate sugars inherent to foods from sugars that are not naturally occurring in foods.

Added Sugars

The U.S. Department of Agriculture (USDA) has defined "added sugars" for the purpose of analyzing the nutrient intake of Americans using nationwide surveys, as well as for use in the Food Guide Pyramid. The Food Guide Pyramid, which is the food guide for the United States, translates recommendations on nutrient intakes into recommendations for food intakes (Welsh et al., 1992). Added sugars are defined as sugars and syrups that are added to foods during processing or preparation. Major sources of added sugars include soft drinks, cakes, cookies, pies, fruitades, fruit punch, dairy desserts, and candy (USDA/HHS, 2000). Specifically, added sugars include white sugar, brown sugar, raw sugar, corn syrup, corn-syrup

solids, high-fructose corn syrup, malt syrup, maple syrup, pancake syrup, fructose sweetener, liquid fructose, honey, molasses, anhydrous dextrose, and crystal dextrose. Added sugars do not include naturally occurring sugars such as lactose in milk or fructose in fruits.

The Food Guide Pyramid places added sugars at the tip of the pyramid and advises consumers to use them sparingly (USDA, 1996). Table 6-1 shows the amounts of added sugars that could be included in diets that meet the Food Guide Pyramid for three different calorie levels.

Since USDA developed the added sugars definition, the added sugars term has been used in the scientific literature (Bowman, 1999; Britten et al., 2000; Forshee and Storey, 2001; Guthrie and Morton, 2000). The 2000 *Dietary Guidelines for Americans* used the term to aid consumers in identifying beverages and foods that are high in added sugars (USDA/HHS, 2000). Although added sugars are not chemically different from naturally occurring sugars, many foods and beverages that are major sources of added sugars have lower micronutrient densities compared with foods and beverages that are major sources of naturally occurring sugars (Guthrie and Morton, 2000). Currently, U.S. food labels contain information on total sugars per serving, but do not distinguish between sugars naturally present in foods and added sugars.

Definition of Starch

Starch consists of less than 1,000 to many thousands of α-linked glucose units. Amylose is the linear form of starch that consists of α-(1,4) linkages of glucose polymers. Amylopectin consists of the linear

TABLE 6-1 Amount of Sugars That Can Be Added for Three Different Energy Intakes That Meet the Food Guide Pyramid

Food Guide Pyramid Patterns at Three Calorie Levels	Pattern A	Pattern B	Pattern C
Kilocalories (approximate)	1,600	2,200	2,800
Bread/grain group (servings)	6	9	11
Vegetable group (servings)	3	4	5
Fruit group (servings)	2	3	4
Milk group (servings)	2–3	2–3	2–3
Meat group (oz)	5	6	7
Total fat (g)	53	73	93
Total added sugars (tsp)[a]	6	12	18

[a] 1 tsp added sugars = 4 g added sugars.
SOURCE: USDA (1996).

α-(1,4) glucose polymers, as well as branched 1-6 glucose polymers. The amylose starches are compact, have low solubility, and are less rapidly digested. They are prone to retrogradation (hydrogen bonding between amylose units) to form resistant starches (RS_3). The amylopectin starches are digested more rapidly, presumably because of the more effective enzymatic attack of the more open-branched structure.

Definition of Glycemic Response, Glycemic Index, and Glycemic Load

Foods containing carbohydrate have a wide range of effects on blood glucose concentration during the time course of digestion (glycemic response), with some resulting in a rapid rise followed by a rapid fall in blood glucose concentration, and others resulting in a slow extended rise and a slow extended fall. Prolonging the time over which glucose is available for absorption in healthy individuals greatly reduces the postprandial glucose response (Jenkins et al., 1990). Holt and coworkers (1997), however, reported that the insulin response to consumption of carbohydrate foods is influenced by the level of the glucose response, but varies among individuals and with the amount of carbohydrate consumed. Adults with type 1 or type 2 diabetes have been shown to have similar glycemic responses to specific foods (Wolever et al., 1987), whereas glycemic responses were shown to vary with severity of diabetes (Gannon and Nuttall, 1987). Individuals with lactose maldigestion have reduced glycemic responses to lactose-containing items (Maxwell et al., 1970).

The glycemic index (GI) is a classification proposed to quantify the relative blood glucose response to foods containing carbohydrate (Jenkins et al., 1981). It is defined as the area under the curve for the increase in blood glucose after the ingestion of a set amount of carbohydrate in an individual food (e.g., 50 g) in the 2-hour postingestion period as compared with ingestion of the same amount of carbohydrate from a reference food (white bread or glucose) tested in the same individual, under the same conditions, using the initial blood glucose concentration as a baseline. The average daily dietary GI of a meal is calculated by summing the products of the carbohydrate content per serving for each food, times the average number of servings of that food per day, multiplied by the GI, and all divided by the total amount of carbohydrate (Wolever and Jenkins, 1986). Individual foods have characteristic values for GI (Foster-Powell and Brand Miller, 1995), although within-subject and between-subject variability is relatively large (Wolever et al., 1991). Because GI has been determined by using 50-g carbohydrate portions of food, it is possible that there is a nonlinear response between the amount of food ingested, as is the case for fructose (Nuttall et al., 1992) and the glycemic response.

The average glycemic load is derived the same way as the GI, but without dividing by the total amount of carbohydrate consumed. Thus, glycemic load is an indicator of glucose response or insulin demand that is induced by total carbohydrate intake.

GI is referred to throughout this chapter because many studies have used this classification system. This does not imply that it is the best or only system for classifying glycemic responses or other statistical associations. The GI approach does not consider different metabolic responses to the ingestion of sugars versus starches, even though they may have the same GI values (Jenkins et al., 1988b).

Utilization of the Glycemic Index

Several food characteristics that influence GI are summarized in Table 6-2. Broadly speaking, the two main factors that influence GI are carbohydrate type and physical determinants of the rate of digestion, such as whether grains are intact or ground into flour, food firmness resulting from cooking, ripeness, and soluble fiber content (Wolever, 1990). Intrinsic factors such as amylose:amylopectin ratio, particle size and degree of gelatinization, as well as extrinsic factors such as enzyme inhibitors and food preparation and processing, affect GI in their ability to interact with digestive enzymes and the consequent production of monosaccharides. With progressive ripeness of foods, there is a decrease in starch and an increase in free sugar content. The ingestion of fat and protein has been shown to decrease the GI of foods by increasing plasma glucose disposal through the increased secretion of insulin and possibly other hormones (Gannon et al., 1993; Nuttall et al., 1984). Significantly high correlations between GI and protein, fat, and total caloric content were observed and

TABLE 6-2 Factors That Reduce the Rate of Starch Digestibility and the Glycemic Index

Intrinsic	Extrinsic
High amylose:amylopectin ratio	Protective insoluble fiber seed coat as in whole intact grains
Intact grain/large particle size	Viscous fibers
Intact starch granules	Enzyme inhibitors
Raw, ungelatinized or unhydrated starch	Raw foods (vs. cooked foods)
Physical interaction with fat or protein	Minimal food processing
	Reduced ripeness in fruit
	Minimal (compared to extended) storage

explained 87 percent of the variation in glycemic response among foods (Hollenbeck et al., 1986). In addition to these factors, the GI of a meal can affect the glycemic response of the subsequent meal (Ercan et al., 1994; Wolever et al., 1988). Examples of published values for the GI of pure carbohydrates and other food items are shown in Table 6-3.

A number of research groups have reported a significant relationship between mixed-meal GI predicted from individual food items and either the GI measured directly (Chew et al., 1988; Collier et al., 1986; Gulliford et al., 1989; Indar-Brown et al., 1992; Järvi et al., 1995; Wolever and Jenkins, 1986; Wolever et al., 1985, 1990) or metabolic parameters such as high

TABLE 6-3 Glycemic Index (GI) of Common Foods

Food Item	GI (White Bread = 100)
Rice, white, low-amylose	126
Baked potato	121
Corn flakes	119
Rice cakes	117
Jelly beans	114
Cheerios	106
Carrots	101
White bread	101
Wheat bread	99
Soft drink	97
Angel food cake	95
Sucrose	92
Cheese pizza	86
Spaghetti (boiled)	83
Popcorn	79
Sweet corn	78
Banana	76
Orange juice	74
Rice, Uncle Ben's converted long-grain	72
Green peas	68
Oat bran bread	68
Orange	62
All-Bran cereal	60
Apple juice	58
Pumpernickel bread	58
Apple	52
Chickpeas	47
Skim milk	46
Kidney beans	42
Fructose	32

SOURCE: Foster-Powell and Brand Miller (1995).

density lipoprotein cholesterol concentration that are known to be influenced by GI (Liu et al., 2001). Although the glycemic response of diabetics is distinctly higher than that of healthy individuals, the relative response to different types of mixed meals is similar (Indar-Brown et al., 1992; Wolever et al., 1985). The prediction of GI in mixed meals by Wolever and Jenkins (1986) is shown in Figure 6-1. In contrast, some studies reported no such relationship between the calculated and measured GI of mixed meals (Coulston et al., 1984; Hollenbeck et al., 1986; Laine et al., 1987).

There are a number of reasons why different groups have reported different findings on the calculation of GI in mixed meals. As previously discussed, there are a number of intrinsic (e.g., particle size) and extrinsic (e.g., ingestion of fat and protein, degree of food preparation) factors that can affect the glycemic response of a meal (Table 6-2), some of which are known to also affect the absorption of other nutrients such as vitamins and minerals. For instance, coingestion of dietary fat and protein can sometimes have a significant influence on the glucose response of a carbohydrate-containing food, with a reduction in the glucose response generally seen with increases in fat or protein content (Gulliford et al., 1989; Holt et al.,

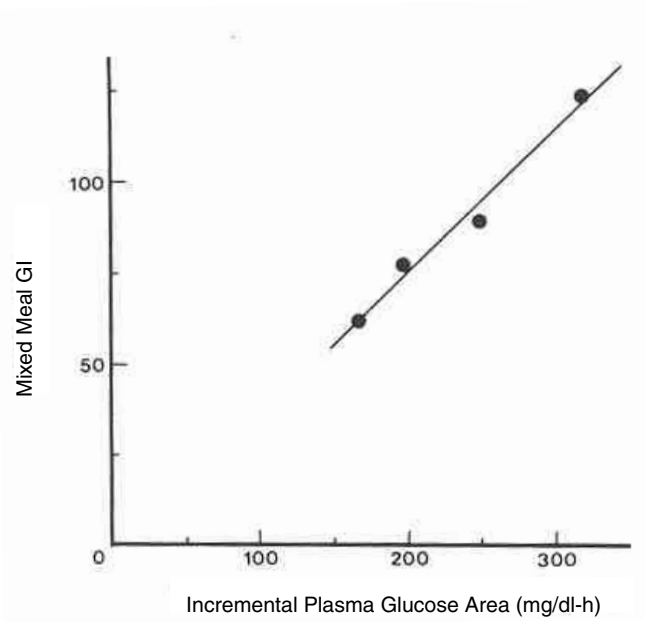

FIGURE 6-1 Correlation between calculated glycemic index (GI) of four test meals (•) and incremental blood glucose response areas. Based on data from Coulston et al. (1984). Reproduced, with permission, from Wolever and Jenkins (1986). Copyright 1986 by the American Society for Clinical Nutrition.

1997). Palatability can have an influence on GI, independent of food type and composition (Sawaya et al., 2001). Furthermore, there are expected inherent biological variations in glucose control and carbohydrate tolerance that are unrelated to the GI of a meal. Finally, varied experimental design and methods for calculating the area under the blood glucose curve can result in a different glycemic response to meals of a similar predicted GI (Coulston et al., 1984; Wolever and Jenkins, 1986). For instance, it is important that the incremental area, rather than the absolute area, under the blood glucose curve be measured (Wolever and Jenkins, 1986). Taken together, the results from these different studies indicate that the GI of mixed meals can usually be predicted from the GI of individual food components.

Physiology of Digestion, Absorption, and Metabolism

Digestion

Starch. The breakdown of starch begins in the mouth where salivary amylase acts on the interior α-(1,4) linkages of amylose and amylopectin. The digestion of these linkages continues in the intestine where pancreatic amylase is released. Amylase digestion produces large oligosaccharides (α-limit dextrins) that contain approximately eight glucose units of one or more α-(1,6) linkages. The α-(1,6) linkages are cleaved more easily than the α-(1,4) linkages.

Oligosaccharides and Sugars. The microvilli of the small intestine extend into an unstirred water layer phase of the intestinal lumen. When a limit dextrin, trisaccharide, or disaccharide enters the unstirred water layer, it is rapidly hydrolyzed by enzymes bound to the brush border membrane. These limit dextrins, produced from starch digestion, are degraded by glucoamylase, which removes glucose units from the nonreducing end to yield maltose and isomaltose. Maltose and isomaltose are degraded by intestinal brush border disaccharidases (e.g., maltase and sucrase). Maltase, sucrase, and lactase digest sucrose and lactose to monosaccharides prior to absorption.

Intestinal Absorption

Monosaccharides first diffuse across to the enterocyte surface, followed by movement across the brush border membrane by one of two mechanisms: active transport or facilitated diffusion.

Active Transport. The intestine is one of two organs that vectorially transports hexoses across the cell into the bloodstream. The mature enterocytes capture the hexoses directly ingested from food or produced from the digestion of di- and polysaccharides. Active transport of sugars involves sodium dependent glucose transporters (SGLTs) in the brush border membrane (Díez-Sampedro et al., 2001). Sodium is pumped from the cell to create a gradient between the interior of the cell and the lumen of the intestine, requiring the hydrolysis of adenosine triphosphate (ATP). The resultant gradient results in the cotransport of one molecule each of sodium and glucose. Glucose is then transported across the basolateral membrane of the small intestine by glucose transporter (GLUT) 2. Similar to glucose, galactose utilizes SGLT cotransporters and basolateral GLUT 2. Fructose is not transported by SGLT cotransporters.

Facilitated Diffusion. There are also transporters of glucose that require neither sodium nor ATP. The driving force for glucose transport is the glucose gradient and the energy change that occurs when the unstirred water layer is replaced with glucose. In this type of transport, called facilitated diffusion, glucose is transported down its concentration gradient (from high to low). Fructose is also transported by facilitated diffusion. One facilitated glucose transporter, GLUT 5, has been identified in the small intestine (Levin, 1999). GLUT 5 appears to transport glucose poorly and is the main transporter of fructose.

Metabolism

Cellular Uptake. Absorbed sugars are transported throughout the body to cells as a source of energy. The concentration of glucose in the blood is highly regulated by the release of insulin. Uptake of glucose by the adipocyte and muscle cell is dependent upon the binding of insulin to a membrane-bound insulin receptor that increases the translocation of intracellular glucose transporters (GLUT 4) to the cell membrane surface for uptake of glucose. GLUT 1 is the transporter of the red blood cell; however, it is also present in the plasma membrane of many other tissues (Levin, 1999). Besides its involvement in the small intestine, GLUT 2 is expressed in the liver and can also transport galactose, mannose, and fructose (Levin, 1999). GLUT 3 is important in the transport of glucose into the brain (Levin, 1999).

Intracellular Utilization of Galactose. Absorbed galactose is primarily the result of lactose digestion. The majority of galactose is taken up by the liver where it is metabolized to galactose-1-phosphate, which is then con-

verted to glucose-1-phosphate. Most of the glucose-1-phosphate derived from galactose metabolism is converted to glycogen for storage.

Intracellular Utilization of Fructose. Absorbed fructose, from either direct ingestion of fructose or digestion of sucrose, is transported to the liver and phosphorylated to fructose-1-phosphate, an intermediate of the glycolytic pathway, which is further cleaved to glyceraldehyde and dihydroxyacetone phosphate (DHAP). DHAP is an intermediary metabolite in both the glycolytic and gluconeogenic pathways. The glyceraldehyde can be converted to glycolytic intermediary metabolites that serve as precursors for glycogen synthesis. Glyceraldehyde can also be used for triacylglycerol synthesis, provided that sufficient amounts of malonyl coenzyme A (CoA) (a precursor for fatty acid synthesis) are available.

Intracellular Utilization of Glucose. Glucose is a major fuel used by most cells in the body. In muscle, glucose is metabolized anaerobically to lactate via the glycolytic pathway. Pyruvate is decarboxylated to acetyl CoA, which enters the tricarboxylic acid (TCA) cycle. Reduced coenyzmes generated in the TCA cycle pass off their electrons to the electron transport system, where it is completely oxidized to carbon dioxide and water. This results in the production of the high-energy ATP that is needed for many other metabolic reactions. After the consumption of carbohydrates, fat oxidation is markedly curtailed, allowing glucose oxidation to provide most of the body's energy needs. In this manner, the body's glucose and glycogen content can be reduced toward more normal concentrations.

Gluconeogenesis. Glucose can be synthesized via gluconeogenesis, a metabolic pathway that requires energy. Gluconeogenesis in the liver and renal cortex is inhibited via insulin following the consumption of carbohydrates and is activated during fasting, allowing the liver to continue to release glucose to maintain adequate blood glucose concentrations.

Glycogen Synthesis and Utilization. Glucose can also be converted to glycogen (glycogenesis), which contains α-(1-4) and α-(1-6) linkages of glucose units. Glycogen is present in the muscle for storage and utilization and in the liver for storage, export, and maintenance of blood glucose concentrations. Glycogenesis is activated in skeletal muscle by a rise in insulin concentration following the consumption of carbohydrate. In the liver, glycogenesis is activated directly by an increase in circulating glucose, fructose, galactose, or insulin concentration. Muscle glycogen is mainly used in the muscle. Following glycogenolysis, glucose can be exported from the liver for maintenance of normal blood glucose concentrations and for use by other tissues.

Formation of Amino Acids and Fatty Acids from Carbohydrates. Pyruvate and intermediates of the TCA cycle are precursors of certain nonessential amino acids. A limited amount of carbohydrate is converted to fat because de novo lipogenesis is generally quite minimal (Hellerstein, 1999; Parks and Hellerstein, 2000). This finding is true for those who are obese, indicating that the vast majority of deposited fat is not derived from dietary carbohydrate when consumed at moderate levels.

Insulin. Based on the metabolic functions of insulin discussed above, the ingestion of carbohydrate produces an immediate increase in plasma insulin concentrations. This immediate rise in plasma insulin concentration minimizes the extent of hyperglycemia after a meal. The effects of insulin deficiency (elevated blood glucose concentration) are exemplified by type 1 diabetes. Individuals who have type 2 diabetes may or may not produce insulin and insulin-dependent muscle and adipose tissue cells may or may not respond to increased insulin concentrations (insulin resistant); therefore, circulating glucose is not effectively taken up by these tissues and metabolized.

Clinical Effects of Inadequate Intake

The lower limit of dietary carbohydrate compatible with life apparently is zero, provided that adequate amounts of protein and fat are consumed. However, the amount of dietary carbohydrate that provides for optimal health in humans is unknown. There are traditional populations that ingested a high fat, high protein diet containing only a minimal amount of carbohydrate for extended periods of time (Masai), and in some cases for a lifetime after infancy (Alaska and Greenland Natives, Inuits, and Pampas indigenous people) (Du Bois, 1928; Heinbecker, 1928). There was no apparent effect on health or longevity. Caucasians eating an essentially carbohydrate-free diet, resembling that of Greenland natives, for a year tolerated the diet quite well (Du Bois, 1928). However, a detailed modern comparison with populations ingesting the majority of food energy as carbohydrate has never been done.

It has been shown that rats and chickens grow and mature successfully on a carbohydrate-free diet (Brito et al., 1992; Renner and Elcombe, 1964), but only if adequate protein and glycerol from triacylglycerols are provided in the diet as substrates for gluconeogenesis. It has also been shown that rats grow and thrive on a 70 percent protein, carbohydrate-free diet (Gannon et al., 1985). Azar and Bloom (1963) also reported that nitrogen balance in adults ingesting a carbohydrate-free diet required the ingestion of 100 to 150 g of protein daily. This, plus the glycerol obtained from triacylglycerol in the diet, presumably supplied adequate substrate

for gluconeogenesis and thus provided at least a minimal amount of completely oxidizable glucose.

The ability of humans to starve for weeks after endogenous glycogen supplies are essentially exhausted is also indicative of the ability of humans to survive without an exogenous supply of glucose or monosaccharides convertible to glucose in the liver (fructose and galactose). However, adaptation to a fat and protein fuel requires considerable metabolic adjustments.

The only cells that have an absolute requirement for glucose as an oxidizable fuel are those in the central nervous system (i.e., brain) and those cells that depend upon anaerobic glycolysis (i.e., the partial oxidation of glucose to produce lactate and alanine as a source of energy), such as red blood cells, white blood cells, and medulla of the kidney. The central nervous system can adapt to a dietary fat-derived fuel, at least in part (Cahill, 1970; Sokoloff, 1973). Also, the glycolyzing cells can obtain their complete energy needs from the indirect oxidation of fatty acids through the lactate and alanine-glucose cycles.

In the absence of dietary carbohydrate, de novo synthesis of glucose requires amino acids derived from the hydrolysis of endogenous or dietary protein or glycerol derived from fat. Therefore, the marginal amount of carbohydrate required in the diet in an energy-balanced state is conditional and dependent upon the remaining composition of the diet. Nevertheless, there may be subtle and unrecognized, untoward effects of a very low carbohydrate diet that may only be apparent when populations not genetically or traditionally adapted to this diet adopt it. This remains to be determined but is a reasonable expectation.

Of particular concern in a Western, urbanized society is the long-term consequences of a diet sufficiently low in carbohydrate such that it creates a chronically increased production of β-hydroxybutyric and acetoacetic acids (i.e., keto acids). The concern is that such a diet, deficient in water-soluble vitamins and some minerals, may result in bone mineral loss, may cause hypercholesterolemia, may increase the risk of urolithiasis (Vining, 1999), and may affect the development and function of the central nervous system. It also may adversely affect an individual's general sense of well being (Bloom and Azar, 1963), although in men starved for an extended period of time, encephalographic tracings remained unchanged and psychometric testing showed no deficits (Owen et al., 1967). It also may not provide for adequate stores of glycogen. The latter is required for hypoglycemic emergencies and for maximal short-term power production by muscles (Hultman et al., 1999).

EVIDENCE CONSIDERED FOR ESTIMATING THE AVERAGE REQUIREMENT FOR CARBOHYDRATE

The endogenous glucose production rate, and thus the utilization rate, depends on the duration of starvation. Glucose production has been determined in a number of laboratories using isotopically labeled glucose (Amiel et al., 1991; Arslanian and Kalhan, 1992; Bier et al., 1977; Denne and Kalhan, 1986; Kalhan et al., 1986; King et al., 1982; Patel and Kalhan, 1992). In overnight fasted adults (i.e., postabsorptive state), glucose production is approximately 2 to 2.5 mg/kg/min, or approximately 2.8 to 3.6 g/kg/d. In a 70-kg man, this represents approximately 210 to 270 g/d. In the postabsorptive state, approximately 50 percent of glucose production comes from glycogenolysis in liver and 50 percent from gluconeogenesis in the liver (Chandramouli et al., 1997; Landau et al., 1996).

The minimal amount of carbohydrate required, either from endogenous or exogenous sources, is determined by the brain's requirement for glucose. The brain is the only true carbohydrate-dependent organ in that it oxidizes glucose completely to carbon dioxide and water. Normally, the brain uses glucose almost exclusively for its energy needs. The endogenous glucose production rate in a postabsorptive state correlates very well with the estimated size of the brain from birth to adult life. However, not all of the glucose produced is utilized by the brain (Bier et al., 1977; Felig, 1973). The requirement for glucose has been reported to be approximately 110 to 140 g/d in adults (Cahill et al., 1968). Nevertheless, even the brain can adapt to a carbohydrate-free, energy-sufficient diet, or to starvation, by utilizing ketoacids for part of its fuel requirements. When glucose production or availability decreases below that required for the complete energy requirements for the brain, there is a rise in ketoacid production in the liver in order to provide the brain with an alternative fuel. This has been referred to as "ketosis." Generally, this occurs in a starving person only after glycogen stores in the liver are reduced to a low concentration and the contribution of hepatic glycogenolysis is greatly reduced or absent (Cahill et al., 1968). It is associated with approximately a 20 to 50 percent decrease in circulating glucose and insulin concentration (Carlson et al., 1994; Owen et al., 1998; Streja et al., 1977). These are signals for adipose cells to increase lipolysis and release nonesterified fatty acids and glycerol into the circulation. The signal also is reinforced by an increase in circulating epinephrine, norepinephrine, glucagon, and growth hormone concentration (Carlson et al., 1994). The nonesterified fatty acids are removed by the liver and converted into ketoacids, which then diffuse out of the liver into the circulation. The increase in nonesterified fatty acids results in a concentration-dependent exponential increase in ketoacids (Hanson et al., 1965); glucagon facilitates this process (Mackrell and Sokal, 1969).

In an overnight fasted person, the circulating ketoacid concentration is very low, but with prolonged starvation the concentration increases dramatically and may exceed the molar concentration of glucose (Cahill, 1970; Streja et al., 1977). In individuals fully adapted to starvation, ketoacid oxidation can account for approximately 80 percent of the brain's energy requirements (Cahill et al., 1973). Thus, only 22 to 28 g/d of glucose are required to fuel the brain. This is similar to the total glucose oxidation rate integrated over 24 hours determined by isotope-dilution studies in these starving individuals (Carlson et al., 1994; Owen et al., 1998).

Overall, the key to the metabolic adaptation to extended starvation is the rise in circulating nonesterified fatty acid concentrations and the large increase in ketoacid production. The glycerol released from the hydrolysis of triacylglycerols stored in fat cells becomes a significant source of substrate for gluconeogenesis, but the conversion of amino acids derived from protein catabolism into glucose is also an important source. Interestingly, in people who consumed a protein-free diet, total nitrogen excretion was reported to be in the range of 2.5 to 3.5 g/d (35 to 50 mg/kg), or the equivalent of 16 to 22 g of catabolized protein in a 70-kg man (Raguso et al., 1999). Thus, it is similar to that in starving individuals (3.7 g/d) (Owen et al., 1998). Overall, this represents the minimal amount of protein oxidized through gluconeogenic pathways (Du Bois, 1928). This amount of protein is considerably less than the Recommended Dietary Allowance (RDA) of 0.8 g/kg/d for adults with a normal body mass index (Chapter 10). For a 70-kg lean male, this equals 56 g/d of protein, which is greater than the estimated obligate daily loss in body protein from the shedding of cells, secretions, and other miscellaneous functions (approximately 6 to 8 g/d for a 70-kg man; see Chapter 10) and has been assumed to be due to inefficient utilization of amino acids for synthesis of replacement proteins and other amino acid-derived products (Gannon and Nuttall, 1999). In part, it also may represent the technical difficulty in determining a minimal daily protein requirement (see Chapter 10).

If 56 g/d of dietary protein is required for protein homeostasis, but the actual daily loss of protein is only approximately 7 g, then presumably the remaining difference (49 g) is metabolized and may be utilized for new glucose production. It has been determined that for ingested animal protein, approximately 0.56 g of glucose can be derived from every 1 g of protein ingested (Janney, 1915). Thus, from the 49 g of protein not directly utilized to replace loss of endogenous protein or not used for other synthetic processes, approximately 27 g (0.56×49) of glucose may be produced. In people on a protein-free diet or who are starving, the 16 to 22 g of catabolized protein could provide 10 to 14 g of glucose.

If the starving individual's energy requirement is 1,800 kcal/d and 95 percent is supplied by fat oxidation either directly or indirectly through

oxidation of ketoacids (Cahill et al., 1973), then fat oxidation represents 1,710 kcal/d, or 190 g based upon approximately 9 kcal/g fat. The glycerol content of a typical triacylglycerol is 10 percent by weight, or in this case 19 g of glycerol, which is equivalent to approximately 19 g of glucose. This, plus the amount of glucose potentially derived from protein, gives a total of approximately 30 to 34 g ([10 to 14] + 19). Thus, a combination of protein and fat utilization is required to supply the small amount of glucose still required by the brain in a person fully adapted to starvation. Presumably this also would be the obligatory glucose requirement in people adapted to a carbohydrate-free diet. Thus, the normal metabolic adaptation to a lack of dietary protein, as occurs in a starving person in whom the protein metabolized is in excess of that lost daily, is to provide the glucose required by the brain. Nevertheless, utilization of this amount of glucose by the brain is vitally important. Without it, function deteriorates dramatically, at least in the brain of rats (Sokoloff, 1973).

The required amount of glucose could be derived easily from ingested protein alone if the individual was ingesting a carbohydrate-free, but energy-adequate diet containing protein sufficient for nitrogen balance. However, ingested amounts of protein greater than 30 to 34 g/d would likely stimulate insulin secretion unless ingested in small amounts throughout a 24-hour period. For example, ingestion of 25 to 50 g of protein at a single time stimulates insulin secretion (Krezowski et al., 1986; Westphal et al., 1990), despite a lack of carbohydrate intake. This rise in insulin would result in a diminution in the release of fatty acids from adipose cells and as a consequence, reduce ketoacid formation and fatty acid oxidation. The ultimate effect would be to increase the requirement for glucose of the brain and other organs. Thus, the minimal amount of glucose irreversibly oxidized to carbon dioxide and water requires utilization of a finely balanced ratio of dietary fat and protein.

Azar and Bloom (1963) reported that 100 to 150 g/d of protein was necessary for maintenance of nitrogen balance. This amount of protein could typically provide amino acid substrate sufficient for the production of 56 to 84 g of glucose daily. However, daily infusion of 90 g of an amino acid mixture over 6 days to both postoperative and nonsurgical starving adults has been reported to reduce urinary nitrogen loss without a significant change in glucose or insulin concentration, but with a dramatic increase in ketoacids (Hoover et al., 1975). Thus, the issue becomes complex in nonstarving people.

Glucose utilization by the brain has been determined either by measuring arteriovenous gradients of glucose, oxygen, lactate, and ketones across the brain and the respiratory quotient (Kety, 1957; Sokoloff, 1973), or with estimates of brain blood flow determined by different methods (e.g., NO_2 diffusion). A major problem with studies based on arteriovenous

differences is the limited accuracy of the blood flow methods used (Settergren et al., 1976, 1980). Using ^{18}F-2-fluoro-2-deoxyglucose and positron emission tomography, the rate of glucose accumulation in the brain also has been determined (Chugani, 1993; Chugani and Phelps, 1986; Chugani et al., 1987; Hatazawa et al., 1987). This is an indirect method for measuring glucose utilization, and also has limitations (Hatazawa et al., 1987). Brain O_2 consumption in association with the brain respiratory quotient also has been used as an indirect estimate of glucose utilization (Kalhan and Kiliç, 1999).

Only data determined by direct measurement of glucose arteriovenous difference across the brain in association with determination of brain blood flow can be considered for setting an Estimated Average Requirement (EAR), although the other, indirect methods yield similar results. The glucose consumption by the brain can be used along with information from Dobbing and Sands (1973) and Dekaban and Sadowsky (1978), which correlated weight of the brain with body weight to calculate glucose utilization.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants Ages 0 Through 12 Months

Methods Considered to Set the AI

Carbohydrate Utilization by the Brain. In infants, the brain size relative to body size is greater than that in adults. The brain utilizes approximately 60 percent of the infant's total energy intake (Gibbons, 1998). Therefore, the turnover of glucose per kilogram of body weight can be up to fourfold greater in the infant compared to the adult (Kalhan and Kiliç, 1999).

The infant brain is fully capable of using ketoacids as fuel. In species in which the mothers' milk is very high in fat, such as in rats, the circulating ketoacid concentration is very high in the suckling pups, and the ketoacids are an important source of fuel for the developing brain (Edmond et al., 1985; Sokoloff, 1973). In addition, the gluconeogenic pathway is well developed even in premature human infants (Sunehag et al., 1999). Indeed, provided that adequate lipid and protein substrates are supplied, gluconeogenesis can account for the majority of glucose turnover. Whether gluconeogenesis can account for the entire glucose requirement in infants has not been tested.

Growth. Studies have been performed using artificial formula feedings and varying the fat and carbohydrate content while keeping the protein

content constant (9 percent) (Fomon et al., 1976). Fomon and coworkers (1976) provided infants with formulas containing either 34 or 62 percent of energy from carbohydrate for 104 days. There were no significant differences in the length or weight of the infants fed the two formulas. Interestingly, it also did not affect the total food energy consumed over the 6 or 12 months of life. From the limited data available, the lowest intake that has been documented to be adequate is 30 percent of total food energy. However, it is likely that infants also may grow and develop normally on a very low or nearly carbohydrate-free diet since their brains' enzymatic machinery for oxidizing ketoacids is more efficient than it is in adults (Sokoloff, 1973).

Human Milk. The lower limit of dietary carbohydrate compatible with life or for optimal health in infants is unknown. Human milk is recognized as the optimal milk source for infants throughout at least the first year of life and is recommended as the sole nutritional milk source for infants during the first 4 to 6 months of life (IOM, 1991). Carbohydrate in human milk is almost exclusively lactose (Table 6-4). The only source of lactose in the animal kingdom is from the mammary gland and therefore is found only in mammals. Lactose is readily hydrolyzed in the infant intestine. The resulting glucose and galactose also readily pass into the portal venous system. They are carried to the liver where the galactose is converted to glucose and either stored as glycogen or released into the general circulation and oxidized. The net result is the provision of two glucose molecules for each lactose molecule ingested. The reason why lactose developed as the carbohydrate fuel produced by the mammary gland is not understood. One reason may be that the provision of a disaccharide compared to a monosaccharide reduces the osmolality of milk. Lactose has also been reported to facilitate calcium absorption from the gut, which otherwise is not readily absorbed from the immature infant intestine (Condon et al., 1970; Ziegler and Fomon, 1983). However, isotopic tracer data have not confirmed this (Kalhan and Kiliç, 1999).

The lactose content of human milk is approximately 74 g/L and changes little over the total nursing period (Dewey and Lönnerdal, 1983; Dewey et al., 1984; Lammi-Keefe et al., 1990; Nommsen et al., 1991) (Table 6-4). However, the volume of milk consumed by the infant decreases gradually over the first 12 months of life as other foods are gradually introduced into the feeding regimen. Over the first 6 months of life, the volume consumed is about 0.78 L/d (see Chapter 2); therefore approximately 60 g of carbohydrate represents about 37 percent of total food energy (see Chapter 5) (Nommsen et al., 1991). This amount of carbohydrate and the ratio of carbohydrate to fat in human milk can be assumed to be optimal for infant growth and development over the first 6 months of life.

TABLE 6-4 Total Carbohydrate Content of Human Milk

Reference	Stage of Lactation	Total Carbohydrate Content (g/L)	Total Lactose Content (g/L)	Total Glucose Content (g/L)
Anderson et al., 1981	3–5 d		51.4 ± 2.2	
	8–11 d		59.8 ± 2.3	
	26–29 d		65.1 ± 2.3	
Anderson et al., 1983	3 d	62 ± 9		
	7 d	67 ± 5		
	14 d	67 ± 6		
Dewey and Lönnerdal, 1983	1 mo		70.5 ± 5.6	
	2 mo		72.1 ± 6.2	
	3 mo		71.3 ± 7.9	
	4 mo		76.1 ± 4.0	
	5 mo		76.2 ± 3.3	
	6 mo		77.5 ± 2.7	
Dewey et al., 1984	4–6 mo		77.1 ± 3.0	
	7–11 mo		75.7 ± 3.6	
	12–20 mo		72.3 ± 4.3	
Neville et al., 1984	33–210 d		Mid-feed: 72.1	Mid-feed: 0.27
	Median 115 d		Pooled pumped: 71.8	Pooled pumped: 0.27
Ferris et al., 1988	2 wk		62.5 ± 6.5	
	6 wk		67.8 ± 6.4	
	12 wk		68.5 ± 7.3	
	16 wk		70.0 ± 6.5	
Lammi-Keefe et al., 1990	8 wk		76.2 ± 3.2	0.26 ± 0.05
			73.6 ± 3.8	0.31 ± 0.05
			77.4 ± 6.7	0.33 ± 0.06
			74.2 ± 4.7	0.33 ± 0.08
			80.1 ± 4.6	0.33 ± 0.06
Allen et al., 1991	21 d		63.4 ± 0.7	0.27 ± 0.01
	45 d		65.6 ± 0.4	0.27 ± 0.01
	90 d		67.7 ± 0.7	0.31 ± 0.01
	180 d		68.8 ± 1.4	0.32 ± 0.02
Nommsen et al., 1991	3 mo		74.4 ± 1.5	
	6 mo		74.4 ± 1.9	
	9 mo		73.5 ± 2.9	
	12 mo		74.0 ± 2.7	

continued

TABLE 6-4 Continued

Reference	Stage of Lactation	Total Carbohydrate Content (g/L)	Total Lactose Content (g/L)	Total Glucose Content (g/L)
Coppa et al., 1993	4 d	78.1 ± 8.08	56.0 ± 6.06	
	10 d	83.8 ± 6.45	62.5 ± 5.74	
	30 d	80.6 ± 6.90	64.1 ± 6.45	
	60 d	79.8 ± 7.01	66.2 ± 6.88	
	90 d	79.3 ± 7.03	66.3 ± 7.08	
	120 d	82.2 ± 10.31	68.9 ± 8.16	

The method used to set the Adequate Intake (AI) for older infants is carbohydrate intake from human milk and complementary foods (see Chapter 2). According to the Third National Health and Nutrition Examination Survey, the median carbohydrate intake from weaning food for ages 7 through 12 months was 50.7 ± 5 g/d (standard error of the mean). Based on an average volume of 0.6 L/d of human milk that is secreted (Chapter 2), the carbohydrate intake from human milk is 44 g/d (0.6 L/d × 74 g/L). Therefore, the total intake of carbohydrate from human milk and complementary foods is 95 g/d (44 + 51).

Carbohydrate AI Summary, Ages 0 Through 12 Months

The AI is based on the average intake of carbohydrate consumed from human milk and complementary foods.

AI for Infants

0–6 months	**60 g/d of carbohydrate**
7–12 months	**95 g/d of carbohydrate**

Special Considerations

The carbohydrate content of milk protein-based formulas for term infants is similar to that of human milk (70 to 74 g/L). Whole cow milk contains lower concentrations of carbohydrate than human milk (48 g/L) (Newburg and Neubauer, 1995). In addition to lactose, conventional infant formulas can also contain sucrose or glucose polymers.

Children and Adolescents Ages 1 Through 18 Years

Evidence Considered in Estimating the Average Requirement

In the newborn, the brain weight is approximately 380 g; by age 1 year this has increased to approximately 1,000 g in boys and approximately 980 g in girls (Dekaban and Sadowsky, 1978; Dobbing and Sands, 1973), with a corresponding increase in energy requirement. After 1 year of age, there is a further increase in brain weight up to 5 years of age (approximately 1,300 g in boys and 1,150 g in girls). Subsequently, the brain size increases only modestly. The consumption of glucose by the brain after age 1 year also remains rather constant or increases modestly and is in the range reported for adults (approximately 31 μmol/100 g of brain/min) (Kennedy and Sokoloff, 1957; Sokoloff et al., 1977). Therefore, the Estimated Average Requirement (EAR) for carbohydrate is set based on information used for adults (see "Adults Ages 19 Years and Older"). As for adults, the EAR is the same for both genders since differences in brain glucose utilization are small.

The amount of glucose produced from obligatory endogenous protein catabolism in children is not known. Therefore, this information was not considered in the derivation of the EAR for children. Children ages 2 to 9 years have requirements for carbohydrate that are similar to adults. This is based on population data in which animal-derived foods are ingested exclusively (e.g., Alaska and Greenland natives), as well as in children with epilepsy who have been treated with ketogenic diets for extended periods of time (Swink et al., 1997; Vining, 1999). In these children, the ketoacid concentration was in the range of 2 to 3 mmol/L (i.e., similar to that in a starving adult) (Nordli et al., 1992).

Carbohydrate EAR and RDA Summary, Ages 1 Through 18 Years

EAR for Children

1–3 years	**100 g/d of carbohydrate**
4–8 years	**100 g/d of carbohydrate**

EAR for Boys

9–13 years	**100 g/d of carbohydrate**
14–18 years	**100 g/d of carbohydrate**

EAR for Girls

9–13 years	**100 g/d of carbohydrate**
14–18 years	**100 g/d of carbohydrate**

The Recommended Dietary Allowance (RDA) for carbohydrate is set by using a coefficient of variation (CV) of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR).

RDA for Children

1–3 years	**130 g/d of carbohydrate**
4–8 years	**130 g/d of carbohydrate**

RDA for Boys

9–13 years	**130 g/d of carbohydrate**
14–18 years	**130 g/d of carbohydrate**

RDA for Girls

9–13 years	**130 g/d of carbohydrate**
14–18 years	**130 g/d of carbohydrate**

Adults Ages 19 Years and Older

Evidence Considered in Estimating the Average Requirement

Glucose Utilization by the Brain. Long-term data in Westernized populations, which could determine the minimal amount of carbohydrate compatible with metabolic requirements and for optimization of health, are not available. Therefore, it is provisionally suggested that an EAR for carbohydrate ingestion in the context of overall food energy sufficiency be based on an amount of digestible carbohydrate that would provide the brain (i.e., central nervous system) with an adequate supply of glucose fuel without the requirement for additional glucose production from ingested protein or triacylglycerols. This amount of glucose should be sufficient to supply the brain with fuel in the absence of a rise in circulating acetoacetate and β-hydroxybutyrate concentrations greater than that observed in an individual after an overnight fast (see "Evidence Considered for Estimating the Average Requirement for Carbohydrate"). This assumes the consumption of an energy-sufficient diet containing an Acceptable Macronutrient Distribution Range of carbohydrate intake (approximately 45 to 65 percent of energy) (see Chapter 11).

Brain glucose utilization based on O_2 consumption is summarized in Table 6-5. Only data determined by direct measurement of glucose arteriovenous difference across the brain in association with determination of

TABLE 6-5 Indirect Estimates of Glucose Utilization by Measuring Brain Oxygen (O_2) Consumption

Reference	Study Population	O_2 Consumption (mL/100 g/min)	O_2 Consumption (L/100 g/d)
Kennedy and Sokoloff, 1957	2 children, 3 y	6.2 5.6	8.93 8.06
Kennedy and Sokoloff, 1957	5 children, 4–7 y	5.3 4.3 4.4 5.7 4.4	7.63 6.19 6.34 8.21 6.34
Kennedy and Sokoloff, 1957	2 children, 10 and 11 y	5.7 4.9	8.21 7.06
Kennedy and Sokoloff, 1957	12 adults	4.18	6.02

[a] For males, based on Dekaban and Sadowsy (1978) and Dobbing and Sands (1973).
[b] O_2 = 4.8 kcal/L = 1.2 g of glucose/L.

brain blood flow (Table 6-6) were considered for setting an EAR, although both methods yielded similar results. Data on glucose consumption by the brain for various age groups using information from Dobbing and Sands (1973) and Dekaban and Sadowsky (1978) were also used, which correlated weight of the brain with body weight. The average rate of brain glucose utilization in the postabsorptive state of adults based on several studies is approximately 33 μmol/100 g of brain/min (5.5 mg/100 g of brain/min or 8.64 g/100 g of brain/d) (Table 6-6). Based on these data, the brain's requirement for carbohydrate is in the range of approximately 117 to 142 g/d (Gottstein and Held, 1979; Reinmuth et al., 1965; Scheinberg and Stead, 1949; Sokoloff et al., 1977). Regardless of age and the associated change in brain mass, the glucose utilization rate/100 g of brain tissue remains rather constant, at least up to age 73 years (Reinmuth et al., 1965). In 351 men (aged 21 to 39 years), the average brain weight at autopsy was reported to be 1.45 kg, with a standard deviation of only 0.02 kg. In 201 women of the same age range, the average brain weight was 1.29 kg with a standard deviation of 0.03 kg. There was excellent correlation between body weight and height and brain weight in adults of all ages.

The glucose produced from the obligatory turnover of protein plus the glucose produced from glycerol is approximately 30 g/d (see "Evi-

Estimated Brain Weight (g)[a]	O_2 Consumption (L/d)	Glucose Consumption (g/d)[b]
1,200	107.1	129
1,200	96.8	116
1,260	96.2	115
1,260	78.0	94
1,300	82.4	99
1,300	109.2	131
1,300	84.3	101
1,360	111.6	134
1,360	96.0	115
1,450	84.3	101

dence Considered for Estimating the Average Requirement for Carbohydrate"). Therefore, the overall dietary carbohydrate requirement in the presence of an energy-adequate diet would be approximately 87 (117 – 30) to 112 (142 – 30) g/d. This amount of carbohydrate is similar to that reported to be required for the prevention of ketosis (50 to 100 g) (Bell et al., 1969; Calloway, 1971; Gamble, 1946; Sapir et al., 1972) and to that reported to have a maximal protein sparing effect when glucose was ingested daily (Gamble, 1946). The carbohydrate requirement is modestly greater than the potential glucose that can be derived from an amount of ingested protein required for nitrogen balance in people ingesting a carbohydrate-free diet (Azar and Bloom, 1963).

This amount of carbohydrate will not provide sufficient fuel for those cells that are dependent on anaerobic glycolysis for their energy supply (e.g., red and white blood cells). For glycolyzing cells, approximately 36 g/d are necessary (Cahill, 1970). Glycolyzing cells can obtain energy through the functioning of the Cori cycle (i.e., lactate to glucose to lactate) and the alanine-glucose cycle. That is, the cyclic interconversion of glucose with lactate or alanine occurs without a net loss of carbon.

In the absence of carbohydrate in the diet, and in the absence of a rise in ketoacids above the overnight fasting reference range, ingested protein

TABLE 6-6 Direct Estimates of Glucose Utilization by Measuring Brain Glucose Consumption

Reference	Study Population	Glucose Consumption (μmol/100 g of brain/min)	Estimated Brain Weight (g)[a]	Glucose Consumption	
				(mg/min)	(g/d)
Settergren et al., 1976	12 infants, average 5 mo	27	400	19.4	28
Mehta et al., 1977	10 infants, average 11 mo	66	1,000	118	170
Settergren et al., 1980	42 infants and children, 3 wk–14 y	25	400–1,450	18–65	26–94
Scheinberg and Stead, 1949	18 adults, 18–36 y	34	1,450	88	127
Reinmuth et al., 1965	13 adults, 21–29 y	38	1,450	99	142
Sokoloff et al., 1977	Adults	31	1,450	81	117
Gottstein and Held, 1979	24 adults, 21–43 y	31	1,450	81	117

[a] Based on Dekaban and Sadowsy (1978) and Dobbing and Sands (1973).

sufficient to provide the brain with glucose fuel is theoretically possible, but is not likely to be acceptable. The amount of dietary protein required approaches the theoretical maximal rate of gluconeogenesis from amino acids in the liver (135 g of glucose/24 h) (Brosnan, 1999).

In summary, the EAR for total carbohydrate is set at 100 g/d. This amount should be sufficient to fuel central nervous system cells without having to rely on a partial replacement of glucose by ketoacids. Although the latter are used by the brain in a concentration-dependent fashion (Sokoloff, 1973), their utilization only becomes quantitatively significant when the supply of glucose is considerably reduced and their circulating concentration has increased several-fold over that present after an overnight fast.

Diets contain a combination of carbohydrate, fat, and protein, and therefore available glucose is not limiting to the brain unless carbohydrate energy intake is insufficient to meet the glucose needs of the brain. Nevertheless, it should be recognized that the brain can still receive enough glucose from the metabolism of the glycerol component of fat and from the gluconeogenic amino acids in protein when a very low carbohydrate diet is consumed.

Aging. It is well known that the overall rate of energy metabolism decreases with aging (Roberts, 2000a). Also, the total body glucose oxidation rate is decreased, but only modestly. In adults 70 years of age or older, the glucose oxidation rate was only about 10 percent less than in young adults between 19 and 29 years of age (Robert et al., 1982).

The actual brain mass slowly decreases after age 45 to 55 years. In 76- to 80-year-old men, the average brain mass was 1.33 kg, and for women in the same age range it was 1.19 kg (i.e., a loss of 8 to 9 percent of mass) (Dekaban and Sadawosky, 1978). This decrease is similar to that reported from autopsy data in Japan (mean 1,422 to 1,336 g) (Yamaura et al., 1980). Whether glucose oxidation changes out of proportion to brain mass remains a controversial issue (Gottstein and Held, 1979; Leenders et al., 1990). In any case, the decrease in brain glucose oxidation rate is not likely to be substantially less. Therefore, the EAR is the same for all adults. There is no evidence to indicate that a certain amount of carbohydrate should be provided as starch or sugars. However, most individuals do not choose to eat a diet in which sugars exceed approximately 30 percent of energy (Nuttall and Gannon, 1981).

Carbohydrate EAR and RDA Summary, Ages 19 Years and Older

EAR for Men

19–30 years	**100 g/d of carbohydrate**
31–50 years	**100 g/d of carbohydrate**
51–70 years	**100 g/d of carbohydrate**
> 70 years	**100 g/d of carbohydrate**

EAR for Women

19–30 years	**100 g/d of carbohydrate**
31–50 years	**100 g/d of carbohydrate**
51–70 years	**100 g/d of carbohydrate**
> 70 years	**100 g/d of carbohydrate**

The RDA for carbohydrate is set by using a CV of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the

EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR).

RDA for Men

19–30 years	**130 g/d of carbohydrate**
31–50 years	**130 g/d of carbohydrate**
51–70 years	**130 g/d of carbohydrate**
> 70 years	**130 g/d of carbohydrate**

RDA for Women

19–30 years	**130 g/d of carbohydrate**
31–50 years	**130 g/d of carbohydrate**
51–70 years	**130 g/d of carbohydrate**
> 70 years	**130 g/d of carbohydrate**

Pregnancy

Evidence Considered in Estimating the Average Requirement

Pregnancy results in an increased metabolic rate and thus an increased fuel requirement. This increased fuel requirement is due to the establishment of the placental–fetal unit and an increased energy supply for growth and development of the fetus. It is also necessary for the maternal adaptation to the pregnant state and for moving about the increased mass of the pregnant woman. This increased need for metabolic fuel often includes an increased maternal storage of fat early in pregnancy, as well as sufficient energy to sustain the growth of the fetus during the last trimester of pregnancy (Knopp et al., 1973).

In spite of the recognized need for increased energy-yielding substrates imposed by pregnancy, the magnitude of need, as well as how much of the increased requirement needs to be met from exogenous sources, remains incompletely understood and is highly variable (Tables 5-23 through 5-27). There is general agreement that the additional food energy requirement is relatively small. Several doubly labeled water studies indicate a progressive increase in total energy expenditure over the 36 weeks of pregnancy (Forsum et al., 1992; Goldberg et al., 1993; Kopp-Hoolihan et al., 1999) (Table 5-27). The mean difference in energy expenditure between week 0 and 36 in the studies was approximately 460 kcal/d and is proportional to body weight.

The developing fetus utilizes glucose as an energy-yielding substrate. However, there is some evidence that the fetus can utilize maternally pro-

vided ketoacids. The fetus does not utilize significant amounts of free fatty acids (Rudolf and Sherwin, 1983).

As part of the adaptation to pregnancy, there is a decrease in maternal blood glucose concentration, a development of insulin resistance, and a tendency to develop ketosis (Burt and Davidson, 1974; Cousins et al., 1980; Phelps et al., 1981; Rudolf and Sherwin, 1983; Ryan et al., 1985).

A higher mean respiratory quotient for both the basal metabolic rate and total 24-hour energy expenditure has also been reported in pregnant women when compared to the postpartum period. This indicates an increased utilization of glucose by the maternal–fetal unit. The increased glucose utilization rate persists after fasting, indicating an increased endogenous production rate as well (Assel et al., 1993; Kalhan et al., 1997) (see Chapter 5). Thus, irrespective of whether there is an increase in total energy expenditure, these data indicate an increase in glucose utilization. Earlier, it was reported that the glucose turnover in the overnight fasted state based on maternal weight gain remains unchanged from that in the nonpregnant state (Cowett et al., 1983; Kalhan et al., 1979).

The fetus reportedly uses approximately 8 ml O_2/kg/min or 56 kcal/kg/d (Sparks et al., 1980). For a 3-kg term fetus, this is equivalent to 168 kcal/d. The transfer of glucose from the mother to the fetus has been estimated to be 17 to 26 g/d in late gestation (Hay, 1994). If this is the case, then glucose can only account for approximately 51 percent of the total oxidizable substrate transferred to the fetus at this stage of gestation.

The mean newborn infant brain weight is reported to be approximately 380 g (Dekaban and Sadowsky, 1978). Assuming the glucose consumption rate is the same for infants and adults (approximately 33 μmol/100 g of brain/min or 8.64 g/100 g of brain/d) (see "Adults Ages 19 Years and Older"), and that ketoacids do not supply a significant amount of oxidizable substrate for the fetal brain in utero, the glucose requirement at the end of pregnancy would be approximately 32.5 g/d. This is greater than the total amount of glucose transferred daily from the mother to the fetus.

Data obtained in newborns indicate that glucose oxidation can only account for approximately 70 percent of the brain's estimated fuel requirement (Denne and Kalhan, 1986). Whether this is the case in the late-term fetus is not known. However, the fetal brain can clearly utilize ketoacids (Patel et al., 1975). In addition, an increase in circulating ketoacids is common in pregnant women (Homko et al., 1999). Taken together, these data suggest that ketoacids may be utilized by the fetal brain in utero. If nonglucose sources (largely ketoacids) supply 30 percent of the fuel requirement of the fetal brain, then the brain glucose utilization rate would be 23 g/d (32.5 g × 0.70). This is essentially the same as the average maternal–fetal glucose transfer rate (mean 22 g, range 17 to 26 g) (Hay,

1994). These data also indicate that the fetal brain utilizes essentially all of the glucose derived from the mother.

In order to assure provision of glucose to the fetal brain (approximately 33 g/d) as a fuel in the absence of utilization of a lipid-derived fuel, as well as to supply the glucose fuel requirement for the mother's brain independent of utilization of ketoacids (or other substrates), the EAR for metabolically available dietary carbohydrate is the EAR for nonpregnant women (100 g/d) plus the additional amount required during the last trimester of pregnancy (35 g/d), or 135 g/d. There is no evidence to indicate that a certain portion of the carbohydrate must be consumed as starch or sugars.

EAR and RDA Summary, Pregnancy

EAR for Pregnancy

14–18 years	**135 g/d of carbohydrate**
19–30 years	**135 g/d of carbohydrate**
31–50 years	**135 g/d of carbohydrate**

The RDA for carbohydrate is set by using a CV of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR). The calculated values for the RDAs have been rounded.

RDA for Pregnancy

14–18 years	**175 g/d of carbohydrate**
19–30 years	**175 g/d of carbohydrate**
31–50 years	**175 g/d of carbohydrate**

Lactation

Evidence Considered in Estimating the Average Requirement

The requirement for carbohydrate is increased during lactation. The lactose content of human milk is approximately 74 g/L; this concentration changes very little during the nursing period. Therefore, the amount of precursors necessary for lactose synthesis must increase. Lactose is synthesized from glucose and as a consequence, an increased supply of glucose must be obtained from ingested carbohydrate or from an increased supply of amino acids in order to prevent utilization of the lactating woman's endogenous proteins. Glycerol derived from endogenous or exogenous

fat may contribute to the increased production of glucose through gluconeogenesis. However, the amount of fat that can be oxidized daily greatly limits the contribution of glycerol to glucose production and thus lactose formation.

The EAR during lactation is the sum of the carbohydrate intake necessary to replace the carbohydrate secreted in human milk (60 g/d) and the EAR for adolescent girls and women (100 g/d). The EAR for carbohydrate during lactation is set at 160 g/d.

EAR and RDA Summary, Lactation

EAR for Lactation

14–18 years	**160 g/d of carbohydrate**
19–30 years	**160 g/d of carbohydrate**
31–50 years	**160 g/d of carbohydrate**

The RDA for carbohydrate is set by using a CV of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR). The calculated values for the RDAs have been rounded.

RDA for Lactation

14–18 years	**210 g/d of carbohydrate**
19–30 years	**210 g/d of carbohydrate**
31–50 years	**210 g/d of carbohydrate**

Special Considerations

Individuals adapted to a very low carbohydrate diet can perform adequately for extended periods of time at power outputs represented by exercise at less than 65 percent O_2 max (Miller and Wolfe, 1999). For extended periods of power output exceeding this level, the dependence on carbohydrate as a fuel increases rapidly to near total dependence (Miller and Wolfe, 1999). Therefore, for such individuals there must be a corresponding increase in carbohydrate derived directly from carbohydrate-containing foods. Additional consumption of dietary protein may assist in meeting the need through gluconeogenesis, but it is unlikely to be consumed in amounts necessary to meet the individual's need. A requirement for such individuals cannot be determined since the requirement for carbohydrate will depend on the particular energy expenditure for some defined period of time (Brooks and Mercier, 1994).

INTAKE OF CARBOHYDRATES

Food Sources

White, brown, and raw sugars represent different forms and purification of sucrose. Corn syrups are the hydrolytic products of starch digestion. They are composed of various proportions of glucose (dextrose), maltose, trisaccharides, and higher molecular-weight products including some starch itself. Another source of carbohydrate, high fructose corn syrup, is often misunderstood. These syrups are also derived from cornstarch through the conversion of a portion of the glucose present in starch into fructose. The fructose content present in corn syrup is 42, 55, or 90 percent. The great majority of the remaining content is glucose. Other sources of sugars include malt syrup, comprised largely of sucrose; honey, which resembles sucrose in its composition but is composed of individual glucose and fructose molecules; and molasses, a by-product of table sugar production.

With the introduction of high fructose corn sweeteners in 1967, the amount of "free" fructose in the diet of Americans has increased considerably (Hallfrisch, 1990). Nonalcoholic beverages (e.g., soft drinks and fruit-flavored drinks) are the major dietary sources of added fructose; fruits and fruit products are the major dietary sources of naturally occurring fructose (Park and Yetley, 1993).

Using 1994–1996 U.S. Department of Agriculture food consumption survey data, nondiet soft drinks were the leading source of added sugars in Americans' diets, accounting for one-third of added sugars intake (Guthrie and Morton, 2000). This was followed by sugars and sweets (16 percent), sweetened grains (13 percent), fruit ades/drinks (10 percent), sweetened dairy (9 percent), and breakfast cereals and other grains (10 percent). Together, these foods and beverages accounted for 90 percent of Americans' added sugars intake. Gibney and colleagues (1995) reported that dairy foods contributed 31 percent of the total sugar intakes in children, and fruits contributed 17 percent of the sugars for all ages.

Grains and certain vegetables are the major contributors of starch. The majority of carbohydrate occurs as starch in corn, tapioca, flour, cereals, popcorn, pasta, rice, potatoes, and crackers. Fruits and darkly colored vegetables contain little or no starch.

Dietary Intake

Data from the 1994–1996, 1998 Continuing Food Survey of Intakes by Individuals (CSFII) indicates that the median intake of carbohydrate was approximately 220 to 330 g/d for men and 180 to 230 g/d for women in the United States (Appendix Table E-2). This represents 49 to 50 percent

of energy intake (Appendix Table E-3). Between 10 and 25 percent of adults consumed less than 45 percent of energy from carbohydrate. Less than 5 percent of adults consumed more than 65 percent of energy from carbohydrate (Appendix Table E-3).

Median carbohydrate intakes of Canadian men and women during 1990 to 1997 ranged from approximately 47 to 50 percent of energy intake (Appendix Table F-2). More than 25 percent of men consumed less than 45 percent of energy from carbohydrate, whereas between 10 and 25 percent of women consumed below this level. Less than 5 percent of Canadian men and women consumed more than 65 percent of energy from carbohydrate.

Data from the Third National Health and Nutrition Examination Survey shows that the median intake of added sugars widely ranged from 10 to 30 tsp/d for adults, which is equivalent to 40 to 120 g/d of sugars (1 tsp = 4 g of sugar) (Appendix Table D-1). Based on data from CFSII, the mean intake of added sugars in the U.S. population aged 2 and older was 82 g, accounting for 15.8 percent of the total energy intake (Guthrie and Morton, 2000).

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Sugars such as sucrose (e.g., white sugar), fructose (e.g., high-fructose corn syrup), and dextrose that are present in foods have been associated with various adverse effects. These sugars may be either naturally occurring or added to foods. Potential adverse effects from consuming a high carbohydrate diet, including sugars and starches, are discussed in detail in Chapter 11.

Behavior

The concept that sugars might adversely affect behavior was first reported by Shannon (1922). The notion that intake of sugars is related to hyperactivity, especially in children, is based on two physiological theories: (1) an allergic reaction to refined sugars (Egger et al., 1985; Speer, 1954) and (2) a hypoglycemic response (Cott, 1977). A number of studies have been conducted to find a correlation between intake of sugars and adverse behavior; some have been reviewed by White and Wolraich (1995). Most of the intervention studies looked at the behavior effects of sugars within a few hours after ingestion, and therefore the long-term effects are unclear. The cross-sectional studies are not capable of determining if the sugars caused adverse behavior or adverse behavior resulted in increased sugar

consumption. A meta-analysis of 23 studies conducted over a 12-year period concluded that sugar intake does not affect either behavior or cognitive performance in children (Wolraich et al., 1995) (Figure 6-2). Therefore, altered behavior cannot be used as an adverse effect for setting a Tolerable Upper Intake Level (UL) for sugars.

Dental Caries

Sugars play a significant role in the development of dental caries (Walker and Cleaton-Jones, 1992), but much less information is known about the role of starch in the development of dental caries (Lingstrom et al., 2000). Early childhood dental caries, also known as baby-bottle tooth decay or nursing caries, affects about 3 to 6 percent of children (Fitzsimons et al., 1998). This is associated with frequent, prolonged use of baby bottles containing fermentable sugars (e.g., cow's milk, infant formula, fruit juice, soft drinks, and other sweetened drinks), at-will breast-feeding, and continual use of a sweetened pacifier (Fitzsimons et al., 1998). Increased consumption of sugar-containing foods has been associated with a deterioration of dental health in 5-year-old children (Holbrook et al., 1995). Children 5 or 8 years of age who consumed sweet snacks between meals more than five times a day had significantly higher mean decayed and missing teeth and filled scores than children with a lower consumption (Kalsbeek and Verrips, 1994). Root caries in middle-aged and elderly adults was significantly associated with sucrose consumption (Papas et al., 1995).

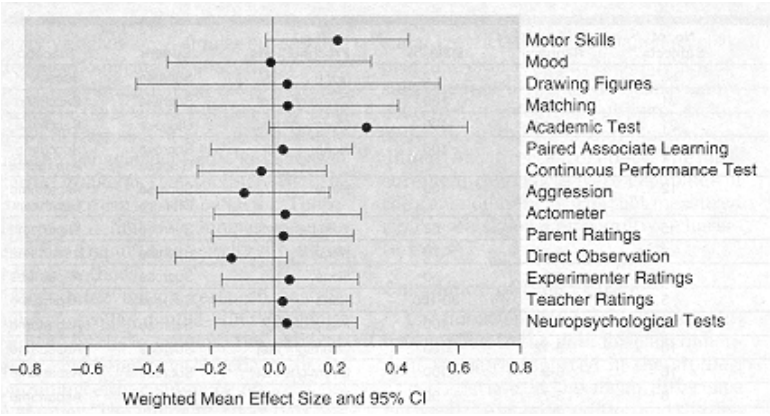

FIGURE 6-2 Weighted mean effect sizes and 95 percent confidence intervals (CI) by measurement construct following meta-analysis of 23 studies on the effect of sugar intake on behavior and cognition. Reprinted, with permission, from Wolraich et al. (1995). Copyright 1995 by the American Medical Association.

Dental caries is a disorder of multifactorial causation. Hence, it is difficult to rationalize the relationship of sugars and dental caries as simply "cause-and-effect" (Walker and Cleaton-Jones, 1992). Caries occurrence is influenced by frequency of meals and snacks, oral hygiene (tooth-brushing frequency), water fluoridation, fluoride supplementation, and fluoride toothpaste (Holbrook et al., 1995; Mascarenhas, 1998; McDonagh et al., 2000; Shaw, 1987). Fluoride alters the sugars–caries dose–response curve. Caries has declined in many industrialized countries and in areas with water fluoridation (McDonagh et al., 2000). Because of the various factors that can contribute to dental caries, it is not possible to determine an intake level of sugars at which increased risk of dental caries can occur.

Triacylglycerol, LDL, and HDL Cholesterol Concentration

Sugars. Fructose is more lipogenic than glucose or starches (Cohen and Schall, 1988; Reiser and Hallfrisch, 1987); however, the precise biochemical basis for this mechanism has not been elucidated (Roche, 1999). There is some evidence that increased intake of sugars is positively associated with plasma triacylglycerol and low density lipoprotein (LDL) cholesterol concentrations (Table 6-7). The data on triacylglycerol concentration is mixed with a number of studies showing an increase in concentration with increased sucrose, glucose, or fructose concentration (Albrink and Ullrich, 1986; Hayford et al., 1979; Kaufmann et al., 1966; Mann et al., 1973, Rath et al., 1974; Reiser et al., 1979a, 1989; Yudkin et al., 1986), whereas other studies have shown no effect (Bossetti et al., 1984; Crapo and Kolterman, 1984; Dunnigan et al., 1970; Hallfrisch et al., 1983; Mann and Truswell, 1972; Surwit et al., 1997; Swanson et al., 1992).

Smith and colleagues (1996) demonstrated that hypertriacylglycerolemia could be reduced in some people with the reduction (73 percent) of extrinsic sucrose in the diet. The investigators reported reduced plasma triacylglycerol concentrations in 32 hypertriacylglycerolemic individuals by greater than 20 percent, and the reduction remained significant with the control of weight loss. Parks and Hellerstein (2000) published an exhaustive review of carbohydrate-induced hypertriacylglycerolemia and concluded that it is more extreme if the carbohydrate content of a high carbohydrate diet consists primarily of monosaccharides, particularly fructose, rather than oligo- and polysaccharides. Purified diets, whether based on starch or monosaccharides, induce hypertriacylglycerolemia more readily than diets higher in fiber in which most of the carbohydrate is derived from unprocessed whole foods, and possibly result in a lower glycemic index and reduced postprandial insulin response (Jenkins et al., 1987b).

TABLE 6-7 Dietary Sugars and Blood Lipid Concentrations in Healthy Subjects

Reference	Study Population/ Dietary Intervention	Triacylglycerol Concentration (mmol/L)			
Kaufmann et al., 1966	3 men and 1 woman, 10–35 d/diet	2 males: no difference between diets			
	30% starch	1 male (ad lib to sucrose to fructose): 0.98–1.98 to 2.76 to 4.50			
	30% sucrose	1 female (starch to fructose): 1.32–1.78 to 2.30–2.58			
	30% fructose				
Dunnigan et al., 1970	9 men and women, 4-wk crossover				
	31% sucrose	1.05[a]			
	sucrose-free	1.04[a]			
Mann and Truswell, 1972	9 men, 2-wk crossover				
	23% sucrose	1.10[a]			
	23% starch	1.11[a]			
Mann et al., 1973	9 men, 2-wk crossover				
	17% sucrose	1.66[a]			
	34% sucrose	1.84[b]			
	34% sucrose + polyunsaturated fatty acids	1.50[a]			
Rath et al., 1974	6 men, 2- to 5-wk crossover	Significant increase with 52% sucrose			
	17% sucrose				
	52% sucrose				
Hayford et al., 1979	8 men, 10-d crossover				
	45% sucrose	0.87[a]			
	65% sucrose	1.31[b]			
	45% glucose	0.80[a]			
	65% glucose	1.33[b]			
Reiser et al., 1979a	19 men and women, 6-wk crossover	Men		Women	
		Baseline	6 wk	Baseline	6 wk
	30% starch	1.28[a]	1.42[a]	1.06[a]	0.98[a]
	30% sucrose	1.54[a]	1.86[b]	1.06[a]	1.23[b]
Hallfrisch et al., 1983	12 men, 5-wk crossover				
	0% fructose, 15% starch	0.97[a]			
	7.5% fructose, 7.5% starch	1.07[a]			
	15% fructose, 0% starch	1.04[a]			
Bossetti et al., 1984	8 men and women, 140-d crossover	Baseline	14 d		
	11–16% sucrose	0.60[a]	0.63[a]		
	11–16% fructose	0.80[a]	0.56[a]		

Low Density Lipoprotein Cholesterol Concentration (mmol/L)	High Density Lipoprotein Cholesterol Concentration (mmol/L)
3.52^a	1.01^a
3.76^b	1.05^a
3.70^b	1.07^a

Baseline	14 d	Baseline	14 d
2.38^a	2.35^a	1.42^a	1.37^a
2.59^a	2.48^a	1.42^a	1.40^a

continued

TABLE 6-7 Continued

Reference	Study Population/ Dietary Intervention	Triacylglycerol Concentration (mmol/L)	
Crapo and Kolterman, 1984	11 men and women, 14-d crossover	No significant difference	
	24% sucrose		
	24% fructose		
Albrink and Ullrich, 1986	6 men per group, 11 d	Significant increase when fed 36% or 52% sucrose and a diet containing less than 14 g of fiber	
	0% sucrose		
	18% sucrose		
	36% sucrose		
	52% sucrose		
Yudkin et al., 1986	14 men, 14-d crossover		
	18% sucrose	1.02[a]	
	37% sucrose	1.11[a]	
	19% sucrose	1.09[a]	
	26 men, 14-d crossover		
	23% sucrose	1.33[a]	
	9% sucrose	1.05[b]	
	24% sucrose	1.23[a]	
Reiser et al., 1989	11 men, 5-wk crossover		
	20% fructose	0.84[a]	
	20% starch	0.70[b]	
Swanson et al., 1992	14 men and women, 4-wk crossover	Baseline	4 wk
	19% fructose, 25% starch	1.16[a]	0.96[a]
	< 3% fructose, 39% starch	1.02[a]	0.94[a]
Surwit et al., 1997	42 women, 6-wk intervention		
	4% sucrose	1.05[a]	
	43% sucrose	1.08[a]	
Marckmann et al., 2000	20 women, 2-wk crossover		
	2.5% sucrose, 59% carbohydrate	0.81[a]	
	23.2% sucrose, 59% carbohydrate	0.96[b]	
Saris et al., 2000	390 adults, 6-mo parallel		
	18.8% sugar, 52% carbohydrate	1.29[a]	
	29.5% sugar, 56% carbohydrate	1.46[a]	

[a,b] Different lettered superscripts within each study indicate that values were significantly different.

Low Density Lipoprotein Cholesterol Concentration (mmol/L)	High Density Lipoprotein Cholesterol Concentration (mmol/L)
	Significant reduction in high density lipoprotein concentration with fructose
Significant decline observed for 0% and 18% sucrose diets	Significantly lower for 18%, 36%, and 52% sucrose diets
	1.27[a] 1.07[b] 1.42[a]
	1.30[a] 1.27[a] 1.26[a]
3.06[a] 2.73[b]	1.16[a] 1.11[a]
Baseline / 4 wk 2.62[a] / 2.73[a] 2.65[a] / 2.46[b]	Baseline / 4 wk 1.28[a] / 1.30[a] 1.32[a] / 1.22[a]
2.38[a] 2.60[b]	1.03[a] 1.06[a]
2.43[a]	1.34[a]
2.72[b]	1.38[a]
3.68[a]	1.20[a]
3.61[a]	1.15[a]

Increases in LDL cholesterol concentration have been observed more consistently with increases in sugar intake (Table 6-7). Increases in LDL cholesterol concentration were reported when 7.5 and 15 percent fructose replaced an equal amount of starch (Hallfrisch et al., 1983), 36 and 52 percent sucrose were fed compared with 0 and 18 percent sucrose (Albrink and Ullrich, 1986), 20 percent fructose replaced an equal amount of starch (Reiser et al., 1989), and 19 percent fructose was fed compared with less than 3 percent fructose (Swanson et al., 1992).

In general, most epidemiological studies have shown an inverse relationship between sugar intake and high density lipoprotein (HDL) cholesterol concentration (Archer et al., 1998; Bolton-Smith et al., 1991; Ernst et al., 1980; Tillotson et al., 1997). Of the nine intervention studies reviewed, five showed no difference in HDL cholesterol concentration with varying intakes of sugars (Bossetti et al., 1984; Hallfrisch et al., 1983; Reiser et al., 1989; Swanson et al., 1992; Surwit et al., 1997). A significant decrease in HDL cholesterol concentration was observed when 24 percent fructose replaced the same amount of sucrose (Crapo and Kolterman, 1984); 37 percent sucrose was fed compared with 18 or 19 percent sucrose (Yudkin et al., 1986); and 18, 36, and 52 percent sucrose was fed compared with 0 percent sucrose (Albrink and Ullrich, 1986).

Kant (2000) used the Third National Health and Nutrition Examination Survey (NHANES III) survey to examine the association between the consumption of energy-dense, nutrient-poor (EDNP) foods on lipid profiles. EDNP foods such as visible fats, nutritive sweeteners and sweetened beverages, desserts, and snacks have high fat and/or high carbohydrate and poor micronutrient content. HDL cholesterol concentration was inversely related and serum homocysteine concentration was positively related to EDNP food intake. Both serum homocysteine and HDL cholesterol concentrations are independent risk factors for cardiovascular disease (Aronow and Ahn, 1998; Boushey et al., 1995).

GI. In controlled studies, the consumption of high glycemic index (GI) diets has generally resulted in modest increases in circulating concentrations of hemoglobin A_{1c}, total serum cholesterol, and triacylglycerols, as well as decreased circulating HDL cholesterol and urinary C-peptide concentrations in diabetic and hyperlipidemic individuals (Table 6-8). Furthermore, studies on dyslipidemic individuals show that a low GI diet can reduce cholesterol and triacylglycerol concentrations (Jenkins et al., 1985, 1987b). Data are limited for healthy individuals as only one study has measured the effect of predicted GI on blood lipid concentrations (Jenkins et al., 1987a). This study showed a 15 and 13 percent reduction in total cholesterol and LDL cholesterol concentration, respectively, when the GI was reduced by 41 (Jenkins et al., 1987a).

A significant negative relationship between GI and HDL cholesterol concentration was reported in two epidemiological studies (Ford and Liu, 2001; Frost et al., 1999) (Table 6-9 and Figure 6-3). Only the negative relationship to glycemic load was significant for postmenopausal women (Liu et al., 2001). HDL cholesterol concentrations were more responsive to changes in GI in women than in men (Figure 6-3). In contrast, Ford and Liu (2001) reported a more pronounced response in men than in women. Thus, although there is evidence for an association between high GI and risk factors for cardiovascular disease (Haffner et al., 1988a; Morris and Zemel, 1999), further controlled studies are needed.

CHD. Four epidemiological studies have shown no risk of coronary heart disease (CHD) from consuming naturally occurring or added sugars (Bolton-Smith and Woodward, 1994a; Kushi et al., 1985; Liu et al., 1982, 2000; McGee et al., 1984) (see Table 11-7). Two epidemiological studies have been conducted to relate the risk of CHD with GI (Liu et al., 2000; van Dam et al., 2000) (Table 6-9). One study showed increased risk of CHD with increasing GI, but for only those with a body mass index greater than 23 (Liu et al., 2000). van Dam and coworkers (2000) observed no association between GI and risk of CHD in elderly men. Thus, there are insufficient data for setting a UL based on increased risk for CHD.

Insulin Sensitivity and Type 2 Diabetes

Sugars. Insulin has three major effects on glucose metabolism: it decreases hepatic glucose output, it increases glucose utilization in muscle and adipose tissue, and it enhances glycogen production in the liver and muscle. Insulin sensitivity measures the ability to do these effectively. Individuals vary genetically in their insulin sensitivity, some being much more efficient than others (Reaven, 1999). Obesity is related to decreased insulin sensitivity (Kahn et al., 2001), which can also be influenced by fat intake (see Chapter 11) and exercise.

Two prospective cohort studies showed no risk of diabetes from consuming increased amounts of sugars (Colditz et al., 1992; Meyer et al., 2000). Furthermore, a negative association was observed between increased sucrose intake and risk of diabetes (Meyer et al., 2000). Intervention studies that have evaluated the effect of sugar intakes on insulin concentration and insulin resistance portray mixed results. Dunnigan and coworkers (1970) reported no difference in glucose tolerance and plasma insulin concentration after 0 or 31 percent sucrose was consumed for 4 weeks. Reiser and colleagues (1979b) reported that when 30 percent starch was replaced with 30 percent sucrose, insulin concentration was significantly elevated; however, serum glucose concentration did not differ.

TABLE 6-8 Controlled Studies of Low Glycemic Index (GI) Diets on Carbohydrate and Lipid Metabolism in Healthy, Diabetic, and Hyperlipidemic Subjects

Reference	Study Design	Change in Diet GI	Type of Glycated Proteins
Healthy subjects			
Jenkins et al., 1987a	6 men, 2 wk	–41	Fructosamine
Kiens and Richter, 1996	7 young men, 30 d	–24	Not reported
Frost et al., 1998	25 women, 3 wk	–18	Not reported
Diabetic subjects			
Collier et al., 1988	7 type I children, 6 wk	–12	Albumin
Fontvieille et al., 1988	8 type I men and women, 3 wk	–14	Fructosamine
Jenkins et al., 1988a	8 type II men and women, 2 wk	–23	HbA_{1c} Fructosamine
Brand et al., 1991	16 type II men and women, 12 wk	–14	HbA_{1c}
Fontvieille et al., 1992	18 type I and II men and women, 5 wk	–26	Fructosamine
Wolever et al., 1992a	15 type II men and women, 2 wk	–27	Fructosamine
Wolever et al., 1992b	6 type II overweight men and women, 6 wk	–28	Fructosamine

Change in Glycated Proteins (%)	Change in Blood Lipids[a] (%)	Comments[b]
–7[c,d]	–15[c,d] TC –13[c,d] LDL-C	–32%[c,e] urinary C-peptide excretion –10%[c,e] creatinine clearance during the day
Not reported	Not reported	Euglycemic hyperinsulinemic clamp showed no difference in glucose uptake between high and low GI diets at low plasma insulin, but glucose uptake was reduced at high plasma insulin with low GI diet
Not reported	Not reported	Using short insulin tolerance test, in vivo insulin sensitivity improved after low GI diet
–19[c,d]	–14[c,d] TC	Reduced postprandial glucose response to standard test meal with low GI diet
–18.1[c,d]	–5.8[c,d] TAG	–8.9%[c,d] plasma phospholipids –6.1%[c,d] daily insulin needs
–6.6[c,d] –6.6[c,d]	–5.8[c,d] TC	–30%[c,d] fasting blood glucose
–11[c,e]	Not significant	–11%[c,e] plasma glucose response to standard meal
–12.1[c,e]	–21.1[c,e] TAG	–11%[c,e] fasting blood glucose –13.3%[c,e] mean daily blood glucose
–3.4[c,e]	–7[c,e] TC	–30%[c,e] urinary C-peptide excretion –29%[c,e] postbreakfast blood glucose TAG rose on high GI diet ($p = 0.027$) and fell on low GI diet, but the difference between the two diets was not significant
–8[c,e]	–6.8[c,e] TC	–22.4%[c,e] TAG for the 5 subjects with TAG > 2.2 mmol/L

continued

TABLE 6-8 Continued

Reference	Study Design	Change in Diet GI	Type of Glycated Proteins
Frost et al., 1994	25 type II men and women, 12 wk	–5	Fructosamine
Järvi et al., 1999	20 type II men and women, 2 d	–26	HbA_{1c} Fructosamine
Luscombe et al., 1999	21 type II men and women, 4 wk	–20	Fructosamine
Hyperlipidemic subjects			
Jenkins et al., 1987b	30 men and women, 4 wk	–17	Fructosamine

[a] TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, TAG = triacylglycerols, HDL-C = high density lipoprotein cholesterol.
[b] PAI-1 = plasminogen activator inhibitor-1.

GI. There are well-recognized, short-term effects of high versus low GI carbohydrates on several key hormones and metabolites. In particular, compared to regular consumption of low GI carbohydrates, regular consumption of high GI carbohydrates results in high concentrations of circulating glucose and insulin (Table 6-8). In healthy individuals, there also appears to be an amplification of glucose and insulin responses to consumption of high GI foods with repeated consumption (Liljeberg et al., 1999). Based on associations between these metabolic parameters and risk of disease (DeFronzo et al., 1992; Groop and Eriksson, 1992; Haffner et al., 1988b, 1990; Martin et al., 1992; Rossetti et al., 1990; Warram et al., 1990), further controlled studies on GI and risk factors for diabetes are needed. Furthermore, studies are needed on the extent to which consumption of high GI diets might influence the development of diabetes compared to other putative dietary variables that also influence insulin secretion (e.g., dietary fiber).

In prospective epidemiological studies, three of the four published studies support an association between GI and the development of type 2 diabetes (Table 6-9). Data from the Nurses' Health Study illustrated a significant association between the dietary glycemic index and risk of type 2 diabetes that was significant both with and without an adjustment for

Change in Glycated Proteins (%)	Change in Blood Lipids[a] (%)	Comments[b]
–15.8[c,d]	–11.3[c,d] TC –26.3[c,d] TAG	–21.3%[c,d] fasting blood glucose
–5.9[c,d] –2.5[c,e]	–5.2[c,e] TC –8.3[c,e] LDL-C	–31%[c,e] 9-h blood glucose profile –53%[c,d] PAI-1 activity
Not significant	+5.7[c,e] HDL-C	Fasting plasma glucose did not significantly differ between the diets
Not significant	When TAG > 2 mmol/L –8.8[c,e] TC –9.1[c,e] LDL-C –19.3[c,e] TAG	24-h urinary C-peptide was not significantly different Changes in weight loss and fat intake did not explain the lipid effects

[c] Significant effect ($p < 0.05$).
[d] Treatment difference (across treatment).
[e] Endpoint difference (between treatment).

cereal fiber intake (Salmerón et al., 1997b). In contrast, the Iowa Women's Health Study showed no significant relationship between GI and the development of type 2 diabetes after adjusting for total dietary fiber, although the association was positive in the GI range of 59 to 71 and then declined with GI values greater than 71 (Meyer et al., 2000). The reasons for the discrepancy between studies are not known, but may be related to the accuracy of dietary intake records, the imprecision in calculating GI from reported diets, and the age of individuals entering the investigations. There are currently no intervention trials in which dietary GI is manipulated and development of chronic diseases monitored; such studies are needed.

Obesity

Sugars. Several studies have been conducted to determine the relationship between total (intrinsic plus added) and added sugars intake and energy intake (Table 6-10). The Department of Health Survey of British School Children showed that as total sugar intake increased from less than 20.7 percent of energy to up to 25.2 percent of energy, intake increased by approximately 100 kcal/d (Gibson, 1993). In contrast, the Bogalusa Heart

TABLE 6-9 Cross-Sectional and Cohort Studies on the Relation of Glycemic Index (GI) to the Risk of Diabetes, Coronary Heart Disease (CHD), and Cancer and Its Association with High Density Lipoprotein Cholesterol (HDL-C) Concentration and Glucated Hemoglobin (HbA_{1c}) in Diabetes

References	Study Design	GI
Diabetes		
Salmerón et al., 1997a	42,759 healthy, male health professionals Cohort, 6-y follow-up	Quintile mean 65 70 73 75 79
Salmerón et al., 1997b	65,173 healthy, female nurses Cohort, 6-y follow-up	Quintile mean 64 68 71 73 77
Meyer et al., 2000	35,988 postmenopausal women Cohort, 6-y follow-up	< 58 59–65 66–71 72–80 > 80
Buyken et al., 2001	2,810 type I diabetic men and women Cross-sectional study	58.2–77.7 79.8–81.5 81.5–85.5 85.5–111.5
Hu et al., 2001	84,941 healthy, female nurses Cohort, 16-y follow-up	
CHD and related parameters		
Frost et al., 1999	1,420 British adults Cross-sectional study	Mean: 86

Main Effect[a]	Comments[b]
RR of diabetes 1.00 1.16 1.19 1.20 1.37	p for trend = 0.03 after adjustment for cereal fiber intake For high GL plus low cereal fiber intake, the RR of diabetes was 2.17 (1.04–4.54)
RR of diabetes 1.00 1.21 1.37 1.37 1.37	p for trend = 0.005 after adjustment for cereal fiber intake Significant association between glycemic load and risk of diabetes (RR = 1.47 for 5th quintile)
RR of diabetes 1.00 1.19 1.26 0.96 0.89	GI and GL were not associated with risk of diabetes
HbA_{1c} (%) 6.05 6.27 6.59 6.55	Using bivariate model, serum HDL-C was inversely associated with GI (p for trend = 0.0001), and TAG was positively associated with GI (p for trend = 0.01) Significant association between GL and risk of diabetes (p trend < 0.001); this is an updated analysis from Salmerón et al. (1997b) that includes 3,300 new cases of type 2 diabetes
Negative relationship between GI and HDL-C ($p < 0.0001$)	

continued

TABLE 6-9 Continued

References	Study Design	GI
Liu et al., 2000	75,521 female nurses Cohort, 10-y follow-up	GI quintile mean by GL score 72 75 77 78 80
van Dam et al., 2000	646 elderly Dutch men Prospective analysis	Tertile median 77 82 85
Ford and Liu, 2001	13,907 men and women Cross-sectional study	< 76 76–79 80–83 84–87 > 87
Liu et al., 2001	280 postmenopausal women Prospective analysis	Quintile mean 68 73 75 77 81
Cancer		
Franceschi et al., 2001	Italian men and women with colon cancer 1,953 cases 4,154 controls	< 70.8 70.8–73.8 73.9–76.5 76.6–79.6 > 79.6

[a] RR = relative risk, OR = odds ratio.
[b] GL = glycemic load, TAG = triacylglycerol, BMI = body mass index.

Study reported a significant decrease in energy intake with increased total sugar intake (Nicklas et al., 1996). A negative correlation between total sugar intake and body mass index (BMI) has been consistently reported for children and adults (Bolton-Smith and Woodward, 1994b; Dreon et al., 1988; Dunnigan et al., 1970; Fehily et al., 1984; Gibson, 1993, 1996b; Miller

Main Effect[a]		Comments[b]
RR of CHD		RR of CHD associated with high glycemic load only for those with BMI > 23
1.00		
1.01		
1.25		
1.51		
1.98		
RR of CHD		No association between GI and risk of CHD (p for trend = 0.7)
1.00		
1.12		
1.11		
Serum HDL-C (mmol/L)		p for trend < 0.001
1.36		The decrease in HDL-C was similar for subjects with BMI < 25 and those with BMI ≥ 25
1.31		
1.30		
1.27		
1.28		
Plasma HDL-C (mmol/L)	Plasma TAG (mmol/L)	Nonsignificant negative association between GI and HDL-C concentration (p for trend = 0.1)
1.45	1.16	
1.42	1.20	Nonsignificant positive association between GI and TAG concentration (p for trend = 0.03)
1.42	1.14	
1.40	1.27	
1.29	1.37	
OR of colon and rectum cancer		p for trend < 0.001
1.0		Similar findings for glycemic load
1.3		
1.6		
1.5		
1.7		

et al., 1990) (Table 6-11). A study of 42 women compared the effects of a high sucrose (43 percent of total energy) and low sucrose (4 percent of total energy), low fat (11 percent total energy) hypoenergetic diet (Surwit et al., 1997). There were no significant differences between groups in total body weight lost during the intervention. On the other hand, a study using

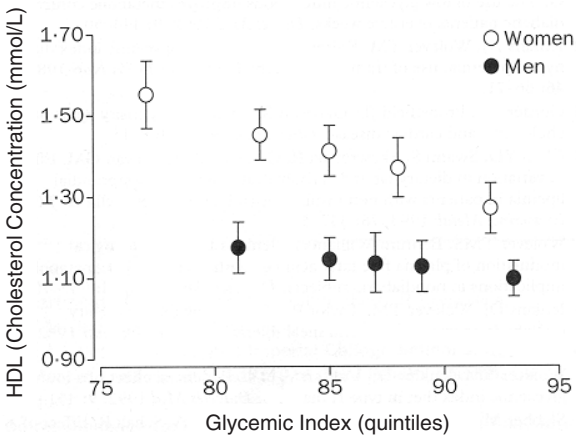

FIGURE 6-3 Relation between high density lipoprotein (HDL) cholesterol concentration and five quintiles of glycemic index in men and women. Reprinted, with permission, from Frost et al. (1999). Copyright 1999 by Elsevier Science (*The Lancet*).

23 lean men, 23 obese men, 17 lean women, and 15 obese women found that lean and obese individuals of the same gender had similar total sugar intake (Miller et al., 1994). However, the obese individuals derived a greater percentage (38.0 to 47.9 percent) of their sugar intake from added sugars compared with lean individuals (25.2 to 31.4 percent).

Increased added sugars intakes have been shown to result in increased energy intakes for children and adults (Bowman, 1999; Gibson 1996a, 1997; Lewis et al., 1992). Despite these observations, a negative correlation between added sugars intake and BMI has been observed (Bolton-Smith and Woodward, 1994b; Gibson, 1996a; Lewis et al., 1992). For adolescents, nonconsumers of soft drinks consumed 1,984 kcal/d in contrast to 2,604 kcal/d for those teens who consumed 26 or more oz of soft drinks per day (Harnack et al., 1999). Using NHANES III data, Troiano and colleagues (2000) found that soft drinks contributed a higher proportion of daily energy intake for overweight than for nonoverweight children and adolescents. Kant (2000) demonstrated a positive association between energy-dense, micronutrient-poor food and beverage consumption (visible fats, nutritive sweeteners, sweetened beverages, desserts, and snacks) and energy intake.

Ludwig and colleagues (2001) examined the relationship between consumption of drinks sweetened with sugars and childhood obesity. They concluded that for each additional serving of the drinks consumed, the

odds of becoming obese increased by 60 percent. Drinks sweetened with sugars, such as soft drinks, have been suggested to promote obesity because compensation at subsequent meals for energy consumed in the form of a liquid could be less complete than for energy consumed as solid food (Mattes, 1996).

Published reports disagree about whether a direct link exists between the trend toward increased intakes of sugars and increased rates of obesity. The lack of association in some studies may be partially due to the pervasive problem of underreporting food intake, which is known to occur with dietary surveys (Johnson, 2000). Underreporting is more prevalent and severe by obese adolescents and adults than by their lean counterparts (Johnson, 2000). In addition, foods high in added sugars are selectively underreported (Krebs-Smith et al., 2000). Thus, it can be difficult to make conclusions about associations between sugars intake and BMI by using self-reported data.

Based on the above data, it appears that the effects of increased intakes of total sugars on energy intake are mixed, and the increased intake of added sugars are most often associated with increased energy intake. There is no clear and consistent association between increased intake of added sugars and BMI. Therefore, the above data cannot be used to set a UL for either added or total sugars.

GI. Although there have been several short-term studies on the relationship between dietary GI and hunger, satiety, and energy intake at single meals, many of the studies are confounded by differences between test diets in variables other than GI (Roberts, 2000b). Among relatively controlled studies (Guss et al., 1994; Holt and Brand Miller, 1995; Ludwig et al., 1999; Rodin, 1991; Spitzer and Rodin, 1987), voluntary energy intake was 29 percent higher following consumption of high GI test meals or preloads compared to those of low GI, as summarized in Figure 6-4 (Roberts, 2000b). These data strongly suggest an effect of GI on short-term energy intake, but there are currently little data on the effect of GI on energy intake from longer-term clinical trials. Such data are necessary before the effects of the GI of carbohydrate-containing foods on energy regulation can be appropriately evaluated because the effects of GI on energy intake might become smaller over time. Obtaining data from clinical trials is especially important because although one nonblinded study reported greater weight loss success in obese patients treated with a low GI diet compared with a conventional low fat diet (Spieth et al., 2000), the two epidemiological studies reporting BMI in their evaluations of the relationship between GI and development of chronic diseases observed no significant association between GI and BMI (Liu et al., 2000; Salmerón et al., 1997a, 1997b).

TABLE 6-10 Sugar and Energy Intake

Reference	Design and Study	Sugar Intake (% of Energy)
Total sugar		
Gibson, 1993	2,705 boys and girls Department of Health Survey of British School Children	< 20.7 20.7–25.2 > 25.2
Nicklas et al., 1996	568 boys and girls, 10 y Bogalusa Heart Study	18.0 22.0 26.4 31.2
Farris et al., 1998	568 boys and girls, 10 y Bogalusa Heart Study	16.1 23.5 28.2 35.6
Added sugar		
Lewis et al., 1992	Nationwide Food Consumption Survey (1977–1978)	
Gibson, 1996a	1,087 men and 1,110 women Dietary and Nutritional Survey of British Adults	< 10 10–13 14–16 17–20 > 20
Gibson, 1997	1,675 boys and girls, 1.5–4.5 y U.K. National Diet and Nutrition Survey of Children	< 12 12–16 16–20 20–25 > 25
Bowman, 1999	Continuing Survey of Food Intakes by Individuals (1994–1996)	< 10 10–18 > 18

[a,b,c] Different lettered superscripts within each study indicate that values were significantly different.

Energy Intake (kcal)

Boys		Girls	
10–11 y	14–15 y	10–11 y	14–15 y
1,954[a]	2,401[a]	1,753[a]	1,819[a]
2,095[b]	2,526[b]	1,838[b]	1,961[b]
2,066[b]	2,549[b]	1,871[b]	1,901[a,b]
2,291			
2,245			
2,274			
2,016			
2,249			
2,286			
2,144			
2,061			

High consumers of added sugars had greater energy intakes than consumers of moderate and low added sugars

Men	Women
2,219[a]	1,438[a]
2,430[b]	1,681[b]
2,455[b,c]	1,738[b]
2,549[b,c]	1,773[b]
2,596[c]	1,774[b]
Boys	Girls
1,129[a]	1,097[a]
1,168[a,b]	1,102[a]
1,187[a,b]	1,139[a]
1,188[a,b]	1,115[a]
1,217[b]	1,116[a]
1,860[a]	
2,040[b]	
2,049[b]	

TABLE 6-11 Interventional and Epidemiological Data on Sugar Intake and Body Mass Index (BMI)

Reference	Study Design	Sugar Intake (% of energy)
Total sugars		
Dunnigan et al., 1970	9 men and women, 4-wk crossover	31% sucrose sucrose-free
Fehily et al., 1984	493 men, 45–59 y 7-d weighed dietary record	
Dreon et al., 1988	155 obese men, 30–59 y 7-d dietary record	13.7 ± 8.4 g/1,000 kcal
Miller et al., 1990	107 men and 109 women, 18–71 y 24-h recall and 2-d dietary questionnaire	
Gibson, 1993	2,705 boys and girls Department of Health Survey of British School Children	< 20.7 20.7–25.2 < 25.2
Bolton-Smith and Woodward, 1994b	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Quintile 1 2 3 4 5
Gibson, 1996b	1,087 men and 1,110 women, 16–64 y Dietary and Nutritional Survey of British Adults	Quintile 1 2 3 4 5

BMI (kg)

62.4
63.8

Significant negative association between sucrose intake and BMI

Significant negative correlation between sucrose intake and BMI

Significant negative correlation between sugar intake and percentage of body fat for women; no association for men

Boys		Girls	
10–11 y	14–15 y	10–11 y	14–15 y
18.6[a]	20.2[a]	18.2[a]	21.2[a]
17.9[a,b]	20.0[a,b]	18.1[a]	20.2[b]
17.5[b]	19.2[b]	17.9[a]	19.8[b]

Men	Women
27.0	26.5
26.4	26.0
26.0	25.5
25.5	25.1
24.7	24.4

Significant negative correlation between sugar intake and BMI

Men	Women
24.9	25.4
25.3	24.7
25.2	24.5
24.8	23.8
24.4	24.4

Weak negative association between sugar intake and BMI

continued

TABLE 6-11 Continued

Reference	Study Design	Sugar Intake (% of energy)
Added sugars		
Lewis et al., 1992	Nationwide Food Consumption Survey (1977–1978)	
Bolton-Smith and Woodward, 1994b	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Quintile 1 2 3 4 5
Gibson, 1996a	1,087 men and 1,110 women, 16–64 y Dietary and Nutritional Survey of British Adults	< 10 10–13 14–16 17–20 > 20
Ludwig et al., 2001	Planet Health intervention and evaluation project	

[a,b,c,d] Different lettered superscripts within each study indicate that values were significantly different.

Physical Activity

Although consumption of high GI test foods increases glucose oxidation and suppresses the availability of free fatty acids (Ritz et al., 1991), for factors that would be predicted to have an adverse effect on the capacity for endurance exercise there are conflicting reports on whether consumption of high GI diets prior to exercise results in measurably adverse exercise performance. Some studies report a negative effect of consumption of high GI carbohydrates prior to exercise compared with consumption of low GI carbohydrates (DeMarco et al., 1999; Gleeson et al., 1986; Okano et al., 1988; Thomas et al., 1991), while other studies report no effect on exercise performance (Chryssanthopoulos et al., 1994; Décombaz et al., 1985; Febbraio et al., 2000; Hargreaves et al., 1987; Sparks et al., 1998). It is possible that the level and duration of exercise and amount of test food have critical influences on the results obtained in such studies. Since the

BMI (kg)	
High consumers of added sugars tended to weigh less than moderate consumers	
Men	Women
27.2	26.5
26.4	25.8
26.1	25.6
25.4	25.4
24.5	24.1
Significant negative correlation between added sugar intake and BMI	
Men	Women
25.9[a]	26.0[a]
25.5[a,b]	24.9[a,b]
24.8[b,c]	24.2[b]
24.4[c,d]	24.1[b]
24.1[c,d]	23.8[b]
Significant negative correlation between added sugar intake and BMI	
For each additional serving of sugar-sweetened drink consumed, BMI and frequency of obesity increased; baseline consumption of sugar-sweetened drinks was independently associated with change in BMI	

available studies are in considerable conflict, the potential for GI to impact exercise performance at submaximal levels of exercise seems limited.

Lung Cancer

One case-control study in Uruguay (463 cases and 465 controls) suggested that foods rich in sugars, total sucrose intake, sucrose-to-dietary fiber ratio, and GI were associated with increased risk of lung cancer (De Stefani et al., 1998).

Breast Cancer

The data examining sugars intake and breast cancer have been inconsistent (World Cancer Research Fund/American Institute for Cancer

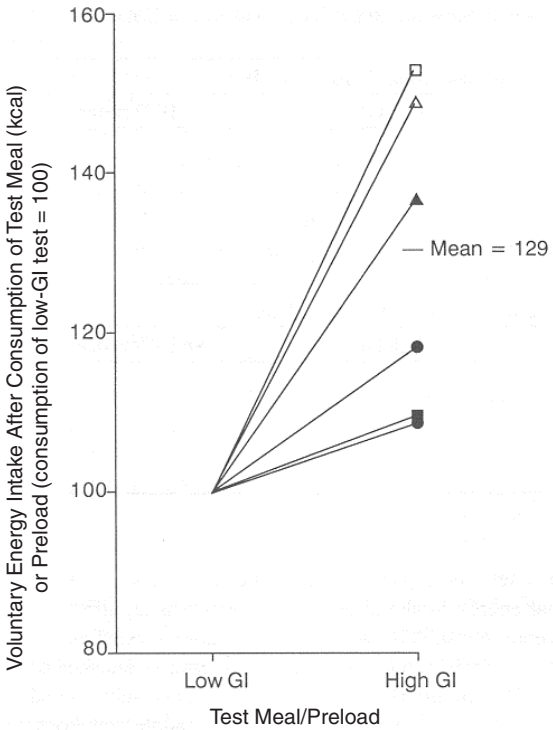

FIGURE 6-4 Summary of data from crossover studies examining the effects of the glycemic index (GI) of test meals or preloads on subsequent energy intake. Δ from Spitzer and Rodin (1987), ▲ from Rodin (1991), ■ from Guss et al. (1994), • from Holt and Brand Miller (1995), □ from Ludwig et al. (1999). All published studies that used pairs of diets differing in GI that contained physiologic amounts of energy, were isocaloric, and were approximately matched for all factors are summarized (i.e., data from 10% sugar solutions in Guss et al. [1994] and the high and medium GI meals only in Ludwig et al. [1999]). Where energy intake was assessed at more than one time point, data from the longest period were used. Reprinted, with permission, from Roberts (2000b). Copyright 2000 by the International Life Sciences Institute.

Research, 1997) and therefore are insufficient to determine a role of sugars in breast cancer (Burley, 1998). There are indications that insulin resistance and insulin-like growth factors may play a role in the development of breast cancer (Bruning et al., 1992; Kazer, 1995).

Prostate Cancer

The Health Professionals Follow-Up Study (n = 47,781 men) demonstrated a reduced risk of advanced prostate cancer associated with increased fructose intakes. Both fruit intake and nonfruit sources of fructose predicted reduced risk of advanced prostate cancer (Giovannucci et al., 1998), but evidence to suggest a role of sugars in prostate cancer is lacking (Burley, 1998).

Colorectal Cancer

The World Cancer Research Fund and American Institute for Cancer Research (1997) reviewed the literature linking foods, nutrients, and dietary patterns with the risk of human cancers worldwide. Data from five case-control studies showed an increase in colorectal polyps and colorectal cancer risk across intakes of sugars and foods rich in sugars (Benito et al., 1990; Macquart-Moulin et al., 1986, 1987; Miller et al., 1983; Tuyns et al., 1988). The subgroups studied showed an elevated risk for those consuming 30 g or more per day compared with those eating less than 10 g/d. Others have concluded that high consumption of fruits and vegetables, as well as the avoidance of foods containing highly refined sugars, are likely to reduce the risk of colon cancer (Giovannucci and Willett, 1994). In many of the studies, sugars increased the risk of colorectal cancer while fiber and starch had the opposite effect. One investigator suggested that the positive association between high sugars consumption and colorectal cancer reflects a global dietary habit that is generally associated with an increased risk of colorectal cancer and may not indicate a biological effect of sugars on colon carcinogenesis (Macquart-Moulin et al., 1987). Burley (1997) concluded from a review of the available literature that there was insufficient evidence to conclude whether sugars had a role in colon cancer.

Concerning a possible relationship between GI and colon cancer, two groups recently reported a case-control study suggesting increased risk of colon cancer among individuals consuming a high versus a low GI diet (Franceschi et al., 2001; Slattery et al., 1997). However, data from other types of investigations are currently unavailable.

Summary

GI

There is a significant body of data suggesting that more slowly absorbed starchy foods that are less processed, or have been processed in traditional ways, may have health advantages over those that are rapidly

digested and absorbed. These foods have been classified as having a low GI and reduce the glycemic load of the diet. Not all studies of low GI or low glycemic load diets have resulted in beneficial effects. However, none have shown negative effects. At a time when populations are increasingly obese, inactive, and prone to insulin resistance, there are theoretical reasons that dietary interventions that reduce insulin demand may have advantages. In this section of the population, it is likely that more slowly absorbed carbohydrate foods and low glycemic load diets will have the greatest advantage.

Dietary GI and glycemic load have relatively predicable effects on circulating glucose, hemoglobin A_{1c}, insulin, triacylglycerol, HDL cholesterol, and urinary C-peptide concentrations, particularly in individuals with diabetes and hyperlipidemia. Although the data are lacking in healthy individuals, on theoretical grounds, these effects would be expected to result in reduced risks of type 2 diabetes and cardiovascular disease in individuals consuming low GI versus high GI carbohydrates. However, the results of epidemiological studies are not always consistent, perhaps because of the difficulty of predicting dietary GI precisely from the relatively simple dietary assessment tools used in some studies. Thus, although there may be beneficial metabolic and disease prevention effects of consuming a greater proportion of carbohydrate from low GI sources, further studies are needed before general recommendations on this issue can be made for the general healthy population.

Further research is especially needed because recommendations to reduce the GI of carbohydrate consumed by the general healthy population would have a significant impact on recommended food sources. Currently, recommended healthy carbohydrate sources with a high GI include whole wheat breads, some breakfast cereals, and potatoes. A recommendation to replace bread and potatoes in the U.S. diet with foods of lower GI would involve major changes in current dietary patterns, and thus substantial evidence of significant beneficial effects of GI is needed. Another important practical issue in considering recommendations on GI is that dietary fiber somewhat decreases GI and may have a beneficial role in several chronic diseases, including the prevention of cardiovascular disease (see Chapter 7). Currently, the median intake of *Dietary Fiber* is only about half the Adequate Intake (AI) for *Total Fiber* (see Appendix Table E-4 and Chapter 7), and the question of whether lowering the GI has measurable beneficial effects on chronic diseases among individuals consuming recommended fiber intakes has received little attention (Luscombe et al., 1999).

Concerning obesity, there is limited evidence suggesting an effect of GI on short-term energy intake. Data from long-term clinical trials on the effects on energy intake are lacking and further studies are needed in this area.

In summary, a UL based on GI is not made at the present time because, although several lines of evidence suggest adverse effects of high GI carbohydrates, it is difficult to eliminate other contributing factors, and the critical mass of evidence necessary for recommending substantial dietary change is not available. Furthermore, it should be noted that sugars have a lower GI than starch yet are rapidly absorbed. However, the principle of slowing carbohydrate absorption, which may underpin the positive findings made in relation to GI, is a potentially important principal with respect to the beneficial health effects of carbohydrate. Further research in this area is needed.

Sugars

Based on the data available on dental caries, behavior, cancer, risk of obesity, and risk of hyperlipidemia, there is insufficient evidence to set a UL for total or added sugars. Although a UL is not set for sugars, a maximal intake level of 25 percent or less of energy from added sugars is suggested based on the decreased intake of some micronutrients of American subpopulations exceeding this level (see Chapter 11 and Appendix J). Because not all micronutrients and other nutrients such as fiber were not examined, the association between added sugars and these nutrients it is not known. While it is recognized that hypertriglyceridemia can occur with increasing intakes of total (intrinsic plus added) sugars, total sugars intake can be limited by minimizing the intake of added sugars and consuming naturally occurring sugars present in nutrient-rich milk, dairy products, and fruits.

Intake Assessment

Median intakes of added sugars were highest in young adults, particularly adolescent males (35.7 tsp or 143 g), and progressively declined with age (Appendix Table D-1). At the 95th percentile of intake, added sugars intakes were as high as 52 tsp (208 g or 832 kcal) for men aged 19 to 50 years.

RESEARCH RECOMMENDATIONS

- There is a need for more research to elucidate the metabolic and long-term health differences resulting from the ingestion of high versus low glycemic index carbohydrates using larger, diverse sample sizes and whole-food diets.
- There is a need for research to determine if the energy density approach to weight reduction is effective in the long-term.

- Experimental studies are needed to determine whether there is a metabolic effect of sugars in enhancing energy expenditure or in suppressing fat intake at a fixed level of energy.
- Research is needed to determine the effect of low glycemic index foods and low glycemic-load diets on serum lipids and other risk factors for chronic disease and complications, especially in high-risk groups.

REFERENCES

Albrink MJ, Ullrich IH. 1986. Interaction of dietary sucrose and fiber on serum lipids in healthy young men fed high carbohydrate diets. *Am J Clin Nutr* 43:419–428.

Allen JC, Keller RP, Archer P, Neville MC. 1991. Studies in human lactation: Milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutr* 54:69–80.

Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV. 1991. Insulin resistance of puberty: A defect restricted to peripheral glucose metabolism. *J Clin Endocrinol Metab* 72:277–282.

Anderson DM, Williams FH, Merkatz RB, Schulman PK, Kerr DS, Pittard WB. 1983. Length of gestation and nutritional composition of human milk. *Am J Clin Nutr* 37:810–814.

Anderson GH, Atkinson SA, Bryan MH. 1981. Energy and macronutrient content of human milk during early lactation from mothers giving birth prematurely and at term. *Am J Clin Nutr* 34:258–265.

Archer SL, Liu K, Dyer AR, Ruth KJ, Jacobs DR, Van Horn L, Hilner JE, Savage PJ. 1998. Relationship between changes in dietary sucrose and high density lipoprotein cholesterol: The CARDIA Study. *Ann Epidemiol* 8:433–438.

Aronow WS, Ahn C. 1998. Risk factors for new coronary events in older African-American men and women. *Am J Cardiol* 82:902–904.

Arslanian S, Kalhan S. 1992. Effects of growth hormone releasing hormone on insulin action and insulin secretion in a hypopituitary patient evaluated by the clamp technique. *Acta Endocrinol* 127:93–96.

Assel B, Rossi K, Kalhan S. 1993. Glucose metabolism during fasting through human pregnancy: Comparison of tracer method with respiratory calorimetry. *Am J Physiol* 265:E351–E356.

Azar GJ, Bloom WL. 1963. Similarities of carbohydrate deficiency and fasting. II. Ketones, nonesterified fatty acids, and nitrogen excretion. *Arch Intern Med* 112:338–343.

Bell JD, Margen S, Calloway DH. 1969. Ketosis, weight loss, uric acid, and nitrogen balance in obese women fed single nutrients at low caloric levels. *Metabolism* 18:193–208.

Benito R, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Muñoz N, Kaldor J. 1990. A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* 45:69–76.

Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM. 1977. Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* 26:1016–1023.

Bloom WL, Azar GJ. 1963. Similarities of carbohydrate deficiency and fasting. I. Weight loss, electrolyte excretion, and fatigue. *Arch Intern Med* 112:333–337.

Bolton-Smith C, Woodward M. 1994a. Coronary heart disease: Prevalence and dietary sugars in Scotland. *J Epidemiol Community Health* 48:119–122.

Bolton-Smith C, Woodward M. 1994b. Dietary composition and fat to sugar ratios in relation to obesity. *Int J Obes Relat Metab Disord* 18:820–828.

Bolton-Smith C, Woodward M, Smith WCS, Tunstall-Pedoe H. 1991. Dietary and non-dietary predictors of serum total and HDL-cholesterol in men and women: Results from the Scottish Heart Health Study. *Int J Epidemiol* 20:95–104.

Bossetti BM, Kocher LM, Moranz JF, Falko JM. 1984. The effects of physiologic amounts of simple sugars on lipoprotein, glucose, and insulin levels in normal subjects. *Diabetes Care* 7:309–312.

Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. 1995. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. *J Am Med Assoc* 274:1049–1057.

Bowman SA. 1999. Diets of individuals based on energy intakes from added sugars. *Fam Econ Nutr Rev* 12:31–38.

Brand JC, Colagiuri S, Crossman S, Allen A, Roberts DCK, Truswell AS. 1991. Low-glycemic index foods improve long-term glycemic control in NIDDM. *Diabetes Care* 14:95–101.

Brito MN, Brito NA, Migliorini RH. 1992. Thermogenic capacity of brown adipose tissue is reduced in rats fed a high protein, carbohydrate-free diet. *J Nutr* 122:2081–2086.

Britten P, Basiotis PP, Davis CA, Anand R. 2000. Is intake of added sugars associated with diet quality? Online. *Nutrition Insights* No 21. USDA Center for Nutrition Policy and Promotion. Available at http://www.usda.gov/cnpp/insights.htm. Accessed June 8, 2001.

Brooks GA, Mercier J. 1994. Balance of carbohydrate and lipid utilization during exercise: The "crossover" concept. *J Appl Physiol* 76:2253–2261.

Brosnan JT. 1999. Comments on metabolic needs for glucose and the role of gluconeogenesis. *Eur J Clin Nutr* 53:S107–S111.

Bruning PF, Bonfrèr JMG, van Noord PAH, Hart AAM, de Jong-Bakker M, Nooijen WJ. 1992. Insulin resistance and breast-cancer risk. *Int J Cancer* 52:511–516.

Burley VJ. 1997. Sugar consumption and cancers of the digestive tract. *Eur J Cancer Prev* 6:422–434.

Burley VJ. 1998. Sugar consumption and human cancer in sites other than the digestive tract. *Eur J Cancer Prev* 7:253–277.

Burt RL, Davidson IWF. 1974. Insulin half-life and utilization in normal pregnancy. *Obstet Gynecol* 43:161–170.

Buyken AE, Toeller M, Heitkamp G, Karamanos B, Rottiers R, Muggeo M, Fuller JH. 2001. Glycemic index in the diet of European outpatients with type 1 diabetes: Relations to glycated hemoglobin and serum lipids. *Am J Clin Nutr* 73:574–581.

Cahill GF. 1970. Starvation in man. *N Engl J Med* 282:668–675.

Cahill GF, Owen OE, Morgan AP. 1968. The consumption of fuels during prolonged starvation. *Adv Enzyme Reg* 6:143–150.

Cahill GF, Aoki TT, Ruderman NB. 1973. Ketosis. *Trans Am Clin Climatol Assoc* 84:184–202.

Calloway DH. 1971. Dietary components that yield energy. *Environ Biol Med* 1:175–186.

Carlson MG, Snead WL, Campbell PJ. 1994. Fuel and energy metabolism in fasting humans. *Am J Clin Nutr* 60:29–36.

Chandramouli V, Ekberg K, Schumann WC, Kalhan SC, Wahren J, Landau BR. 1997. Quantifying gluconeogenesis during fasting. *Am J Physiol* 273:E1209–E1215.

Chew I, Brand JC, Thornburn AW, Truswell AS. 1988. Application of glycemic index to mixed meals. *Am J Clin Nutr* 47:53–56.

Chryssanthopoulos C, Hennessy LCM, Williams C. 1994. The influence of pre-exercise glucose ingestion on endurance running capacity. *Br J Sports Med* 28:105–109.

Chugani HT. 1993. Positron emission tomography scanning: Applications in newborns. *Clin Perinatol* 20:395–409.

Chugani HT, Phelps ME. 1986. Maturational changes in cerebral function in infants determined by ^{18}FDG positron emission tomography. *Science* 231:840–843.

Chugani HT, Phelps ME, Mazziotta JC. 1987. Positron emission tomography study of human brain functional development. *Ann Neurol* 22:487–497.

Cohen JC, Schall R. 1988. Reassessing the effects of simple carbohydrates on the serum triglyceride responses to fat meals. *Am J Clin Nutr* 48:1031–1034.

Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. 1992. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023.

Collier GR, Wolever TMS, Wong GS, Josse RG. 1986. Prediction of glycemic response to mixed meals in noninsulin-dependent diabetic subjects. *Am J Clin Nutr* 44:349–352.

Collier GR, Giudici S, Kalmusky J, Wolever TMS, Helman G, Wesson V, Ehrlich RM, Jenkins DJA. 1988. Low glycaemic index starchy foods improve glucose control and lower serum cholesterol in diabetic children. *Diabetes Nutr Metab* 1:11–19.

Condon JR, Nassim JR, Millard FJC, Hilbe A, Stainthorpe EM. 1970. Calcium and phosphorus metabolism in relation to lactose tolerance. *Lancet* 1:1027–1029.

Coppa GV, Gabrielli O, Pierani P, Catassi C, Carlucci A, Giorgi PL. 1993. Changes in carbohydrate composition in human milk over 4 months of lactation. *Pediatrics* 91:637–641.

Cott A. 1977. Treatment of learning disabilities. In: Williams RJ, Kalita DK, eds. *A Physician's Handbook on Orthomolecular Medicine.* New York: Pergamon Press. Pp. 90–94.

Coulston AM, Hollenbeck CB, Liu GC, Williams RA, Starich GH, Mazzaferri EL, Reaven GM. 1984. Effect of source of dietary carbohydrate on plasma glucose, insulin, and gastric inhibitory polypeptide responses to test meals in subjects with noninsulin-dependent diabetes mellitus. *Am J Clin Nutr* 40:965–970.

Cousins L, Rigg L, Hollingsworth D, Brink G, Aurand J, Yen SSC. 1980. The 24-hour excursion and diurnal rhythm of glucose, insulin, and C-peptide in normal pregnancy. *Am J Obstet Gynecol* 136:483–488.

Cowett RM, Susa JB, Kahn CB, Giletti B, Oh W, Schwartz R. 1983. Glucose kinetics in nondiabetic and diabetic women during the third trimester of pregnancy. *Am J Obstet Gynecol* 146:773–780.

Crapo PA, Kolterman OG. 1984. The metabolic effects of 2-week fructose feeding in normal subjects. *Am J Clin Nutr* 39:525–534.

Décombaz J, Sartori D, Arnaud M-J, Thélin A-L, Schürch P, Howald H. 1985. Oxidation and metabolic effects of fructose or glucose ingested before exercise. *Int J Sports Med* 6:282–286.

DeFronzo RA, Bonadonna RC, Ferrannini E. 1992. Pathogenesis of NIDDM. A balanced overview. *Diabetes Care* 15:318–368.

Dekaban AS, Sadowsky D. 1978. Changes in brain weights during the span of human life: Relation of brain weights to body heights and body weights. *Ann Neurol* 4:345–356.

DeMarco HM, Sucher KP, Cisar CJ, Butterfield GE. 1999. Pre-exercise carbohydrate meals: Application of glycemic index. *Med Sci Sports Exerc* 31:164–170.

Denne SC, Kalhan SC. 1986. Glucose carbon recycling and oxidation in human newborns. *Am J Physiol* 251:E71–E77.

De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco A, Carzoglio JC. 1998. Dietary sugar and lung cancer: A case-control study in Uruguay. *Nutr Cancer* 31:132–137.

Dewey KG, Lönnerdal B. 1983. Milk and nutrient intake of breast-fed infants from 1 to 6 months: Relation to growth and fatness. *J Pediatr Gastroenterol Nutr* 2:497–506.

Dewey KG, Finley DA, Lönnerdal B. 1984. Breast milk volume and composition during late lactation (7–20 months). *J Pediatr Gastroenterol Nutr* 3:713–720.

Díez-Sampedro A, Eskandari S, Wright EM, Hirayama BA. 2001. Na^+-to-sugar stoichiometry of SGLT3. *Am J Physiol Renal Physiol* 280:F278–F282.

Dobbing J, Sands J. 1973. Quantitative growth and development of human brain. *Arch Dis Child* 48:757–767.

Dreon DM, Frey-Hewitt B, Ellsworth N, Williams PT, Terry RB, Wood PD. 1988. Dietary fat:carbohydrate ratio and obesity in middle-aged men. *Am J Clin Nutr* 47:995–1000.

Du Bois EF. 1928. The control of protein in the diet. *J Am Diet Assoc* 4:53–76.

Dunnigan MG, Fyfe T, McKiddie MT, Crosbie SM. 1970. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. *Clin Sci* 38:1–9.

Edmond J, Austad N, Robbins RA, Bergstrom JD. 1985. Ketone body metabolism in the neonate: Development and effect of diet. *Fed Proc* 44:2359–2364.

Egger J, Carter CM, Graham PJ, Gumley D, Soothill JF. 1985. Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome. *Lancet* 1:540–545.

Ercan N, Gannon MC, Nuttall FQ. 1994. Effect of added fat on the plasma glucose and insulin response to ingested potato given in various combinations as two meals in normal individuals. *Diabetes Care* 17:1453–1459.

Ernst N, Fisher M, Smith W, Gordon T, Rifkind BM, Little JA, Mishkel MA, Williams OD. 1980. The association of plasma high-density lipoprotein cholesterol with dietary intake and alcohol consumption. The Lipid Research Clinics Program Prevalence Study. *Circulation* 62:IV41–IV52.

FAO/WHO (Food and Agriculture Organization/World Health Organization). 1998. *Carbohydrates in Human Nutrition.* Rome: FAO.

Farris RP, Nicklas TA, Myers L, Berenson GS. 1998. Nutrient intake and food group consumption of 10-year-olds by sugar intake level: The Bogalusa Heart Study. *J Am Coll Nutr* 17:579–585.

Febbraio MA, Keenan J, Angus DJ, Campbell SE, Garnham AP. 2000. Preexercise carbohydrate ingestion, glucose kinetics, and muscle glycogen use: Effect of the glycemic index. *J Appl Physiol* 89:1845–1851.

Fehily AM, Phillips KM, Yarnell JWG. 1984. Diet, smoking, social class, and body mass index in the Caerphilly Heart Disease Study. *Am J Clin Nutr* 40:827–833.

Felig P. 1973. The glucose-alanine cycle. *Metabolism* 22:179–207.

Ferris AM, Dotts MA, Clark RM, Ezrin M, Jensen RG. 1988. Macronutrients in human milk at 2, 12, and 16 weeks postpartum. *J Am Diet Assoc* 88:694–697.

Fitzsimons D, Dwyer JT, Palmer C, Boyd LD. 1998. Nutrition and oral health guidelines for pregnant women, infants, and children. *J Am Diet Assoc* 98:182–189.

Fomon SJ, Thomas LN, Filer LJ, Anderson TA, Nelson SE. 1976. Influence of fat and carbohydrate content of diet on food intake and growth of male infants. *Acta Paediatr Scand* 65:136–144.

Fontvieille AM, Acosta M, Rizkalla SW, Bornet F, David P, Letanoux M, Tchobroutsky G, Slama G. 1988. A moderate switch from high to low glycaemic-index foods for 3 weeks improves the metabolic control of type I (IDDM) diabetic subjects. *Diabetes Nutr Metab* 1:139–143.

Fontvieille AM, Rizkalla SW, Penfornis A, Acosta M, Bornet FRJ, Slama G. 1992. The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks. *Diabet Med* 9:444–450.

Ford ES, Liu S. 2001. Glycemic index and serum high-density lipoprotein cholesterol concentration among US adults. *Arch Intern Med* 161:572–576.

Forshee RA, Storey ML. 2001. The role of added sugars in the diet quality of children and adolescents. *J Am Coll Nutr* 20:32–43.

Forsum E, Kabir N, Sadurskis A, Westerterp K. 1992. Total energy expenditure of healthy Swedish women during pregnancy and lactation. *Am J Clin Nutr* 56:334–342.

Foster-Powell K, Brand Miller J. 1995. International tables of glycemic index. *Am J Clin Nutr* 62:871S–890S.

Franceschi S, Dal Maso L, Augustin L, Negri E, Parpinel M, Boyle P, Jenkins DJA, La Vecchia C. 2001. Dietary glycemic load and colorectal cancer risk. *Ann Oncol* 12:173–178.

Frost G, Wilding J, Beecham J. 1994. Dietary advice based on the glycaemic index improves dietary profile and metabolic control in type 2 diabetic patients. *Diabet Med* 11:397–401.

Frost G, Leeds A, Trew G, Margara R, Dornhorst A. 1998. Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic diet. *Metabolism* 47:1245–1251.

Frost G, Leeds AA, Doré CJ, Madeiros S, Brading S, Dornhorst A. 1999. Glycaemic index as a determinant of serum HDL-cholesterol concentration. *Lancet* 353:1045–1048.

Gamble JL. 1946. Physiological information gained from studies on the life raft ration. *Harvey Lect* 42:247–273.

Gannon MC, Nuttall FQ. 1987. Factors affecting interpretation of postprandial glucose and insulin areas. *Diabetes Care* 10:759–763.

Gannon MC, Nuttall FQ. 1999. Protein and diabetes. In: Franz MJ, Bantle JP, eds. *American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes.* Alexandria, VA: American Diabetes Association. Pp. 107–125.

Gannon MC, Niewoehner CB, Nuttall FQ. 1985. Effect of insulin administration on cardiac glycogen synthase and synthase phosphatase activity in rats fed diets high in protein, fat or carbohydrate. *J Nutr* 115:243–251.

Gannon MC, Nuttall FQ, Westphal SA, Seaquist ER. 1993. The effect of fat and carbohydrate on plasma glucose, insulin, C-peptide, and triglycerides in normal male subjects. *J Am Coll Nutr* 12:36–41.

Gibbons A. 1998. Solving the brain's energy crisis. *Science* 280:1345–1347.

Gibney M, Sigman-Grant M, Stanton JL, Keast DR. 1995. Consumption of sugars. *Am J Clin Nutr* 62:178S–194S.

Gibson SA. 1993. Consumption and sources of sugars in the diets of British schoolchildren: Are high-sugar diets nutritionally inferior? *J Hum Nutr Diet* 6:355–371.

Gibson SA. 1996a. Are diets high in non-milk extrinsic sugars conducive to obesity? An analysis from the Dietary and Nutritional Survey of British Adults. *J Hum Nutr Diet* 9:283–292.

Gibson SA. 1996b. Are high-fat, high-sugar foods and diets conducive to obesity? *Int J Food Sci Nutr* 47:405–415.

Gibson SA. 1997. Non-milk extrinsic sugars in the diets of pre-school children: Association with intakes of micronutrients, energy, fat and NSP. *Br J Nutr* 78:367–378.

Giovannucci E, Willett WC. 1994. Dietary factors and risk of colon cancer. *Ann Med* 26:443–452.

Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. 1998. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* 58:442–447.

Gleeson M, Maughan RJ, Greenhaff PL. 1986. Comparison of the effects of pre-exercise feeding of glucose, glycerol and placebo on endurance and fuel homeostasis in man. *Eur J Appl Physiol* 55:645–653.

Glinsmann WH, Irausquin H, Park YK. 1986. Evaluation of health aspects of sugars contained in carbohydrate sweeteners. Report of Sugars Task Force. *J Nutr* 116:S1–S216.

Goldberg GR, Prentice AM, Coward WA, Davies HL, Murgatroyd PR, Wensing C, Black AE, Harding M, Sawyer M. 1993. Longitudinal assessment of energy expenditure in pregnancy by the doubly labeled water method. *Am J Clin Nutr* 57:494–505.

Gottstein U, Held K. 1979. Effects of aging on cerebral circulation and metabolism in man. *Acta Neurologica Scand* 60:54–55.

Groop LC, Eriksson JG. 1992. The etiology and pathogenesis of non-insulin-dependent diabetes. *Ann Med* 24:483–489.

Gulliford MC, Bicknell EJ, Scarpello JH. 1989. Differential effect of protein and fat ingestion on blood glucose responses to high- and low-glycemic-index carbohydrates in noninsulin-dependent diabetic subjects. *Am J Clin Nutr* 50:773–777.

Guss JL, Kissileff HR, Pi-Sunyer FX. 1994. Effects of glucose and fructose solutions on food intake and gastric emptying in nonobese women. *Am J Physiol* 267:R1537–R1544.

Guthrie JF, Morton JF. 2000. Food sources of added sweeteners in the diets of Americans. *J Am Diet Assoc* 100:43–48, 51.

Haffner SM, Fong D, Hazuda HP, Pugh JA, Patterson JK. 1988a. Hyperinsulinemia, upper body adiposity, and cardiovascular risk factors in non-diabetics. *Metabolism* 37:338–345.

Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. 1988b. Increased insulin concentrations in nondiabetic offspring of diabetic parents. *N Engl J Med* 319:1297–1301.

Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK. 1990. Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes* 39:283–288.

Hallfrisch J. 1990. Metabolic effects of dietary fructose. *FASEB J* 4:2652–2660.

Hallfrisch J, Reiser S, Prather ES. 1983. Blood lipid distribution of hyperinsulinemic men consuming three levels of fructose. *Am J Clin Nutr* 37:740–748.

Hanson PG, Johnson RE, Zaharko DS. 1965. Correlation between ketone body and free fatty acid concentrations in the plasma during early starvation in man. *Metabolism* 14:1037–1040.

Hargreaves M, Costill DL, Fink WJ, King DS, Fielding RA. 1987. Effect of pre-exercise carbohydrate feedings on endurance cycling performance. *Med Sci Sports Exerc* 19:33–36.

Harnack L, Stang J, Story M. 1999. Soft drink consumption among US children and adolescents: Nutritional consequences. *J Am Diet Assoc* 99:436–441.

Hatazawa J, Brooks RA, Di Chiro G, Bacharach SL. 1987. Glucose utilization rate versus brain size in humans. *Neurology* 37:583–588.

Hay WW. 1994. Placental supply of energy and protein substrates to the fetus. *Acta Paediatr Suppl* 405:13–19.

Hayford JT, Danney MM, Wiebe D, Roberts S, Thompson RG. 1979. Triglyceride integrated concentrations: Effect of variation of source and amount of dietary carbohydrate. *Am J Clin Nutr* 32:1670–1678.

Heinbecker P. 1928. Studies on the metabolism of Eskimos. *J Biol Chem* 80:461–475.

Hellerstein MK. 1999. De novo lipogenesis in humans: Metabolic and regulatory aspects. *Eur J Clin Nutr* 53:S53–S65.

Holbrook WP, Árnadóttir IB, Takazoe E, Birkhed D, Frostell G. 1995. Longitudinal study of caries, cariogenic bacteria and diet in children just before and after starting school. *Eur J Oral Sci* 103:42–45.

Hollenbeck CB, Coulston AM, Reaven GM. 1986. Glycemic effects of carbohydrates: A different perspective. *Diabetes Care* 9:641–647.

Holt SH, Brand Miller J. 1995. Increased insulin responses to ingested foods are associated with lessened satiety. *Appetite* 24:43–54.

Holt SHA, Brand Miller JC, Petocz P. 1997. An insulin index of foods: The insulin demand generated by 1000-kJ portions of common foods. *Am J Clin Nutr* 66:1264–1276.

Homko CJ, Sivan E, Reece EA, Boden G. 1999. Fuel metabolism during pregnancy. *Semin Reprod Endocrinol* 17:119–125.

Hoover HC, Grant JP, Gorschboth C, Ketcham AS. 1975. Nitrogen-sparing intravenous fluids in postoperative patients. *N Engl J Med* 293:172–175.

Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. 2001. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345:790–797.

Hultman E, Harris RC, Spriet LL. 1999. Diet in work and exercise performance. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*, 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 761–782.

Indar-Brown K, Norenberg C, Madar Z. 1992. Glycemic and insulinemic responses after ingestion of ethnic foods by NIDDM and healthy subjects. *Am J Clin Nutr* 55:89–95.

IOM (Institute of Medicine). 1991. *Nutrition During Lactation*. Washington, DC: National Academy Press.

Janney NW. 1915. The metabolic relationship of the proteins to glucose. *J Biol Chem* 20:321–350.

Järvi AE, Karlström BE, Granfeldt YE, Björk IME, Vessby BOH, Asp N-GL. 1995. The influence of food structure on postprandial metabolism in patients with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 61:837–842.

Järvi AE, Karlström BE, Granfeldt YE, Björck IE, Asp N-GL, Vessby BOH. 1999. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. *Diabetes Care* 22:10–18.

Jenkins DJA, Wolever TMS, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL, Goff DV. 1981. Glycemic index of foods: A physiological basis for carbohydrate exchange. *Am J Clin Nutr* 34:362–366.

Jenkins DJA, Wolever TMS, Kalmusky J, Giudici S, Giordano C, Wong GS, Bird JN, Patten R, Hall M, Buckley G, Little JA. 1985. Low glycemic index carbohydrate foods in the management of hyperlipidemia. *Am J Clin Nutr* 42:604–617.

Jenkins DJA, Wolever TMS, Collier GR, Ocana A, Rao AV, Buckley G, Lam Y, Mayer A, Thompson LU. 1987a. Metabolic effects of a low-glycemic-index diet. *Am J Clin Nutr* 46:968–975.

Jenkins DJA, Wolever TMS, Kalmusky J, Guidici S, Girodano C, Patten R, Wong GS, Bird J, Hall M, Buckley G, Csima A, Little JA. 1987b. Low-glycemic index diet in hyperlipidemia: Use of traditional starchy foods. *Am J Clin Nutr* 46:66–71.

Jenkins DJA, Wolever TMS, Buckley G, Lam KY, Giudici S, Kalmusky J, Jenkins AL, Patten RL, Bird J, Wong GS, Josse RG. 1988a. Low-glycemic-index starchy food in the diabetic diet. *Am J Clin Nutr* 48:248–254.

Jenkins DJA, Wolever TMS, Jenkins AL. 1988b. Starchy foods and glycemic index. *Diabetes Care* 11:149–159.

Jenkins DJA, Jenkins AL, Wolever TM, Vuksan V, Brighenti F, Testolin G. 1990. Fiber and physiological and potentially therapeutic effects of slowing carbohydrate absorption. *Adv Exp Med Biol* 270:129–134.

Johnson RK. 2000. What are people really eating and why does it matter? *Nutr Today* 35:40–46.

Kahn SE, Prigeon RL, Schwartz RS, Fujimoto WY, Knopp RH, Brunzell JD, Porte D. 2001. Obesity, body fat distribution, insulin sensitivity and islet β-cell function as explanations for metabolic diversity. *J Nutr* 131:354S–360S.

Kalhan SC, Kiliç Ì. 1999. Carbohydrate as nutrient in the infant and child: Range of acceptable intake. *Eur J Clin Nutr* 53:S94–S100.

Kalhan SC, D'Angelo LJ, Savin SM, Adam PAJ. 1979. Glucose production in pregnant women at term gestation. Sources of glucose for human fetus. *J Clin Invest* 63:388–394.

Kalhan SC, Oliven A, King KC, Lucero C. 1986. Role of glucose in the regulation of endogenous glucose production in the human newborn. *Pediatr Res* 20:49–52.

Kalhan S, Rossi K, Gruca L, Burkett E, O'Brien A. 1997. Glucose turnover and gluconeogenesis in human pregnancy. *J Clin Invest* 100:1775–1781.

Kalsbeek H, Verrips GH. 1994. Consumption of sweet snacks and caries experience of primary school children. *Caries Res* 28:477–483.

Kant AK. 2000. Consumption of energy-dense, nutrient-poor foods by adult Americans: Nutritional and health implications. The Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 72:929–936.

Kaufmann NA, Poznanski R, Blondheim SH, Stein Y. 1966. Effect of fructose, glucose, sucrose and starch on serum lipids in carbohydrate induced hypertriglyceridemia and in normal subjects. *Israel J Med Sci* 2:715–726.

Kazer RR. 1995. Insulin resistance, insulin-like growth factor I and breast cancer: A hypothesis. *Int J Cancer* 62:403–406.

Kennedy C, Sokoloff L. 1957. An adaptation of the nitrous oxide method to the study of the cerebral circulation in children: Normal values for cerebral blood flow and cerebral metabolic rate in childhood. *J Clin Invest* 36:1130–1137.

Kety SS. 1957. The general metabolism of the brain in vivo. In: Richter D, ed. *Metabolism of the Nervous System.* London: Pergamon Press. Pp. 221–237.

Kiens B, Richter EA. 1996. Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans. *Am J Clin Nutr* 63:47–53.

King KC, Tserng K-Y, Kalhan SC. 1982. Regulation of glucose production in newborn infants of diabetic mothers. *Pediatr Res* 16:608–612.

Knopp RH, Saudek CD, Arky RA, O'Sullivan JB. 1973. Two phases of adipose tissue metabolism in pregnancy: Maternal adaptations for fetal growth. *Endocrinology* 92:984–988.

Kopp-Hoolihan LE, van Loan MD, Wong WW, King JC. 1999. Longitudinal assessment of energy balance in well-nourished, pregnant women. *Am J Clin Nutr* 69:697–704.

Krebs-Smith SM, Graubard BI, Kahle LL, Subar AF, Cleveland LE, Ballard-Barbash R. 2000. Low energy reporters vs. others: A comparison of reported food intakes. *Eur J Clin Nutr* 54:281–287.

Krezowski PA, Nuttall FQ, Gannon MC, Bartosh NH. 1986. The effect of protein ingestion on the metabolic response to oral glucose in normal individuals. *Am J Clin Nutr* 44:847–856.

Kushi LK, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. 1985. Diet and 20-year mortality from coronary heart disease. The Ireland–Boston Diet–Heart Study. *N Engl J Med* 312:811–888.

Laine DC, Thomas W, Levitt MD, Bantle JP. 1987. Comparison of predictive capabilities of diabetic exchange lists and glycemic index of foods. *Diabetes Care* 10:387–394.

Lammi-Keefe CJ, Ferris AM, Jensen RG. 1990. Changes in human milk at 0600, 1000, 1400, 1800, and 2200 h. *J Pediatr Gastroenterol Nutr* 11:83–88.

Landau BR, Wahren J, Chandramouli V, Schumann WC, Ekberg K, Kalhan SC. 1996. Contributions of gluconeogenesis to glucose production in the fasted state. *J Clin Invest* 98:378–385.

Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJR, Gibbs JM, Wise RJS, Hatazawa J, Herold S, Beaney RP, Brooks DJ, Spinks T, Rhodes C, Frackowiak RSJ, Jones T. 1990. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain* 113:27–47.

Levin RJ. 1999. Carbohydrates. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*, 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 49–65.

Lewis CJ, Park YK, Dexter PB, Yetley EA. 1992. Nutrient intakes and body weights of persons consuming high and moderate levels of added sugars. *J Am Diet Assoc* 92:708–713.

Liljeberg HGM, Åkerberg AKE, Björck IME. 1999. Effect of the glycemic index and content of indigestible carbohydrates of cereal-based breakfast meals on glucose tolerance at lunch in healthy subjects. *Am J Clin Nutr* 69:647–655.

Lingstrom P, van Houte J, Kashket S. 2000. Food starches and dental caries. *Crit Rev Oral Biol Med* 11:366–380.

Liu K, Stamler J, Trevisan M, Moss D. 1982. Dietary lipids, sugar, fiber, and mortality from coronary heart disease. Bivariate analysis of international data. *Arteriosclerosis* 2:221–227.

Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. 2000. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 71:1455–1461.

Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. 2001. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr* 73:560–566.

Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. 1999. High glycemic index foods, overeating, and obesity. *Pediatrics* 103:E26.

Ludwig DS, Peterson KE, Gortmaker SL. 2001. Relation between consumption of sugar-sweetened drinks and childhood obesity: A prospective, observational analysis. *Lancet* 357:505–508.

Luscombe ND, Noakes M, Clifton PM. 1999. Diets high and low in glycemic index versus high monounsaturated fat diets: Effects on glucose and lipid metabolism in NIDDM. *Eur J Clin Nutr* 53:473–478.

Mackrell DJ, Sokal JE. 1969. Antagonism between the effects of insulin and glucagon on the isolated liver. *Diabetes* 18:724–732.

Macquart-Moulin G, Riboli E, Cornée J, Charnay B, Berthezène P, Day N. 1986. Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* 38:183–191.

Macquart-Moulin G, Riboli E, Cornée J, Kaaks R, Berthezène P. 1987. Colorectal polyps and diet: A case-control study in Marseilles. *Int J Cancer* 40:179–188.

Mann JI, Truswell AS. 1972. Effects of isocaloric exchange of dietary sucrose and starch on fasting serum lipids, postprandial insulin secretion and alimentary lipaemia in human subjects. *Br J Nutr* 27:395–405.

Mann JI, Watermeyer GS, Manning EB, Randles J, Truswell AS. 1973. Effects on serum lipids of different dietary fats associated with a high sucrose diet. *Clin Sci* 44:601–604.

Marckmann P, Raben A, Astrup A. 2000. Ad libitum intake of low-fat diets rich in either starchy foods or sucrose: Effects on blood lipids, factor VII coagulant activity, and fibrinogen. *Metabolism* 49:731–735.

Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. 1992. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: Results of a 25-year follow-up study. *Lancet* 340:925–929.

Mascarenhas AK. 1998. Oral hygiene as a risk indicator of enamel and dentin caries. *Community Dent Oral Epidemiol* 26:331–339.

Mattes RD. 1996. Dietary compensation by humans for supplemental energy provided as ethanol or carbohydrate in fluids. *Physiol Behav* 59:179–187.

Maxwell JD, McKiddie MT, Ferguson A, Buchanan KD. 1970. Plasma insulin response to oral carbohydrate in patients with glucose and lactose malabsorption. *Gut* 11:962–965.

McDonagh MS, Whiting PF, Wilson PM, Sutton AJ, Chestnutt I, Cooper J, Misso K, Bradley M, Treasure E, Kleijnen J. 2000. Systemic review of water fluoridation. *Br Med J* 321:855–859.

McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. 1984. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. *Am J Epidemiol* 119:667–676.

Mehta S, Kalsi HK, Nain CK, Menkes JH. 1977. Energy metabolism of brain in human protein-calorie malnutrition. *Pediatr Res* 11:290–293.

Meyer KA, Kushi LH, Jacobs DR, Slavin J, Sellers TA, Folsom AR. 2000. Carbohydrates, dietary fiber, and incident of type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930.

Miller AB, Howe GR, Jain M, Craib KJP, Harrison L. 1983. Food items and food groups as risk factors in a case-control study of diet and colorectal cancer. *Int J Cancer* 32:155–161.

Miller SL, Wolfe RR. 1999. Physical exercise as a modulator of adaptation to low and high carbohydrate and low and high fat intakes. *Eur J Clin Nutr* 53:S112–S119.

Miller WC, Lindeman AK, Wallace J, Niederpruem M. 1990. Diet composition, energy intake, and exercise in relation to body fat in men and women. *Am J Clin Nutr* 52:426–430.

Miller WC, Niederpruem MG, Wallace JP, Lindman AK. 1994. Dietary fat, sugar, and fiber predict body fat content. *J Am Diet Assoc* 94:612–615.

Morris KL, Zemel MB. 1999. Glycemic index, cardiovascular disease, and obesity. *Nutr Rev* 57:273–276.

Neville MC, Keller RP, Seacat J, Casey CE, Allen JC, Archer P. 1984. Studies on human lactation. I. Within-feed and between-breast variation in selected components of human milk. *Am J Clin Nutr* 40:635–646.

Newburg DS, Neubauer SH. 1995. Carbohydrates in milks: Analysis, quantities, and significance. In: Jensen RG, ed. *Handbook of Milk Composition*. New York: Academic Press. Pp. 273–349.

Nicklas TA, Myers L, Farris RP, Srinivasan SR, Berenson GS. 1996. Nutritional quality of a high carbohydrate diet as consumed by children: The Bogalusa Heart Study. *J Nutr* 126:1382–1388.

Nommsen LA, Lovelady CA, Heinig MJ, Lönnerdal B, Dewey KG. 1991. Determinants of energy, protein, lipid, and lactose concentrations in human milk during the first 12 mo of lactation: The DARLING Study. *Am J Clin Nutr* 53:457–465.

Nordli DR, Koenigsberger D, Schroeder J, deVivo DC. 1992. Ketogenic diets. In: Resor SR, Kutt H, eds. *The Medical Treatment of Epilepsy*. New York: Marcel Dekker. Pp. 455–472.

Nuttall FQ, Gannon MC. 1981. Sucrose and disease. *Diabetes Care* 4:305–310.

Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P. 1984. Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load. *Diabetes Care* 7:465–470.

Nuttall FQ, Gannon MC, Burmeister LA, Lane JT, Pyzdrowski KL. 1992. The metabolic response to various doses of fructose in type II diabetic subjects. *Metabolism* 41:510–517.

Okano G, Takeda H, Morita I, Katoh M, Mu Z, Miyake S. 1988. Effect of pre-exercise fructose ingestion on endurance performance in fed men. *Med Sci Sports Exerc* 20:105–109.

Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF. 1967. Brain metabolism during fasting. *J Clin Invest* 46:1589–1595.

Owen OE, Smalley KJ, D'Alessio DA, Mozzoli MA, Dawson EK. 1998. Protein, fat, and carbohydrate requirements during starvation: Anaplerosis and cataplerosis. *Am J Clin Nutr* 68:12–34.

Papas AS, Joshi A, Palmer CA, Giunta JL, Dwyer JT. 1995. Relationship of diet to root caries. *Am J Clin Nutr* 61:423S–429S.

Park YK, Yetley EA. 1993. Intakes and food sources of fructose in the United States. *Am J Clin Nutr* 58:737S–747S.

Parks EJ, Hellerstein MK. 2000. Carbohydrate-induced hypertriacylglycerolemia: Historical perspective and review of biological mechanisms. *Am J Clin Nutr* 71:412–433.

Patel D, Kalhan S. 1992. Glycerol metabolism and triglyceride-fatty acid cycling in the human newborn: Effect of maternal diabetes and intrauterine growth retardation. *Pediatr Res* 31:52–58.

Patel MS, Johnson CA, Rajan R, Owen OE. 1975. The metabolism of ketone bodies in developing human brain: Development of ketone-body-utilizing enzymes and ketone bodies as precursors for lipid synthesis. *J Neurochem* 25:905–908.

Phelps RL, Metzger BE, Freinkel N. 1981. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. *Am J Obstet Gynecol* 140:730–736.

Raguso CA, Pereira P, Young VR. 1999. A tracer investigation of obligatory oxidative amino acid losses in healthy, young adults. *Am J Clin Nutr* 70:474–483.

Rath R, Masˇek J, Kujalová V, Slabochová Z. 1974. Effect of a high sugar intake on some metabolic and regulatory indicators in young men. *Nahrung* 18:343–353.

Reaven GM. 1999. Insulin resistance: A chicken that has come to roost. *Ann N Y Acad Sci* 892:45–57.

Reinmuth OM, Scheinberg P, Bourne B. 1965. Total cerebral blood flow and metabolism. *Arch Neurol* 12:49–66.

Reiser S, Hallfrisch J. 1987. *Metabolic Effects of Dietary Fructose.* Boca Raton, FL: CRC Press.

Reiser S, Hallfrisch J, Michaelis OE, Lazar FL, Martin RE, Prather ES. 1979a. Isocaloric exchange of dietary starch and sucrose in humans. I. Effects on levels of fasting blood lipids. *Am J Clin Nutr* 32:1659–1669.

Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OE, Prather ES. 1979b. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. *Am J Clin Nutr* 32:2206–2216.

Reiser S, Powell AS, Scholfield DJ, Panda P, Ellwood KC, Canary JJ. 1989. Blood lipids, lipoproteins, apoproteins, and uric acid in men fed diets containing fructose or high-amylose cornstarch. *Am J Clin Nutr* 49:832–839.

Renner R, Elcombe AM. 1964. Factors affecting the utilization of "carbohydrate-free" diets by the chick. II. Level of glycerol. *J Nutr* 84:327–330.

Ritz P, Krempf M, Cloarec D, Champ M, Charbonnel B. 1991. Comparative continuous-indirect-calorimetry study of two carbohydrates with different glycemic indices. *Am J Clin Nutr* 54:855–859.

Robert J-J, Cummins JC, Wolfe RR, Durkot M, Matthews DE, Zhao XH, Bier DM, Young VR. 1982. Quantitative aspects of glucose production and metabolism in healthy elderly subjects. *Diabetes* 31:203–211.

Roberts SB. 2000a. A review of age-related changes in energy regulation and suggested mechanisms. *Mech Ageing Dev* 116:157–167.

Roberts SB. 2000b. High-glycemic index foods, hunger, and obesity: Is there a connection? *Nutr Rev* 58:163–169.

Roche HM. 1999. Dietary carbohydrates and triacylglycerol metabolism. *Proc Nutr Soc* 58:201–207.

Rodin J. 1991. Effects of pure sugar vs. mixed starch fructose loads on food intake. *Appetite* 17:213–219.

Rossetti L, Giaccari A, DeFronzo RA. 1990. Glucose toxicity. *Diabetes Care* 13:610–630.

Rudolf MCJ, Sherwin RS. 1983. Maternal ketosis and its effects on the fetus. *Clin Endocrinol Metab* 12:413–428.

Ryan EA, O'Sullivan MJ, Skyler JS. 1985. Insulin action during pregnancy. Studies with the euglycemic clamp technique. *Diabetes* 34:380–389.

Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. 1997a. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550.

Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. 1997b. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *J Am Med Assoc* 277:472–477.

Sapir DG, Owen OE, Cheng JT, Ginsberg R, Boden G, Walker WG. 1972. The effect of carbohydrates on ammonium and ketoacid excretion during starvation. *J Clin Invest* 51:2093–2102.

Saris WH, Astrup A, Prentice AM, Zunft HJ, Formiguera X, Verboeket-van de Venne WP, Raben A, Poppitt SD, Seppelt B, Johnston S, Vasilaras TH, Keogh GF. 2000. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs. complex carbohydrates on body weight and blood lipids: The CARMEN study. *Int J Obes Relat Metab Disord* 24:1310–1318.

Sawaya AL, Fuss PJ, Dallal GE, Tsay R, McCrory MA, Young V, Roberts SB. 2001. Meal palatability, substrate oxidation and blood glucose in young and older men. *Physiol Behav* 72:5–12.

Scheinberg P, Stead EA. 1949. The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization, glucose utilization, and peripheral resistance, with observations on the effect of tiliting and anxiety. *J Clin Invest* 28:1163–1171.

Settergren G, Lindblad BS, Persson B. 1976. Cerebral blood flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and amino acids in infants. *Acta Paediatr Scand* 65:343–353.

Settergren G, Lindblad BS, Persson B. 1980. Cerebral blood flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and amino acids in anesthetized children. *Acta Paediatr Scand* 69:457–465.

Shannon WR. 1922. Neuropathologic manifestations in infants and children as a result of anaphylactic reaction to foods contained in their diet. *Am J Dis Child* 24:89–94.

Shaw JH. 1987. Causes and control of dental caries. *N Engl J Med* 317:996–1004.

Slattery ML, Benson J, Berry TD, Duncan D, Edwards SL, Caan BJ, Potter JD. 1997. Dietary sugar and colon cancer. *Cancer Epidemiol Biomarkers Prev* 6:677–685.

Smith JB, Niven BE, Mann JI. 1996. The effect of reduced extrinsic sucrose intake on plasma triglyceride levels. *Eur J Clin Nutr* 50:498–504.

Sokoloff L. 1973. Metabolism of ketone bodies by the brain. *Annu Rev Med* 24:271–280.

Sokoloff L, Fitzgerald GG, Kaufman EE. 1977. Cerebral nutrition and energy metabolism. In: Wurtman RJ, Wurtman JJ, eds. *Nutrition and the Brain*. New York: Raven Press. Pp. 87–139.

Sparks JW, Girard JR, Battaglia FC. 1980. An estimate of the caloric requirements of the human fetus. *Biol Neonate* 38:113–119.

Sparks MJ, Selig SS, Febbraio MA. 1998. Pre-exercise carbohydrate ingestion: Effect of the glycemic index on endurance exercise performance. *Med Sci Sports Exerc* 30:844–849.

Speer F. 1954. The allergenic tension-fatigue syndrome. *Pediatr Clin North Am* 1:1029–1037.

Spieth LE, Harnish JD, Lenders CM, Raezer LB, Pereira MA, Hangen SJ, Ludwig DS. 2000. A low-glycemic index diet in the treatment of pediatric obesity. *Arch Pediatr Adolesc Med* 154:947–951.

Spitzer L, Rodin J. 1987. Effects of fructose and glucose preloads on subsequent food intake. *Appetite* 8:135–145.

Streja DA, Steiner G, Marliss EB, Vranic M. 1977. Turnover and recycling of glucose in man during prolonged fasting. *Metabolism* 26:1089–1098.

Sunehag AL, Haymond MW, Schanler RJ, Reeds PJ, Bier DM. 1999. Gluconeogenesis in very low birth weight infants receiving total parenteral nutrition. *Diabetes* 48:791–800.

Surwit RS, Feinglos MN, McCaskill CC, Clay SL, Babyak MA, Brownlow BS, Plaisted CS, Lin P-H. 1997. Metabolic and behavioral effects of a high-sucrose diet during weight loss. *Am J Clin Nutr* 65:908–915.

Swanson JE, Laine DC, Thomas W, Bantle JP. 1992. Metabolic effects of dietary fructose in healthy subjects. *Am J Clin Nutr* 55:851–856.

Swink TD, Vining EPG, Freeman JM. 1997. The ketogenic diet: 1997. *Adv Pediatr* 44:297–329.

Thomas DE, Brotherhood JR, Brand JC. 1991. Carbohydrate feeding before exercise: Effect of glycemic index. *Int J Sports Med* 12:180–186.

Tillotson JL, Grandits GA, Bartsch GE, Stamler J. 1997. Relation of dietary carbohydrates to blood lipids in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr* 65:314S–326S.

Troiano RP, Briefel RR, Carroll MD, Bialostosky K. 2000. Energy and fat intakes of children and adolescents in the United States: Data from the National Health and Nutrition Examination Surveys. *Am J Clin Nutr* 72:1343S–1353S.

Tuyns AJ, Kaaks R, Haelterman M. 1988. Colorectal cancer and the consumption of foods: A case-control study in Belgium. *Nutr Cancer* 11:189–204.

USDA (U.S. Department of Agriculture). 1996. *The Food Guide Pyramid.* Home and Garden Bulletin No. 252. Washington, DC: U.S. Government Printing Office.

USDA/HHS (U.S. Department of Agriculture/U.S. Department of Health and Human Services). 2000. *Nutrition and Your Health: Dietary Guidelines for Americans.* Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

van Dam RM, Visscher AWJ, Feskens EJM, Verhoef P, Kromhout D. 2000. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: The Zutphen Elderly Study. *Eur J Clin Nutr* 54:726–731.

Vining EPG. 1999. Clinical efficacy of the ketogenic diet. *Epilepsy Res* 37:181–190.

Walker ARP, Cleaton-Jones PE. 1992. Sugar intake and dental caries. *Br Dent J* 172:7.

Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. 1990. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 113:909–915.

Welsh S, Davis C, Shaw A. 1992. Development of the Food Guide Pyramid. *Nutr Today* 27:12–23.

Westphal SA, Gannon MC, Nuttall FQ. 1990. Metabolic response to glucose ingested with various amounts of protein. *Am J Clin Nutr* 52:267–272.

White JW, Wolraich M. 1995. Effect of sugar on behavior and mental performance. *Am J Clin Nutr* 62:242S–249S.

Wolever TMS. 1990. Relationship between dietary fiber content and composition in foods and the glycemic index. *Am J Clin Nutr* 51:72–75.

Wolever TMS, Jenkins DJA. 1986. The use of the glycemic index in predicting the blood glucose response to mixed meals. *Am J Clin Nutr* 43:167–172.

Wolever TMS, Nuttal FQ, Lee R, Wong GS, Josse RG, Csima A, Jenkins DJA. 1985. Prediction of the relative blood glucose response of mixed meals using the white bread glycemic index. *Diabetes Care* 8:418–428.

Wolever TMS, Jenkins DJA, Josse RG, Wong GS, Lee R. 1987. The glycemic index: Similarity of values derived in insulin-dependent and non-insulin-dependent diabetic patients. *J Am Coll Nutr* 6:295–305.

Wolever TMS, Jenkins DJA, Ocana AM, Rao VA, Collier GR. 1988. Second-meal effect: Low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. *Am J Clin Nutr* 48:1041–1047.

Wolever TMS, Jenkins DJA, Vuksan V, Josse RG, Wong GS, Jenkins AL. 1990. Glycemic index of foods in individual subjects. *Diabetes Care* 13:126–132.

Wolever TMS, Jenkins DJA, Jenkins AL, Josse RG. 1991. The glycemic index: Methodology and clinical implications. *Am J Clin Nutr* 54:846–854.

Wolever TMS, Jenkins DJA, Vuksan V, Jenkins AL, Buckley GC, Wong GS, Josse RG. 1992a. Beneficial effect of a low glycaemic index diet in type 2 diabetes. *Diabet Med* 9:451–458.

Wolever TMS, Jenkins DJA, Vuksan V, Jenkins AL, Wong GS, Josse RG. 1992b. Beneficial effect of low-glycemic index diet in overweight NIDDM subjects. *Diabetes Care* 15:562–564.

Wolraich ML, Wilson DB, White JW. 1995. The effect of sugar on behavior or cognition in children. A meta-analysis. *J Am Med Assoc* 274:1617–1621.

World Cancer Research Fund/American Institute for Cancer Research. 1997. *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* Washington, DC: American Institute for Cancer Research.

Yamaura H, Ito M, Kubota K, Matsuzawa T. 1980. Brain atrophy during aging: A quantitative study with computed tomography. *J Gerontol* 35:492–498.

Yudkin J, Eisa O, Kang SS, Meraji S, Bruckdorfer KR. 1986. Dietary sucrose affects plasma HDL cholesterol concentration in young men. *Ann Nutr Metab* 30:261–266.

Ziegler EE, Fomon SJ. 1983. Lactose enhances mineral absorption in infancy. *J Pediatr Gastroenterol Nutr* 2:288–294.

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Dietary, Functional, and Total Fiber

SUMMARY

Dietary Fiber consists of nondigestible carbohydrates and lignin that are intrinsic and intact in plants. *Functional Fiber* consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans. *Total Fiber* is the sum of *Dietary Fiber* and *Functional Fiber*. Fibers have different properties that result in different physiological effects. For example, viscous fibers may delay the gastric emptying of ingested foods into the small intestine, resulting in a sensation of fullness, which may contribute to weight control. Delayed gastric emptying may also reduce postprandial blood glucose concentrations and potentially have a beneficial effect on insulin sensitivity. Viscous fibers can interfere with the absorption of dietary fat and cholesterol, as well as with the enterohepatic recirculation of cholesterol and bile acids, which may result in reduced blood cholesterol concentrations. Consumption of *Dietary* and certain *Functional Fibers*, particularly those that are poorly fermented, is known to improve fecal bulk and laxation and ameliorate constipation. The relationship of fiber intake to colon cancer is the subject of ongoing investigation and is currently unresolved. An Adequate Intake (AI) for *Total Fiber* in foods is set at 38 and 25 g/d for young men and women, respectively, based on the intake level observed to protect against coronary heart disease. Median intakes of *Dietary Fiber* ranged from 16.5 to 17.9 g/d for men and 12.1 to 13.8 g/d for women (Appendix Table E-4). There was insufficient evidence to set a Tolerable Upper Intake Level (UL) for *Dietary Fiber* or *Functional Fiber*.

BACKGROUND INFORMATION

Overview

Definitions of Fiber

A variety of definitions of fiber exist worldwide (IOM, 2001). Some are based solely on one or more analytical methods for isolating fiber, while others are physiologically based. For instance, in the United States fiber is defined by a number of analytical methods that are accepted by the Association of Official Analytical Chemists International (AOAC); these methods isolate nondigestible animal and plant carbohydrates. In Canada, however, a formal definition has been in place that recognizes nondigestible food of plant origin—but not of animal origin—as fiber. As nutrition labeling becomes uniform throughout the world, it is recognized that a single definition of fiber may be needed. Furthermore, new products are being developed or isolated that behave like fiber, yet do not meet the traditional definitions of fiber, either analytically or physiologically.

Without an accurate definition of fiber, compounds can be designed or isolated and concentrated using available methods without necessarily providing beneficial health effects, which most people consider to be an important attribute of fiber. Other compounds can be developed that are nondigestible and provide beneficial health effects, yet do not meet the current U.S. definition based on analytical methods. For these reasons, the Food and Nutrition Board, under the oversight of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, assembled a Panel on the Definition of Dietary Fiber to develop a proposed definition of fiber (IOM, 2001). Based on the panel's deliberations, consideration of public comments, and subsequent modifications, the following definitions have been developed:

Dietary Fiber consists of nondigestible carbohydrates and lignin that are intrinsic and intact in plants.

Functional Fiber consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans.

Total Fiber is the sum of *Dietary Fiber* and *Functional Fiber.*

This two-pronged approach to define edible, nondigestible carbohydrates recognizes the diversity of carbohydrates in the human food supply that are not digested: plant cell wall and storage carbohydrates that predominate in foods, carbohydrates contributed by animal foods, and isolated and low molecular weight carbohydrates that occur naturally or have been synthesized or otherwise manufactured. These definitions recognize a continuum of carbohydrates and allow for flexibility to incorporate new fiber

sources developed in the future (after demonstration of beneficial physiological effects in humans). While it is not anticipated that the new definitions will significantly impact recommended levels of intake, information on both *Dietary Fiber* and *Functional Fiber* will more clearly delineate the source of fiber and the potential health benefits. Although sugars and sugar alcohols could potentially be categorized as *Functional Fibers*, for labeling purposes they are not considered to be *Functional Fibers* because they fall under "sugars" and "sugar alcohols" on the food label.

Distinguishing Features of Dietary Fiber Compared with Functional Fiber

Dietary Fiber consists of nondigestible food plant carbohydrates and lignin in which the plant matrix is largely intact. Specific examples are provided in Table 7-1. Nondigestible means that the material is not digested and absorbed in the human small intestine. Nondigestible plant carbohydrates in foods are usually a mixture of polysaccharides that are integral components of the plant cell wall or intercellular structure. This definition recognizes that the three-dimensional plant matrix is responsible for some of the physicochemical properties attributed to *Dietary Fiber*. Fractions of plant foods are considered *Dietary Fiber* if the plant cells and their three-dimensional interrelationships remain largely intact. Thus, mechanical treatment would still result in intact fiber. Another distinguishing feature of *Dietary Fiber* sources is that they contain other macronutrients (e.g., digestible carbohydrate and protein) normally found in foods. For example, cereal brans, which are obtained by grinding, are anatomical layers of the grain consisting of intact cells and substantial amounts of starch and protein; they would be categorized as *Dietary Fiber* sources.

TABLE 7-1 Characteristics of *Dietary Fiber*

Characteristic	*Dietary Fiber*
Nondigestible animal carbohydrate	No
Carbohydrates not recovered by alcohol precipitation[a]	Yes
Nondigestible mono- and disaccharides and polyols	No
Lignin	Yes
Resistant starch	Some
Intact, naturally occurring food source only	Yes
Resistant to human enzymes	Yes
Specifies physiological effect	No

[a] Includes inulin, oligosaccharides (3–10 degrees of polymerization), fructans, polydextrose, methylcellulose, resistant maltodextrins, and other related compounds.

Resistant starch that is naturally occurring and inherent in a food or created during normal processing of a food, as is the case for flaked corn cereal, would be categorized as *Dietary Fiber*. Examples of oligosaccharides that fall under the category of *Dietary Fiber* are those that are normally constituents of a *Dietary Fiber* source, such as raffinose, stachyose, and verbacose in legumes, and the low molecular weight fructans in foods, such as Jerusalem artichoke and onions.

Functional Fiber consists of isolated or extracted nondigestible carbohydrates that have beneficial physiological effects in humans. *Functional Fibers* may be isolated or extracted using chemical, enzymatic, or aqueous steps. Synthetically manufactured or naturally occurring isolated oligosaccharides and manufactured resistant starch are included in this definition. Also included are those naturally occurring polysaccharides or oligosaccharides usually extracted from their plant source that have been modified (e.g., to a shorter polymer length or to a different molecular arrangement). Although they have been inadequately studied, animal-derived carbohydrates such as connective tissue are generally regarded as nondigestible. The fact that animal-derived carbohydrates are not of plant origin forms the basis for including animal-derived, nondigestible carbohydrates in the *Functional Fiber* category. Isolated, manufactured, or synthetic oligosaccharides of three or more degrees of polymerization are considered to be *Functional Fiber*. Nondigestible monosaccharides, disaccharides, and sugar alcohols are not considered to be *Functional Fibers* because they fall under "sugars" or "sugar alcohols" on the food label. Also, rapidly changing lumenal fluid balance resulting from large amounts of nondigestible mono- and disaccharides or low molecular weight oligosaccharides, such as that which occurs when sugar alcohols are consumed, is not considered a mechanism of laxation for *Functional Fibers*.

Rationale for Definitions

Nondigestible carbohydrates are frequently isolated to concentrate a desirable attribute of the mixture from which it was extracted. Distinguishing a category of *Functional Fiber* allows for the desirable characteristics of such components to be highlighted. In the relatively near future, plant and animal synthetic enzymes may be produced as recombinant proteins, which in turn may be used in the manufacture of fiber-like materials. The definition will allow for the inclusion of these materials and will provide a viable avenue to synthesize specific oligosaccharides and polysaccharides that are part of plant and animal tissues.

In summary, one definition has been proposed for *Dietary Fiber* because many other substances in high fiber foods, including a variety of vitamins and minerals, often have made it difficult to demonstrate a significant

health benefit specifically attributable to the fiber in foods. Thus, it is difficult to separate out the effect of fiber per se from the high fiber food. Attempts have been made to do this, particularly in epidemiological studies, by controlling for other substances in those foods, but these attempts were not always successful. The advantage, then, of adding isolated nondigestible carbohydrates as a fiber source to a food is that one may be able to draw conclusions about *Functional Fiber* itself with regard to its physiological role rather than that of the vehicle in which it is found. The proposed definitions do not preclude research directed towards the health benefits of *Dietary Fiber* in foods, but it is not necessary to demonstrate a physiological effect in order for a food fiber to be listed as *Dietary Fiber*.

An important aspect of the recommended definitions is that a substance is required to demonstrate a beneficial physiological effect to be classified as *Functional Fiber*. Research has shown that extraction or isolation of a polysaccharide, usually through chemical, enzymatic, or aqueous means, can either enhance its health benefit (usually because it is a more concentrated source) or diminish the beneficial effect. These recommendations should be helpful in evaluating diet and disease relationship studies as it will be possible to classify fiber-like components as *Functional Fibers* due to their documented health benefits. Although databases are not currently constructed to delineate potential beneficial effects of specific fibers, there is no reason that this could not be accomplished in the future.

Examples of Dietary and Functional Fibers

As described in the report, *Dietary Reference Intakes: Proposed Definition of Dietary Fiber* (IOM, 2001), *Dietary Fiber* includes plant nonstarch polysaccharides (e.g., cellulose, pectin, gums, hemicellulose, β-glucans, and fibers contained in oat and wheat bran), plant carbohydrates that are not recovered by alcohol precipitation (e.g., inulin, oligosaccharides, and fructans), lignin, and some resistant starch. Potential *Functional Fibers* for food labeling include isolated, nondigestible plant (e.g., resistant starch, pectin, and gums), animal (e.g., chitin and chitosan), or commercially produced (e.g., resistant starch, polydextrose, inulin, and indigestible dextrins) carbohydrates.

How the Definitions Affect the Interpretation of This Report

The reason that a definition of fiber is so important is that what *is* or *is not* considered to be dietary fiber in, for example, a major epidemiological study on fiber and heart disease or fiber and colon cancer, could determine the results and interpretation of that study. In turn, that would affect recommendations regarding fiber intake. Clearly, the definitions described

above were developed after the studies cited in this report, which form the basis for fiber intake recommendations. However, that should not detract from the relevance of the recommendations, as the database used to measure fiber for these studies will be noted.

For example, most epidemiological studies use the U.S. Department of Agriculture (USDA) database for fiber, along with other databases and data added by the investigators for missing values (Hallfrisch et al., 1988; Heilbrun et al., 1989; Miller et al., 1983; Platz et al., 1997). Such a database represents *Dietary Fiber*, since *Functional Fibers* that serve as food ingredients contribute a minor amount to the *Total Fiber* content of foods. In 1987, the U.S. Food and Drug Administration (FDA) adopted AOAC method 985.29 for regulatory purposes to identify fiber as a mixture of nonstarch polysaccharides, lignin, and some resistant starch (FDA, 1987). Related methods that isolated the same components as AOAC method 985.29 were developed independently and accepted by AOAC and FDA in subsequent years. These methods exclude all oligosaccharides (3 to 9 degrees of polymerization) from the definition and include all polysaccharides, lignin, and some of the resistant starch that is resistant to the enzymes (protease, amylase, and amyloglucosidase) used in the AOAC methods. It is these methods that are used to measure the fiber content of foods that is entered into the USDA database.

Other epidemiological studies have assessed intake of specific high fiber foods, such as legumes, breakfast cereals, fruits, and vegetables (Hill, 1997; Thun et al., 1992). Intervention studies often use specific fiber supplements such as pectin, psyllium, and guar gum, which would, by the above definition, be considered *Functional Fibers* if their role in human health is documented. For the above reasons, the type of fiber (*Dietary*, *Functional*, or *Total Fiber*) used in the studies discussed later in this chapter is identified.

Description of the Common Dietary and Functional Fibers

Below is a description of the *Dietary Fibers* that are most abundant in foods and the *Functional Fibers* that are commonly added to foods or provided as supplements. To be classified as a *Functional Fiber* for food labeling purposes, a certain level of information on the beneficial physiological effects in humans will be needed. For some of the known beneficial effects of *Dietary* and potential *Functional Fibers*, see "Physiological Effects of Isolated and Synthetic Fibers" and "Evidence Considered for Estimating the Requirement for *Dietary Fiber* and *Functional Fiber*."

Cellulose. Cellulose, a polysaccharide consisting of linear β-(1,4)–linked glucopyranoside units, is the main structural component of plant cell walls.

Humans lack digestive enzymes to cleave β-(1,4) linkages and thus cannot absorb glucose from cellulose. Powdered cellulose is a purified, mechanically disintegrated cellulose obtained as a pulp from wood or cotton and is added to food as an anticaking, thickening, and texturizing agent. Dietary cellulose can be classified as *Dietary Fiber* or *Functional Fiber*, depending on whether it is naturally occurring in food (*Dietary Fiber*) or added to foods (*Functional Fiber*).

Chitin and Chitosan. Chitin is an amino-polysaccharide containing β-(1,4) linkages as is present in cellulose. Chitosan is the deacetylated product of chitin. Both chitin and chitosan are found in the exoskeletons of arthropods (e.g., crabs and lobsters) and in the cell walls of most fungi. Neither chitin nor chitosan is digested by mammalian digestive enzymes. Chitin and chitosan are primarily consumed as a supplement and potentially can be classified as *Functional Fibers* if sufficient data on physiological benefits in humans are documented.

β-Glucans. β-glucans are homopolysaccharides of branched glucose resides. These β-linked D-glucopyranose polymers are constituents of fungi, algae, and higher plants (e.g., barley and oats). Naturally occurring β-glucans can be classified as *Dietary Fibers*, whereas added or isolated β-glucans are potential *Functional Fibers*.

Gums. Gums consist of a diverse group of polysaccharides usually isolated from seeds and have a viscous feature. Guar gum is produced by the milling of the endosperm of the guar seed. The major polysaccharide in guar gum is galactomannan. Galactomannans are highly viscous and are therefore used as food ingredients for their thickening, gelling, and stabilizing properties. Gums in the diet can be classified as *Dietary* or *Functional Fibers*.

Hemicelluloses. Hemicelluloses are a group of polysaccharides found in plant cell walls that surround cellulose. These polymers can be linear or branched and consist of glucose, arabinose, mannose, xylose, and galacturonic acid. Dietary hemicelluoses are classified as *Dietary Fibers*.

Inulin, Oligofructose, and Fructooligosaccharides. Inulin and oligofructose are naturally occurring in a variety of plants. Most of the commercially available inulin and oligofructose is either synthesized from sucrose or extracted and purified from chicory roots. Oligofructose is also formed by partial hydrolysis of inulin. Inulin is a polydisperse β-(2,1)-linked fructan with a glucose molecule at the end of each fructose chain. The chain length is usually 2 to 60 units, with an average degree of polymerization of

ten. The β-(2,1) linkage is resistant to enzymatic digestion. Synthetic oligofructose contains β-(2,1) fructose chains with and without terminal glucose units. The chain ranges from two to eight monosaccharide residues. Synthetic fructooligosaccharides have the same chemical and structural composition as oligofructose, except that the degree of polymerization ranges from two to four. Because many current definitions of dietary fiber are based on methods involving ethanol precipitation, oligosaccharides and fructans that are endogenous in foods, but soluble in ethanol, are not analyzed as dietary fiber. Thus, the USDA database does not currently include these fiber sources. With respect to the definitions outlined in this chapter, the naturally occurring fructans that are found in plants, such as chicory, onions, and Jerusalem artichoke, would be classified as *Dietary Fibers*; the synthesized or extracted fructans could be classified as *Functional Fibers* when there are sufficient data to show positive physiological effects in humans.

Lignin. Lignin is a highly branched polymer comprised of phenylpropanoid units and is found within "woody" plant cell walls, covalently bound to fibrous polysaccharides (*Dietary Fibers*). Although not a carbohydrate, because of its association with *Dietary Fiber*, and because it affects the physiological effects of *Dietary Fiber*, lignin is classified as a *Dietary Fiber* if it is relatively intact in the plant. Lignin isolated and added to foods could be classified as *Functional Fiber* given sufficient data on positive physiological effects in humans.

Pectins. Pectins, which are found in the cell wall and intracellular tissues of many fruits and berries, consist of galacturonic acid units with rhamnose interspersed in a linear chain. Pectins frequently have side chains of neutral sugars, and the galactose units may be esterified with a methyl group, a feature that allows for its viscosity. While fruits and vegetables contain 5 to 10 percent naturally occurring pectin, pectins are industrially extracted from citrus peels and apple pomace. Isolated, high methoxylated pectins are mainly added to jams due to their gelling properties with high amounts of sugar. Low methoxylated pectins are added to low-calorie gelled products, such as sugar-free jams and yogurts. Thus, pectins in the diet are classified as *Dietary* and/or *Functional Fiber*.

Polydextrose. Polydextrose is a polysaccharide that is synthesized by random polymerization of glucose and sorbitol. Polydextrose serves as a bulking agent in foods and sometimes as a sugar substitute. Polydextrose is not digested or absorbed in the small intestine and is partially fermented in the large intestine, with the remaining excreted in the feces. Polydextrose

can potentially be classified as a *Functional Fiber* when sufficient data on physiological benefits in humans are documented.

Psyllium. Psyllium refers to the husk of psyllium seeds and is a very viscous mucilage in aqueous solution. The psyllium seed, also known as plantago or flea seed, is small, dark, reddish-brown, odorless, and nearly tasteless. *P. ovata*, known as blond or Indian plantago seed, is the species from which husk is usually derived. *P. ramosa* is known as Spanish or French psyllium seed. Psyllium, also known as ispaghula husk, may be classified as a *Functional Fiber.*

Resistant Dextrins. Indigestible components of starch hydrolysates, as a result of heat and enzymatic treatment, yield indigestible dextrins that are also called resistant maltodextrins. Unlike gums, which have a high viscosity that can lead to problems in food processing and unpleasant organoleptic properties, resistant maltodextrins are easily added to foods and have a good mouth feel. Resistant maltodextrins are produced by heat/acid treatment of cornstarch, followed by enzymatic (amylase) treatment. The average molecular weight of resistant maltodextrins is 2,000 daltons and consists of polymers of glucose containing α-(1-4) and α-(1-6) glucosidic bonds, as well as 1-2 and 1-3 linkages. Resistant dextrins can potentially be classified as *Functional Fibers* when sufficient data on physiological benefits in humans are documented.

Resistant Starch. Resistant starch is naturally occurring, but can also be produced by the modification of starch during the processing of foods. Starch that is included in a plant cell wall and thus physically inaccessible to α-amylase is called RS_1. Native starch that can be made accessible to the enzyme by gelatinization is called RS_2. Resistant starch that is formed during processing is called RS_3 or RS_4 and is considered to be fiber that is isolated rather than intact and naturally occurring. RS_3 (retrograded starch) is formed from the cooking and cooling or extrusion of starchy foods (e.g., potato chips and cereals). RS_4 (chemically modified starch) includes starch esters, starch ethers, and cross-bonded starches that have been produced by the chemical modification of starch. RS_3 and RS_4 are not digested by mammalian intestinal enzymes and are partly fermented in the colon (Cummings et al., 1996; Englyst et al., 1992). Resistant starch is estimated to be approximately 10 percent (2 to 20 percent) of the amount of starch consumed in the Western diet (Stephen et al., 1983). Thus, RS_1 and RS_2 are classified as *Dietary Fibers*, and RS_3 and RS_4 may be classified as *Functional Fibers.*

Physiology of Absorption, Metabolism, and Excretion

By definition, *Dietary Fiber* and *Functional Fiber* are not digested by mammalian enzymes. Therefore, they pass into the large intestine relatively intact. Along the gastrointestinal tract, properties of fiber result in different physiological effects.

Effect on Gastric Emptying and Satiety

Consumption of viscous fibers delays gastric emptying (Low, 1990; Roberfroid, 1993) and expands the effective unstirred layer, thus slowing the process of absorption once in the small intestine (Blackburn et al., 1984). This in turn can cause an extended feeling of fullness (Bergmann et al., 1992). A slower emptying rate means delayed digestion and absorption of nutrients (Jenkins et al., 1978; Ritz et al., 1991; Roberfroid, 1993; Truswell, 1992), resulting in decreased absorption of energy (Heaton, 1973). For example, Stevens and coworkers (1987) showed an 11 percent reduction in energy intake with psyllium gum intake. Postprandial glucose concentration in the blood is thus lower after the consumption of viscous fiber than after consumption of digestible carbohydrate alone (Benini et al., 1995; Holt et al., 1992; Leathwood and Pollet, 1988). The extended presence of nutrients in the upper small intestine may promote satiety (Sepple and Read, 1989).

Fermentation

Fibers may be fermented by the colonic microflora to carbon dioxide, methane, hydrogen, and short-chain fatty acids (primarily acetate, propionate, and butyrate). Foods rich in hemicelluloses and pectins, such as fruits and vegetables, contain *Dietary Fiber* that is more completely fermentable than foods rich in celluloses, such as cereals (Cummings, 1984; Cummings and Englyst, 1987; McBurney and Thompson, 1990). There appears to be no relationship between the level of *Dietary Fiber* intake and fermentability up to very high levels (Livesey, 1990). Resistant starch is highly fermentable (van Munster et al., 1994). Butyrate, a four-carbon, short-chain fatty acid, is the preferred energy source for colon cells (Roediger, 1982), and lack of butyrate production, absorption, or metabolism is thought by some to contribute to ulcerative colitis (Roediger, 1980; Roediger et al., 1993). Others have suggested that butyrate may be protective against colon cancer (see "*Dietary Fiber* and the Prevention of Colon Cancer"). However, the relationship between butyrate and colon cancer is controversial and the subject of ongoing investigation (Lupton, 1995).

Contribution of Fiber to Energy

When a metabolizable carbohydrate is absorbed in the small intestine, its energy value is 16.7 kJ/g (4 kcal/g); when fiber is anaerobically fermented by colonic microflora in the large intestine, short-chain fatty acids (e.g., butyrate, acetate, and propionate) are produced and absorbed as an energy source. Once absorbed into the colon cells, butyrate can be used as an energy source by colonocytes (Roediger, 1982); acetate and propionate travel through the portal vein to the liver, where propionate is then utilized by the liver. Acetate can be metabolized peripherally. A small proportion of energy from fermented fiber is used for bacterial growth and maintenance, and bacteria are excreted in feces, which also contain short-chain fatty acids (Cummings and Branch, 1986). Differences in food composition, patterns of food consumption, the administered dose of fiber, the metabolic status of the individual (e.g., obese, lean, malnourished), and the digestive capability of the individual influence the digestible energy consumed and the metabolizable energy available from various dietary fibers. Because the process of fermentation is anaerobic, less energy is recovered from fiber than the 4 kcal/g that is recovered from carbohydrate. While it is still unclear as to the energy yield of fibers in humans, current data indicate that the yield is in the range of 1.5 to 2.5 kcal/g (Livesey, 1990; Smith et al., 1998).

Physiological Effects of Isolated and Synthetic Fibers

This section summarizes the fibers for which there is a sufficient database that documents their beneficial physiological human effects, which is the rationale for categorizing them as *Functional Fibers*. It is important to note that discussions on the potential benefits of what might eventually be classified as *Functional Fibers* should not be construed as endorsements of those fibers. While plant-based foods are a good source of *Dietary Fiber*, isolated or synthetic fibers have been developed for their use as food ingredients and because of their beneficial role in human health. In 1988 Health Canada published guidelines for what they considered to be "novel fiber sources" and food products containing them that could be labeled as a source of fiber in addition to those included in their 1985 definition (Health Canada, 1988). The rationale for these guidelines was that there were safety issues unique to novel sources of fiber, and if a product was represented as containing fiber, it should have the beneficial physiological effects associated with dietary fiber that the public expects. The guidelines indicated that both safety and efficacy of the fiber source had to be established in order for the product to be identified as a source of dietary fiber in Canada, and this had to be done through experiments using humans.

Three measures of efficacy were identified: (1) laxation, (2) normalization of blood lipid concentrations, and (3) attenuation of blood glucose responses. Detailed guidelines were later produced for the clinical studies required to assess laxation effects, as this was the physiological function most often used by industry when seeking approval for a novel fiber source (Health Canada, 1997). For each of the fiber sources discussed below, studies will be summarized that relate to one of the three measures of efficacy identified by Health Canada, as these are the three most commonly accepted beneficial effects of fibers. A more complete discussion of these three measures of efficacy may be found later in this chapter. In addition, other potentially efficacious effects will be noted where studies are available.

As interest has increased in fiber, manufacturers have isolated various types of fiber from a wide range of carbohydrate sources added to foods. Many of these isolated materials are used as food additives based on functional properties such as thickening or fat reduction. As enzymatic and other technologies evolve, many types of polysaccharides will continue to be designed and manufactured using plant and animal synthetic enzymes. Examples in this category include modified cellulose, in which the hydroxyl groups on the glucose residues have been substituted to varying degrees with alkyl groups such as methyl and propyl; fructooligosaccharides manufactured from sucrose; and polydextrose synthesized from glucose. In some instances, fibers isolated from plants or manufactured chemically or synthetically have demonstrated more powerful beneficial physiological effects than a food source of the fiber polysaccharide.

Cellulose

Laxation. From a meta-analysis of about 100 studies of changes in stool weight with various fiber sources, investigators have calculated the increase in fecal weight due to fiber ingestion (Cummings, 1993). As noted later in this chapter, an increase in fecal weight does not necessarily equate with enhanced laxation, so this needs to be considered in interpreting the results of fecal bulking studies. Cellulose was shown to increase fecal bulk by 3 g/g of cellulose fed. This is lower than that achieved by bran (5.7 g/g of bran), but higher than that of isolated, fermentable fibers such as pectin (1.3 g/g of pectin) (Cummings, 1993). In a randomized, crossover study designed to compare the effects of supplemental pectin (12 g/d), cellulose (15 g/d), and lignin (12 g/d) on stool characteristics of healthy volunteers, cellulose was the only fiber that significantly decreased (–27 percent) mean stool transit time and increased mean wet stool weight (+57 percent) (Hillman et al., 1983).

Normalization of Blood Lipid Concentrations. Cellulose is often used as the placebo in studies designed to test the efficacy of fibers on decreasing serum cholesterol concentrations. Cellulose is either neutral with respect to blood cholesterol concentrations (Hillman et al., 1985; Niemi et al., 1988) or, in some studies, it actually shows a slight increase (Anderson et al., 1999).

Attenuation of Blood Glucose Responses. Similar to the relationship between cellulose and serum cholesterol concentrations, cellulose is also often used as a placebo in studies that evaluate the effect of fiber on blood glucose and insulin concentrations. Cellulose is ineffective in decreasing the postprandial glucose response (Librenti et al., 1992; Niemi et al., 1988).

Chitin and Chitosan

Laxation. There is no evidence that chitin or chitosan function as laxatives in humans.

Normalization of Blood Lipid Concentrations. There are a number of animal studies that have suggested that chitin and chitosan may decrease lipid absorption and thus the amount of fat entering the blood (Gallaher et al., 2000; Razdan and Pettersson, 1994; Sugano et al., 1980; Zacour et al., 1992). Therefore, blood cholesterol and triacylglycerol concentrations have been shown to be reduced with chitosan intake in animals (Chiang et al., 2000; Jennings et al., 1988; Razdan and Pettersson, 1994, 1996; Razdan et al., 1997).

These results, however, have not always been observed in controlled intervention trials with humans. When adult volunteers were given 2.7 g of chitosan for 7 days, there was no effect on fecal fat excretion (Guerciolini et al., 2001). When 2.4 g of chitosan was consumed daily by women, a significant reduction in low density lipoprotein (LDL) cholesterol concentration was observed (Wuolijoki et al., 1999). More intervention studies are needed to further understand the role of chitin and chitosan in the attenuation of blood lipid concentration in humans.

Attenuation of Blood Glucose Responses. There are no known reports in humans on chitin or chitosan intake and the attenuation of blood glucose responses.

Other Potential Physiological Effects. Because chitosan has been shown in some animal studies to reduce fat absorption, it has been proposed that chitosan intake can aid in weight reduction. When rats were fed up to

5 percent of their diet as chitosan, there was no effect on weight gain (Jennings et al., 1988; Sugano et al., 1980). Significantly reduced body weights were observed when chickens were fed 30 g/kg of chitosan (Razdan et al., 1997). There was no change in body weight in women consuming 2.4 g/d of chitosan for 8 weeks (Wuolijoki et al., 1999). Furthermore, no change in body weight was observed in women who consumed 2 g/d of chitosan for 28 days (Pittler et al., 1999). Similarly, in a study of 88 obese Asians, Ho and colleagues (2001) found no effect of chitosan supplementation (3 g/d) on weight, body mass index, or lean body mass compared to placebo.

Guar Gum

Laxation. As a viscous, highly fermentable fiber, guar gum has little effect on fecal bulk or laxation (Slavin, 1987).

Normalization of Blood Lipid Concentrations. Jenkins and coworkers (1975) reported the hypocholesterolemic effect of guar gum, which is often added to foods. Since 1975 there have been a number of studies with guar gum supplementation and findings of an 11 to 16 percent reduction in serum cholesterol concentration (Anderson and Tietyen-Clark, 1986; Penagini et al., 1986). For example, when type 2 diabetics were provided guar gum (21 g/d) for 3 months, the mean serum total and LDL cholesterol concentrations were significantly lower than controls (Aro et al., 1981). Furthermore, hypercholesterolemic men who received 15 g/d of guar gum had significantly lower serum total cholesterol and LDL cholesterol concentrations compared to the placebo controls after 6 weeks (Aro et al., 1984). Blake and coworkers (1997) evaluated the effect of depolymerized guar galactomannan on fasting plasma lipid concentrations in volunteers with moderately raised plasma cholesterol. There were significant reductions in plasma total cholesterol (9.7 percent) and LDL cholesterol (11 percent) concentrations after the guar treatment ($p < 0.001$). In addition to decreasing blood cholesterol concentrations, guar gum has also been shown to decrease concentrations of triacylglycerols (Bosello et al., 1984), as well as systolic and diastolic blood pressure (Krotkiewski, 1987).

Attenuation of Blood Glucose Responses. Viscous fibers, such as pectin and guar gum and those present in oat products and beans, produced significant reductions in glycemic response in 33 of 50 studies (66 percent) as reviewed in Wolever and Jenkins (1993). This is in contrast to only 3 of 14 studies conducted with insoluble fiber (21 percent). For example, when individuals with type 2 diabetes were given 21 g/d of guar gum,

there was a significant reduction in both basal and postprandial hyperglycemia compared to the placebo controls (Aro et al., 1981). In addition, the provision of 30 g/d of guar gum decreased fasting blood glucose concentration and increased insulin sensitivity (Landin et al., 1992).

In a dose–response study to determine the amount of guar gum needed to decrease postprandial glycemia and insulinemia, guar gum was supplied at 0, 2.9, 6.0, and 9.1 g/d in the form of biscuits to eight nondiabetics (Ellis et al., 1988). A reduction of 209 mU/min/L in the integrated insulin curve was estimated for every 1 g of guar gum incorporated into the biscuit. The addition of 10 g/d of guar gum to a test meal generated an overall decrease in blood glucose concentrations in both normal ($n = 5$) and diabetic ($n = 6$) individuals (Goulder et al., 1978).

Guar gum has also been shown to be effective when sprinkled on food. In a study with 18 type 2-diabetic patients, 5 g of guar gum granules or 5 g of wheat bran were sprinkled over food at each main meal for 4 weeks (Fuessl et al., 1987). There was a 50 percent reduction in the incremental area under the postprandial glycemic curve with the guar gum. Mean fasting plasma glucose and glycosylated hemoglobin concentrations were lower after treatment with guar gum compared with the wheat bran control.

Not all studies, however, have found a glycemic benefit from guar administration. In one study with type 2 diabetics with near-normal fasting plasma glucose concentrations, 15 g/d of guar gum did not reduce the excessive postprandial glycemic response (Holman et al., 1987). Although the mechanism for improved glycemic response seen with guar gum in most studies is not entirely clear, guar gum has been shown to increase C-peptide response over time, thus suggesting enhanced insulin secretion by guar gum (Groop et al., 1993). When the standard glucose test was performed after ingestion of 15 g/d of guar gum, improved glucose tolerance was observed in all but one pregnant women. In addition, guar gum generated significant reductions in mean serum glucose concentrations at 1, 2, and 3 hours after feeding (Gabbe et al., 1982).

Inulin, Oligofructose, and Fructooligosaccharides

Laxation. A few studies have demonstrated an increase in fecal bulk and increased stool frequency upon the ingestion of inulin or oligofructose. Fecal weight was increased after consuming 15 g/d of inulin or oligofructose (Gibson et al., 1995), and inulin (20 to 40 g/d) was shown to reduce constipation (Kleessen et al., 1997). A multicenter trial was conducted to test whether fructooligosaccharides worsen gastrointestinal symptoms in people with irritable bowel syndrome (Olesen and Gudmand-

Høyer, 2000). After 2 to 6 weeks of treatment with 20 g/d of fructo-oligosaccharides or placebo, symptoms of irritable bowel syndrome improved more in the placebo group than in the fructooligosaccharide group; however, there was no difference between the groups after continuous treatment for 12 weeks.

Normalization of Blood Lipid Concentrations. Studies on the effect of inulin or oligofructose ingestion on plasma lipid concentrations have provided mixed results. Significant reductions in plasma triacylglycerol concentrations occurred with the intake of 10 g/d of inulin, particularly in those individuals with a baseline triacylglycerol concentration greater than 1.5 mmol/L (Jackson et al., 1999). The ingestion of 9 g/d of inulin significantly reduced plasma total cholesterol and triacylglycerol concentrations in young men (Brighenti et al., 1999). Nonsignificant changes in plasma total or high density lipoprotein (HDL) cholesterol and triacylglycerol concentrations were reported for individuals consuming 14 g/d of inulin (Pedersen et al., 1997) or 20 g/d of fructooligosaccharide (Luo et al., 1996). In young, healthy males, 15 g/d of nondigestible oligosaccharides (inulin or fructooligosaccharides) did not decrease blood lipids or affect glucose absorption compared to controls (van Dokkum et al., 1999).

Attenuation of Blood Glucose Responses. A placebo-controlled parallel study showed that a daily intake of 10 g of inulin significantly reduced fasting insulin concentrations (Jackson et al., 1999). Fasting blood glucose concentrations were significantly reduced by 15 mg/dL in type 2 diabetics who were fed 8 g/d of fructooligosaccharides (Yamashita et al., 1984). Daily intake of 20 g of fructooligosaccharides significantly decreased basal hepatic glucose production (Luo et al., 1996). No difference, however, was observed in the incremental area under the curve for glucose when individuals were fed 50 g of a rice-based cereal containing 0 or 9 g of inulin (Brighenti et al., 1999).

Other Potential Physiological Effects. An important effect of inulin intake is considered to be the production of *Bifidobacteria*. *Bifidobacteria* contain high amounts of β-fructosidase, which are specific for the β-(1,2) bond present in inulin and oligofructose. A number of studies in humans have shown that the ingestion of fructooligosaccharides leads to an increase in fecal *Bifidobacteria* (Bouhnik et al., 1996, 1999; Buddington et al., 1996; Tuohy et al., 2001; Williams et al., 1994). *Bifidobacteria* have been shown to promote beneficial health effects in animals (Grizard and Barthomeuf, 1999); however, potential beneficial effects in humans are not well understood.

Oat Products and β-Glucans

Laxation. Extracted β-glucans are highly fermentable and therefore their contribution to fecal bulk is minimal (McBurney, 1991). This may contribute, in part, to the lack of an effect in preventing constipation. Oat bran increases stool weight by supplying rapidly fermented viscous fiber to the proximal colon for bacterial growth (Chen et al., 1998).

Normalization of Blood Lipid Concentrations. In one study, oat gum supplementation (9 g/d of β-glucan) did not significantly decrease serum total cholesterol concentration compared to the placebo, leading the authors to conclude that the cholesterol-lowering capacity of oat gum in healthy young men is weak (Beer et al., 1995). In contrast, when hypercholesterolemic individuals were fed oat gum providing 5.8 g/d of β-glucan or a maltodextrin placebo for 4 weeks, mean total and LDL cholesterol concentrations decreased throughout the oat gum phase, and both concentrations were reduced 9 percent relative to initial values (Braaten et al., 1994b). In a larger study, adults with multiple risk factors and LDL cholesterol concentrations above 4.14 mmol/L or between 3.37 and 4.14 mmol/L were randomized to one of seven groups to receive either oatmeal or oat bran at various levels or a placebo control (Davidson et al., 1991). There was a dose-dependent reduction in LDL cholesterol concentrations with the oat cereals. However, when a modest level of β-glucan (3 g/d) was provided to 62 healthy adults with mild to moderate hyperlipidemia, there was no significant reduction in plasma total or LDL cholesterol concentrations (Lovegrove et al., 2000).

Oat bran concentrate has been incorporated into bread products. The long-term effects of such products were tested in men with type 2 diabetes (Pick et al., 1996). Total plasma and LDL cholesterol concentrations were lower in the oat bran concentrate period (9 g/d of viscous fiber) than in the white bread period.

Attenuation of Blood Glucose Responses. In one study, individuals with type 2 diabetes were fed meals containing wheat farina, wheat farina with oat gum, or oat bran (Braaten et al., 1994a). Both the oat bran and wheat farina with oat gum meals reduced the postprandial rise in plasma glucose and insulin concentrations compared to the wheat farina meal without the oat gum. This is an example of the extracted form of oat bran (*Functional Fiber*) having a similar effect to the native form (*Dietary Fiber*). Oat gum has also been compared to guar gum with respect to glucose and insulin responses after an oral glucose load in healthy, fasting individuals (Braaten et al., 1991). In this study, the glucose and insulin responses to the oat and guar gum meals were nearly identical. In addition, both gum meals

resulted in increases in plasma glucose and insulin concentrations that were lower than glucose alone ($p < 0.01$). Hallfrisch and colleagues (1995) studied glucose responses in 16 women and 7 men with moderately high cholesterol concentrations who supplemented their normal diets with oat extracts in which either 1 or 10 percent viscous β-glucans were added. Glucose responses were reduced at both the 1 and 10 percent β-glucan supplementation level.

Pectin

Laxation. In a meta-analysis of approximately 100 studies on stool weight changes with various fiber sources, investigators were able to calculate the increase in fecal weight due to fiber ingestion (Cummings, 1993). This meta-analysis concluded that pectin ingestion leads to an increase of about 1.3 g of stool/g of pectin as compared to 5.4 g/g produced from wheat bran, suggesting that pectin is not an important fecal bulking agent (Cummings, 1993). In a randomized crossover study designed to compare the effects of pectin (12 g/d), cellulose (15 g/d), and lignin (12 g/d) on stool characteristics in healthy volunteers, pectin did not alter transit time or increase 24-hour stool wet weight, whereas cellulose decreased mean stool transit time and increased mean wet stool weight (Hillman et al., 1983).

Normalization of Blood Lipid Concentrations. Pectin has been tested in a number of studies for its hypocholesterolemic effect. For example, in a 16-week, double-blind crossover study, grapefruit pectin supplementation decreased plasma cholesterol concentration by 7.6 percent and LDL cholesterol concentration by 10.8 percent in individuals at moderate to high risk of coronary heart disease (Cerda et al., 1988). When 12 g/d of pectin was taken with meals for 3 weeks, there was a mean decrease in total serum cholesterol concentration of 0.48 ± 0.18 mmol/L (Durrington et al., 1976). This decrease was mainly due to a reduction in LDL cholesterol concentration. When 15 g/d of citrus pectin was provided in metabolically controlled diets for 3 weeks, plasma cholesterol concentrations were reduced by 13 percent and fecal fat excretion increased by 44 percent; however, plasma triacylglycerol concentrations did not change (Kay and Truswell, 1977). Gold and coworkers (1980) did not observe reductions in serum cholesterol concentrations following the consumption of 10 g of pectin with 100 g of glucose. The consumption of 7.2 g/d of psyllium that had been added to foods did not result in a significant decrease in LDL cholesterol concentration. However, total cholesterol and triacylglycerol concentrations were significantly decreased (Jenkins et al., 2002).

There is some documentation that the hypocholesterolemic effects of pectin are due to increased excretion of bile acids and cholesterol. Supplementation with 15 g of pectin increased bile acid excretion by 35 percent and net cholesterol excretion by 14 percent in ileostomy patients, whereas 16 g of wheat bran produced no significant changes (Bosaeus et al., 1986).

Attenuation of Blood Glucose Responses. Viscous fibers such as pectin have been found to produce a significant reduction in glycemic response in 33 of 50 studies (66 percent) (Wolever and Jenkins, 1993). This is in contrast to only 3 of 14 studies with insoluble fiber (21 percent).

Polydextrose

Laxation. Polydextrose has been shown to increase fecal mass and sometimes stool frequency. Tomlin and Read (1988) showed that 30 g/d of polydextrose increased fecal mass without affecting transit time and stool frequency. Achour and coworkers (1994) observed no significant changes in fecal weight or transit time when seven men consumed 30 g/d of polydextrose. When 4, 8, or 12 g/d of polydextrose was provided, fecal weight increased and ease and frequency of defecation improved in a dose–response manner (Jie et al., 2000).

Findings on the effect of polydextrose intake on fecal bacterial production are mixed. Achour and colleagues (1994) reported no changes in bacterial mass in the feces of individuals who consumed 30 g/d of polydextrose. This lack of difference may be explained, in part, by the findings of Jie and coworkers (2000). Following the ingestion of 4, 8, or 12 g/d of polydextrose (n = 30 treatment), there was a dose-dependent decrease in *Bacteriodes*, whereas the beneficial *Lactobacillus* and *Bifidobacteria* species increased.

Normalization of Blood Lipid Concentrations. Sixty-one healthy volunteers received 15 g/d of polydextrose for 2 months. Serum concentrations of total cholesterol, triacylglycerols, and LDL cholesterol did not change during this period; however, concentrations of HDL cholesterol decreased (Saku et al., 1991).

Psyllium

Laxation. Psyllium is the active ingredient in laxatives, and thus from an over-the-counter drug viewpoint, there is extensive literature on its efficacy in this regard. After 8 weeks of psyllium treatment to patients with

idiopathic constipation, both stool frequency and stool weight increased significantly, stool consistency improved, and pain on defecation was reduced (Ashraf et al., 1995). The authors concluded that the beneficial effects of psyllium with regard to constipation are largely related to a facilitation of the defecatory process (Ashraf et al., 1995). Similarly, psyllium was tested in a multisite study of 170 individuals with chronic idiopathic constipation for 2 weeks (McRorie et al., 1998). Psyllium increased stool water content, stool water weight, total stool output, bowel movement frequency, and a score combining objective measures of constipation. Four months of psyllium treatment significantly improved bowel function and fecal output in 12 elderly patients (Burton and Manninen, 1982). In a multicenter trial with 394 individuals, psyllium improved bowel function better than other laxatives (mainly lactulose), with superior stool consistency and decreased incidence of adverse events (Dettmar and Sykes, 1998). Prior and Whorwell (1987) tested psyllium (ispaghula husk) in 80 patients with irritable bowel syndrome and found that constipation was significantly improved and transit time decreased in patients taking psyllium.

Normalization of Blood Lipid Concentrations. A number of studies have been conducted to ascertain the beneficial effects of psyllium on blood lipid concentrations. Several of these studies provided 10.2 g/d of psyllium for up to 26 weeks and all showed marked reductions in serum total and LDL cholesterol concentrations compared to cellulose (Anderson et al., 1988, 1999, 2000b; Levin et al., 1990). The dose–response effect of psyllium at 0, 3.4, 6.8, or 10.2 g/d was tested in a double-blind controlled study in 286 adults with LDL cholesterol concentrations between 3.36 and 5.68 mmol/L (Davidson et al., 1998). The effects of 10.2 g/d of psyllium seed husk on serum LDL cholesterol concentrations were modest, with levels 5.3 percent below that of the control group at week 24 ($p < 0.05$).

In a 3-week intervention with 21 g/d of psyllium ($n = 7$), plasma total, LDL, and HDL cholesterol concentrations were significantly reduced (Abraham and Mehta, 1988). Psyllium decreased plasma concentrations of total cholesterol by 5.6 percent and LDL cholesterol by 8.6 percent; concentrations were unchanged in the cellulose group. Serum cholesterol concentration was reduced by 20 percent in 12 elderly patients receiving psyllium supplementation (Burton and Manninen, 1982). In a large, multicenter trial conducted in the United Kingdom, 7 or 10.5 g/d of psyllium was provided to 340 patients with mild to moderate hypercholesterolemia over 12 weeks (MacMahon and Carless, 1998). After 12 weeks, LDL cholesterol concentrations decreased by 8.7 percent for the 7-g/d group and 9.7 percent for the 10.5-g/d group. After a 6-month follow-up period, psyllium combined with diet modification was shown to reduce LDL cholesterol concentrations by 10.6 to 13.2 percent and total choles-

terol concentrations by 7.7 to 8.9 percent (MacMahon and Carless, 1998). Danielsson and coworkers (1979) treated 13 patients with essential hyperlipoproteinemia over 2 to 29 months with psyllium hydrophilic colloid. Serum cholesterol and triacylglycerol concentrations were reduced an average of 16.9 and 52.0 percent, respectively. If blood lipid concentrations were normal at baseline, no reductions were observed when individuals consumed psyllium colloid (Danielsson et al., 1979).

Studies also have been conducted using a ready-to-eat cereal enriched with psyllium. Hypercholesterolemic individuals consuming 114 g/d of a psyllium-flake cereal for 6 weeks showed significantly lower serum total and LDL cholesterol concentrations than those consuming the same amount of wheat-bran flake cereal (Anderson et al., 1992b). Similarly, Bell and coworkers (1990) tested the cholesterol-lowering effects of viscous fiber (psyllium or pectin) cereals as part of a diet in 58 men with mild to moderate hypercholesterolemia. During the cereal-plus-diet phase of the study, total and LDL cholesterol concentrations in the psyllium-enriched cereal group decreased by 5.9 and 5.7 percent, respectively.

A meta-analysis was conducted to determine the effect of consumption of psyllium-enriched cereal products on blood lipid concentrations in 404 adults with mild to moderate hypercholesterolemia consuming a low fat diet (Olson et al., 1997). Compared to the control cereals, individuals who consumed psyllium cereals had lower total and LDL cholesterol concentrations, whereas HDL cholesterol concentrations were not affected. Anderson and coworkers (2000a) conducted a meta-analysis of eight controlled trials to define the hypolipidemic effects of psyllium when used in combination with a low fat diet in hypercholesterolemic men and women. There were a total of 384 individuals receiving psyllium in the eight studies covered by the meta-analysis and these individuals were compared to those consuming cellulose ($n = 272$). Consumption of 10.2 g/d of psyllium ($n = 384$) lowered serum total cholesterol by 4 percent and serum LDL cholesterol by 7 percent, relative to the cellulose control ($n = 272$).

Everson and colleagues (1992) evaluated the mechanisms of the hypocholesterolemic effect of psyllium by measuring intestinal cholesterol absorption, cholesterol synthesis in isolated peripheral blood mononuclear cells, bile acid kinetics, gallbladder motility, and intestinal transit. The researchers concluded that psyllium decreases LDL cholesterol concentrations mainly by the stimulation of bile acid production.

Attenuation of Blood Glucose Responses. In an 8-week intervention study in 34 men with type 2 diabetes and hypercholesterolemia consuming either 10.2 g/d of psyllium or cellulose, daily and postlunch postprandial glucose concentration were 11.0 and 19.2 percent lower, respectively, in the psyllium group (Anderson et al., 1999). Also, psyllium has been shown to

reduce the glycemic index of foods when added to a meal (Frati-Munari et al., 1998). The effect of psyllium or placebo on postprandial serum glucose and insulin concentrations was tested in 18 type 2 diabetic patients in a crossover design (Pastors et al., 1991). Compared to placebo, postprandial glucose elevation was reduced by 14 percent at breakfast and 20 percent at dinner, and postprandial serum insulin concentration was reduced by 12 percent after breakfast. However, this depression of the normal postprandial increase in serum glucose and insulin concentrations seen with psyllium does not appear to be due to a delay in gastric emptying (Rigaud et al., 1998).

Resistant Dextrins

Laxation. There are no human studies to support a laxative benefit from ingestion of indigestible dextrins.

Normalization of Blood Lipid Concentrations. The intake of 60 g/d of resistant maltodextrin was shown to reduce serum total cholesterol and triacylglycerol concentrations in type 2 diabetics as compared with type 2 diabetics or healthy adults who consumed 30 g/d of resistant maltodextrin (Ohkuma and Wakabayashi, 2001). No difference was observed in the concentration of HDL cholesterol.

Attenuation of Blood Glucose Responses. Reduced blood glucose concentrations and insulin secretion were observed when rats were given resistant maltodextrins after sucrose or maltose loading (Wakabayashi et al., 1993, 1995). Furthermore, an intake of 5 g of resistant maltodextrin reduced the postprandial blood glucose concentrations in healthy men and women (Tokunaga and Matsuoka, 1999). The ingestion of 60 g/d, but not 30 g/d, of resistant maltodextrin resulted in a significant reduction of fasting blood glucose concentrations in type 2 diabetics (Ohkuma and Wakabayashi, 2001).

Resistant Starch

Laxation. Increased fecal bulk due to increased starch intake has been reported (Shetty and Kurpad, 1986). The impact of resistant starch (RS_3) from a corn-based cereal on colonic function was measured in eight male volunteers (Tomlin and Read, 1990). After consuming 10.33 g/d of RS_3 for 1 week, there was no significant difference in fecal output, stool frequency, ease of defecation, whole-gut transit time, or degree of flatulence compared to an intake of 0.86 g/d of RS_3 from a rice-based cereal. A

significant increase in stool weight, however, was observed when men consumed 32 g/d RS_3 for 4 weeks (Heijnen et al., 1998). Jenkins and coworkers (1998) determined the effects of low fiber (control), wheat bran supplements providing an additional 30 g of fiber (high fiber control), or the equivalent amount of resistant starch as RS_2 or RS_3. Compared to the low fiber control, the wheat bran supplement increased fecal bulk by 96 ± 14 g/d ($p < 0.001$) and the mean for both resistant starches was 22 ± 8 g/d greater than controls ($p = 0.013$). This is consistent with the small increase in fecal bulk seen with resistant starch intake in other studies (Behall and Howe, 1996; Cummings et al., 1996; Heijnen et al., 1998; Hylla et al., 1998; Phillips et al., 1995).

Because resistant starch is partly fermented in the colon, intake may lead to increased production of short-chain fatty acids. When 39 g/d of a mixture of naturally occurring and processed resistant starch was consumed, there was a significant increase in fecal butyrate and acetate concentrations, and therefore a significant reduction in fecal pH (Phillips et al., 1995). However, when glucose or 32 g/d of RS_3 was consumed for 4 weeks, there was no difference in fecal pH, fecal short-chain fatty acid concentrations, or fecal secondary bile acid concentrations (Heijnen et al., 1998).

Normalization of Blood Lipid Concentrations. Several animal studies have demonstrated a lowering of blood cholesterol and triacylglycerol concentrations with resistant starch intake (de Deckere et al., 1993; Ranhotra et al., 1997; Younes et al., 1995). When healthy, normolipidemic individuals were given glucose or 30 g/d of RS_3 supplements for 3 weeks, there were no significant differences in fasting serum total, LDL, and HDL cholesterol concentrations or triacylglycerol concentrations (Heijnen et al., 1996). Resistant starch does not appear to provide the cholesterol-lowering effects of viscous fiber, but rather acts more like nonviscous fiber (Jenkins et al., 1998). Neither Jenkins and coworkers (1998) nor Heijnen and coworkers (1996) showed a lowering effect of resistant starch on serum lipids.

Attenuation of Blood Glucose Responses. Adding resistant starch to bread at various levels (0, 5, 10, and 20 percent) was shown to reduce the glycemic index in a dose-dependent manner (100, 96, 74, and 53) (Brown et al., 1995). The consumption of 30 g/d of RS_3 was shown to significantly reduce the urinary excretion of C-peptide, indicating reduced insulin secretion (de Roos et al., 1995).

Clinical Effects of Inadequate Intake

Dietary and *Functional Fibers* are not essential nutrients, so inadequate intakes do not result in biochemical or clinical symptoms of a deficiency. A

lack of these fibers in the diet, however, can result in inadequate fecal bulk and may detract from optimal health in a variety of different ways depending on other factors, such as the rest of the diet and the stage of the life cycle.

EVIDENCE CONSIDERED FOR ESTIMATING THE REQUIREMENT FOR *DIETARY FIBER* AND *FUNCTIONAL FIBER*

There is no biochemical assay that reflects *Dietary Fiber* or *Functional Fiber* nutritional status. Clearly one cannot measure blood fiber concentration since, by definition, fiber is not absorbed. Instead, the potential health benefits of fiber consumption, which may be compromised by a lack of fiber in the diet, have been reviewed. Throughout each section and the discussion of each indicator, a delineation is made between *Dietary Fiber* and *Functional Fiber*. It should be kept in mind that although high *Dietary Fiber* intake is associated with decreased risk or improvements in several chronic diseases, a report of the National Academy of Sciences states "there is no conclusive evidence that it is dietary fiber rather than the other components of vegetables, fruits, and cereal products that reduces the risk of those diseases" (NRC, 1989). The definition of *Dietary Fiber* in this report states that it must be "intrinsic and intact in plants." Thus, the reported benefits are due to the fiber *source*, not necessarily to the fiber per se. In contrast, *Functional Fiber* (which consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans), by definition, must show that the beneficial physiological effect in humans is due to the isolated or synthesized fiber itself.

A number of epidemiological studies have been conducted to evaluate the relationship between fiber intake and risk of chronic disease. While *Functional Fibers*, such as pectins and gums, are added to foods as ingredients, these levels are minimal and therefore fiber intakes that are estimated from food composition tables generally represent *Dietary Fiber*.

Dietary Fiber, Functional Fiber, *and the Prevention of Hyperlipidemia, Hypertension, and Coronary Heart Disease*

Epidemiological Studies

There are no epidemiological studies that have evaluated the relationship between *Functional Fiber* and the risk of coronary heart disease (CHD). A number of epidemiological studies, however, have found reduced CHD rates in individuals consuming high amounts of *Dietary Fiber* and fiber-rich foods (Bolton-Smith et al., 1992; Fraser et al., 1992; Humble et al., 1993; Jacobs et al., 1998; Khaw and Barrett-Connor, 1987; Kushi et al., 1985;

Morris et al., 1977; Pietinen et al., 1996; Rimm et al., 1996; Todd et al., 1999; Wolk et al., 1999). For example, Fraser and colleagues (1992) reported that in a cohort of 31,208 California Seventh-day Adventists, there was a 44 percent reduced risk of nonfatal CHD and an 11 percent reduced risk of fatal CHD for those who ate whole wheat bread compared with those who ate white bread. In the Iowa Women's Health Study, Jacobs and coworkers (1998) found that the risk of CHD death was reduced by approximately one-third for women consuming one or more servings of a whole grain product each day compared with those rarely eating any whole grain products. Similarly, Morris and coworkers (1977) followed 337 men in London, England for 10 to 20 years and found that men with a high intake of cereal fiber had a lower rate of CHD than men with a low cereal fiber intake.

In the Health Professionals Follow-up Study, the relative risk for fatal coronary disease and total myocardial infarction were 0.45 and 0.59, respectively, for men in the highest quintile of *Dietary Fiber* intake (28.9 g/d) compared with the lowest quintile (12.4 g/d) (Rimm et al., 1996) (Table 7-2). Cereal fiber was more strongly associated with the reduced risk of CHD than were fiber from fruits and vegetables. Wolk and coworkers (1999) examined the relationship between intake of *Dietary Fiber* and risk of CHD in the Nurses' Health Study and found a significant inverse association, which was confined to *Dietary Fiber* from cereal sources (Table 7-2). Compared with the lowest quintile of cereal fiber intake (2.2 g/d), women in the highest quintile (7.7 g/d) had a 34 percent lower risk of total CHD. In a large cohort of 21,930 Finnish men, there was a significant inverse association between *Dietary Fiber* intake and CHD, with a multivariate relative risk of 0.84 for men in the highest quintile of intake (34.8 g/d) compared with the lowest quintile of intake (16.1 g/d) (Pietinen et al., 1996) (Table 7-2).

In summary, the large-scale, adequately powered, prospective studies all show a substantial protective effect of *Dietary Fiber* for CHD. Specifically, these three studies—which used multivariate models to control for energy, saturated fat, alcohol, body mass index, and various vitamins—showed a strong relationship between cereal fibers and a weak or no relationship between vegetable and fruit fibers. In terms of setting intake recommendations and actual numbers as a primary determinant of fiber requirements, these studies are most useful as they are adequately powered, divide *Dietary Fiber* into quintiles of intake, and provide data on energy intake (Pietinen et al., 1996; Rimm et al., 1996; Wolk et al., 1999). Using these studies, it is also possible to relate the number of grams of *Dietary Fiber* per day to the decrease in CHD incidence.

Although not reporting quintiles of intake, a fourth study by Khaw and Barrett-Connor (1987) can be considered because it showed that an

TABLE 7-2 Prospective Cohort Studies on *Dietary Fiber* Intake and Risk of Coronary Heart Disease (CHD)

Reference	Study Design	Quintile	Relative Risk for CHD
Pietinen et al., 1996	21,930 Finnish men, 50–69 y 6-y follow-up	1	1.00
		2	0.91
		3	0.88
		4	0.86
		5	0.84
			p for trend = 0.03
Rimm et al., 1996	43,757 U.S. men, 40–75 y 6-y follow-up	1	1.00
		2	0.97
		3	0.91
		4	0.87
		5	0.59
			p for trend < 0.001
Wolk et al., 1999	68,782 U.S. women, 37–64 y 10-y follow-up	1	1.00
		2	0.98
		3	0.92
		4	0.87
		5	0.77
			p for trend = 0.07

[a] *Dietary Fiber* intake is energy-adjusted to 2,000 kcals.
[b] *Dietary Fiber* intake is energy-adjusted to 1,600 kcals.

increased intake of 6 g/d of *Dietary Fiber* was associated with a 33 percent risk reduction for CHD in women and 24 percent in men, and the reduction in CHD mortality was independent of other dietary variables. The Health Professionals Follow-up Study reported a 19 percent decrease in risk for total myocardial infarction per 10-g/d increase of *Dietary Fiber* and a 29 percent decrease per 10-g/d increase of cereal fiber (Rimm et al., 1996). A similar result for women was reported by Wolk and coworkers (1999) with a 19 percent decrease in risk for total CHD events per 10-g/d increase of *Dietary Fiber*, but a stronger relationship was reported for cereal fiber (37 percent decrease per 5-g/d increase).

Dietary Fiber Intake (g/d)	Energy Intake (kcal/d)	Grams of *Dietary Fiber*/ 1,000 kcal
16.1	2,722	5.9
20.7	2,787	7.4
24.3	2,781	8.7
28.3	2,754	10.3
34.8	2,705	12.9
12.4	2,000[a]	6.2
16.6	2,000	8.3
19.6	2,000	9.8
23.0	2,000	11.5
28.9	2,000	14.45
11.5	1,600[b]	7.2
14.3	1,600	8.9
16.4	1,600	10.25
18.8	1,600	11.75
22.9	1,600	14.31

Intervention Trials

There have been a large number of intervention trials to ascertain whether fiber supplementation can alter blood lipid concentrations and therefore alter the risk of CHD. These trials are briefly summarized below. All but one are small trials; often these interventions are performed in people with high initial serum cholesterol concentrations. The strongest data are for oat products and beans (*Dietary Fiber*). In addition, viscous *Functional Fibers* such as guar, pectin, and psyllium, have been tested in intervention trials and found to decrease serum total and low density lipoprotein (LDL) cholesterol concentration in most studies. For example,

Anderson and coworkers (1984b) compared the effects of oat bran or bean supplementation on 20 hypercholesterolemic adult males, providing approximately 47 g/d of plant *Dietary Fiber* and 17 g/d of viscous *Dietary Fiber*. Both the oat bran and bean diets significantly decreased serum total cholesterol concentrations by 19 percent. In a similar metabolic ward study of 10 hypercholesterolemic men, oat bran and bean diets decreased both serum total and LDL cholesterol concentrations by 23 percent after 3 weeks on the test diets (Anderson et al., 1984a). A review of the oat bran and bean fiber intervention trials where *Dietary Fiber* supplementation was combined with a low fat diet shows that reductions in serum total cholesterol concentrations ranged from 8 to 26 percent (Anderson and Gustafson, 1988; Anderson et al., 1984a, 1984b; Judd and Truswell, 1981; Kirby et al., 1981). Smaller portions of oat bran or oat meal (60 g, dry measure) have been shown to decrease serum total cholesterol concentrations by approximately 8 to 11 percent (Bartram et al., 1992; Van Horn et al., 1986).

Other viscous fibers, in addition to those from oats and beans, have also been shown to decrease serum cholesterol concentrations. For example, Jenkins and coworkers (1975) reported the hypocholesterolemic effect of guar gum (*Functional Fiber*), which is often added to foods. Since that time, there have been a number of studies with guar gum supplementation that resulted in a reduction in serum cholesterol concentrations of between 11 and 15 percent (Anderson and Tietyen-Clark, 1986). In a 3-week intervention that provided 21 g/d of psyllium, total, LDL, and high density lipoprotein cholesterol concentrations were all significantly reduced (Abraham and Mehta, 1988). A meta-analysis testing the effects of pectin, oat bran, guar gum, and psyllium on blood lipid concentrations showed that 2 to 10 g/d of viscous fiber were associated with small but significant decreases in total and LDL cholesterol concentrations (Brown et al., 1999). The different viscous fibers reduced serum total and LDL cholesterol concentrations by similar amounts. Resistant starch does not appear to provide the cholesterol-lowering effects of viscous fibers, but rather acts more like nonviscous fibers (Jenkins et al., 1998). Neither Heijnen and coworkers (1996) nor Jenkins and coworkers (1998) showed a lipid-lowering effect of resistant starch on serum lipid concentrations.

It should also be noted that the effect of fiber on decreasing serum cholesterol concentration is not due to its replacement of fat in the diet. In a prospective, randomized, controlled trial with a low fat and a low fat plus high *Dietary Fiber* groups, the group consuming high *Dietary Fiber* exhibited a greater average reduction (13 percent) in serum total cholesterol concentration than the low fat (9 percent) and the usual diet (7 percent) groups (Anderson et al., 1992a). Mathur and coworkers (1968) conducted a study in 20 men supplemented with Bengal gram. Serum

total cholesterol concentrations averaged 23 percent lower on the high fat, Bengal gram diet than on the high fat diet alone.

Not all fibers decrease serum cholesterol concentration. For example, Anderson and coworkers (1991) randomly allocated 20 hypercholesterolemic men to either a wheat bran or oat bran diet. After 21 days, oat bran significantly decreased serum total cholesterol concentration by 12.8 percent; however, there was no effect with wheat bran. Behall (1990) compared a low fiber diet with a diet containing an average of 19.5 g/d of added cellulose (a nonviscous fiber) or the viscous fibers carboxymethylcellulose gum, karaya gum, or locust bean gum. The diets containing the viscous fibers led to significantly lower plasma cholesterol concentrations. Although these relatively small-scale intervention trials using viscous *Functional Fibers* have reported substantial cholesterol-lowering effects and therefore should be protective against CHD, no protective effect against CHD was seen in a large-scale clinical trial with individuals who had a previous myocardial infarction (Burr et al., 1989). These individuals were encouraged to increase grain fiber intake by increasing consumption of whole meal bread, high fiber breakfast cereals, and wheat bran, which resulted in an increased grain fiber intake from 9 to 17 g/d in the intervention group. Wheat bran and other poorly fermented fibers (e.g., cellulose) have also failed to decrease serum lipids in animal studies. Increasing the intake of *Dietary Fiber* by increasing the consumption of fruits and vegetables can attenuate plasma triacylglycerol concentrations. Obarzanek and coworkers (2001) showed that increasing *Dietary Fiber* intake from 11 to 30 g/d as a result of increased consumption of fruits, vegetables, and whole grains prevented a rise in plasma triacylglycerol concentrations in those fed a low fat diet, especially in those individuals with initially high concentrations. Plasma triacylglycerol concentrations were significantly reduced (Chandalia et al., 2000) or unchanged (Lichtenstein et al., 2002) by increasing *Dietary Fiber* intake when consuming a low fat diet. These studies suggest that *Dietary Fiber* prevents the rise in plasma triacylglycerol concentrations that occurs when consuming a low fat, high carbohydrate diet (see Chapter 11).

Summary of the Intervention Trials

Viscous *Functional Fibers* and foods sources of viscous *Dietary Fiber* reduce both total and LDL cholesterol concentrations, and may also reduce serum triglycerides. The amount of cholesterol reduction appears to be related to the amount of fiber consumed, although only a few studies report dose–response data. A meta-analysis of 20 trials that used high doses of oat bran, which is rich in viscous *Dietary Fiber*, showed that the reductions in serum cholesterol concentrations ranged from 0.1 to 2.5 percent/g of intake (Ripsin et al., 1992). If one accepts the proposed 2 percent risk reduction

for CHD for every 1 percent reduction in serum cholesterol (Lipid Research Clinics Program, 1984), these results suggest substantial benefits from consumption of high amounts of viscous *Dietary* and *Functional Fibers* and support the epidemiological findings regarding fiber and CHD. It is of interest to compare the hypothetical risk reduction for CHD per gram of oat bran consumed (in the clinical intervention trials) to that for total dietary fiber intake in the epidemiological studies. For example, in the oat bran meta-analysis, using a 1.2 percent reduction in serum cholesterol per gram of oat bran (the midpoint of the range of 0.1 to 2.5 percent) and multiplying by 2 (proposed 2 percent reduction for risk of CHD for every 1 percent reduction in serum cholesterol) would suggest a reduced risk of CHD of 2.4 percent/g of oat bran consumed. This can then be compared with the data on total fiber consumption and risk for CHD in the three primary epidemiological studies shown in Table 7-2.

In the Health Professionals Follow-Up Study (Rimm et al., 1996), there is a difference of 16.5 g of fiber intake between the highest and lowest intake groups (28.9–12.4), and a reported relative risk of 0.45 for fatal coronary disease and 0.59 for total myocardial infarction for men in the highest compared to the lowest quintile for fiber intake. This equates to a risk reduction of 3.3 percent/g of fiber for fatal coronary disease and 2.5 percent/g of fiber for total myocardial infarction. In the Nurses' Health Study (Wolk et al., 1999) there is a difference of 11.4 g of fiber between the highest and lowest intake groups (22.9–11.5) and a relative risk of 0.77 for total CHD. This equates to a risk reduction of 2.02 percent/g of fiber. Finally, in a study of Finnish men (Pietinen et al., 1996), there is a difference of 18.7 g of fiber between the highest and lowest intake groups (34.8–16.1) and a relative risk of 0.68 for coronary death. This equates to a risk reduction of 1.71 percent/g of fiber.

Although the calculations above are hypothetical and are based on a number of assumptions, (including the linearity of response of fiber consumption to risk reduction), the finding that the degree of risk reductions per gram of fiber consumed are within a reasonable range of each other are suggestive that the results of the clinical trials for viscous fibers are supportive of the epidemiological finding. It is also clear that the effect of viscous fibers on decreasing blood cholesterol concentrations cannot explain the multitude of studies cited above that generally show *Dietary Fiber* to be protective against CHD, even though a mixed fiber diet is only approximately one-third viscous fiber. This suggests that mechanisms in addition to cholesterol-lowering may be involved.

Mechanisms by Which Dietary Fibers May Protect Against CHD

While not explicit, several hypotheses exist to explain the mechanisms by which *Dietary Fiber* may protect against CHD. The lowering of serum cholesterol concentration by viscous *Dietary* or *Functional Fibers* is thought to involve changes in cholesterol or bile acid absorption, hepatic production of lipoproteins, or peripheral clearance of lipoproteins (Chen and Anderson, 1986). Viscous fibers may interfere with the absorption and enterohepatic recirculation of bile acids and cholesterol in the intestine, forcing the liver to synthesize more cholesterol to meet the need for bile acid synthesis, and thus decreasing circulating cholesterol. This cannot be the sole explanation, however, since not all viscous fibers increase fecal bile acid excretion, and the magnitude of the increase, when present, is often small. In addition to delaying or interfering with the absorption of cholesterol and bile acids, viscous fibers may delay the absorption of macronutrients, including fat and carbohydrate. Delayed carbohydrate absorption, in turn, could lead to increased insulin sensitivity (Hallfrisch et al., 1995) and decreased triacylglycerol concentrations (Rivellese et al., 1980), also considered risk factors for CHD. Ascherio and coworkers (1992) have shown a strong inverse association between *Dietary Fiber* intake and risk of hypertension in men, with hypertension being an important risk factor for CHD.

Diets high in *Dietary Fiber* also may favorably affect plasminogen activator inhibitor type 1 and factor VII activity (Djoussé et al., 1998; Mennen et al., 1997; Sundell and Ranby, 1993). In addition, a large number of studies (described above) show whole-grain cereal products as being protective against CHD. Whole grain cereals are also sources of phytochemicals, such as phytate and phytoestrogens, which may independently impact CHD.

Summary

On the basis of the evidence provided on fiber intake and CHD, certain sources of *Dietary Fiber* (cereal foods) and certain *Functional Fibers* (viscous) are associated with reduced risk of CHD. In prospective population studies, there is a strong relationship between *Total Fiber* intake from foods and CHD. Therefore, a recommended intake level can be set for *Total Fiber* based on prevention of CHD and recognizing that the greatest benefit comes from the ingestion of cereal fibers and viscous *Functional Fibers*, including gums and pectins. Further discussion is provided in the later section, "Findings by Life Stage and Gender Group."

Fiber Intake and Gastrointestinal Health

Fiber Intake and Duodenal Ulcer

In a prospective cohort of 47,806 men with 138 newly diagnosed cases of duodenal ulcer, *Dietary Fibers*, and particularly the viscous fibers, were strongly associated with a decreased risk of duodenal ulcer (relative risk of 0.40 for the highest quintile of viscous fiber intake) (Aldoori et al., 1997). In this study, fiber from fruit, vegetable, and leguminous sources, but not cereal fiber, was associated with a reduced risk of duodenal ulcer. Although the mechanism behind this proposed positive effect of viscous fibers on duodenal ulcer is not known, one hypothesis is that the delay in gastric emptying, known to result from the ingestion of viscous fibers, may play a role.

Dietary Fiber, Functional Fiber, and Colon Health

Constipation, Laxation, and the Contribution of Fiber to Fecal Weight. Consumption of certain *Dietary* and *Functional Fibers* is known to improve laxation and ameliorate constipation (Burkitt et al., 1972; Cummings et al., 1978; Kelsay et al., 1978; Lupton et al., 1993). In most reports there is a strong positive correlation between intake of *Dietary Fiber* and daily fecal weight (Birkett et al., 1997). Also, *Dietary Fiber* intake is usually negatively correlated with transit time (Birkett et al., 1997). Although what constitutes "constipation" is variously defined, diets that increase the number of bowel movements per day, improve the ease with which a stool is passed, or increase fecal bulk are considered to be of benefit. For example, in a weight-loss study, obese individuals were put on a very low energy diet with or without 30 g/d of isolated plant fiber (Astrup et al., 1990). Those receiving the fiber supplement had a higher number of bowel movements per day (1.0) compared to those not receiving the fiber supplement (0.7/d). Not all reports, however, support the concept that fiber serves as a laxative (Cameron et al., 1996; Kochen et al., 1985). Because water is also important for laxation, some have suggested that increasing fiber intake alone is not sufficient, and that more water should be consumed as well (Anti et al., 1998). Determining a stool weight that might promote laxation and ameliorate constipation is very difficult. In one study, although fecal weight ranged from 41 to 340 g and transit time ranged from 22 to 123 hours, no subject reported suffering either constipation or diarrhea (Birkett et al., 1997). At the same time, a number of studies have shown that low fiber intake is associated with constipation. For example, Morais and coworkers (1999) reported that children with chronic constipation had lower *Dietary*

Fiber intake than the control group. The authors concluded that a low intake of fiber is a risk factor for chronic constipation in children.

In a meta-analysis of about 100 studies of stool-weight changes with various fiber sources, investigators were able to calculate the increase in fecal weight due to *Dietary* or *Functional Fiber* ingestion (Cummings, 1993). Such calculations yielded the following increases in fecal weight: 5.4 g of stool/g of wheat-bran fiber, 4.9 g/g of fruits and vegetables, 3 g/g of isolated cellulose, and 1.3 g/g of isolated pectin (Cummings, 1993). The contribution of resistant starch to fecal bulk has also been assessed. For example, Jenkins and colleagues (1998) determined the bulking effects of wheat bran supplements (30 g) or the equivalent amount as resistant starch (RS_2 or RS_3). Compared to the low fiber control, the wheat bran supplement increased fecal bulk by 96 ± 14 g/d ($p < 0.001$) and the mean for both resistant starches was 22 ± 8 g/d greater ($p = 0.013$). This is consistent with the small increase in fecal bulk seen with resistant starch intake in other studies (Behall and Howe, 1996; Cummings et al., 1996; Heijnen et al., 1998; Hylla et al., 1998; Phillips et al., 1995). Additional discussion of the effects of *Functional Fibers*, such as psyllium, is included in the earlier section, "Physiological Effects of Isolated and Synthetic Fibers."

Fiber Fermentation Products as an Energy Source for the Colon. Butyrate is the primary energy source for the colonocyte (Roediger, 1982). One study showed high acetate and low butyrate ratios of short-chain fatty acids in patients with adenomatous polyps and colon cancer (Weaver et al., 1988). Increased fecal butyrate outputs have been demonstrated using both whole food and commercial sources of resistant starch in some studies (Jenkins et al., 1998; Macfarlane and Englyst, 1986; Phillips et al., 1995; Silvester et al., 1995), but not in others (Heijnen et al., 1998; Hylla et al., 1998). It has been proposed that colonic diseases, including ulcerative colitis, are disorders of energy utilization (Roediger, 1980), although this remains an unresolved issue.

Fiber and the Prevention of Diverticular Disease. Diverticular disease is characterized by saccular herniations of the colonic wall and is highly prevalent in elderly populations in Western societies (Watters and Smith, 1990). Although usually asymptomatic, when diverticula become inflamed, the condition is known as diverticulitis. Current estimates for the North American population indicate that one-third of those older than 45 years and two-thirds of those older than 85 years have diverticular disease (Roberts and Veidenheimer, 1990).

Several types of studies have shown a relationship between fiber intake and diverticular disease. In the prospective Health Professionals Follow-Up Study, there was a strong negative association between *Dietary Fiber*

intake and the incidence of symptomatic diverticular disease (Aldoori et al., 1994, 1995), which persisted after adjustment for several other risk factors. The data showed that the inverse relationship was particularly strong for the nonviscous *Dietary Fiber*, particularly cellulose (Aldoori et al., 1998). Case-control studies have consistently found that patients with diverticula consumed less *Dietary Fiber* than did nonpatients. For example, Gear and coworkers (1979) reported on the prevalence of symptomless diverticular disease in vegetarians and nonvegetarians in England. Twelve percent of the vegetarians had diverticular disease compared with 33 percent of the nonvegetarians. In addition, the vegetarians had a mean daily *Dietary Fiber* intake of 41.5 g/d in comparison to 21.4 g/d for the nonvegetarians. Similarly, Manousos and coworkers (1985) reported a lower prevalence of diverticular disease in rural Greece compared with that found in urban areas. In addition, those individuals with diverticular disease consumed fewer vegetables, brown bread, potatoes, and fruit. In an intervention trial, Findlay and coworkers (1974) showed a protective effect of unprocessed bran. In another study, Brodribb (1977) treated 18 patients with diverticular disease by providing either a high fiber, bran-containing bread (6.7 g) or ordinary wheat bread (0.6 g). Relief of symptoms was significantly greater in the high fiber group compared with the low fiber control group.

Although the mechanism by which fiber may be protective against diverticular disease is unknown, several hypotheses have been proposed. For example, some scientists report that it is due to decreased transit time, increased stool weight, and decreased intracolonic pressure with fiber supplementation (Cummings, 2000).

Summary and Conclusions. The majority of the studies cited above show a relationship between *Dietary Fiber* and gastrointestinal health. There are data that show the benefits of certain *Dietary* and *Functional Fibers* on gastrointestinal health, including the effect of fiber on duodenal ulcers, constipation, laxation, fecal weight, energy source for the colon, and prevention of diverticular disease. For duodenal ulcer and diverticular disease, the data are promising for a protective effect, but insufficient data exist at this time upon which to base a recommended intake level. It is clear that fiber fermentation products provide energy for colonocytes and other cells of the body, but again this is not sufficient to use as a basis for a recommendation for fiber intake. With regard to the known fecal bulking and laxative effects of certain fibers, these are very well documented in numerous studies. A recommended intake level for *Total Fiber* based on prevention of CHD should be sufficient to reduce constipation in most normal people given adequacy of hydration of the large bowel.

Dietary Fiber *and the Prevention of Colon Cancer*

Marked international differences in rates of colon cancer (Boyle et al., 1985), coupled with findings from migratory studies showing that individuals take on the cancer demographics of the population to which they move (Haenszel and Kurihara, 1968), have suggested a strong role for environmental factors in colon cancer incidence.

Epidemiological Studies

Thun and coworkers (1992) found a significant inverse relation between the intake of citrus fruits, vegetables, and high fiber grains and colon cancer, although *Dietary Fiber* intake was not specifically analyzed. Fuchs and colleagues (1999) prospectively examined the relationship between *Dietary Fiber* intake and the risk of colon cancer in a large cohort of women. The same study group found a minimal nonsignificant inverse association in an earlier report that was based on 150 cases of colon cancer reported during 6 years of follow-up (Willett et al., 1990). In addition, the follow-up study revealed no relationship (Fuchs et al., 1999). Likewise, in six large, prospective studies, inverse associations between *Dietary Fiber* intake and the risk of colon cancer were weak or nonexistent (Giovannucci et al., 1994; Heilbrun et al., 1989; Kato et al., 1997; Key et al., 1996; Pietinen et al., 1999; Steinmetz et al., 1994).

Inverse relationships have been reported between *Dietary Fiber* intake and risk of colon cancer in some case-control studies (Bidoli et al., 1992; Dales et al., 1979; Freudenheim et al., 1990; Gerhardsson de Verdier et al., 1990; Iscovich et al., 1992; Lyon et al., 1987; Modan et al., 1975; Tuyns et al., 1987; West et al., 1989), but not all (Berta et al., 1985; Jain et al., 1980; Macquart-Moulin et al., 1986). A critical review of 37 observational epidemiological studies and a meta-analysis of 23 case-control studies showed that the majority suggest that *Dietary Fiber* is protective against colon cancer, with an odds ratio of 0.57 for the highest fiber group compared with the lowest (Trock et al., 1990). Furthermore, a meta-analysis of case-control studies demonstrated a combined relative risk of 0.53 for colon cancer in the highest as compared with the lowest quintile of fiber intake (Howe et al., 1992).

Lanza (1990) reviewed 48 epidemiological studies on the relationship between diets containing *Total Fiber* and colon cancer and found that 38 reported an inverse relationship, 7 reported no association, and 3 reported a direct association. In the Netherlands, *Dietary Fiber* intake was reported to be inversely related to total cancer deaths, as the 10-year cancer death rate was approximately threefold higher in individuals with low fiber intake compared with high fiber intake (Kromhout et al., 1982). Despite these

and other positive findings, a number of important studies (Fuchs et al., 1999; Giovannucci and Willett, 1994) and three recent clinical intervention trials (Alberts et al., 2000; Bonithon-Kopp et al., 2000; Schatzkin et al., 2000) do not support a protective effect of *Dietary Fiber* intake against colon cancer. This issue remains to be resolved.

Intervention Studies

There have been a number of small clinical interventions addressing various surrogate markers for colon cancer, primarily changes in rectal cell proliferation and polyp recurrence. Generally, the small intervention trials have shown either no effect of fiber on the marker of choice or a very small effect. For example, Alberts and coworkers (1990) supplemented individuals with 13.5 g/d of wheat-bran fiber (*Dietary Fiber*) for 8 weeks and analyzed rectal mucosa cell biopsies for changes in cell proliferation. There was no overall decrease in rectal cell proliferation as a result of fiber supplementation unless the groups were divided into those with initially high and those with initially normal labeling indices. With this statistical division, there was a significant decrease in cell proliferation as a result of the fiber supplementation in six of the eight patients with initially high labeling indices and three of the eight patients with initially low indices, which suggests that wheat-bran fiber is protective against colon cancer. In a separate trial from the same group, supplemental dietary wheat-bran fiber (2.0 or 13.5 g/d) was provided to participants with a history of colon adenoma resection (Alberts et al., 1997). Wheat-bran fiber did not reduce the labeling index at either 3 or 9 months. Additionally, two randomized, placebo-controlled trials found no significant reduction in the incidence of colon tumor indicators among subjects who supplemented their diet with wheat bran or consumed high fiber diets (MacLennan et al., 1995; McKeown-Eyssen et al., 1994).

Recently, findings from three major trials on fiber and colonic polyp recurrence were reported (Alberts et al., 2000; Bonithon-Kopp et al., 2000; Schatzkin et al., 2000). All were well-designed, well-executed trials in individuals who previously had polyps removed. The Polyp Prevention Trial, which incorporated eight clinical centers, included an intervention that consisted of a diet that was low in fat, high in fiber, and high in fruits and vegetables (*Dietary Fiber*) (Schatzkin et al., 2000). There was no difference in polyp recurrence between the intervention and control groups. The Arizona Wheat-bran Fiber Trial provided 13.5 g/d versus 2 g/d of wheat-bran fiber (*Dietary Fiber*) (Alberts et al., 2000). Again, there was no difference between the control group and the intervention group in terms of polyp recurrence. The third trial used 3.5 g/d of psyllium (ispaghula husk) as the intervention (a potential *Functional Fiber*) (Bonithon-Kopp et al.,

2000). The adjusted odds ratio for the psyllium fiber intervention on polyp recurrence was 1.67 ($p = 0.042$).

Potential Mechanisms

Many hypotheses have been proposed as to how fiber might protect against colon cancer development; these hypotheses have been tested primarily in animal models. The hypotheses include the dilution of carcinogens, procarcinogens, and tumor promoters in a bulky stool; a more rapid rate of transit through the colon with high fiber diets; a reduction in the ratio of secondary bile acids to primary bile acids by acidifying colonic contents; the production of butyrate from the fermentation of dietary fiber by the colonic microflora; and the reduction of ammonia, which is known to be toxic to cells (Harris and Ferguson, 1993; Jacobs, 1986; Klurfeld, 1992; Van Munster and Nagengast, 1993; Visek, 1978). Unfortunately, most of the epidemiological and even the clinical intervention trials did not measure functional aspects of potential mechanisms by which fiber may be protective, and they did not attempt to relate aspects of colon physiology such as fecal weight or transit time to a protective effect against tumor development. Cummings and colleagues (1992) suggest that a daily fecal weight greater than 150 g is protective against colon cancer. In a study by Birkett and coworkers (1997), it was necessary to achieve a stool weight of 150 g to improve fecal markers for colon cancer, including fecal bulk, primary to secondary bile acid ratios, fecal pH, ammonia, and transit time. *Dietary Fiber* intake was 18 ± 8 g in the less than 150-g fecal-weight group and 28 ± 9 g in the greater than 150-g group ($p < 0.01$).

Dietary Fiber Intake and Colonic Adenomas

People with colonic adenomas are at elevated risk of developing colon cancer (Lev, 1990). Several epidemiological studies have reported that high *Dietary Fiber* and low fat intakes are associated with a lower incidence of colonic adenomas (Giovannucci et al., 1992; Hoff et al., 1986; Little et al., 1993; Macquart-Moulin et al., 1987; Neugut et al., 1993). For example, Giovannucci and coworkers (1992) studied a population of 7,284 men from the Health Professionals Follow-up Study and found a significant negative relationship between *Dietary Fiber* intake and colonic adenomas. The inverse relationship with *Dietary Fiber* persisted when they adjusted for other nutrients commonly found in fruits and vegetables. The overall median dietary intake of *Dietary Fiber* in this population was 21 g/d, with a median intake of 13 g/d for the lowest quintile and 34 g/d for the highest quintile. A reanalysis of 16,448 men from the Health Professionals Follow-Up Study that controlled for folate intake did not find a significant associa-

tion between intake of *Dietary Fiber* and colon adenomas, although a slight reduction in risk was observed with increasing intake of fruit fiber (Platz et al., 1997).

Possible Reasons for the Lack of a Protective Effect of Dietary Fiber in Some Trials

There is considerable debate and speculation as to why clinical intervention trials on the relationship between fiber intake and colon cancer have not shown the expected beneficial effect of fiber. Some of the possible reasons for these results are discussed below.

Timing of the Intervention. Some of the recent prospective studies, such as the Nurses' Health Study (Fuchs et al., 1999) and the Health Professionals Follow-Up Study (Giovannucci et al., 1994), have failed to show a protective effect of *Dietary Fiber* intake against colon cancer when early indications from these same cohorts suggested that they would. As noted above, the Health Professionals Follow-up Study showed a protective effect of *Dietary Fiber* from the diet against colonic adenomas (Giovannucci et al., 1992). However, when the same cohort was later investigated for the relationship between intake of *Dietary Fiber* and colon carcinoma, no relationship was found (Giovannucci et al., 1994). A partial explanation for the difference is due to differences in ways that the data were analyzed based on information that was known at the time of analysis.

A similar situation was found in the Nurses' Health Study cohort, which initially found that the combination of high *Dietary Fiber* and low saturated or animal fat intake was associated with a reduced risk of adenomas (Willett et al., 1990), whereas a low intake of fiber alone did not contribute to the risk of colon cancer. Again, at follow-up in the same cohort, no relationship was found between *Dietary Fiber* intake and colon cancer incidence (Fuchs et al., 1999). This may also account for the lack of a protective effect of *Dietary Fiber* in the three recently reported clinical intervention trials (Alberts et al., 2000; Bonithon-Kopp et al., 2000; Schatzkin et al., 2000) since the participants already had colonic adenomas. Perhaps, as Giovannucci and colleagues (1992) suggest, intake of *Dietary Fiber* may influence the early stages of carcinogenesis, whereas dietary fat may have a greater influence on the progression of initiated cells into cancer.

The Confounding Role of Other Dietary Factors. Another possible explanation for the lack of a positive effect of fiber on colon cancer involves the potential confounding role of starch. As discussed in Chapter 6, starch may be divided into glycemic and nonglycemic starch, with nonglycemic starch being resistant to digestion by mammalian enzymes and thus reach-

ing the colon. Resistant starch intake has been associated with increased concentrations of fecal ammonia (Birkett et al., 1997). This association was reversed when nonstarch polysaccharides were added. Ammonia is toxic to normal colonic cells and stimulates the growth of malignant cells (Visek, 1978). Thus, diets that are high in resistant starch, but low in fiber, may have adverse effects (Birkett et al., 1997).

Individuals May Not Consume Sufficient Amounts of Fiber or the Right Type of Fiber. Neither the prospective studies nor the three large intervention trials reported aspects of colonic function (Alberts et al., 2000; Bonithon-Kopp et al., 2000; Schatzkin et al., 2000). It is possible that bulkier stools or faster transit through the colon reduce the risk of bowel cancer (Cummings et al., 1992), but that the amounts or types of *Dietary Fibers* consumed did not result in these physiological effects. In addition, positive benefits of fiber with respect to colon cancer may not occur until *Dietary Fiber* intake is sufficiently high; for example, greater than the median 32 g/d for the highest quintile in The Health Professionals Follow-Up Study of men (Giovannucci et al., 1994; Platz et al., 1997) and 25 g/d in the Nurses' Health Study (Fuchs et al., 1999).

Summary

All but one of the studies (Bonithon-Kopp et al., 2000) cited in this section examined the relationship of *Dietary Fiber* to colon cancer. Information is lacking on the role of *Functional Fibers* in the incidence of colon cancer because of the lack of intake data on specific *Functional Fibers* collected in epidemiological studies. Most animal studies on fiber and colon cancer, however, have used what could be termed *Functional Fibers* (Jacobs, 1986). Because evidence available is either too conflicting or inadequately understood, a recommended intake level based on the prevention of colon cancer cannot be set.

Dietary Fiber *and Protection Against Breast Cancer*

A growing number of studies have reported on the relationship of *Dietary Fiber* intake and breast cancer incidence, and the strongest case can be made for cereal consumption rather than consumption of *Dietary Fiber* per se (for an excellent review see Gerber [1998]). Between-country studies, such as England versus Wales (Ingram, 1981), southern Italy versus northern Italy versus the United States (Taioli et al., 1991), and China versus the United States (Yu et al., 1991), and one study within Spain (Morales and Llopis, 1992), all showed an inverse correlation between bread and cereal consumption and breast cancer risk. The findings of

Caygill and coworkers (1998) showed an inverse correlation between breast cancer incidence and both the current diet ($p < 0.001$) and the diet 20 years previously ($p < 0.001$). However, starchy root, vegetable, and fruit intakes were not related to breast cancer risk for either diet.

Prospective Studies

There have been at least two prospective studies relating *Dietary Fiber* intake to breast cancer incidence in the United States and both found no significant association (Graham et al., 1992; Willett et al., 1992). A Canadian study showed a significant protective trend for the intake of cereals, with borderline significance for *Dietary Fiber* (Rohan et al., 1993). Verhoeven and coworkers (1997) investigated the relationship between *Dietary Fiber* intake and breast cancer risk in The Netherlands Cohort Study. This prospective cohort study showed no evidence that a high intake of *Dietary Fiber* decreased the risk of breast cancer.

Case-Control Studies

Eight of eleven reported case-control studies showed a protective effect of *Dietary Fiber* against breast cancer (Baghurst and Rohan, 1994; De Stefani et al., 1997; Franceschi et al., 1996; Freudenheim et al., 1996; Graham et al., 1991; Lubin et al., 1986; Rohan et al., 1988; Ronco et al., 1999; van't Veer et al., 1990; Witte et al., 1997; Yuan et al., 1995). For studies that showed this protection, the range of the odds ratio or relative risk was 0.40 to 0.74.

Intervention Studies

Most intervention studies on fiber and breast cancer have examined fiber intake and plasma or urinary indicators of estrogen (e.g., estrone, estradiol). Since certain breast cancers are hormone dependent, the concept is that fiber may be protective by decreasing estrogen concentrations. Rose and coworkers (1991) provided three groups of premenopausal women with a minimum of 30 g/d of *Dietary Fiber* from wheat, oats, or corn. After 2 months, wheat bran was shown to decrease plasma estrone and estradiol concentrations, but oats and corn were not effective. Bagga and coworkers (1995) provided 12 premenopausal women a very low fat diet (10 percent of energy) that provided 25 to 35 g/d of *Dietary Fiber*. After 2 months there were significant decreases in serum estradiol and estrone concentrations, with no effects on ovulation. Woods and colleagues (1989) found that a low fat (25 percent of energy), high fiber (40 g of *Dietary Fiber*) diet significantly reduced serum estrone sulfate concentra-

tions in healthy premenopausal women compared with consumption of a typical Western diet (40 percent of energy from fat, 12 g of *Dietary Fiber*). In a separate study, the same researchers again provided a low fat (20 percent of energy), high fiber (40 g of *Dietary Fiber*) diet to premenopausal African-American women and observed reduced concentrations of serum estradiol and estrone sulfate when compared with a typical Western diet (Woods et al., 1996).

Mechanisms

A variety of different mechanisms have been proposed as to how fiber might protect against breast cancer, but the primary hypothesis is through decreasing serum estrogen concentrations. Fiber can reduce the enterohepatic circulation of estrogen by binding unconjugated estrogens in the gastrointestinal tract (Shultz and Howie, 1986), making them unavailable for absorption (Gorbach and Goldin, 1987). Goldin and coworkers (1982) reported decreased plasma concentrations of estrone and increased fecal excretion of estrogens with increasing fecal weight. Alternatively, certain fibers can modify the colonic microflora to produce bacteria with low deconjugating activity (Rose, 1990), and deconjugated estrogens are reabsorbed. With less reabsorption of estrogens, plasma concentrations decrease. Another related hypothesis is that fiber speeds up transit through the colon, thus allowing less time for bacterial deconjugation. In fact, Petrakis and King (1981) noted abnormal cells in the mammary fluid of severely constipated women. Also, fiber sources contain phytoestrogens, which may compete with endogenous estrogens and act as antagonists (Lee et al., 1991; Rose, 1992). Finally, one report showed that *Dietary Fiber* intake was negatively correlated with total body fat mass, intra-abdominal adipose tissue, and subcutaneous abdominal adipose tissue in 135 men and 214 women (Larson et al., 1996). Since estrogen synthesis can occur in lipid stores, a decreased lipid mass should result in decreased synthesis. In addition to decreasing serum estrogen concentrations, fiber may be protective by adsorbing carcinogens or speeding their transit through the colon and providing less opportunity for their absorption. Carcinogens known to be related to breast cancer that may be affected include heterocyclic amines (Ito et al., 1991; Knekt et al., 1994), which have been shown to adsorb to fiber (Harris et al., 1996).

Summary

There are no reports on the role of *Functional Fibers* in the risk of breast cancer. Clearly, fiber has the potential capacity to decrease blood

estrogen concentrations by a variety of different mechanisms, but whether or not this is sufficient to decrease the risk of breast cancer has not been thoroughly investigated. Because of the lack of evidence to support a role of *Dietary Fiber* in preventing breast cancer, this clinical endpoint cannot be used to set a recommended intake level.

Dietary Fiber *and Other Cancers*

Although the preponderance of the literature on fiber intake and cancer involves colon cancer and breast cancer, several studies have shown decreased risk for other types of cancer. Because *Dietary Fiber* has been shown to decrease serum estrogen concentrations, some researchers have hypothesized a protective effect against hormone-related cancers such as endometrial, ovarian, and prostate. Studies on *Dietary Fiber* intake and endometrial cancer have shown both significant and nonsignificant decreases in risk (Barbone et al., 1993; Goodman et al., 1997; McCann et al., 2000). In addition, studies have shown a decreased risk in ovarian cancer with a high intake of *Dietary Fiber* (McCann et al., 2001; Risch et al., 1994; Tzonou et al., 1993). However, no significant associations have been observed between *Dietary Fiber* intake and risk of prostate cancer (Andersson et al., 1996; Ohno et al., 1988; Rohan et al., 1995). Although interesting to note, this literature is in its infancy and cannot be used to set a recommended intake level for *Dietary Fiber*.

Dietary Fiber *and* Functional Fiber *and Glucose Tolerance, Insulin Response, and Amelioration of Diabetes*

Epidemiological Studies

Epidemiological evidence suggests that intake of certain fibers may delay glucose uptake and attenuate the insulin response, thus providing a protective effect against diabetes. Evidence for the protective effect of *Dietary Fiber* intake against type 2 diabetes comes from several prospective studies that have reported on the relationship between food intake and type 2 diabetes (Colditz et al., 1992; Meyer et al., 2000; Salmerón et al., 1997a, 1977b). One study examined the relationship between specific dietary patterns and risk of type 2 diabetes in a cohort of 42,759 men, while controlling for major known risk factors (Salmerón et al., 1997a). The results suggest that diets with a high glycemic load and low cereal fiber content are positively associated with risk of type 2 diabetes, independent of other currently known risk factors (Figure 7-1). In a second study, diet and risk of type 2 diabetes in a cohort of 65,173 women were evaluated (Salmerón et al., 1997b). Again, diets with a high glycemic load and

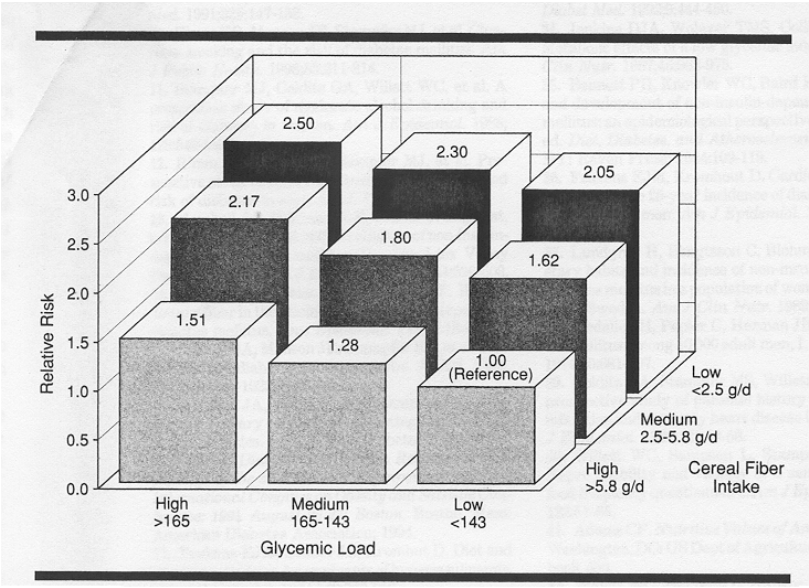

FIGURE 7-1 Relative risk of type 2 diabetes by different levels of cereal fiber intake and glycemic load. Reprinted, with permission, from Salmerón et al. (1997b). Copyright 1997 by the American Medical Association.

low cereal fiber content were positively associated with risk of type 2 diabetes, independent of other dietary factors and currently known risk factors. Of particular importance is that this combination resulted in a relative risk of 2.17 for men (Salmerón et al., 1997a) and 2.5 for women (Salmerón et al., 1997b), which is more than twofold greater relative to consumption of a diet high in cereal fiber and low in glycemic load (Figure 7-1).

In theory, the hypothesis as to how *Dietary Fiber* may be protective against type 2 diabetes is that it attenuates the glucose response and decreases insulin concentrations. This theory is supported by results from the Zutphen Elderly Study, where a negative relationship was observed between *Dietary Fiber* intake and insulin concentrations (Feskens et al., 1994).

Intervention Studies

In some clinical intervention trials ranging from 2 to 17 weeks, consumption of *Dietary Fiber* was shown to decrease insulin requirements in type 2 diabetics (Anderson et al., 1987; Rivellese et al., 1980; HCR Simpson

et al., 1981). However, Behall (1990) compared the addition of 19.5 g of one of four different *Functional Fibers* (cellulose, carboxymethycellulose gum, karaya gum, and locust bean gum) to a low fiber diet with respect to glucose and insulin response curves from a standard glucose tolerance test and found no significant differences between the diets after 4 weeks. In addition, resistant starch has not been shown to have an effect on glycemic index. This is in contrast to the differences in "slow release" versus "fast release" starches, which have differential effects on postprandial glycemic and insulinemic profiles (Golay et al., 1992; Jenkins et al., 1987).

Viscous *Dietary* and *Functional Fibers*, such as are found in oat products, beans, isolated pectin, and isolated guar gum, have been found to produce significant reductions in glycemic response in 33 of 50 studies (66 percent) reviewed by Wolever and Jenkins (1993), which is in contrast to only 3 of 14 studies with nonviscous fiber (21 percent). Mechanistic data and hypotheses support this effect of viscous fibers as they delay gastric emptying and delay the absorption of glucose and other nutrients (Jenkins et al., 1978; Wood et al., 1994). However, a seeming anomaly is that the blood glucose response of foods is more closely related to their nonviscous fiber content than to their viscous fiber content (Wolever, 1995). It is not clear as to how significant the viscosity of fiber is to its contribution to the reduction in glycemic response in the overall observation of a lower incidence of type 2 diabetes with high fiber diets. Therefore, viscosity should not be considered the most important attribute of fiber with respect to this endpoint.

Summary

There is evidence that *Total Fiber* reduces the risk of diabetes; this can be used as a secondary endpoint to support a recommended intake level for *Total Fiber* that is primarily based on prevention of CHD. Further discussion is provided in the later section, "Findings by Life Stage and Gender Group."

Fiber Intake, Satiety, and Weight Maintenance

Epidemiological Studies

Since foods rich in fiber tend to be low in energy, researchers have hypothesized that fiber consumption may help with weight maintenance. This is an important consideration since obesity is such a prevalent problem and contributes to the risk of many diseases. Support for the concept that fiber consumption helps with weight maintenance is provided by studies showing that daily *Dietary Fiber* intake is lower for obese men (20.9 ± 1.8 g)

and women (15.7 ± 1.1 g) than for lean men (26.9 ± 1.8 g) and women (22.7 ± 2.1 g) (Miller et al., 1994). Furthermore, in a study of 1,914 men and 3,378 women, mean body mass index (BMI) was significantly lower in the high *Dietary Fiber* group for both men and women (Appleby et al., 1998).

Intervention Studies

Several intervention studies suggest that diets high in fiber may assist in weight loss (Birketvedt et al., 2000; Eliasson et al., 1992; Rigaud et al., 1990; Rössner et al., 1987; Ryttig et al., 1989), although other studies have not found this effect (Astrup et al., 1990; Baron et al., 1986). For example, Birketvedt and coworkers (2000) conducted a study in which 53 moderately overweight females consumed a reduced energy diet (1,200 kcal/d) with or without a fiber supplement, which was 6 g/d for 8 weeks and then 4 g/d thereafter. The women on the fiber-supplemented diets lost 8.0 kg versus 5.8 kg for the placebo group ($p < 0.05$). High fiber diets are characterized by a very low energy density compared to diets high in fat, and a greater volume must be consumed in order to reach a certain energy level (Duncan et al., 1983; Tremblay et al., 1991), which again could result in cessation of eating. The issue of whether fiber has implications in the modulation of appetite has been reviewed (Blundell and Burley, 1987; Levine and Billington, 1994). Consumption of viscous fibers delays gastric emptying (Roberfroid, 1993), which in turn can cause an extended feeling of fullness (Bergmann et al., 1992) and delayed absorption of glucose and other nutrients (Jenkins et al., 1978; Ritz et al., 1991; Roberfroid, 1993; Truswell, 1992). Some investigators suggest that the delayed absorption of nutrients is associated with an extended feeling of satiety and delayed return of appetite (Grossman, 1986; Holt et al., 1992; Leathwood and Pollet, 1988), but not all investigators have found this effect (de Roos et al., 1995; Krishnamachar and Mickelsen, 1987; Sepple and Read, 1989).

A number of studies investigated the effect of consumption of a high fiber meal and food intake at a later eating occasion. For example, eating a breakfast supplemented with 29 g of sugar beet fiber resulted in 14 percent less energy consumption at the subsequent lunch (Burley et al., 1993). In contrast, other investigators have failed to demonstrate any postingestive effect of fiber on food intake (Delargy et al., 1995; Levine and Billington, 1994). One study found that there was no difference between a high fiber and a low fiber diet on later food intake if the energy content of the initial diets was similar (Delargy et al., 1995). These authors used 20 g of *Dietary Fiber* for their test breakfast meal, which is much lower than the 29 g used by Burley and coworkers (1993). The authors concluded that for *Dietary Fiber* to have an effect, there has to be greater than 20 g in the test meal

(Delargy et al., 1995). Similar findings of no effect of a test meal on appetite throughout the day have been found for substituting resistant starch for digestible starch (Raben et al., 1994). In addition, much of the data on chitin and chitosan in promoting weight loss have been negative (see earlier section, "Physiological Effects of Isolated and Synthetic Fibers").

Summary

The strongest data supporting a relationship between fiber and weight maintenance come from the few epidemiological studies showing that *Dietary Fiber* intake is lower for obese men and women than for lean men and women and that BMI is lower with higher fiber consumption for both men and women. Efforts to show that eating specific fibers increases satiety and thus results in a decreased food intake have been inconclusive. In terms of the attribute of fiber that may result in decreased food intake, some have suggested that viscosity is important as it delays gastric emptying and may lead to feeling more full for a longer period of time. However, this hypothesis has not been validated in clinical trials.

Although the finding that the overall data on *Dietary Fiber* intake are negatively correlated with BMI is suggestive of a role for fiber in weight control, the studies designed to determine how fiber intake might impact overall energy intake have not shown a major effect. In fact, it appears that very high amounts of fiber (e.g., 30 g/meal) are required to diminish subsequent energy intake after that meal. For humans, there is no overwhelming evidence that *Dietary Fiber* has an effect on satiety or weight maintenance, therefore this endpoint is not used to set a recommended intake level.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Expression of the Total Fiber Requirement

Total Fiber requirements (the sum of *Dietary Fiber* and *Functional Fiber*) may be expressed in a variety of different ways, including age plus number of grams per day (Williams et al., 1995), grams per kilogram of body weight (AAP, 1993), grams per day (Health and Welfare Canada, 1985; LSRO, 1987), and grams per 1,000 kcal (LSRO, 1987). Each of these methods has its advantages and disadvantages. Because the available evidence suggests that the beneficial effects of fiber in humans are most likely related to the amount of food consumed—not to the individual's age or body weight—the best approach is to set an Adequate Intake (AI) based on grams per 1,000 kcal. However, since many people do not know how many kilocalories they consume in a day, the AI is based on the usual daily intake of

energy (Appendix Table E-1) for each age group and is expressed in grams per day. Those with energy intakes significantly above or below the reference intakes for their age and gender may want to consider adjusting their total fiber intake accordingly.

Infants Ages 0 Through 12 Months

There are no functional criteria for fiber status that reflect response to dietary intake in infants. Since human milk is recognized as the optimal source of nourishment for infants throughout at least the first year of life and as a sole nutritional source for infants during the first 4 to 6 months of life (IOM, 1991), and because human milk contains no *Dietary Fiber*, there is no AI for infants 0 through 6 months of age. During the 7- through 12-month age period, the intake of solid foods becomes more significant, and *Dietary Fiber* intake may increase. However, there are no data on *Dietary Fiber* intake in this age group and no theoretical reason to establish an AI for infants 7 through 12 months of age.

Children and Adolescents Ages 1 Through 18 Years

Method Used to Set the AI

Although guidelines have been endorsed for recommended dietary intakes of total fat and fatty acids, protein, carbohydrate, and cholesterol in children 2 years of age and older by a variety of different organizations (AHA, 1983; Dwyer, 1980; USDA/HHS, 2000), none of these guidelines recommend a specific level of fiber intake during childhood. Data suggest that North American children, like adults, consume inadequate amounts of fiber for optimal health, and that consumption of fiber should be increased to promote normal laxation, to help prevent diet-related cancer, to help reduce serum cholesterol concentrations and therefore the risk of coronary heart disease (CHD), and to help prevent obesity and the risk of adult-onset diabetes (AHA, 1983; AMA Council on Scientific Affairs, 1989; Wynder and Berenson, 1984). National pediatric dietary goals are targeted for children older than 2 years of age, with a suggestion that age 2 to 3 years be a transition year (National Cholesterol Education Program, 1991).

Constipation is a common problem during childhood, as it is in adults, and accounts for 25 percent of visits to pediatric gastroenterology clinics (Loening-Baucke, 1993). As discussed in the earlier section, "*Dietary Fiber, Functional Fiber,* and Colon Health," there are strong data showing the contribution of high fiber diets, along with adequate fluid intake, to laxation in adults. However, fiber intake and constipation data in children are limited. Studies correlate low *Dietary Fiber* intake with constipation

(Hunt et al., 1993; Roma et al., 1999). Two studies by the same research group addressed fiber intake in American children and found that children with constipation consumed, on average, about half as much fiber as the healthy control group (McClung et al., 1993, 1995). Morais and coworkers (1999) reported that children with chronic constipation ingested less *Dietary Fiber* than age-matched controls.

The AI for *Total Fiber* for children and adolescents is based on the data cited for adults, which showed that 14 g/1,000 kcal reduced the risk of CHD (see "Adults Ages 19 Years and Older"). The AI (14 g/1,000 kcal × median energy intake [kcal/1,000 kcal/d]) is then set for each age and gender group. The median energy intake for 1- to 3-year-old children is 1,372 kcal/d (Appendix Table E-1). Thus, 19 g/d (14 × 1.37) of total fiber would be recommended for this age group. It should be kept in mind that recommendations for fiber intake are based on a certain amount of total fiber as a function of energy intake. This means that those who consume less than the median energy intake of a particular category need less fiber than the recommendation (which is based on the mean energy intake). For example, the median energy intake for 1- to 3-year-old children is 1,372 kcal/d and the recommendation for total fiber is 19 g/d. However, 1-year-old children not meeting this energy consumption level will not require 19 g/d and their intake should be scaled back accordingly.

The median energy intake for 4- to 8-year-old children is 1,759 kcal/d (Appendix Table E-1). Thus, 25 g/d (14 × 1.76) of *Total Fiber* would be recommended for these children. The AIs for *Total Fiber* for boys and girls 9 to 18 years of age have been calculated in a similar manner using the energy intake values in Appendix Table E-1.

Total Fiber *AI Summary, Ages 1 Through 18 Years*

AI for Children

1–3 years	**19 g/d of *Total Fiber***
4–8 years	**25 g/d of *Total Fiber***

AI for Boys

9–13 years	**31 g/d of *Total Fiber***
14–18 years	**38 g/d of *Total Fiber***

AI for Girls

9–13 years	**26 g/d of *Total Fiber***
14–18 years	**26 g/d of *Total Fiber***

Adults Ages 19 Years and Older

Methods Used to Set the AI

Fiber Intake and Risk of CHD. Although the preponderance of the data shows a protective effect of consumption of high fiber and high fiber-containing foods against CHD (see earlier section, "*Dietary Fiber, Functional Fiber,* and the Prevention of Hyperlipidemia, Hypertension, and Coronary Heart Disease"), there are exceptions to these findings. A more important consideration for establishing a requirement for fiber is the fact that the dietary intake data from epidemiological studies are on fiber-containing foods, which are considered *Dietary Fiber.* Certain investigators specifically analyzed diets for *Dietary Fiber* (Burr and Sweetnam, 1982; Hallfrisch et al., 1988; Khaw and Barrett-Connor, 1987; Kromhout et al., 1982; Kushi et al., 1985; Morris et al., 1977; Pietinen et al., 1996; Rimm et al., 1996), but others used indicators of *Dietary Fiber* intake such as cereals, vegetables, fruits, whole grains, or legumes. There are many constituents of whole grains, in addition to *Dietary Fiber*, that may reduce the risk of CHD (Slavin et al., 1997; Thompson, 1994). Despite these cautions, the data on the relationship between *Dietary Fiber* intake and risk of CHD based on epidemiological, clinical, and mechanistic data are strong enough to warrant using this relationship as a basis for setting a recommended level of intake. Both men and women appear to benefit from increasing their intake of foods rich in fibers, particularly cereal fibers, with women appearing to benefit more from increasing fiber consumption than men.

Because the prospective studies of Pietinen and coworkers (1996), Rimm and coworkers (1996), and Wolk and coworkers (1999) are adequately powered, divide fiber intake into quintiles, and provide data on energy intake (Table 7-2), it is possible to set a recommended intake level. Data from 21,930 Finnish men showed that at the highest quintile of *Dietary Fiber* intake (34.8 g/d), median energy intake was 2,705 kcal/d, which equates to 12.9 g of *Dietary Fiber*/1,000 kcal (Pietinen et al., 1996). The Health Professionals Follow-up Study of men reported a *Dietary Fiber* intake of 28.9 g/d in the highest quintile, with a normalized energy intake of 2,000 kcal/d, which equates to 14.45 g of *Dietary Fiber*/1,000 kcal (Rimm et al., 1996). In the Nurses' Health Study of women, the median *Dietary Fiber* intake at the highest quintile was 22.9 g/d, with a normalized energy intake of 1,600 kcal/d (Wolk et al., 1999), which equates to 14.3 g of *Dietary Fiber*/1,000 kcal. In these three studies, there was a significant negative trend in *Dietary Fiber* intake and risk of CHD. Specifically, there was a strong nega-

tive correlation between cereal fiber intake and risk of CHD, whereas the correlation was weak or nonexistent for fruit and vegetable fibers. Taken collectively and averaging to the nearest gram, these data suggest an intake of 14 g of *Dietary Fiber*/1,000 kcal, particularly from cereals, to promote heart health. Data from the intervention trials are in line with these recommendations, as are data from epidemiological studies.

Fiber Intake and Risk of Type 2 Diabetes. The literature on *Dietary Fiber* intake and glucose tolerance, insulin response, and amelioration of diabetes alone is insufficient at this time to use as a basis for a recommendation (see "Evidence Considered for Estimating the Requirement for *Dietary Fiber* and *Functional Fiber*"). However, it should be noted that the positive effects seen in two large prospective studies (Salmerón et al., 1997a, 1997b) were achieved with the same levels of fiber that have previously been reported as being protective against CHD (Pietinen et al., 1996; Rimm et al., 1996; Wolk et al., 1999). Therefore, the recommendations made using the effect of *Dietary Fiber* intake on CHD are supported by the data on *Dietary Fiber* intake and type 2 diabetes.

Summary. Prospective studies have shown that the impact of *Dietary Fiber* on the advent of CHD occurs continuously across a range of intakes. Therefore, an Estimated Average Requirement (EAR) cannot be set.

Based on the average intake of *Dietary Fiber* and its effect on CHD, as well as the beneficial role of *Functional Fibers* (such as gums, pectin and psyllium), an AI for *Total Fiber* is set for each age and gender group by multiplying 14 g/1,000 kcal × median energy intake (kcal/1,000 kcal/d). The highest median intake level for each gender-specific age group (from Appendix Table E-1) was used in the equation to set the AI for young adults (19 to 50 years of age) and older adults (51 years of age and older). There is no information to indicate that fiber intake as a function of energy intake differs during the life cycle.

By definition, the AI is expected to meet or exceed the EAR or the average amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of a specific healthy population. Thus, where data are insufficient to be used as the basis of an AI, *Total Fiber* at the recommended levels may also help to ameliorate constipation and diverticular disease, provide fuel for colonic cells, attenuate blood glucose and lipid concentrations, and provide a source of nutrient-rich, low energy-dense foods that could contribute to satiety.

Total Fiber AI Summary, Ages 19 Years and Older

AI for Men

19–30 years	**38 g/d of *Total Fiber***
31–50 years	**38 g/d of *Total Fiber***
51–70 years	**30 g/d of *Total Fiber***
> 70 years	**30 g/d of *Total Fiber***

AI for Women

19–30 years	**25 g/d of *Total Fiber***
31–50 years	**25 g/d of *Total Fiber***
51–70 years	**21 g/d of *Total Fiber***
> 70 years	**21 g/d of *Total Fiber***

Pregnancy

Method Used to Set the AI

There is no evidence to suggest the beneficial effects of fiber in reducing the risk of CHD for pregnant adolescent girls and women is different from nonpregnant adolescent girls and women. Therefore, the AI for *Total Fiber* is 28 g/d (14 g/1,000 kcal × 1,978 kcal/1,000 kcal/d).

Total Fiber *AI Summary, Pregnancy*

AI for Pregnant Women

14–18 years	**28 g/d of *Total Fiber***
19–30 years	**28 g/d of *Total Fiber***
31–50 years	**28 g/d of *Total Fiber***

Lactation

Method Used to Set the AI

There is no evidence to suggest the beneficial effects of fiber in reducing the risk of CHD for lactating adolescent girls and women are different from nonpregnant adolescent girls and women. Therefore, the AI for *Total Fiber* is 29 g/d (14 g/1,000 kcal × 2,066 kcal/1,000 kcal/d).

Total Fiber *AI Summary, Lactation*

AI for Lactating Women

14–18 years	**29 g/d of *Total Fiber***
19–30 years	**29 g/d of *Total Fiber***
31–50 years	**29 g/d of *Total Fiber***

INTAKE OF *DIETARY FIBER*

Food Sources

Marlett (1992) reported on the *Dietary Fiber* content of 117 frequently consumed foods. *Dietary Fiber* was present in the majority of fruits, vegetables, refined grains, and miscellaneous foods such as ketchup, olives, and soups, at concentrations of 1 to 3 percent, or 1 to 3 g/100 g of fresh weight. Nuts, legumes, and high fiber grains typically contained more than 3 percent *Dietary Fiber*. About one-third of the fiber in legumes, nuts, fruits, and vegetables was present as hemicelluloses. Approximately one-fourth of the fiber in grains and fruit and one-third in nuts and vegetables consisted of cellulose. Although fruits contained the greatest amount of pectin, 15 to 20 percent of the fiber content in legumes, nuts, and vegetables was pectin.

The major sources of naturally occurring inulin and oligofructose are wheat and onions, which provide about 70 and 25 percent of these components, respectively (Moshfegh et al., 1999). Isolated inulin provides a creamy texture and is added to replace fat in table spreads, dairy products, frozen desserts, baked goods, fillings, and dressings. Oligofructose is most commonly added to cereals, fruit preparations for yogurt, cookies, dairy products, and frozen desserts.

Depending on one's chosen diet, naturally occurring and manufactured resistant starch, as well as that produced during normal processing of foods for human consumption, could make a significant contribution to daily *Total Fiber* intake. Legumes are the largest source of naturally occurring resistant starch (Marlett and Longacre, 1996). In addition, green bananas (Englyst and Cummings, 1986) and cooled, cooked potatoes (Englyst and Cummings, 1987) can provide a significant amount of resistant starch. Resistant starch resulting from normal processing of a foodstuff is a more modest contributor to a typical daily intake. Starches specifically manufactured to be resistant to endogenous human digestion are a rapidly growing segment of commercially available resistant starches.

Dietary Intake

National nutrition surveys use the U.S. Department of Agriculture (USDA) food composition database to estimate the intake of various nutrients. This database primarily measures *Dietary Fiber* intake because isolated *Functional Fibers*, such as pectins and gums, that are used as ingredients represent a very minor amount of the fiber present in foods. For instance, the fiber content of fat-free ice creams and yogurts, which contain *Functional Fibers* as additives, is much less than 1 g/serving and therefore is often labeled as having 0 g of fiber. Based on intake data from the Continuing Survey of Food Intakes by Individuals (CSFII) (1994–1996, 1998), median *Dietary Fiber* intakes ranged from 16.5 to 17.9 g/d for men and 12.1 to 13.8 g/d for women (Appendix Table E-4). Based on the Adequate Intakes (AI) set for the various age and gender groups, 10 percent or less of a particular group consumed greater than the AI.

Based on additional intake data from CSFII, American diets provided on average 2.6 g/d of inulin and 2.5 g/d of oligofructose (Moshfegh et al., 1999). Since inulin and oligofructose have not been analyzed as fiber previously, they would not be in the USDA database. This would mean that people are actually consuming approximately 5.1 g/d more fiber than reported in the CSFII database (Appendix Table E-4). Although there is a seemingly large gap between current fiber intake and the recommended intake, it is not difficult to consume recommended levels of *Total Fiber* by choosing foods recommended by the Food Guide Pyramid. Two sample menus are provided that meet the Estimated Energy Requirement (EER) and AI for *Total Fiber* for men (Table 7-3) and women (Table 7-4).

These menus show that a 19-year-old active male and a 19-year-old active female can meet their AI for *Total Fiber* without exceeding their EER. These diets also meet the Recommended Dietary Allowances and AIs for all of the micronutrients.

ADVERSE EFFECTS OF OVERCONSUMPTION

Adverse Effects of Dietary Fiber

Mineral Bioavailability

Within the last 20 years, several animal and human studies have shown that foods or diets rich in fibers may alter mineral metabolism, especially when phytate is present (Sandstead, 1992). Fibers may reduce the bioavailability of minerals such as iron, calcium, and zinc (AAP, 1981; Williams and Bollella, 1995). However, levels of 10 to 12 g of *Dietary Fiber*/1,000 kcal have been suggested as safe even for Japanese adolescents, who tradition-

TABLE 7-3 Fiber Intake from an Omnivorous Diet Adequate in Essential Micronutrients to Meet the Estimated Energy Requirement for a Male 19 Years of Age (3,078 kcal/d)

Meal	Foods Eaten	Energy (kcal)	*Total Fiber* (g)
Breakfast	Grapefruit, pink or red ($^1/_2$ medium)	38	1.4
	Banana (1 medium)	109	2.8
	Cereal, ready-to-eat shredded oats (1 cup)	112	3.0
	English muffin (white, 1 whole)	134	1.5
	Margarine (2 tsp)	68	0
	Milk, 1% (1 cup)	102	0
	Total for meal	563	8.7
Snack	Crackers, whole wheat (6 each)	109	0.9
	Cheddar cheese (1.5 oz)	171	0
	Juice ($^3/_4$ cup)	78	0.4
	Total for snack	358	1.3
Lunch	Tossed salad (1 cup)	16	1.5
	Salad dressing (1 tbs)	66	0
	Chili with beans and beef (1 cup)	273	6.5
	Cornbread (1 piece)	173	1.3
	Margarine (1 tsp)	34	0
	Grapes ($^1/_2$ cup)	57	0.8
	Fig bar cookies (2)	111	1.5
	Milk, 1% (1 cup)	102	0
	Total for meal	832	11.6
Dinner	Salmon in soy sauce (3.5 oz)	169	0.2
	Rice with vegetables ($^3/_4$ cup)	167	1.4
	Broccoli (1-$^1/_2$ cup)	40	4.4
	Roll, whole wheat (2 medium)	177	5.0
	Margarine (2 tsp)	68	0
	Ice cream ($^1/_2$ cup)	98	0.3
	Total for meal	719	11.3
Snack	Carrots, raw (12 medium baby)	51	3.6
	Spinach dip (2 tbs)	58	0.4
	Turkey sandwich	344	1.2
	Cola (1 can)	153	0
	Total for snack	606	5.2
Daily total		3,078	38.1

NOTE: Source of food composition data: NDS-R Food and Nutrient Data Base, Version 4.04_32, 2001, Nutrition Coordinating Center, University of Minnesota.

TABLE 7-4 Fiber Intake from an Omnivorous Diet Adequate in Essential Micronutrients to Meet the Estimated Energy Requirement for a Female 19 Years of Age (2,393 kcal/d)

Meal	Foods Eaten	Energy (kcal)	*Total Fiber* (g)
Breakfast	Banana ($^1/_2$ medium)	54	1.4
	Cereal, ready-to-eat shredded oats ($^3/_4$ cup)	84	2.3
	English muffin (white, 1 whole)	134	1.5
	Margarine (2 tsp)	68	0
	Milk, skim (1 cup)	86	0
	Total for meal	426	5.2
Snack	Crackers, whole wheat (5 each)	90	0.7
	Cheddar cheese (1.5 oz)	171	0
	Juice ($^3/_4$ cup)	78	0.4
	Total for snack	339	1.1
Lunch	Tossed salad ($^3/_4$ cup)	12	1.1
	Salad dressing (1 tbs)	66	0
	Chili with beans and beef ($^3/_4$ cup)	205	4.9
	Cornbread (1 piece)	173	1.3
	Margarine (1 tsp)	34	0
	Grapes ($^1/_2$ cup)	57	0.8
	Milk, skim (1 cup)	86	0
	Total for meal	633	8.1
Dinner	Salmon in soy sauce (3.5 oz)	169	0.2
	Rice with vegetables ($^1/_2$ cup)	111	1.0
	Broccoli ($^1/_2$ cup)	14	1.5
	Roll, whole wheat (1 medium)	89	2.5
	Margarine (1 tsp)	34	0
	Ice cream ($^1/_2$ cup)	98	0.3
	Total for meal	515	5.5
Snack	Apple (1 medium)	81	3.7
	Pretzels (1 oz)	108	0.9
	Peanut butter sandwich	138	1.3
	Cola (1 can)	153	0
	Total for snack	480	5.9
Daily total		2,393	25.8

NOTE: Source of food composition data: NDS-R Food and Nutrient Data Base, Version 4.04_32, 2001, Nutrition Coordinating Center, University of Minnesota.

ally have low levels of calcium intake (Nishimune et al., 1993). Most studies that assess the effect of fiber intake on mineral status have looked at calcium, magnesium, iron, or zinc.

Calcium. Most studies investigating the effects of cereal, vegetable, and fruit fibers on the absorption of calcium in animals and humans have reported no effect on calcium absorption or balance (Spencer et al., 1991; Wisker et al., 1991). However, some studies described a decrease in calcium absorption with ingestion of *Dietary Fiber* under certain conditions (Knox et al., 1991; O'Brien et al., 1993). Slavin and Marlett (1980) found that supplementing the diet with 16 g/d of cellulose resulted in significantly greater fecal excretion of calcium resulting in an average loss of approximately 200 mg/d. There was no effect on the apparent absorption of calcium after the provision of 15 g/d of citrus pectin (Sandberg et al., 1983).

Magnesium. Studies report no differences in magnesium balance with intake of certain *Dietary Fibers* (Behall et al., 1987; Hallfrisch et al., 1987; Spencer et al., 1991). Astrup and coworkers (1990) showed no effect of the addition of 30 g/d of plant fiber to a very low energy diet on plasma concentrations of magnesium. There was no effect on the apparent absorption of magnesium after the provision of 15 g/d of citrus pectin (Sandberg et al., 1983). Magnesium balance was not significantly altered with the consumption of 16 g/d of cellulose (Slavin and Marlett, 1980).

Iron and Zinc. A number of studies have looked at the impact of fiber-containing foods, such as cereal fibers, on iron and zinc absorption. These cereals typically contain levels of phytate that are known to impair iron and zinc absorption. Coudray and colleagues (1997) showed no effect of isolated viscous inulin or partly viscous sugar beet fibers on either iron or zinc absorption when compared to a control diet. Metabolic balance studies conducted in adult males who consumed four oat bran muffins daily showed no changes in zinc balance due to the supplementation (Spencer et al., 1991). Brune and coworkers (1992) have suggested that the inhibitory effect of bran on iron absorption is due to its phytate content rather than its *Dietary Fiber* content. However, the addition of 12 g/d of bran to a meal decreased iron absorption by 51 to 74 percent, and the inhibition was not explained by the presence of phytate (KM Simpson et al., 1981).

Gastrointestinal Distress. There are limited studies to suggest that chronic high intakes of *Dietary Fibers* can cause gastrointestinal distress. The consumption of wheat bran at levels up to 40 g/d did not result in significant increases in gastrointestinal distress compared to a placebo (McRorie et al., 2000). However, flatulence did increase with increased intake of *Dietary*

Fiber (Bolin and Stanton, 1998; Tomlin et al., 1991). Adverse effects have been observed under certain special circumstances. For instance, 75 to 80 g/d of *Dietary Fiber* has been associated with sensations of excessive abdominal fullness and increased flatulence in individuals with pancreatic disease (Dutta and Hlasko, 1985). Furthermore, the consumption of 160 to 200 g/d of unprocessed bran resulted in intestinal obstruction in a woman who was taking an antidepressant (Kang and Doe, 1979).

Summary

Dietary Fiber can have variable compositions and therefore it is difficult to link a specific fiber with a particular adverse effect, especially when phytate is also often present. It is concluded that as part of an overall healthy diet, a high intake of *Dietary Fiber* will not produce significant deleterious effects in healthy people. Therefore, a Tolerable Upper Intake Level (UL) is not set for *Dietary Fiber*.

Special Considerations

Dietary Fiber is a cause of gastrointestinal distress in people with irritable bowel syndrome. Those who suffer from excess gas production can consume a low gas-producing diet, which is low in dietary fiber (Cummings, 2000).

Hazard Identification for Isolated and Synthetic Fibers

Unlike *Dietary Fiber*, it may be possible to concentrate large amounts of *Functional Fiber* in foods, beverages, and supplements. Since the potential adverse health effects of *Functional Fiber* are not completely known, they should be evaluated on a case-by-case basis. In addition, projections regarding the potential contribution of *Functional Fiber* to daily *Total Fiber* intake at anticipated patterns of food consumption would be informative. *Functional Fiber*, like *Dietary Fiber*, is not digested by mammalian enzymes and passes into the colon. Thus, like *Dietary Fiber*, most potentially deleterious effects of *Functional Fiber* ingestion will be on the interaction with other nutrients in the gastrointestinal tract. Data from human studies on adverse effects of consuming what may be considered as *Functional Fibers* (if sufficient data exist to show a potential health benefit) are summarized below under the particular fiber.

Chitin and Chitosan

Studies on the adverse effects of chitin and chitosan are limited. A study in rats fed up to 5 percent chitin for 13 weeks showed no adverse

effects based on clinical signs, hematology, serum biochemistry, and histopathology analysis (Niho et al., 1999).

Gums

Gastrointestinal Distress. While the adverse gastrointestinal effects of gums are limited, incidences of moderate to severe degrees of flatulence were reported from a trial in which 4 to 12 g/d of a hydrolyzed guar gum were provided to 16 elderly patients (Patrick et al., 1998).

Allergic Reactions. Gums such as the exudate gums, gum arabic, and gum tragacanth have been shown to elicit an immune response in mice (Strobel et al., 1982). Occupational asthma caused by guar gum has been reported (Lagier et al., 1990).

Inulin, Oligofructose, and Fructooligosaccharide

Cancer. When F-344 rats, known to have a high incidence of neoplastic lesions, were given 0, 8,000, 20,000, or 50,000 ppm doses of fructooligosaccharide, the incidence of pituitary adenomas was 20, 26, 38, and 44 percent, respectively (Haseman et al., 1990). The incidence was significantly higher for intakes at 20,000 and 50,000 ppm. Clevenger and coworkers (1988) reported no difference in the onset of cancer in F-344 rats fed 0, 8,000 (341 to 419 mg/kg/d), 20,000 (854 to 1,045 mg/kg/d), or 50,000 ppm (2,170 to 2,664 mg/kg/d) doses of fructooligosaccharide compared with the controls.

Development and Reproduction. Henquin (1988) observed a lack of developmental toxicity when female rats were fed a diet containing 20 percent fructooligosaccharide during gestation. When pregnant rats were fed diets containing 5, 10, or 20 percent fructooligosaccharide during gestation, no adverse developmental effects were observed (Sleet and Brightwell, 1990).

Genotoxicity. Fructooligosaccharide has been tested for genotoxicity using a wide range of test doses (0 to 50,000 ppm); the results indicated no genotoxic potential from use of fructooligosaccharide (Clevenger et al., 1988).

Gastrointestinal Distress. A number of studies have observed gastrointestinal distress (e.g., diarrhea, flatulence, bloating, and cramping) with

inulin, oligofructose, or fructooligosaccharide intake. Cramping, bloating, flatulence, and diarrhea was observed at intakes ranging from 14 to 18 g/d of inulin (Davidson and Maki, 1999; Pedersen et al., 1997). Consumption of 5 or 15 g/d of fructooligosaccharide produced a gaseous response in healthy men (Alles et al., 1996). Briet and coworkers (1995) reported increased flatulence as a result of consuming more than 30 g/d of fructo-oligosaccharide, increased bloating at greater than 40 g/d, and cramps and diarrhea at 50 g/d. Increased flatulence and bloating were observed when 10 g/d of fructooligosaccharide was consumed (Stone-Dorshow and Levitt, 1987).

The role carbohydrate malabsorption plays in the onset of diarrhea most likely depends upon the balance between the osmotic force of the carbohydrate and the capacity of the colon to remove the carbohydrate via bacterial fermentation. In order to evaluate the significance of osmolarity, Clausen and coworkers (1998) compared the severity of diarrhea after consumption of fructooligosaccharide and lactulose, both of which are nonabsorbable carbohydrates. Although both carbohydrates are fermented by colonic microflora, they differ in osmolarity. The osmotic force is twice as high for lactulose as for frutooligosaccharide. In a crossover design, 12 individuals were given fructooligosaccharide or lactulose in increasing doses of 0, 20, 40, 80, and 160 g/d. The increase in fecal volume measured as a function of the dose administered was twice as high for lactulose as for fructooligosaccharide; however, there was substantial interindividual variation in the response. The researchers concluded that fecal volume in carbohydrate-induced diarrhea is proportional to the osmotic force of the malabsorbed saccharide, even though most is degraded by colonic bacteria (Clausen et al., 1998).

Allergic Reactions. Data on the allergenicity of inulin and oligofructose is very limited. Anaphylaxis was observed following the intravenous administration of inulin for determining the glomerular filtration rate (Chandra and Barron, 2002). Separate episodes of anaphylaxis were observed following the ingestion of artichoke leaves, a margarine containing inulin extracted from chicory (Raftiline HP), and a candy containing inulin (Raftiline HP) or oligofructose (Raftilose P95) (Gay-Crosier et al., 2000). A skin-pricking test revealed hypersensitivity to each of the above foods or ingredients (Gay-Crosier et al., 2000).

Pectin

Pectin has been shown to have a negligible effect on zinc retention in humans (Lei et al., 1980). Also, Behall and coworkers (1987) found that refined fibers had no effect on mineral balance as long as people were

consuming recommended dietary allowance levels of iron and zinc when fed as part of their control diet.

Polydextrose

Polydextrose has showed no reproductive toxicity, teratology, mutagenicity, genotoxicity, or carcinogenesis in experimental animals (Burdock and Flamm, 1999). In humans, no reports of abdominal cramping or diarrhea were reported in men and women who were given up to 12 g/d of polydextrose (Jie et al., 2000). Furthermore, there were no complaints of abdominal distress with the consumption of 30 g/d of polydextrose (Achour et al., 1994). However, flatulence and gas-related problems were reported following the intake of 30 g/d of polydextrose (Tomlin and Read, 1988). Diarrhea was reported with the consumption of 15 g/d of polydextrose; however, this symptom ceased after 1 month of intake (Saku et al., 1991).

Psyllium

Gastrointestinal Distress. In a meta-analysis of eight studies regarding psyllium intake, the authors found that psyllium was well tolerated and safe (Anderson et al., 2000a). There have been certain situations in which adverse effects have been observed. Esophageal obstruction was noted in an elderly man who regularly took a "heaping" teaspoon with some water (Noble and Grannis, 1984). Furthermore, an elderly woman who was given 2 tbs of a psyllium-based laxative three times daily suffered from small-bowel obstruction (Berman and Schultz, 1980). It was determined that her water intake was insufficient for this dose. Thus, psyllium generally does not cause gastrointestinal distress provided adequate amounts of water are consumed.

Cancer. In the European Center Prevention Organization Study, psyllium (*Functional Fiber*) was provided at a level of 3.5 g/d (Bonithon-Kopp et al., 2000). Patients ($n = 655$) with a history of colon adenomas were randomly assigned to one of three treatment groups: 2 g/d of calcium, 3.5 g/d of psyllium, or placebo. Participants in the study also had a colonoscopy after 3 years of follow-up. The adjusted odds ratio for colon adenoma recurrence for the psyllium fiber intervention was 1.67 ($p = 0.042$). The authors concluded that supplementation with psyllium may have adverse effects on colon adenoma recurrence.

Allergic Reactions. Several reports of anaphylaxis have been reported following the ingestion of psyllium-containing cereals (Drake et al., 1991; James et al., 1991; Lantner et al., 1990). Subsequent IgE antibodies to psyllium were confirmed in these reports. Symptoms of asthma have also been reported in individuals exposed to psyllium powder (Busse and Schoenwetter, 1975).

Resistant Starch

Ninety-one percent of individuals who consumed 32 g/d of RS_3 (retrograded starch; formed from the cooking and cooling or extrusion of starchy foods) experienced flatulence and 41 percent reported bloated feelings (Heijnen et al., 1998). Other gastrointestinal discomforts were reported by 14 percent of those consuming 32 g/d of RS_3, whereas only 5 percent of individuals consuming an equal amount of glucose reported such discomforts.

Summary

While occasional adverse gastrointestinal symptoms are observed when consuming some of the isolated or synthetic fibers, serious chronic adverse effects have not been observed. Furthermore, due to the bulky nature of fibers, excess consumption is likely to be self-limiting. Therefore, a UL was not set for these individual fibers.

RESEARCH RECOMMENDATIONS

The relationship of fiber to health is of great importance, particularly since novel fiber sources are appearing on the market, and these fiber sources may or may not produce the same physiological effects as fiber from traditional foods. Research that provides human data and does the following is assigned the highest priority:

- Evaluate the protective effect of fiber against colon cancer in subsets of the population by applying genotyping and phenotyping to those participating in fiber and colon cancer trials. There also needs to be increased validation of intermediate markers, such as polyp recurrence, and assessment of functional markers (e.g., fecal bulk) and its relationship to these endpoints.
- Conduct a dose–response study to determine the amount of fiber that needs to be ingested to promote optimum laxation so that this could form the basis for a recommendation for fiber intake and provide a basis for determining functional fibers.

- Attempt to relate changes in the colonic microflora due to fiber ingestion to functional endpoints (e.g., decreased irritable bowel syndrome, increased laxation).
- Conduct longer-term studies on low energy-dense food sources (high in dietary fiber) and satiety and weight control to see if a higher fiber diet will help with weight maintenance or promote adherence to reduced calorie diets for weight reduction.
- Examine the relation between *Dietary Fiber* intake, energy intake, and long-term body weight in existing prospective epidemiological studies in addition to intervention studies.
- Conduct long-term studies on the effects of both viscous and whole-grain cereal fibers on coronary heart disease and diabetes risk factors.

REFERENCES

AAP (American Academy of Pediatrics). 1981. Plant fiber intake in the pediatric diet. *Pediatrics* 67:572–575.

AAP. 1993. Carbohydrate and dietary fiber. In: Barness LA, ed. *Pediatric Nutrition Handbook*, 3rd ed. Elk Grove Village, IL: AAP. Pp. 100–106.

Abraham ZD, Mehta T. 1988. Three-week psyllium-husk supplementation: Effect on plasma cholesterol concentrations, fecal steroid excretion, and carbohydrate absorption in men. *Am J Clin Nutr* 47:67–74.

Achour L, Flourié B, Briet F, Pellier P, Marteau P, Rambaud J-C. 1994. Gastrointestinal effects and energy value of polydextrose in healthy nonobese men. *Am J Clin Nutr* 59:1362–1368.

AHA (American Heart Association). 1983. AHA committee report. Diet in the healthy child. Task Force Committee of the Nutrition Committee and the Cardiovascular Disease in the Young Council of the American Heart Association. *Circulation* 67:1411A–1414A.

Alberts DS, Einspahr J, Rees-McGee S, Ramanujam P, Buller MK, Clark L, Ritenbaugh C, Atwood J, Pethigal P, Earnest D, Villar H, Phelps J, Lipkin M, Wargovich M, Meyskens FL. 1990. Effects of dietary wheat-bran fiber on rectal epithelial cell proliferation in patients with resection for colorectal cancers. *J Natl Cancer Inst* 82:1280–1285.

Alberts DS, Einspahr J, Ritenbaugh C, Aickin M, Rees-McGee S, Atwood J, Emerson S, Mason-Liddil N, Bettinger L, Patel J, Bellapravalu S, Ramanujam PS, Phelps J, Clark L. 1997. The effect of wheat-bran fiber and calcium supplementation on rectal mucosal proliferation rates in patients with resected adenomatous colorectal polyps. *Cancer Epidemiol Biomarkers Prev* 6:161–169.

Alberts DS, Martínez ME, Roe DJ, Guillén-Rodríguez JM, Marshall JR, van Leeuwen JB, Reid ME, Ritenbaugh C, Vargas PA, Bhatacharyya AB, Earnest DL, Sampliner RE. 2000. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. *N Engl J Med* 342:1156–1162.

Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. 1994. A prospective study of diet and the risk of symptomatic diverticular disease in men. *Am J Clin Nutr* 60:757–764.

Aldoori WH, Giovannucci EL, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Wing AL, Trichopoulos DV, Willett WC. 1995. Prospective study of physical activity and the risk of symptomatic diverticular disease in men. *Gut* 36:276–282.

Aldoori WH, Giovannucci EL, Stampfer MJ, Rimm EB, Wing AL, Willett WC. 1997. Prospective study of diet and the risk of duodenal ulcer in men. *Am J Epidemiol* 145:42–50.

Aldoori WH, Giovannucci EL, Rockett HRH, Sampson L, Rimm EB, Willett WC. 1998. A prospective study of dietary fiber types and symptomatic diverticular disease in men. *J Nutr* 128:714–719.

Alles MS, Hautvast JG, Nagengast FM, Hartemink R, Van Laere KM, Jansen JB. 1996. Fate of fructo-oligosaccharides in the human intestine. *Br J Nutr* 76:211–221.

AMA (American Medical Association) Council on Scientific Affairs. 1989. Dietary fiber and health. *J Am Med Assoc* 262:542–546.

Anderson JW, Gustafson NJ. 1988. Hypocholesterolemic effects of oat and bean products. *Am J Clin Nutr* 48:749–753.

Anderson JW, Tietyen-Clark J. 1986. Dietary fiber: Hyperlipidemia, hypertension, and coronary heart disease. *Am J Gastroenterol* 81:907–919.

Anderson JW, Story L, Sieling B, Chen W-JL. 1984a. Hypocholesterolemic effects of high-fibre diets rich in water-soluble plant fibres. *J Can Diet Assoc* 45:140–148.

Anderson JW, Story L, Sieling B, Chen W-JL, Petro MS, Story J. 1984b. Hypocholesterolemic effects of oat-bran or bean intake for hypercholesterolemic men. *Am J Clin Nutr* 40:1146–1155.

Anderson JW, Gustafson NJ, Bryant CA, Tietyen-Clark J. 1987. Dietary fiber and diabetes: A comprehensive review and practical application. *J Am Diet Assoc* 87:1189–1197.

Anderson JW, Zettwoch N, Feldman T, Tietyen-Clark J, Oeltgen P, Bishop CW. 1988. Cholesterol-lowering effects of psyllium hydrophilic mucilloid for hypercholesterolemic men. *Arch Intern Med* 148:292–296.

Anderson JW, Gilinsky NH, Deakins DA, Smith SF, O'Neal DS, Dillon DW, Oeltgen PR. 1991. Lipid responses of hypercholesterolemic men to oat-bran and wheat-bran intake. *Am J Clin Nutr* 54:678–683.

Anderson JW, Garrity TF, Wood CL, Whitis SE, Smith BM, Oeltgen PR. 1992a. Prospective, randomized, controlled comparison of the effects of low-fat and low-fat plus high-fiber diets on serum lipid concentrations. *Am J Clin Nutr* 56:887–894.

Anderson JW, Riddell-Mason S, Gustafson NJ, Smith SF, Mackey M. 1992b. Cholesterol-lowering effects of psyllium-enriched cereal as an adjunct to a prudent diet in the treatment of mild to moderate hypercholesterolemia. *Am J Clin Nutr* 56:93–98.

Anderson JW, Allgood LD, Turner J, Oeltgen PR, Daggy BP. 1999. Effects of psyllium on glucose and serum lipid responses in men with type 2 diabetes and hypercholesterolemia. *Am J Clin Nutr* 70:466–473.

Anderson JW, Allgood LD, Lawrence A, Altringer LA, Jerdack GR, Hengehold DA, Morel JG. 2000a. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: Meta-analysis of 8 controlled trials. *Am J Clin Nutr* 71:472–479.

Anderson JW, Davidson MH, Blonde L, Brown WV, Howard JW, Ginsberg H, Allgood LD, Weingand KW. 2000b. Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am J Clin Nutr* 71:1433–1438.

Andersson S-O, Wolk A, Bergström R, Giovannucci E, Lindgren C, Baron J, Adami H-O. 1996. Energy, nutrient intake and prostate cancer risk: A population-based case-control study in Sweden. *Int J Cancer* 68:716–722.

Anti M, Pignataro G, Armuzzi A, Valenti A, Iascone E, Marmo R, Lamazza A, Pretaroli AR, Pace V, Leo P, Castelli A, Gasbarrini G. 1998. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. *Hepatogastroenterology* 45:727–732.

Appleby PN, Thorogood M, Mann JI, Key TJ. 1998. Low body mass index in non-meat eaters: The possible roles of animal fat, dietary fibre and alcohol. *Int J Obes Relat Metab Disord* 22:454–460.

Aro A, Uusitupa M, Voutilainen E, Hersio K, Korhonen T, Siitonen O. 1981. Improved diabetic control and hypocholesterolaemic effect induced by long-term dietary supplementation with guar gum in type-2 (insulin-independent) diabetes. *Diabetologia* 21:29–33.

Aro A, Uusitupa M, Voutilainen E, Korhonen T. 1984. Effects of guar gum in male subjects with hypercholesterolemia. *Am J Clin Nutr* 39:911–916.

Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ. 1992. A prospective study of nutritional factors and hypertension among US men. *Circulation* 86:1475–1484.

Ashraf W, Park F, Lof J, Quigley EM. 1995. Effects of psyllium therapy on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation. *Aliment Pharmacol Ther* 9:639–647.

Astrup A, Vrist E, Quaade F. 1990. Dietary fibre added to very low calorie diet reduces hunger and alleviates constipation. *Int J Obes* 14:105–112.

Bagga D, Ashley JM, Geffrey SP, Wang HJ, Barnard RJ, Korenman S, Heber D. 1995. Effects of a very low fat, high fiber diet on serum hormones and menstrual function. Implications for breast cancer prevention. *Cancer* 76:2491–2496.

Baghurst PA, Rohan TE. 1994. High-fiber diets and reduced risk of breast cancer. *Int J Cancer* 56:173–176.

Barbone F, Austin H, Partridge EE. 1993. Diet and endometrial cancer: A case-control study. *Am J Epidemiol* 137:393–403.

Baron JA, Schori A, Crow B, Carter R, Mann JI. 1986. A randomized controlled trial of low carbohydrate and low fat/high fiber diets for weight loss. *Am J Public Health* 76:1293–1296.

Bartram P, Gerlach S, Scheppach W, Keller F, Kasper H. 1992. Effect of a single oat bran cereal breakfast on serum cholesterol, lipoproteins, and apolipoproteins in patients with hyperlipoproteinemia type IIa. *J Parenter Enteral Nutr* 16:533–537.

Beer MU, Arrigoni E, Amado R. 1995. Effects of oat gum on blood cholesterol levels in healthy young men. *Eur J Clin Nutr* 49:517–522.

Behall KM. 1990. Effect of soluble fibers on plasma lipids, glucose tolerance and mineral balance. *Adv Exp Med Biol* 270:7–16.

Behall KM, Howe JC. 1996. Resistant starch as energy. *J Am Coll Nutr* 15:248–254.

Behall KM, Scholfield DJ, Lee K, Powell AS, Moser PB. 1987. Mineral balance in adult men: Effect of four refined fibers. *Am J Clin Nutr* 46:307–314.

Bell LP, Hectorn KJ, Reynolds H, Hunninghake DB. 1990. Cholesterol-lowering effects of soluble-fiber cereals as part of a prudent diet for patients with mild to moderate hypercholesterolemia. *Am J Clin Nutr* 52:1020–1026.

Benini L, Castellani G, Brighenti F, Heaton KW, Brentegani MT, Casiraghi MC, Sembenini C, Pellegrini N, Fioretta A, Minniti G. 1995. Gastric emptying of a solid meal is accelerated by the removal of dietary fibre naturally present in food. *Gut* 36:825–830.

Bergmann JF, Chassany O, Petit A, Triki R, Caulin C, Segrestaa JM. 1992. Correlation between echographic gastric emptying and appetite: Influence of psyllium. *Gut* 33:1042–1043.

Berman JI, Schultz MJ. 1980. Bulk laxative ileus. *J Am Geriatr Soc* 28:224–226.

Berta JL, Coste T, Rautureau J, Guilloud-Bataille M, Pequignot G. 1985. Diet and rectocolonic cancers. Results of a case-control study. *Gastroenterol Clin Biol* 9:348–353.

Bidoli E, Franceschi S, Talamini R, Barra S, La Vecchia C. 1992. Food consumption and cancer of the colon and rectum in north-eastern Italy. *Int J Cancer* 50:223–229.

Birkett AM, Jones GP, de Silva AM, Young GP, Muir JG. 1997. Dietary intake and faecal excretion of carbohydrate by Australians: Importance of achieving stool weights greater than 150 g to improve faecal markers relevant to colon cancer risk. *Eur J Clin Nutr* 51:625–632.

Birketvedt GS, Aaseth J, Florholmen JR, Ryttig K. 2000. Long term effect of fibre supplement and reduced energy intake on body weight and blood lipids in overweight subjects. *Acta Medica (Hradec Králové)* 43:129–132.

Blackburn NA, Holgate AM, Read NW. 1984. Does guar gum improve post-prandial hyperglycaemia in humans by reducing small intestinal contact area? *Br J Nutr* 52:197–204.

Blake DE, Hamblett CJ, Frost PG, Judd PA, Ellis PR. 1997. Wheat bread supplemented with depolymerized guar gum reduces the plasma cholesterol concentration in hypercholesterolemic human subjects. *Am J Clin Nutr* 65:107–113.

Blundell JE, Burley VJ. 1987. Satiation, satiety and the action of fibre on food intake. *Int J Obesity* 11:9–25.

Bolin TD, Stanton RA. 1998. Flatus emission patterns and fibre intake. *Eur J Surg* 582:115–118.

Bolton-Smith C, Woodward M, Tunstall-Pedoe H. 1992. The Scottish Heart Health Study. Dietary intake by food frequency questionnaire and odds ratios for coronary heart disease risk. II. The antioxidant vitamins and fibre. *Eur J Clin Nutr* 46:85–93.

Bonithon-Kopp C, Kronborg O, Giacosa A, Räth U, Faivre J. 2000. Calcium and fibre supplementation in prevention of colorectal adenoma recurrance: A randomised intervention trial. *Lancet* 356:1300–1306.

Bosaeus I, Carlsson NG, Sandberg AS, Andersson H. 1986. Effect of wheat bran and pectin on bile acid and cholesterol excretion in ileostomy patients. *Hum Nutr Clin Nutr* 40:429–440.

Bosello O, Cominacini L, Zocca I, Garbin U, Ferrari F, Davoli A. 1984. Effects of guar gum on plasma lipoproteins and apolipoproteins C-II and C-III in patients affected with familial combined hyperlipoproteinemia. *Am J Clin Nutr* 40:1165–1174.

Bouhnik Y, Flourié B, Riottot M, Bisetti N, Gailing M-F, Guibert A, Bornet F, Rambaud J-C. 1996. Effects of fructo-oligosaccharides ingestion on fecal bifidobacteria and selected metabolic indexes of colon carcinogenesis in healthy humans. *Nutr Cancer* 26:21–29.

Bouhnik Y, Vahedi K, Achour L, Attar A, Salfati J, Pochart P, Marteau P, Flourié B, Bornet F, Rambaud J-C. 1999. Short-chain fructo-oligosaccharide administration dose-dependently increases fecal bifidobacteria in healthy humans. *J Nutr* 129:113–116.

Boyle P, Zaridze DG, Smans M. 1985. Descriptive epidemiology of colorectal cancer. *Int J Cancer* 36:9–18.

Braaten JT, Wood PJ, Scott FW, Riedel KD, Poste LM, Collins MW. 1991. Oat gum lowers glucose and insulin after an oral glucose load. *Am J Clin Nutr* 53:1425–1430.

Braaten JT, Scott FW, Wood PJ, Riedel KD, Wolynetz MS, Brulé D, Collins MW. 1994a. High β-glucan oat bran and oat gum reduce postprandial blood glucose and insulin in subjects with and without type 2 diabetes. *Diabetic Med* 11:312–318.

Braaten JT, Wood PJ, Scott FW, Wolynetz MS, Lowe MK, Bradley-White P, Collins MW. 1994b. Oat beta-glucan reduces blood cholesterol concentration in hypercholesterolemic subjects. *Eur J Clin Nutr* 48:465–474.

Briet F, Achour L, Flourié B, Beaugerie L, Pellier P, Franchisseur C, Bornet F, Rambaud JC. 1995. Symptomatic response to varying levels of fructo-oligosaccharides consumed occasionally or regularly. *Eur J Clin Nutr* 49:501–507.

Brighenti F, Casiraghi MC, Canzi E, Ferrari A. 1999. Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal milieu and blood lipids in healthy male volunteers. *Eur J Clin Nutr* 53:726–733.

Brodribb AJM. 1977. Treatment of symptomatic diverticular disease with a high-fibre diet. *Lancet* 1:664–666.

Brown IL, McNaught KJ, Moloney E. 1995. Hi-maize: New directions in starch technology and nutrition. *Food Aust* 47:273–279.

Brown L, Rosner B, Willett W, Sacks FM. 1999. Cholesterol-lowering effects of dietary fiber: A meta-analysis. *Am J Clin Nutr* 69:30–42.

Brune M, Rossander-Hulten L, Hallberg L, Gleerup A, Sandberg AS. 1992. Iron absorption from bread in humans: Inhibiting effects of cereal fiber, phytate and inositol phosphates with different numbers of phosphate groups. *J Nutr* 122:442–449.

Buddington RK, Williams CH, Chen S-C, Witherly SA. 1996. Dietary supplementation of neosugar alters the fecal flora and decreases activities of some reductive enzymes in human subjects. *Am J Clin Nutr* 63:709–716.

Burdock GA, Flamm WG. 1999. A review of the studies of the safety of polydextrose in food. *Food Chem Toxicol* 37:233–264.

Burkitt DP, Walker ARP, Painter NS. 1972. Effect of dietary fibre on stools and transit-times, and its role in the causation of disease. *Lancet* 2:1408–1412.

Burley VJ, Paul AW, Blundell JE. 1993. Sustained post-ingestive action of dietary fibre: Effects of a sugar-beet-fibre-supplemented breakfast on satiety. *J Hum Nutr Diet* 6:43–50.

Burr ML, Sweetnam PM. 1982. Vegetarianism, dietary fiber, and mortality. *Am J Clin Nutr* 36:873–877.

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. 1989. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet* 2:757–761.

Burton R, Manninen V. 1982. Influence of psyllium-based fibre preparation on faecal and serum parameters. *Acta Med Scand Suppl* 668:91–94.

Busse WW, Schoenwetter WF. 1975. Asthma from psyllium in laxative manufacture. *Ann Intern Med* 83:361–362.

Cameron KJ, Nyulasi IB, Collier GR, Brown DJ. 1996. Assessment of the effect of increased dietary fibre intake on bowel function in patients with spinal cord injury. *Spinal Cord* 34:277–283.

Caygill CPJ, Charlett A, Hill MJ. 1998. Relationship between the intake of high-fibre foods and energy and the risk of cancer of the large bowel and breast. *Eur J Cancer Prev* 7:S11–S17.

Cerda JJ, Robbins FL, Burgin CW, Baumgartner TG, Rice RW. 1988. The effects of grapefruit pectin on patients at risk for coronary heart disease without altering diet or lifestyle. *Clin Cardiol* 11:589–594.

Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ. 2000. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 342:1392–1398.

Chandra R, Barron JL. 2002. Anaphylactic reaction to intravenous sinistrin (Inutest). *Ann Clin Biochem* 39:76.

Chen H-L, Haack VS, Janecky CW, Vollendorf NW, Marlett JA. 1998. Mechanisms by which wheat bran and oat bran increase stool weight in humans. *Am J Clin Nutr* 68:711–719.

Chen WJL, Anderson JW. 1986. Hypocholesterolemic effects of soluble fibers. In: Vahouny GV, Kritchevsky D, eds. *Dietary Fiber: Basic and Clinical Aspects.* New York: Plenum Press. Pp. 275–286.

Chiang MT, Yao HT, Chen HC. 2000. Effect of dietary chitosans with different viscosity on plasma lipids and lipid peroxidation in rats fed on a diet enriched with cholesterol. *Biosci Biotechnol Biochem* 64:965–971.

Clausen MR, Jorgensen J, Mortensen PB. 1998. Comparison of diarrhea induced by ingestion of fructooligosaccharide Idolax and disaccharide lactulose (role of osmolarity versus fermentation of malabsorbed carbohydrate). *Dig Dis Sci* 43:2696–2707.

Clevenger MA, Turnbill D, Inoue H, Enomoto M, Allen JA, Henderson LM, Jones E. 1988. Toxicological evaluation of neosugar: Genotoxicity, carcinogenicity, and chronic toxicity. *J Am Coll Toxicol* 7:643–662.

Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. 1992. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023.

Coudray C, Bellanger J, Castiglia-Delavaud C, Remesy C, Vermorel M, Rayssignuier Y. 1997. Effect of soluble or partly soluble dietary fibres supplementation on absorption and balance of calcium, magnesium, iron and zinc in healthy young men. *Eur J Clin Nutr* 51:375–380.

Cummings JH. 1984. Microbial digestion of complex carbohydrates in man. *Proc Nutr Soc* 43:35–44.

Cummings JH. 1993. The effect of dietary fiber on fecal weight and composition. In: Spiller GA, ed. *CRC Handbook of Dietary Fiber in Human Nutrition*, 2nd ed. Boca Raton, FL: CRC Press. Pp. 263–349.

Cummings JH. 2000. Nutritional management of diseases of the gut. In: Garrow JS, James WPT, Ralph A, eds. *Human Nutrition and Dietetics*, 10th ed. Edinburgh: Churchill Livingston. Pp. 547–573.

Cummings JH, Branch WJ. 1986. Fermentation and the production of short-chain fatty acids in the human large intestine. In: Vahouny GV, Kritchevsky D, eds. *Dietary Fiber: Basic and Clinical Aspects.* New York: Plenum Press. Pp. 131–149.

Cummings JH, Englyst HN. 1987. Fermentation in the human large intestine and the available substrates. *Am J Clin Nutr* 45:1243–1255.

Cummings JH, Southgate DAT, Branch W, Houston H, Jenkins DJA, James WPT. 1978. Colonic responses to dietary fibre from carrot, cabbage, apple, bran, and guar gum. *Lancet* 1:5–9.

Cummings JH, Bingham SA, Heaton KW, Eastwood MA. 1992. Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). *Gastroenterology* 103:1783–1789.

Cummings JH, Beatty ER, Kingman SM, Bingham SA, Englyst HN. 1996. Digestion and physiological properties of resistant starch in the human large bowel. *Br J Nutr* 75:733–747.

Dales LG, Friedman GD, Ury HK, Grossman S, Williams SR. 1979. A case-control study of relationships of diet and other traits to colorectal cancer in American blacks. *Am J Epidemiol* 109:132–144.

Danielsson A, Ek B, Nyhlin H, Steen L. 1979. Effect of long term treatment with hydrophilic colloid on serum lipids. *Acta Hepatogastroenterol (Stuttg)* 26:148–153.

Davidson MH, Maki KC. 1999. Effects of dietary inulin on serum lipids. *J Nutr* 129:1474S–1477S.

Davidson MH, Dugan LD, Burns JH, Bova J, Story K, Drennan KB. 1991. The hypocholesterolemic effects of β-glucan in oatmeal and oat bran. A dose-controlled study. *J Am Med Assoc* 265:1833–1839.

Davidson MH, Maki KC, Kong JC, Dugan LD, Torri SA, Hall HA, Drennan KB, Anderson SM, Fulgoni VL, Saldanha LG, Olson BH. 1998. Long-term effects of consuming foods containing psyllium seed husk on serum lipids in subjects with hypercholesterolemia. *Am J Clin Nutr* 67:367–376.

de Deckere EA, Kloots WJ, van Amelsvoort JM. 1993. Resistant starch decreases serum total cholesterol and triacylglycerol concentrations in rats. *J Nutr* 123:2142–2151.

Delargy HJ, Burley VJ, O'Sullivan KR, Fletcher RJ, Blundell JE. 1995. Effects of different soluble:insoluble fibre ratios at breakfast on 24-h pattern of dietary intake and satiety. *Eur J Clin Nutr* 49:754–766.

de Roos N, Heijnen M-L, de Graaf C, Woestenenk G, Hobbel E. 1995. Resistant starch has little effect on appetite, food intake and insulin secretion of healthy young men. *Eur J Clin Nutr* 49:532–541.

De Stefani E, Correa P, Ronco A, Mendilaharsu M, Guidobono M, Deneo-Pellegrini H. 1997. Dietary fiber and risk of breast cancer: A case-control study in Uruguay. *Nutr Cancer* 28:14–19.

Dettmar PW, Sykes J. 1998. A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation. *Curr Med Res Opin* 14:227–233.

Djoussé L, Ellison RC, Zhang Y, Arnett DK, Sholinsky P, Borecki I. 1998. Relation between dietary fiber consumption and fibrinogen and plasminogen activator inhibitor type 1: The National Heart, Lung, and Blood Institute Family Heart Study. *Am J Clin Nutr* 68:568–575.

Drake CL, Moses ES, Tandberg D. 1991. Systemic anaphylaxis after ingestion of a psyllium-containing breakfast cereal. *Am J Emerg Med* 9:449–451.

Duncan KH, Bacon JA, Weinsier RL. 1983. The effects of high and low energy density diets on satiety, energy intake, and eating time of obese and nonobese subjects. *Am J Clin Nutr* 37:763–767.

Durrington PN, Manning AP, Bolton CH, Hartog M. 1976. Effect of pectin on serum lipids and lipoproteins, whole-gut transit-time, and stool weight. *Lancet* 2:394–396.

Dutta SK, Hlasko J. 1985. Dietary fiber in pancreatic disease: Effect of high fiber diet on fat malabsorption in pancreatic insufficiency and in vitro study of the interaction of dietary fiber with pancreatic enzymes. *Am J Clin Nutr* 41:517–525.

Dwyer J. 1980. Diets for children and adolescents that meet the dietary goals. *Am J Dis Child* 134:1073–1080.

Eliasson K, Ryttig KR, Hylander B, Rossner S. 1992. A dietary fibre supplement in the treatment of mild hypertension. A randomized, double-blind, placebo-controlled trial. *J Hypertens* 10:195–199.

Ellis PR, Kamalanathan T, Dawoud FM, Strange RN, Coultate TP. 1988. Evaluation of guar biscuits for use in the management of diabetes: Tests of physiological effects and palatability in non-diabetic volunteers. *Eur J Clin Nutr* 42:425–435.

Englyst HN, Cummings JH. 1986. Digestion of the carbohydrates of banana (*Musa paradisiaca sapientum*) in the human small intestine. *Am J Clin Nutr* 44:42–50.

Englyst HN, Cummings JH. 1987. Digestion of polysaccharides of potato in the small intestine of man. *Am J Clin Nutr* 45:423–431.

Englyst HN, Kingman SM, Cummings JH. 1992. Classification and measurement of nutritionally important starch fractions. *Eur J Clin Nutr* 46:S33–S50.

Everson GT, Daggy BP, McKinley C, Story JA. 1992. Effects of psyllium hydrophilic muccilloid on LDL-cholesterol and bile acid synthesis in hypercholesterolemic men. *J Lipid Res* 33:1183–1192.

FDA (U.S. Food and Drug Administration). 1987. Nutrition labeling of food; calorie content. *Fed Regis* 52:28590–28691.

Feskens EJM, Loeber JG, Kromhout D. 1994. Diet and physical activity as determinants of hyperinsulinemia: The Zutphen Elderly Study. *Am J Epidemiol* 140:350–360.

Findlay JM, Smith AN, Mitchell WD, Anderson AJB, Eastwood MA. 1974. Effects of unprocessed bran on colon function in normal subjects and in diverticular disease. *Lancet* 1:146–149.

Franceschi S, Favero A, Decarli A, Negri E, La Vecchia C, Ferraroni M, Russo A, Salvini S, Amadori D, Conti E, Montella M, Giacosa A. 1996. Intake of macronutrients and risk of breast cancer. *Lancet* 347:1351–1356.

Fraser GE, Sabaté J, Beeson WL, Strahan TM. 1992. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch Intern Med* 152:1416–1424.

Frati-Munari AC, Benitez-Pinto W, Raul Ariza-Andraca C, Casarrubias M. 1998. Lowering glycemic index of food by acarbose and Plantago psyllium mucilage. *Arch Med Res* 29:137–141.

Freudenheim JL, Graham S, Horvath PJ, Marshall JR, Haughey BP, Wilkinson G. 1990. Risks associated with source of fiber and fiber components in cancer of the colon and rectum. *Cancer Res* 50:3295–3300.

Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure JR, Swanson MK, Nemoto T, Graham S. 1996. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *J Natl Cancer Inst* 88:340–348.

Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, Speizer FE, Willett WC. 1999. Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med* 340:169–176.

Fuessl HS, Williams G, Adrian TE, Bloom SR. 1987. Guar sprinkled on food: Effect on glycaemic control, plasma lipids and gut hormones in non-insulin dependent diabetic patients. *Diabetic Med* 4:463–468.

Gabbe SG, Cohen AW, Herman GO, Schwartz S. 1982. Effect of dietary fiber on the oral glucose tolerance test in pregnancy. *Am J Obstet Gynecol* 143:514–517.

Gallaher CM, Munion J, Hesslink R, Wise J, Gallaher DD. 2000. Cholesterol reduction by glucomannan and chitosan is mediated by changes in cholesterol absorption and bile acid and fat excretion in rats. *J Nutr* 130:2753–2759.

Gay-Crosier F, Schreiber G, Hauser C. 2000. Anaphylaxis from inulin in vegetables and processed food. *N Engl J Med* 342:1372.

Gear JSS, Ware A, Fursdon P, Mann JI, Nolan DJ, Brodribb AJM, Vessey MP. 1979. Symptomless diverticular disease and intake of dietary fibre. *Lancet* 1:511–514.

Gerber M. 1998. Fibre and breast cancer. *Eur J Cancer Prev* 7:S63–S67.

Gerhardsson de Verdier M, Hagman U, Steineck G, Rieger Å, Norell SE. 1990. Diet, body mass and colorectal cancer: A case-referent study in Stockholm. *Int J Cancer* 46:832–838.

Gibson GR, Beatty ER, Wang X, Cummings JH. 1995. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology* 108:975–982.

Giovannucci E, Willett WC. 1994. Dietary factors and risk of colon cancer. *Ann Med* 26:443–452.

Giovannucci E, Stampfer MJ, Colditz G, Rimm EB, Willett WC. 1992. Relationship of diet to risk of colorectal adenoma in men. *J Natl Cancer Inst* 84:91–98.

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. 1994. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54:2390–2397.

Golay A, Koellreutter B, Bloise D, Assal JP, Wursch P. 1992. The effect of muesli or cornflakes at breakfast on carbohydrate metabolism in type 2 diabetic patients. *Diabetes Res Clin Pract* 15:135–141.

Gold LA, McCourt JP, Merimee TJ. 1980. Pectin: An examination in normal subjects. *Diabetes Care* 3:50–52.

Goldin BR, Adlercreutz H, Gorbach SL, Warram JH, Dwyer JT, Swenson L, Woods MN. 1982. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Engl J Med* 307:1542–1547.

Goodman MT, Wilkens LR, Hankin JH, Lyu L-C, Wu AH, Kolonel LN. 1997. Association of soy and fiber consumption with the risk of endometrial cancer. *Am J Epidemiol* 146:294–306.

Gorbach SL, Goldin BR. 1987. Diet and the excretion and enterohepatic cycling of estrogens. *Prev Med* 16:525–529.

Goulder TJ, Alberti KGMM, Jenkins DA. 1978. Effect of added fiber on the glucose and metabolic response to a mixed meal in normal and diabetic subjects. *Diabetes Care* 1:351–355.

Graham S, Hellmann R, Marshall J, Freudenheim J, Vena J, Swanson M, Zielezny M, Nemoto T, Stubbe N, Raimondo T. 1991. Nutritional epidemiology of postmenopausal breast cancer in western New York. *Am J Epidemiol* 134:552–566.

Graham S, Zielezny M, Marshall J, Priore R, Freudenheim J, Brasure J, Haughey B, Nasca P, Zdeb M. 1992. Diet in the epidemiology of postmenopausal breast cancer in the New York State Cohort. *Am J Epidemiol* 136:1327–1337.

Grizard D, Barthomeuf C. 1999. Non-digestible oligosaccharides used as prebiotic agents: Mode of production and beneficial effects on animal and human health. *Reprod Nutr Dev* 39:563–588.

Groop P-H, Aro A, Stenman S, Groop L. 1993. Long-term effects of guar gum in subjects with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 58:513–518.

Grossman SP. 1986. The role of glucose, insulin and glucagon in the regulation of food intake and body weight. *Neurosci Biobehav Rev* 10:295–315.

Guerciolini R, Radu-Radulescu L, Boldrin M, Dallas J, Moore R. 2001. Comparative evaluation of fecal fat excretion induced by orlistat and chitosan. *Obes Res* 9:364–367.

Haenszel W, Kurihara M. 1968. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst* 40:43–68.

Hallfrisch J, Powell A, Carafelli C, Reiser S, Prather ES. 1987. Mineral balances of men and women consuming high fiber diets with complex or simple carbohydrate. *J Nutr* 117:48–55.

Hallfrisch J, Tobin JD, Muller DC, Andres R. 1988. Fiber intake, age, and other coronary risk factors in men of the Baltimore Longitudinal Study (1959–1975). *J Gerontol Med Sci* 43:M64–M68.

Hallfrisch J, Scholfield DJ, Behall KM. 1995. Diets containing soluble oat extracts improve glucose and insulin responses of moderately hypercholesterolemic men and women. *Am J Clin Nutr* 61:379–384.

Harris PJ, Ferguson LR. 1993. Dietary fibre: Its composition and role in protection against colorectal cancer. *Mutat Res* 290:97–110.

Harris PJ, Triggs CM, Roberton AM, Watson ME, Ferguson LR. 1996. The adsorption of heterocyclic aromatic amines by model dietary fibres with contrasting compositions. *Chem Biol Interact* 100:13–25.

Haseman JK, Arnold J, Eustis SL. 1990. Tumor incidences in Fischer 344 rats: NTP historical data. In: GA Boorman, ed. *Pathology of the Fischer Rat.* San Diego, CA: Academic Press. Pp. 557–564.

Health and Welfare Canada. 1985. *Report of the Expert Advisory Committee on Dietary Fibre.* Ottawa: Supply and Services Canada.

Health Canada. 1988. *Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them.* Ottawa: Food Directorate, Health Protection Branch, Health Canada.

Health Canada. 1997. Appendix 2. Guideline for planning and statistical review of clinical laxation studies for dietary fibre. In: *Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them.* Ottawa: Food Directorate, Health Protection Branch, Health Canada.

Heaton KW. 1973. Food fibre as an obstacle to energy intake. *Lancet* 2:1418–1421.

Heijnen M-LA, van Amelsvoort JMM, Deurenberg P, Beynen AC. 1996. Neither raw nor retrograded resistant starch lowers fasting serum cholesterol concentrations in healthy normolipidemic subjects. *Am J Clin Nutr* 64:312–318.

Heijnen M-LA, van Amelsvoort JMM, Deurenberg P, Beynen AC. 1998. Limited effect of consumption of uncooked (RS_2) or retrograded (RS_3) resistant starch on putative risk factors for colon cancer in healthy men. *Am J Clin Nutr* 67:322–331.

Heilbrun LK, Nomura A, Hankin JH, Stemmermann GN. 1989. Diet and colorectal cancer with special reference to fiber intake. *Int J Cancer* 44:1–6.

Henquin JC. 1988. *Reproduction Toxicity: Study on the Influence of Fructooligosaccharides on the Development of Foetal and Postnatal Rat.* Raffinerie Tirlemontoise Internal Report. Photocopy.

Hill MJ. 1997. Cereals, cereal fibre and colorectal cancer risk: A review of the epidemiological literature. *Eur J Cancer Prev* 6:219–225.

Hillman LC, Peters SG, Fisher CA, Pomare EW. 1983. Differing effects of pectin, cellulose and lignin on stool pH, transit time and weight. *Br J Nutr* 50:189–195.

Hillman LC, Peters SG, Fisher CA, Pomare EW. 1985. The effects of the fiber components pectin, cellulose and lignin on serum cholesterol levels. *Am J Clin Nutr* 42:207–213.

Ho SC, Tai ES, Eng PHK, Tan CE, Fok ACK. 2001. In the absence of dietary surveillance, chitosan does not reduce plasma lipids or obesity in hypercholesterolaemic obese Asian subjects. *Singapore Med J* 42:6–10.

Hoff G, Moen IE, Trygg K, Frølich W, Sauar J, Vatn M, Gjone E, Larsen S. 1986. Epidemiology of polyps in the rectum and sigmoid colon. Evaluation of nutritional factors. *Scand J Gastroenterol* 21:199–204.

Holman RR, Steemson J, Darling P, Turner RC. 1987. No glycemic benefit from guar administration in NIDDM. *Diabetes Care* 10:68–71.

Holt S, Brand J, Soveny C, Hansky J. 1992. Relationship of satiety to postprandial glycaemic, insulin and cholecystokinin responses. *Appetite* 18:129–141.

Howe GR, Benito E, Castelleto R, Cornée J, Estéve J, Gallagher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA, Kune S, L'Abbé KA, Lee HP, Lee M, Miller AB, Peters RK, Potter JD, Riboli E, Slattery ML, Trichopoulos D, Tuyns A, Tzonou A, Whittemore AS, Wu-Williams AH, Shu Z. 1992. Dietary intake of fiber and decreased risk of cancers of the colon and rectum: Evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* 84:1887–1896.

Humble CG, Malarcher AM, Tyroler HA. 1993. Dietary fiber and coronary heart disease in middle-aged hypercholesterolemic men. *Am J Prev Med* 9:197–202.

Hunt R, Fedorak R, Frohlich J, McLennan C, Pavilanis A. 1993. Therapeutic role of dietary fibre. *Can Fam Physician* 39:897–910.

Hylla S, Gostner A, Dusel G, Anger H, Bartram H-P, Christl SU, Kasper H, Scheppach W. 1998. Effects of resistant starch on the colon in healthy volunteers: Possible implications for cancer prevention. *Am J Clin Nutr* 67:136–142.

Ingram DM. 1981. Trends in diet and breast cancer mortality in England and Wales 1928–1977. *Nutr Cancer* 3:75–80.

IOM (Institute of Medicine). 1991. *Nutrition During Lactation.* Washington, DC: National Academy Press.

IOM. 2001. *Dietary Reference Intakes: Proposed Definition of Dietary Fiber.* Washington, DC: National Academy Press.

Iscovich JM, L'Abbé KA, Castelleto R, Calzona A, Bernedo A, Chopita NA, Jmelnitzsky AC, Kaldor J, Howe GR. 1992. Colon cancer in Argentina. II: Risk from fibre, fat and nutrients. *Int J Cancer* 51:858–861.

Ito N, Hasegawa R, Sano M, Tamano S, Esumi H, Takayama S, Sugimura T. 1991. A new colon and mammary carcinogen in cooked food, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). *Carcinogenesis* 12:1503–1506.

Jackson KG, Taylor GRJ, Clohessy AM, Williams CM. 1999. The effect of the daily intake of inulin fasting lipid, insulin and glucose concentrations in middle-aged men and women. *Br J Nutr* 82:23–30.

Jacobs DR, Meyer KA, Kushi LH, Folsom AR. 1998. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: The Iowa Women's Health Study. *Am J Clin Nutr* 68:248–257.

Jacobs LR. 1986. Relationship between dietary fiber and cancer: Metabolic, physiologic, and cellular mechanisms. *Proc Soc Exp Biol Med* 183:299–310.

Jain M, Cook GM, Davis FG, Grace MG, Howe GR, Miller AB. 1980. A case-control study of diet and colo-rectal cancer. *Int J Cancer* 26:757–768.

James JM, Cooke SK, Barnett A, Sampson HA. 1991. Anaphylactic reactions to a psyllium-containing cereal. *J Allergy Clin Immunol* 88:402–408.

Jenkins DJA, Newton C, Leeds AR, Cummings JH. 1975. Effect of pectin, guar gum, and wheat fibre on serum cholesterol. *Lancet* 1:1116–1117.

Jenkins DJA, Wolever TMS, Leeds AR, Gassull MA, Haisman P, Dilawari J, Goff DV, Metz GL, Alberti KGMM. 1978. Dietary fibres, fibre analogues, and glucose tolerance: Importance of viscosity. *Br Med J* 1:1392–1394.

Jenkins DJA, Wolever TMS, Collier GR, Ocana A, Rao AV, Buckley G, Lam Y, Mayer A, Thompson LU. 1987. Metabolic effects of a low-glycemic-index diet. *Am J Clin Nutr* 46:968–975.

Jenkins DJA, Vuksan V, Kendall CWC, Würsch P, Jeffcoat R, Waring S, Mehling CC, Vidgen E, Augustin LSA, Wong E. 1998. Physiological effects of resistant starches on fecal bulk, short chain fatty acids, blood lipids and glycemic index. *J Am Coll Nutr* 17:609–616.

Jenkins DJA, Kendall CWC, Vuksan V, Vidgen E, Parler T, Faulkner D, Mehling CC, Garsetti M, Testolin G, Cunnane SC, Ryan MA, Corey PN. 2002. Soluble fiber intake at a dose approved by the US Food and Drug Administration for a health claim of health benefits: Serum lipid risk factors for cardiovascular disease assessed in a randomized controlled crossover trial. *Am J Clin Nutr* 75:834–839.

Jennings CD, Boleyn K, Bridges SR, Wood PJ, Anderson JW. 1988. A comparison of the lipid-lowering and intestinal morphological effects of cholestyramine, chitosan, and oat gum in rats. *Proc Soc Exp Biol Med* 189:13–20.

Jie Z, Bang-Yao L, Ming-Jie X, Hai-Wei L, Zu-Kang Z, Ting-Song W, Craig SAS. 2000. Studies on the effects of polydextrose intake on physiologic function in Chinese people. *Am J Clin Nutr* 72:1503–1509.

Judd PA, Truswell AS. 1981. The effect of rolled oats on blood lipids and fecal steroid excretion in man. *Am J Clin Nutr* 34:2061–2067.

Kang JY, Doe WF. 1979. Unprocessed bran causing intestinal obstruction. *Br Med J* 1:1249–1250.

Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E. 1997. Prospective study of diet and female colorectal cancer: The New York University Women's Health Study. *Nutr Cancer* 28:276–281.

Kay RM, Truswell AS. 1977. Effect of citrus pectin on blood lipids and fecal steroid excretion in man. *Am J Clin Nutr* 30:171–175.

Kelsay JL, Behall KM, Prather ES. 1978. Effect of fiber from fruits and vegetables on metabolic responses of human subjects. I. Bowel transit time, number of defecations, fecal weight, urinary excretions of energy and nitrogen and apparent digestibilities of energy, nitrogen, and fat. *Am J Clin Nutr* 31:1149–1153.

Key TJA, Thorogood M, Appleby PN, Burr ML. 1996. Dietary habits and mortality in 11,000 vegetarians and health conscious people: Results of a 17 year follow up. *Br Med J* 313:775–779.

Khaw K, Barrett-Connor E. 1987. Dietary fiber and reduced ischemic heart disease mortality rates in men and women: A 12-year prospective study. *Am J Epidemiol* 126:1093–1102.

Kirby RW, Anderson JW, Sieling B, Rees ED, Chen W-JL, Miller RE, Kay RM. 1981. Oat-bran intake selectively lowers serum low-density lipoprotein cholesterol concentrations of hypercholesterolemic men. *Am J Clin Nutr* 34:824–829.

Kleessen B, Sykura B, Zunft HJ, Blaut M. 1997. Effects of inulin and lactose on fecal microflora, microbial activity, and bowel habit in elderly constipated persons. *Am J Clin Nutr* 65:1397–1402.

Klurfeld DM. 1992. Dietary fiber-mediated mechanisms in carcinogenesis. *Cancer Res* 52:2055S–2059S.

Knekt P, Steineck G, Järvinen R, Hakulinen T, Aromaa A. 1994. Intake of fried meat and risk of cancer: A follow-up study in Finland. *Int J Cancer* 59:756–760.

Knox TA, Kassarjian Z, Dawson-Hughes B, Golner BB, Dallal GE, Arora S, Russell RM. 1991. Calcium absorption in elderly subjects on high- and low-fiber diets: Effect of gastric acidity. *Am J Clin Nutr* 53:1480–1486.

Kochen MM, Wegscheider K, Abholz HH. 1985. Prophylaxis of constipation by wheat bran: A randomized study in hospitalized patients. *Digestion* 31:220–224.

Krishnamachar S, Mickelsen O. 1987. The influence of different carbohydrate sources on blood glucose levels and satiety: Effect of physical activity on blood glucose response. *Hum Nutr Food Sci Nutr* 41F:29–39.

Kromhout D, Bosschieter EB, de Lezenne Coulander C. 1982. Dietary fibre and 10-year mortality from coronary heart disease, cancer, and all causes. The Zutphen Study. *Lancet* 2:518–522.

Krotkiewski M. 1987. Effect of guar gum on the arterial blood pressure. *Acta Med Scand* 222:43–49.

Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. 1985. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. *N Engl J Med* 312:811–818.

Lagier F, Cartier A, Somer J, Dolovich J, Malo JL. 1990. Occupational asthma caused by guar gum. *J Allergy Clin Immunol* 85:785–790.

Landin K, Holm G, Tengborn L, Smith U. 1992. Guar gum improves insulin sensitivity, blood lipids, blood pressure, and fibrinolysis in healthy men. *Am J Clin Nutr* 56:1061–1065.

Lantner RR, Espiritu BR, Zumerchik P, Tobin MC. 1990. Anaphylaxis following ingestion of a psyllium-containing cereal. *J Am Med Assoc* 264:2534–2536.

Lanza E. 1990. National Cancer Institute Satellite Symposium on Fiber and Colon Cancer. In: Kritchevsky D, Bonfield C, Anderson JW, eds. *Dietary Fiber: Chemistry, Physiology, and Health Effects.* New York: Plenum Press. Pp. 383–387.

Larson DE, Hunter GR, Williams MJ, Kekes-Szabo T, Nyikos I, Goran MI. 1996. Dietary fat in relation to body fat and intraabdominal adipose tissue: A cross-sectional analysis. *Am J Clin Nutr* 64:677–684.

Leathwood P, Pollet P. 1988. Effects of slow release carbohydrates in the form of bean flakes on the evolution of hunger and satiety in man. *Appetite* 10:1–11.

Lee HP, Gourley L, Duffy SW, Estève J, Lee J, Day NE. 1991. Dietary effects on breast-cancer risk in Singapore. *Lancet* 337:1197–1200.

Lei KY, Davis MW, Fang MM, Young LC. 1980. Effect of pectin on zinc, copper and iron balances in humans. *Nutr Rep Int* 22:459–466.

Lev R. 1990. Malignant potential of adenomatous polyps. In: *Adenomatous Polyps of the Colon: Pathobiological and Clinical Features.* New York: Springer-Verlag. Pp. 53–89.

Levin EG, Miller VT, Muesing RA, Stoy DB, Balm TK, LaRosa JC. 1990. Comparison of psyllium hydrophilic mucilloid and cellulose as adjuncts to a prudent diet in the treatment of mild to moderate hypercholesterolemia. *Arch Intern Med* 150:1822–1827.

Levine AS, Billington CJ. 1994. Dietary fiber: Does it affect food intake and body weight? In: Fernstrom JD, Miller GD, eds. *Appetite and Body Weight Regulation: Sugar, Fat, and Macronutrient Substitutes.* Boca Raton, FL: CRC Press. Pp. 191–200.

Librenti MC, Cocchi M, Orsi E, Pozza G, Micossi P. 1992. Effect of soya and cellulose fibers on postprandial glycemic response in type II diabetic patients. *Diabetes Care* 15:111–113.

Lichtenstein AH, Ausman LM, Jalbert SM, Vilella-Bach M, Jauhiainen M, McGladdery S, Erkkila AT, Ehnholm C, Frohlich J, Schaefer EJ. 2002. Efficacy of a Therapeutic Lifestyle Change/Step 2 diet in moderately hypercholesterolemic middle-aged and elderly female and male subjects. *J Lipid Res* 43:264–273.

Lipid Research Clinics Program. 1984. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *J Am Med Assoc* 251:365–374.

Little J, Logan RFA, Hawtin PG, Hardcastle JD, Turner ID. 1993. Colorectal adenomas and diet: A case-control study of subjects participating in the Nottingham Faecal Occult Blood Screening Programme. *Br J Cancer* 67:177–184.

Livesey G. 1990. Energy values of unavailable carbohydrate and diets: An inquiry and analysis. *Am J Clin Nutr* 51:617–637.

Loening-Baucke V. 1993. Chronic constipation in children. *Gastroenterology* 105:1557–1564.

Lovegrove JA, Clohessy A, Milon H, Williams CM. 2000. Modest doses of β-glucan do not reduce concentrations of potentially atherogenic lipoproteins. *Am J Clin Nutr* 72:49–55.

Low AG. 1990. Nutritional regulation of gastric secretion, digestion and emptying. *Nutr Res Rev* 3:229–252.

LSRO (Life Sciences Research Office). 1987. *Physiological Effects and Health Consequences of Dietary Fiber.* Bethesda, MD: LSRO.

Lubin F, Wax Y, Modan B. 1986. Role of fat, animal protein, and dietary fiber in breast cancer etiology: A case-control study. *J Natl Cancer Inst* 77:605–612.

Luo J, Rizkalla SW, Alamowitch C, Boussairi A, Blayo A, Barry J-L, Laffitte A, Guyon F, Bornet FRJ, Slama G. 1996. Chronic consumption of short-chain fructo-oligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. *Am J Clin Nutr* 63:939–945.

Lupton JR. 1995. Butyrate and colonic cytokinetics: Differences between in vitro and in vivo studies. *Eur J Cancer Prev* 4:373–378.

Lupton JR, Morin JL, Robinson MC. 1993. Barley bran flour accelerates gastrointestinal transit time. *J Am Diet Assoc* 93:881–885.

Lyon JL, Mahoney AW, West DW, Gardner JW, Smith KR, Sorenson AW, Stanish W. 1987. Energy intake: Its relationship to colon cancer risk. *J Natl Cancer Inst* 78:853–861.

Macfarlane GT, Englyst HN. 1986. Starch utilization by the human large intestinal microflora. *J Appl Bacteriol* 60:195–201.

MacLennan R, Macrae F, Bain C, Battistutta D, Chapuis P, Gratten H, Lambert J, Newland RC, Ngu M, Russell A, Ward M, Wahlqvist ML. 1995. Randomized trial of intake of fat, fiber, and beta carotene to prevent colorectal adenomas. *J Natl Cancer Inst* 87:1760–1766.

MacMahon M, Carless J. 1998. Ispaghula husk in the treatment of hypercholesterolemia: A double-blind controlled study. *J Cardiovasc Risk* 5:167–172.

Macquart-Moulin G, Riboli E, Cornée J, Charnay B, Berthezène P, Day N. 1986. Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* 38:183–191.

Macquart-Moulin G, Riboli E, Cornée J, Kaaks R, Berthezène P. 1987. Colorectal polyps and diet: A case-control study in Marseilles. *Int J Cancer* 40:179–188.

Manousos O, Day NE, Tzonou A, Papadimitriou C, Kapetanakis A, Polychronopoulou-Trichopoulou A, Trichopoulos D. 1985. Diet and other factors in the aetiology of diverticulosis: An epidemiological study in Greece. *Gut* 26:544–549.

Marlett JA. 1992. Content and composition of dietary fiber in 117 frequently consumed foods. *J Am Diet Assoc* 92:175–186.

Marlett JA, Longacre MJ. 1996. Comparison of in vitro and in vivo measures of resistant starch in selected grain products. *Cereal Chem* 73:63–68.

Mathur KS, Khan MA, Sharma RD. 1968. Hypocholesterolaemic effect of Bengal gram: A long-term study in man. *Br Med J* 1:30–31.

McBurney MI. 1991. Potential water-holding capacity and short-chain fatty acid production from purified fiber sources in a fecal incubation system. *Nutrition* 7:421–424.

McBurney MI, Thompson LU. 1990. Fermentative characteristics of cereal brans and vegetable fibers. *Nutr Cancer* 13:271–280.

McCann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S. 2000. Diet in the epidemiology of endometrial cancer in western New York (United States). *Cancer Causes Control* 11:965–974.

McCann SE, Moysich KB, Mettlin C. 2001. Intakes of selected nutrients and food groups and risk of ovarian cancer. *Nutr Cancer* 39:19–28.

McClung HJ, Boyne LJ, Linsheid T, Heitlinger LA, Murray RD, Fyda J, Li BUK. 1993. Is combination therapy for encopresis nutritionally safe? *Pediatrics* 91:591–594.

McClung HJ, Boyne L, Heitlinger L. 1995. Constipation and dietary fiber intake in children. *Pediatrics* 96:999–1001.

McKeown-Eyssen GE, Bright-See E, Bruce WR, Jazmaji V. 1994. A randomized trial of a low fat high fibre diet in the recurrence of colorectal polyps. *J Clin Epidemiol* 47:525–536.

McRorie JW, Daggy BP, Morel JG, Diersing PS, Miner PB, Robinson M. 1998. Psyllium is superior to docusate sodium for treatment of chronic constipation. *Aliment Pharmacol Ther* 12:491–497.

McRorie J, Kesler J, Bishop L, Filloon T, Allgood G, Sutton M, Hunt T, Laurent A, Rudolph C. 2000. Effects of wheat bran and Olestra on objective measures of stool and subjective reports of GI symptoms. *Am J Gastroenterol* 95:1244–1252.

Mennen LI, Witteman JCM, den Breeijen JH, Schouten EG, de Jong PTVM, Hofman A, Grobbee DE. 1997. The association of dietary fat and fiber with coagulation factor VII in the elderly: The Rotterdam Study. *Am J Clin Nutr* 65:732–736.

Meyer KA, Kushi LH, Jacobs DR, Slavin J, Sellers TA, Folsom AR. 2000. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930.

Miller AB, Howe GR, Jain M, Craib KJP, Harrison L. 1983. Food items and food groups as risk factors in a case-control study of diet and colo-rectal cancer. *Int J Cancer* 32:155–161.

Miller WC, Niederpruem MG, Wallace JP, Lindeman AK. 1994. Dietary fat, sugar, and fiber predict body fat content. *J Am Diet Assoc* 94:612–615.

Modan B, Barell V, Lubin F, Modan M, Greenberg RA, Graham S. 1975. Low-fiber intake as an etiologic factor in cancer of the colon. *J Natl Cancer Inst* 55:15–18.

Morais MB, Vítolo MR, Aguirre ANC, Fagundes-Neto U. 1999. Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. *J Pediatr Gastroenterol Nutr* 29:132–135.

Morales M, Llopis A. 1992. Breast cancer and diet in Spain. *J Environ Pathol Toxicol Oncol* 11:157–167.

Morris JN, Marr JW, Clayton DG. 1977. Diet and heart: A postscript. *Br Med J* 2:1307–1314.

Moshfegh AJ, Friday JE, Goldman JP, Ahuja JKC. 1999. Presence of inulin and oligofructose in the diets of Americans. *J Nutr* 129:1407S–1411S.

National Cholesterol Education Program. 1991. *Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents.* NIH Publication No. 91-2732. Bethesda, MD: National Heart, Lung, and Blood Institute.

Neugut AI, Garbowski GC, Lee WC, Murray T, Nieves JW, Forde KA, Treat MR, Waye JD, Fenoglio-Preiser C. 1993. Dietary risk factors for the incidence and recurrence of colorectal adenomatous polyps. A case-control study. *Ann Intern Med* 11:91–95.

Niemi MK, Keinänen-Kiukaanniemi SM, Salmela PI. 1988. Long-term effects of guar gum and microcrystalline cellulose on glycaemic control and serum lipids in type 2 diabetes. *Eur J Clin Pharmacol* 34:427–429.

Niho N, Tamura T, Toyoda K, Uneyama C, Shibutani M, Hirose M. 1999. A 13-week subchronic toxicity study of chitin in F344 rats. *Kokuritsu Iyakuhin Shokuhin Eisei Kenkyusho Hokoku* 117:129–134.

Nishimune T, Sumimoto T, Konishi Y, Yakushiji T, Komachi Y, Mitsuhashi Y, Nakayama I, Okazaki K, Tsuda T, Ichihashi A, Adachi T, Imanaka M, Kirigaya T, Ushio H, Kasuga Y, Saeki K, Yamamoto Y, Ichikawa T, Nakahara S, Oda S. 1993. Dietary fiber intake of Japanese younger generations and the recommended daily allowance. *J Nutr Sci Vitaminol (Tokyo)* 39:263–278.

Noble JA, Grannis FW. 1984. Acute esophageal obstruction by a psyllium-based bulk laxative. *Chest* 86:800.

NRC (National Research Council). 1989. *Diet and Health: Implications for Reducing Chronic Disease Risk.* Washington, DC: National Academy Press.

Obarzanek E, Sacks FM, Vollmer WM, Bray GA, Miller ER, Lin P-H, Karanja NM, Most-Windhauser MM, Moore TJ, Swain JF, Bales CW, Proschan MA. 2001. Effects on blood lipids of a blood pressure-lowering diet: The Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr* 74:80–89.

O'Brien KO, Allen LH, Quatromoni P, Siu-Caldera M-L, Vieira NE, Perez A, Holick MF, Yergey AL. 1993. High fiber diets slow bone turnover in young men but have no effect on efficiency of intestinal calcium absorption. *J Nutr* 123:2122–2128.

Ohkuma K, Wakabayashi S. 2001. Fibersol-2: A soluble, non-digestible, starch-derived dietary fibre. In: McCleary BV, Prosky L, eds. *Advanced Dietary Fibre Technology.* Oxford: Blackwell Science. Pp. 510–523.

Ohno Y, Yoshida O, Oishi K, Okada K, Yamabe H, Schroeder FH. 1988. Dietary β-carotene and cancer of the prostate: A case-control study in Kyoto, Japan. *Cancer Res* 48:1331–1336.

Olesen M, Gudmand-Høyer E. 2000. Efficacy, safety, and tolerability of fructo-oligosaccharides in the treatment of irritable bowel syndrome. *Am J Clin Nutr* 72:1570–1575.

Olson BH, Anderson SM, Becker MP, Anderson JW, Hunninghake DB, Jenkins DJA, LaRose JC, Rippe JM, Roberts DCK, Stoy DB, Summerbell CD, Truswell AS, Wolever TMS, Morris DH, Fulgoni VL. 1997. Psyllium-enriched cereals lower blood total cholesterol and LDL cholesterol, but not HDL cholesterol, in hypercholesterolemic adults: Results of a meta-analysis. *J Nutr* 127:1973–1980.

Pastors JG, Blaisdell PW, Balm TK, Asplin CM, Pohl SL. 1991. Psyllium fiber reduces rise in postprandial glucose and insulin concentrations in patients with non-insulin-diabetes mellitus. *Am J Clin Nutr* 53:1431–1435.

Patrick PG, Gohman SM, Marx SC, DeLegge MH, Greenberg NA. 1998. Effect of supplements of partially hydrolyzed guar gum on the occurrence of constipation and use of laxative agents. *J Am Diet Assoc* 98:912–914.

Pedersen A, Sandstrom B, Van Amelsvoort JM. 1997. The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. *Br J Nutr* 78:215–222.

Penagini R, Velio P, Vigorelli R, Bozzani A, Castagnone D, Ranzi T, Bianchi PA. 1986. The effect of dietary guar on serum cholesterol, intestinal transit, and fecal output in man. *Am J Gastroenterol* 81:123–125.

Petrakis NL, King EB. 1981. Cytological abnormalities in nipple aspirates of breast fluid from women with severe constipation. *Lancet* 2:1203–1204.

Phillips J, Muir JG, Birkett A, Lu ZX, Jones GP, O'Dea K, Young GP. 1995. Effect of resistant starch on fecal bulk and fermentation-dependent events in humans. *Am J Clin Nutr* 62:121–130.

Pick ME, Hawrysh ZJ, Gee MI, Toth E, Garg ML, Hardin RT. 1996. Oat bran concentrate bread products improve long-term control of diabetes: A pilot study. *J Am Diet Assoc* 96:1254–1261.

Pietinen P, Rimm EB, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. 1996. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation* 94:2720–2727.

Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, Virtamo J. 1999. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 10:387–396.

Pittler MH, Abbot NC, Harkness EF, Ernst E. 1999. Randomized, double-blind trial of chitosan for body weight reduction. *Eur J Clin Nutr* 53:379–381.

Platz EA, Giovannucci E, Rimm EB, Rockett HRH, Stampfer MJ, Colditz GA, Willett WC. 1997. Dietary fiber and distal colorectal adenoma in men. *Cancer Epidemiol Biomarkers Prev* 6:661–670.

Prior A, Whorwell PJ. 1987. Double blind study of ispagula in irritable bowel syndrome. *Gut* 28:1510–1513.

Raben A, Tagliabue A, Christensen NJ, Madsen J, Holst JJ, Astrup A. 1994. Resistant starch: The effect on postprandial glycemia, hormonal response, and satiety. *Am J Clin Nutr* 60:544–551.

Ranhotra GS, Gelroth JA, Leinen SD. 1997. Hypolipidemic effect of resistant starch in hamsters is not dose dependent. *Nutr Res* 17:317–323.

Razdan A, Pettersson D. 1994. Effect of chitin and chitosan on nutrient digestibility and plasma lipid concentrations in broiler chickens. *Br J Nutr* 72:277–288.

Razdan A, Pettersson D. 1996. Hypolipidaemic, gastrointestinal and related responses of broiler chickens to chitosans of different viscosity. *Br J Nutr* 76:387–397.

Razdan A, Pettersson D, Pettersson J. 1997. Broiler chicken body weights, feed intakes, plasma lipid and small-intestinal bile acid concentrations in response to feeding of chitosan and pectin. *Br J Nutr* 78:283–291.

Rigaud D, Ryttig KR, Angel LA, Apfelbaum M. 1990. Overweight treated with energy restriction and a dietary fibre supplement: A 6-month randomized, double-blind, placebo-controlled trial. *Int J Obes* 14:763–769.

Rigaud D, Paycha F, Meulemans A, Merrouche M, Mignon M. 1998. Effect of psyllium on gastric emptying, hunger feeling and food intake in normal volunteers: A double blind study. *Eur J Clin Nutr* 52:239–245.

Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. 1996. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *J Am Med Assoc* 275:447–451.

Ripsin CM, Keenan JM, Jacobs DR, Elmer PJ, Welch RR, Van Horn L, Liu K, Turnbull WH, Thye FW, Kestin M, Hegsted M, Davidson DM, Davidson MH, Dugan LD, Demark-Wahnefried W, Beling S. 1992. Oat products and lipid lowering. A meta-analysis. *J Am Med Assoc* 267:3317–3325.

Risch HA, Jain M, Marrett LD, Howe GR. 1994. Dietary fat intake and risk of epithelial ovarian cancer. *J Natl Cancer Inst* 86:1409–1415.

Ritz P, Krempf M, Cloarec D, Champ M, Charbonnel B. 1991. Comparative continuous-indirect-calorimetry study of two carbohydrates with different glycemic indices. *Am J Clin Nutr* 54:855–859.

Rivellese A, Riccardi G, Giacco A, Pacioni D, Genovese S, Mattioli PL, Mancini M. 1980. Effect of dietary fibre on glucose control and serum lipoproteins in diabetic patients. *Lancet* 2:447–450.

Roberfroid M. 1993. Dietary fiber, inulin, and oligofructose: A review comparing their physiological effects. *Crit Rev Food Sci Nutr* 33:103–148.

Roberts PL, Veidenheimer MC. 1990. Diverticular disease of the colon. In: Bayless TM, ed. *Current Therapy in Gastroenterology and Liver Disease—3*. Toronto: Decker Mosby. Pp. 416–419.

Roediger WEW. 1980. The colonic epithelium in ulcerative colitis: An energy-deficiency disease? *Lancet* 2:712–715.

Roediger WEW. 1982. Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology* 83:424–429.

Roediger WE, Duncan A, Kapaniris O, Millard S. 1993. Reducing sulfur compounds of the colon impair colonocyte nutrition: Implications for ulcerative colitis. *Gastroenterology* 104:802–809.

Rohan TE, McMichael AJ, Baghurst PA. 1988. A population-based case-control study of diet and breast cancer in Australia. *Am J Epidemiol* 128:478–489.

Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. 1993. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: A cohort study. *Cancer Causes Control* 4:29–37.

Rohan TE, Howe GR, Burch JD, Jain M. 1995. Dietary factors and risk of prostate cancer: A case-control study in Ontario, Canada. *Cancer Causes Control* 6:145–154.

Roma E, Adamidis D, Nikolara R, Constantopoulos A, Messaritakis J. 1999. Diet and chronic constipation in children: The role of fiber. *J Pediatr Gastroenterol Nutr* 28:169–174.

Ronco A, De Stefani E, Boffetta P, Deneo-Pellegrini H, Mendilaharsu M, Leborgne F. 1999. Vegetables, fruits, and related nutrients and risk of breast cancer: A case-control study in Uruguay. *Nutr Cancer* 35:111–119.

Rose DP. 1990. Dietary fiber and breast cancer. *Nutr Cancer* 13:1–8.

Rose DP. 1992. Dietary fiber, phytoestrogens, and breast cancer. *Nutrition* 8:47–51.

Rose DP, Goldman M, Connoly JM, Strong LE. 1991. High-fiber diet reduces serum estrogen concentrations in premenopausal women. *Am J Clin Nutr* 54:520–525.

Rössner S, von Zweigbergk D, Öhlin A, Ryttig K. 1987. Weight reduction with dietary fibre supplements. Results of two double-blind randomized studies. *Acta Med Scand* 222:83–88.

Ryttig KR, Tellnes G, Haegh L, Boe E, Fagerthun H. 1989. A dietary fibre supplement and weight maintenance after weight reduction: A randomized, double-blind, placebo-controlled long-term trial. *Int J Obes* 13:165–171.

Saku K, Yoshinaga K, Okura Y, Ying H, Harada R, Arakawa K. 1991. Effects of polydextrose on serum lipids, lipoproteins, and apolipoproteins in healthy subjects. *Clin Ther* 13:254–258.

Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. 1997a. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550.

Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. 1997b. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *J Am Med Assoc* 277:472–477.

Sandberg AS, Ahderinne R, Andersson H, Hallgren B, Hulten L. 1983. The effect of citrus pectin on the absorption of nutrients in the small intestine. *Hum Nutr Clin Nutr* 37:171–183.

Sandstead HH. 1992. Fiber, phytates, and mineral nutrition. *Nutr Rev* 50:30–31.

Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, Cahill J. 2000. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 342:1149–1155.

Sepple CP, Read NW. 1989. Gastrointestinal correlates of the development of hunger in man. *Appetite* 13:183–191.

Shetty PS, Kurpad AV. 1986. Increasing starch intake in the human diet increases fecal bulking. *Am J Clin Nutr* 43:210–212.

Shultz TD, Howie BJ. 1986. In vitro binding of steroid hormones by natural and purified fibers. *Nutr Cancer* 8:141–147.

Silvester KR, Englyst HN, Cummings JH. 1995. Ileal recovery of starch from whole diets containing resistant starch measured in vitro and fermentation of ileal effluent. *Am J Clin Nutr* 62:403–411.

Simpson HCR, Simpson RW, Lousley S, Carter RD, Geekie M, Hockaday TDR, Mann JI. 1981. A high carbohydrate leguminous fibre diet improves all aspects of diabetic control. *Lancet* 1:1–15.

Simpson KM, Morris ER, Cook JD. 1981. The inhibitory effect of bran on iron absorption in man. *Am J Clin Nutr* 34:1469–1478.

Slavin JL. 1987. Dietary fiber: Classification, chemical analyses, and food sources. *J Am Diet Assoc* 87:1164–1171.

Slavin JL, Marlett JA. 1980. Influence of refined cellulose on human bowel function and calcium and magnesium retention. *Am J Clin Nutr* 33:1932–1939.

Slavin J, Jacobs D, Marquart L. 1997. Whole-grain consumption and chronic disease: Protective mechanisms. *Nutr Cancer* 27:14–21.

Sleet R, Brightwell J. 1990. *FS-Teratology Study in Rats.* Raffinerie Tirlemontoise Internal Report. Photocopy.

Smith T, Brown JC, Livesey G. 1998. Energy balance and thermogenesis in rats consuming nonstarch polysaccharides of various fermentabilities. *Am J Clin Nutr* 68:802–819.

Spencer H, Norris C, Derler J, Osis D. 1991. Effect of oat bran muffins on calcium absorption and calcium, phosphorus, magnesium and zinc balance in men. *J Nutr* 121:1976–1983.

Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. 1994. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* 139:1–15.

Stephen AM, Haddad AC, Phillips SF. 1983. Passage of carbohydrate into the colon. Direct measurements in humans. *Gastroenterology* 85:589–595.

Stevens J, Levitsky DA, VanSoest PJ, Robertson JB, Kalkwarf HJ, Roe DA. 1987. Effect of psyllium gum and wheat bran on spontaneous energy intake. *Am J Clin Nutr* 46:812–817.

Stone-Dorshow T, Levitt MD. 1987. Gaseous response to ingestion of a poorly absorbed fructo-oligosaccharide sweetener. *Am J Clin Nutr* 46:61–65.

Strobel S, Ferguson A, Anderson DM. 1982. Immunogenicity of foods and food additives—In vivo testing of gums arabic, karaya, and tragacanth. *Toxicol Lett* 14:247–252.

Sugano M, Fujikawa T, Hiratsuji Y, Nakashima K, Fukuda N, Hasegawa Y. 1980. A novel use of chitosan as a hypocholesterolemic agent in rats. *Am J Clin Nutr* 33:787–793.

Sundell IB, Ranby M. 1993. Oat husk fiber decreases plasminogen activator inhibitor type 1 activity. *Haemostasis* 23:45–50.

Taioli E, Nicolosi A, Wynder EL. 1991. Dietary habits and breast cancer: A comparative study of United States and Italian data. *Nutr Cancer* 16:259–265.

Thompson LU. 1994. Antioxidants and hormone-mediated health benefits of whole grains. *Crit Rev Food Sci Nutr* 34:473–497.

Thun MJ, Calle EE, Namboodiri MM, Flanders WD, Coates RJ, Byers T, Boffetta P, Garfinkel L, Heath CW. 1992. Risk factors for fatal colon cancer in a large prospective study. *J Natl Cancer Inst* 84:1491–1500.

Todd S, Woodward M, Tunstall-Pedoe H, Bolton-Smith C. 1999. Dietary antioxidant vitamins and fiber in the etiology of cardiovascular disease and all-causes mortality: Results from the Scottish Heart Health Study. *Am J Epidemiol* 150:1073–1080.

Tokunaga K, Matsuoka A. 1999. Effects of a Food for Specified Health Use (FOSHU) which contains indigestible dextrin as an effective ingredient on glucose and lipid metabolism. *J Jpn Diabetes Soc* 42:61–65.

Tomlin J, Read NW. 1988. A comparative study of the effects on colon function caused by feeding ispaghula husk and polydextrose. *Aliment Pharmacol Ther* 2:513–519.

Tomlin J, Read NW. 1990. The effect of resistant starch on colon function in humans. *Br J Nutr* 64:589–595.

Tomlin J, Lowis C, Read NW. 1991. Investigation of normal flatus production in healthy volunteers. *Gut* 32:665–669.

Tremblay A, Lavallée N, Alméras N, Allard L, Després J-P, Bouchard C. 1991. Nutritional determinants of the increase in energy intake associated with a high-fat diet. *Am J Clin Nutr* 53:1134–1137.

Trock B, Lanza E, Greenwald P. 1990. Dietary fiber, vegetables, and colon cancer: Critical review and meta-analyses of the epidemiologic evidence. *J Natl Cancer Inst* 82:650–661.

Truswell AS. 1992. Glycaemic index of foods. *Eur J Clin Nutr* 46:S91–S101.

Tuohy KM, Kolida S, Lustenberger AM, Gibson GR. 2001. The prebiotic effects of biscuits containing partially hydrolysed guar gum and fructo-oligosaccharides—A human volunteer study. *Br J Nutr* 86:341–348.

Tuyns AJ, Haelterman M, Kaaks R. 1987. Colorectal cancer and the intake of nutrients: Oligosaccharides are a risk factor, fats are not. A case-control study in Belgium. *Nutr Cancer* 10:181–196.

Tzonou A, Hsieh C-C, Polychronopoulou A, Kaprinis G, Toupadaki N, Trichopoulou A, Karakatsani A, Trichopoulos D. 1993. Diet and ovarian cancer: A case-control study in Greece. *Int J Cancer* 55:411–414.

USDA/HHS (U.S. Department of Agriculture/U.S. Department of Health and Human Services). 2000. *Nutrition and Your Health: Dietary Guidelines for Americans*. Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

van Dokkum W, Wezendonk B, Srikumar TS, van den Heuvel EGHM. 1999. Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. *Eur J Clin Nutr* 53:1–7.

Van Horn LV, Liu K, Parker D, Emidy L, Liao Y, Pan WH, Giumetti D, Hewitt J, Stamler J. 1986. Serum lipid response to oat product intake with a fat-modified diet. *J Am Diet Assoc* 86:759–764.

van Munster IP, Nagengast FM. 1993. The role of carbohydrate fermentation in colon cancer prevention. *Scand J Gastroenterol* 200:80–86.

van Munster IP, de Boer HM, Jansen MC, de Haan AF, Katan MB, van Amelsvoort JM, Nagengast FM. 1994. Effect of resistant starch on breath-hydrogen and methane excretion in healthy volunteers. *Am J Clin Nutr* 59:626–630.

van't Veer P, Kolb CM, Verhoef P, Kok FJ, Schouten EG, Hermus RJ, Sturmans F. 1990. Dietary fiber, beta-carotene and breast cancer: Results from a case-control study. *Int J Cancer* 45:825–828.

Verhoeven DTH, Assen N, Goldbohm RA, Dorant E, van't Veer P, Sturmans F, Hermus RJJ, van den Brandt PA. 1997. Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: A prospective cohort study. *Br J Cancer* 75:149–155.

Visek WJ. 1978. Diet and cell growth modulation by ammonia. *Am J Clin Nutr* 31:S216–S220.

Wakabayashi S, Ueda Y, Matsuoka A. 1993. Effects of indigestible dextrin on blood glucose and insulin levels after various sugar loads in rats. *J Jpn Soc Nutr Food Sci* 46:131–137.

Wakabayashi S, Kishimoto Y, Matsuoka A. 1995. Effects of indigestible dextrin on glucose tolerance in rats. *J Endocrinol* 144:533–538.

Watters DAK, Smith AN. 1990. Strength of the colon wall in diverticular disease. *Br J Surg* 77:257–259.

Weaver GA, Krause JA, Miller TL, Wolin MJ. 1988. Short chain fatty acid distributions of enema samples from a sigmoidoscopy population: An association of high acetate and low butyrate ratios with adenomatous polyps and colon cancer. *Gut* 29:1539–1543.

West DW, Slattery ML, Robison LM, Schuman KL, Ford MH, Mahoney AW, Lyon JL, Sorensen AW. 1989. Dietary intake and colon cancer: Sex- and anatomic site-specific associations. *Am J Epidemiol* 130:883–894.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. 1990. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 323:1664–1672.

Willett WC, Hunter DJ, Stampfer MJ, Colditz G, Manson JE, Spiegelman D, Rosner B, Hennekens CH, Speizer FE. 1992. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. *J Am Med Assoc* 268:2037–2044.

Williams CH, Witherly SA, Buddington RK. 1994. Influence of dietary neosugar on selected bacterial groups of the human faecal microbiota. *Microb Ecol Health Dis* 7:91–97.

Williams CL, Bollella M. 1995. Is a high-fiber diet safe for children? *Pediatrics* 96:1014–1019.

Williams CL, Bollella M, Wynder EL. 1995. A new recommendation for dietary fiber in childhood. *Pediatrics* 96:985–988.

Wisker E, Nagel R, Tanudjaja TK, Feldheim W. 1991. Calcium, magnesium, zinc, and iron balances in young women: Effects of a low-phytate barley-fiber concentrate. *Am J Clin Nutr* 54:553–559.

Witte JS, Ursin G, Siemiatycki J, Thompson WD, Paganini-Hill A, Haile RW. 1997. Diet and premenopausal bilateral breast cancer: A case-control study. *Breast Cancer Res Treat* 42:243–251.

Wolever TMS. 1995. In vitro and in vivo models for predicting the effect of dietary fiber and starchy foods on carbohydrate metabolism. In: Kritchevsky D, Bonfield C, eds. *Dietary Fiber in Health and Disease.* St. Paul, MN: Eagan Press. Pp. 360–377.

Wolever TMS, Jenkins DJA. 1993. Effect of dietary fiber and foods on carbohydrate metabolism. In: Spiller G, ed. *CRC Handbook of Dietary Fiber in Human Nutrition.* Boca Raton, FL: CRC Press. Pp. 111–162.

Wolk A, Manson JE, Stampfer MJ, Colditz GA, Hu FB, Speizer FE, Hennekens CH, Willett WC. 1999. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *J Am Med Assoc* 281:1998–2004.

Wood PJ, Braaten JT, Scott FW, Riedel KD, Wolynetz MS, Collins MW. 1994. Effect of dose and modification of viscous properties of oat gum on plasma glucose and insulin following an oral glucose load. *Br J Nutr* 72:731–743.

Woods MN, Gorbach SL, Longcope C, Goldin BR, Dwyer JT, Morrill-LaBrode A. 1989. Low-fat, high-fiber diet and serum estrone sulfate in premenopausal women. *Am J Clin Nutr* 49:1179–1183.

Woods MN, Barnett JB, Spiegelman D, Trail N, Hertzmark E, Longcope C, Gorbach SL. 1996. Hormone levels during dietary changes in premenopausal African-American women. *J Natl Cancer Inst* 88:1369–1374.

Wuolijoki E, Hirvelä T, Ylitalo P. 1999. Decrease in serum LDL cholesterol with microcrystalline chitosan. *Methods Find Exp Clin Pharmacol* 21:357–361.

Wynder EL, Berenson GS. 1984. Preventive strategies for reducing hyperlipidemia in childhood. *Prev Med* 13:327–329.

Yamashita K, Kawai K, Itakura M. 1984. Effects of fructo-oligosaccharides on blood glucose and serum lipids in diabetic subjects. *Nutr Res* 4:961–966.

Younes H, Levrat MA, Demigne C, Remesy C. 1995. Resistant starch is more effective than cholestyramine as a lipid-lowering agent in the rat. *Lipids* 30:847–853.

Yu H, Harris RE, Gao Y-T, Gao R, Wynder RL. 1991. Comparative epidemiology of cancers of the colon, rectum, prostate and breast in Shanghai, China versus the United States. *Int J Epidemiol* 20:76–81.

Yuan J-M, Wang Q-S, Ross RK, Henderson BE, Yu MC. 1995. Diet and breast cancer in Shanghai and Tianjin, China. *Br J Cancer* 71:1353–1358.

Zacour AC, Silva ME, Cecon PR, Bambirra EA, Vieira EC. 1992. Effect of dietary chitin on cholesterol absorption and metabolism in rats. *J Nutr Sci Vitaminol (Tokyo)* 38:609–613.

8

Dietary Fats: Total Fat and Fatty Acids

SUMMARY

Fat is a major source of fuel energy for the body and aids in the absorption of fat-soluble vitamins and carotenoids. Neither an Adequate Intake (AI) nor Recommended Dietary Allowance (RDA) is set for total fat because there are insufficient data to determine a defined level of fat intake at which risk of inadequacy or prevention of chronic disease occurs. An Acceptable Macronutrient Distribution Range (AMDR), however, has been estimated for total fat—it is 20 to 35 percent of energy (see Chapter 11). A Tolerable Upper Intake Level (UL) is not set for total fat because there is no defined intake level of fat at which an adverse effect occurs.

Saturated fatty acids are synthesized by the body to provide an adequate level needed for their physiological and structural functions; they have no known role in preventing chronic diseases. Therefore, neither an AI nor RDA is set for saturated fatty acids. There is a positive linear trend between total saturated fatty acid intake and total and low density lipoprotein (LDL) cholesterol concentration and increased risk of coronary heart disease (CHD). A UL is not set for saturated fatty acids because any incremental increase in saturated fatty acid intake increases CHD risk. It is neither possible nor advisable to achieve 0 percent of energy from saturated fatty acids in typical whole-food diets. This is because all fat and oil sources are mixtures of fatty acids, and consuming 0 percent of energy would require extraordinary changes in patterns of dietary intake. Such extraordinary adjustments may introduce undesirable effects (e.g., inadequate intakes of protein and

certain micronutrients) and unknown and unquantifiable health risks. The AMDR for total fat is set at 20 to 35 percent of energy. It is possible to have a diet low in saturated fatty acids by following the dietary guidance provided in Chapter 11.

n-9 *cis* Monounsaturated fatty acids are synthesized by the body and have no known independent beneficial role in human health and are not required in the diet. Therefore, neither an AI nor an RDA is set. There is insufficient evidence to set a UL for *n*-9 *cis* monounsaturated fatty acids.

Linoleic acid is the only *n*-6 polyunsaturated fatty acid that is an essential fatty acid; it serves as a precursor to eicosanoids. A lack of dietary *n*-6 polyunsaturated fatty acids is characterized by rough and scaly skin, dermatitis, and an elevated eicosatrienoic acid:arachidonic acid (triene:tetraene) ratio. The AI for linoleic acid is based on the median intake in the United States where an *n*-6 fatty acid deficiency is nonexistent in healthy individuals. The AI is 17 g/d for young men and 12 g/d for young women. While intake levels much lower than the AI occur in the United States without the presence of a deficiency, the AI can provide the beneficial health effects associated with the consumption of linoleic acid (see Chapter 11). There is insufficient evidence to set a UL for *n*-6 polyunsaturated fatty acids.

n-3 Polyunsaturated fatty acids play an important role as structural membrane lipids, particularly in nerve tissue and the retina, and are precursors to eicosanoids. A lack of α-linolenic acid in the diet can result in clinical symptoms of a deficiency (e.g., scaly dermatitis). An AI is set for α-linolenic acid based on median intakes in the United States where an *n*-3 fatty acid deficiency is nonexistent in healthy individuals. The AI is 1.6 and 1.1 g/d for men and women, respectively. While intake levels much lower than the AI occur in the United States without the presence of a deficiency, the AI can provide the beneficial health effects associated with the consumption of *n*-3 fatty acids (see Chapter 11). There is insufficient evidence to set a UL for *n*-3 fatty acids.

Trans fatty acids are not essential and provide no known benefit to human health. Therefore, no AI or RDA is set. As with saturated fatty acids, there is a positive linear trend between *trans* fatty acid intake and LDL cholesterol concentration, and therefore increased risk of CHD. A UL is not set for *trans* fatty acids because any incremental increase in *trans* fatty acid intake increases CHD risk. Because *trans* fatty acids are unavoidable in ordinary, nonvegan diets, consuming 0 percent of energy would require significant changes in patterns of dietary intake. As with saturated fatty acids, such adjustments may introduce undesirable effects (e.g., elimina-

tion of commercially prepared foods, dairy products, and meats that contain *trans* fatty acids may result in inadequate intakes of protein and certain micronutrients) and unknown and unquantifiable health risks. Nevertheless, it is recommended that *trans* fatty acid consumption be as low as possible while consuming a nutritionally adequate diet. Dietary guidance in minimizing *trans* fatty acid intake is provided in Chapter 11.

BACKGROUND INFORMATION

Total Fat

Fat is a major source of fuel energy for the body. It also aids in the absorption of the fat-soluble vitamins A, D, E, and K and carotenoids. Dietary fat consists primarily (98 percent) of triacylglycerol, which is composed of one glycerol molecule esterified with three fatty acid molecules, and smaller amounts of phospholipids and sterols. Fatty acids are hydrocarbon chains that contain a methyl (CH_3-) and a carboxyl (-COOH) end. The fatty acids vary in carbon chain length and degree of unsaturation (number of double bonds in the carbon chain). The fatty acids can be classified into the following categories:

- Saturated fatty acids
- *Cis* monounsaturated fatty acids
- *Cis* polyunsaturated fatty acids
  — *n*-6 fatty acids
  — *n*-3 fatty acids
- *Trans* fatty acids

Dietary fat derives from both animal and plant products. In general, animal fats have higher melting points and are solid at room temperature, which is a reflection of their high content of saturated fatty acids. Plant fats (oils) tend to have lower melting points and are liquid at room temperature (oils); this is explained by their high content of unsaturated fatty acids. Exceptions to this rule are the seed oils (e.g., coconut oil and palm kernel oil), which are high in saturated fat and solid at room temperature. *Trans* fatty acids have physical properties generally resembling saturated fatty acids and their presence tends to harden fats. In the discussion below, total fat intake refers to the intake of all forms of triacylglycerol, regardless of fatty acid composition, in terms of percentage of total energy intake.

In addition to the functions of fat and fatty acids described above, fatty acids also function in cell signaling and alter expression of specific genes

involved in lipid and carbohydrate metabolism (Jump and Clarke, 1999; Sessler and Ntambi, 1998). Fatty acids may themselves be ligands for, or serve as precursors for, the synthesis of unknown endogenous ligands for nuclear peroxisome proliferator activating receptors (Kliewer et al., 1997; Latruffe and Vamecq, 1997). These receptors are important regulators of adipogenesis, inflammation, insulin action, and neurological function.

Phospholipids

Phospholipids are a form of fat that contains one glycerol molecule that is esterified with two fatty acids and either inositol, choline, serine, or ethanolamine. Phospholipids are primarily located in the membranes of cells in the body and the globule membranes in milk. A very small amount of dietary fat occurs as phospholipid. The metabolism of phospholipids is described below for total fat. The various fatty acids that are contained in phospholipids are the same as those present in triglycerides.

Saturated Fatty Acids

The majority of dietary saturated fatty acids come from animal products such as meat and dairy products (USDA, 1996). The remaining comes from plant sources. These sources provide a series of saturated fatty acids for which the major dietary fatty acids range in chain length from 8 to 18 carbon atoms. These are:

- 8:0 Caprylic acid
- 10:0 Caproic acid
- 12:0 Lauric acid
- 14:0 Myristic acid
- 16:0 Palmitic acid
- 18:0 Stearic acid

The saturated fatty acids are not only a source of body fuel, but are also structural components of cell membranes. Various saturated fatty acids are also associated with proteins and are necessary for their normal function. Saturated fatty acids can be synthesized by the body.

Fats in general, including saturated fatty acids, play a role in providing desirable texture and palatability to foods used in the diet. Palmitic acid is particularly useful for enhancing the organoleptic properties of fats used in commercial products. Stearic acid, in contrast, has physical properties that limit the amount that can be incorporated into dietary fat.

Cis *Monounsaturated Fatty Acids*

Cis monounsaturated fatty acids are characterized by having one double bond with the hydrogen atoms present on the same side of the double bond. Typically, plant sources rich in *cis* monounsaturated fatty acids (e.g., canola oil, olive oil, and the high oleic safflower and sunflower oils) are liquid at room temperature. Monounsaturated fatty acids are present in foods with a double bond located at 7 (*n*-7) or 9 (*n*-9) carbon atoms from the methyl end. Monounsaturated fatty acids that are present in the diet include:

- 18:1*n*-9 Oleic acid
- 14:1*n*-7 Myristoleic acid
- 16:1*n*-7 Palmitoleic acid
- 18:1*n*-7 Vaccenic acid
- 20:1*n*-9 Eicosenoic acid
- 22:1*n*-9 Erucic acid

Oleic acid accounts for about 92 percent of dietary monounsaturated fatty acids. Monounsaturated fatty acids, including oleic acid and nervonic acid (24:1*n*-9), are important in membrane structural lipids, particularly nervous tissue myelin. Other monounsaturated fatty acids, such as palmitoleic acid, are present in minor amounts in the diet.

n-*6 Polyunsaturated Fatty Acids*

The primary *n*-6 polyunsaturated fatty acids are:

- 18:2 Linoleic acid
- 18:3 γ-Linolenic acid
- 20:3 Dihomo-γ-linolenic acid
- 20:4 Arachidonic acid
- 22:4 Adrenic acid
- 22:5 Docosapentaenoic acid

Linoleic acid cannot be synthesized by humans and a lack of it results in adverse clinical symptoms, including a scaly rash and reduced growth. Therefore, linoleic acid is essential in the diet. Linoleic acid is the precursor to arachidonic acid, which is the substrate for eicosanoid production in tissues, is a component of membrane structural lipids, and is also important in cell signaling pathways. Dihomo-γ-linolenic acid, also formed from linoleic acid, is also an eicosanoid precursor. *n*-6 Polyunsaturated fatty acids also play critical roles in normal epithelial cell function (Jones and

Kubow, 1999). Arachidonic acid and other unsaturated fatty acids are involved with regulation of gene expression resulting in decreased expression of proteins that regulate the enzymes involved with fatty acid synthesis (Ou et al., 2001). This may partly explain the ability of unsaturated fatty acids to influence the hepatic synthesis of fatty acids.

n-*3 Polyunsaturated Fatty Acids*

n-3 Polyunsaturated fatty acids tend to be highly unsaturated with one of the double bonds located at 3 carbon atoms from the methyl end. This group includes:

- 18:3 α-Linolenic acid
- 20:5 Eicosapentaenoic acid
- 22:5 Docosapentaenoic acid
- 22:6 Docosahexaenoic acid

α-Linolenic acid is not synthesized by humans and a lack of it results in adverse clinical symptoms, including neurological abnormalities and poor growth. Therefore, α-linolenic acid is essential in the diet. It is the precursor for synthesis of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are formed in varying amounts in animal tissues, especially fatty fish, but not in plant cells. EPA is the precursor of *n*-3 eicosanoids, which have been shown to have beneficial effects in preventing coronary heart disease, arrhythmias, and thrombosis (Kinsella et al., 1990).

Trans *Fatty Acids*

Trans fatty acids are unsaturated fatty acids that contain at least one double bond in the *trans* configuration. The *trans* double-bond configuration results in a larger bond angle than the *cis* configuration, which in turn results in a more extended fatty acid carbon chain more similar to that of saturated fatty acids rather than that of *cis* unsaturated, double-bond–containing fatty acids. The conformation of the double bond impacts on the physical properties of the fatty acid. Those fatty acids containing a *trans* double bond have the potential for closer packing or aligning of acyl chains, resulting in decreased mobility; hence fluidity is reduced when compared to fatty acids containing a *cis* double bond. Partial hydrogenation of polyunsaturated oils causes isomerization of some of the remaining double bonds and migration of others, resulting in an increase in the *trans* fatty acid content and the hardening of fat. Hydrogenation of oils, such as corn oil, can result in both *cis* and *trans* double bonds anywhere between carbon 4 and carbon 16. A major *trans* fatty acid is elaidic acid (9-*trans* 18:1).

During hydrogenation of polyunsaturated fatty acids, small amounts of several other *trans* fatty acids (9-*trans*,12-*cis* 18:2; 9-*cis*,12-*trans* 18:2) are produced. In addition to these isomers, dairy fat and meats contain 9-*trans* 16:1 and conjugated dienes (9-*cis*,11-*trans* 18:2). The *trans* fatty acid content in foods tends to be higher in foods containing hydrogenated oils (Emken, 1995).

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a collective term for a group of geometric and positional isomers of linoleic acid in which the *trans/cis* double bonds are conjugated; that is, the double bonds occur without an intervening carbon atom not part of a double bond. At least nine different isomers of CLA have been reported as minor constituents of food (Ha et al., 1989), but only two of the isomers, *cis*-9,*trans*-11 and *trans*-10,*cis*-12, possess biological activity (Pariza et al., 2001). There is limited evidence to suggest that the *trans*-10,*cis*-12 isomer reduces the uptake of lipids by the adipocyte, and that the *cis*-9,*trans*-11 isomer is active in inhibiting carcinogenesis. Similarly, there are limited data to show that *cis*-9,*trans*-11 and *trans*-10,*cis*-12 isomers inhibit atherogenesis (Kritchevsky et al., 2000).

CLA is naturally present in dairy products and ruminant meats as a consequence of biohydrogenation in the rumen. *Butyrivibrio fibrisolvens*, a ruminant microorganism, is responsible for the production of the *cis*-9,*trans*-11 CLA isomer that is synthesized as a result of the biohydrogenation of linoleic acid (Noble et al., 1974). The *cis*-9,*trans*-11 CLA isomer may be directly absorbed or further metabolized to *trans*-11 octadecenoic acid (vaccenic acid) (Pariza et al., 2001). After absorption, vaccenic acid can then be converted back to *cis*-9,*trans*-11 CLA within mammalian cells by Δ9 desaturase (Adlof et al., 2000; Chin et al., 1994; Griinari et al., 2000; Santora et al., 2000). Additionally, the biohydrogenation of several other polyunsaturated fatty acids has been shown to produce vaccenic acid as an intermediate (Griinari and Bauman, 1999), thus providing additional substrate for the endogenous production of *cis*-9,*trans*-11 CLA. Griinari and coworkers (2000) estimate that approximately 64 percent of the CLA in cow's milk is of endogenous origin.

Verhulst and coworkers (1987) isolated a microorganism, *Propionibacterium acnes*, that appears to have the ability to convert linoleic acid to *trans*-10,*cis*-12 CLA, an isomer of CLA that is found in rumen digesta (Fellner et al., 1999). *Trans*-10 octadecenoic acid is formed in the rumen via biohydrogenation of *trans*-10,*cis*-12 CLA, and both have been reported to be found in cow's milk (Griinari and Bauman, 1999). However, endogenous production of *trans*-10,*cis*-12 CLA from *trans*-10 octadecenoic acid does not occur because mammalian cells do not possess the Δ12 desaturase enzyme (Adlof et al., 2000; Pariza et al., 2001). Therefore, any *trans*-10,*cis*-12 CLA

isomer that is reported in mammalian tissue or sera would likely originate from gastrointestinal absorption.

Physiology of Absorption, Metabolism, and Excretion

Total Fat

Absorption. Dietary fat undergoes lipolysis by lipases in the gastrointestinal tract prior to absorption. Although there are lipases in the saliva and gastric secretion, most lipolysis occurs in the small intestine. The hydrolysis of triacylglycerol is achieved through the action of pancreatic lipase, which requires colipase, also secreted by the pancreas, for activity. In the intestine, fat is emulsified with bile salts and phospholipids secreted into the intestine in bile, hydrolyzed by pancreatic enzymes, and almost completely absorbed. Pancreatic lipase has high specificity for the *sn*-1 and *sn*-3 positions of dietary triacylglycerols, resulting in the release of free fatty acids from the *sn*-1 and *sn*-3 positions and 2-monoacylglycerol. These products of digestion are absorbed into the enterocyte, and the triacylglycerols are reassembled, largely via the 2-monoacylglycerol pathway. This pathway conserves the fatty acid at the *sn*-2 position. The triacylglycerols are then assembled together with cholesterol, phospholipid, and apoproteins into chylomicrons. Following absorption, fatty acids of carbon chain length 12 or less may be transported as unesterified fatty acids bound to albumin directly to the liver via the portal vein, rather than acylated into triacylglycerols.

Dietary phospholipids are hydrolyzed by pancreatic phospholipase A_2 and cholesterol esters by pancreatic cholesterol ester hydrolase. The lysophospholipids are re-esterified and packaged together with cholesterol and triacylglycerols in intestinal lipoproteins or transported as lysophospholipid via the portal system to the liver.

Chylomicrons enter the circulation through the thoracic duct. These particles enter the circulation and within the capillaries of muscle and adipose tissue. Chylomicrons come into contact with the enzyme lipoprotein lipase, which is located on the surface of capillaries. Activation of lipoprotein lipase apolipoprotein CII, an apoprotein present on chylomicrons, results in the hydrolysis of the chylomicron triacylglycerol fatty acids. Most of the fatty acids released in this process are taken up by adipose tissue and re-esterified into triacylglycerol for storage. Triacylglycerol fatty acids also are taken up by muscle and oxidized for energy or are released into the systemic circulation and returned to the liver.

Metabolism. Most newly absorbed fatty acids enter adipose tissue for storage as triacylglycerol. However, in the postabsorptive state or during exercise when fat is needed for fuel, adipose tissue triacylglycerol undergoes lipolysis and free fatty acids are released into the circulation. Hydrolysis occurs via the action of the adipose tissue enzyme hormone-sensitive lipase. The activity of this lipase is suppressed by insulin. When plasma insulin concentrations fall in the postabsorptive state, hormone-sensitive lipase is activated to release more free fatty acids into the circulation. Thus, in the postabsorptive state, free fatty acid concentrations in plasma are high; conversely, in the postprandial state, hormone-sensitive lipase activity is suppressed and free fatty acid concentrations in plasma are low.

Free fatty acids circulate in the blood bound to albumin. The major site of fatty acid oxidation is skeletal muscle. When free fatty acid concentrations are relatively high, muscle uptake of fatty acids is also high. As in liver, fatty acids in the muscle are transported via a carnitine-dependent pathway into mitochondria where they undergo β-oxidation, which involves removal of two carbon fragments. These two carbon units enter the citric acid cycle as acetyl coenzyme A (CoA), through which they are completely oxidized to carbon dioxide with the generation of large quantities of high-energy phosphate bonds, or they condense to form ketone bodies. Muscle can oxidize both fatty acids and glucose for energy. However, the uptake of fatty acids in excess of the needs for oxidation for energy by muscle does result in temporary storage as triacylglycerol (Bessesen et al., 1995). High uptake of fatty acids by skeletal muscle also reduces glucose uptake by muscle and glucose oxidation (Pan et al., 1997; Roden et al., 1996).

Fatty acids released from adipose tissue or to a lesser extent during hydrolysis of chylomicron and very low density lipoprotein (VLDL) triacylglycerols are also taken up and oxidized by the liver. Oxidation of fatty acids containing up to 18 carbon atoms occurs mainly in the mitochondria. Oxidation of excess fatty acids in the liver, which occurs in prolonged fasting and with high intakes of medium-chain fatty acids, results in formation of large amounts of acetyl CoA that exceed the capacity for entry to the citric acid cycle. These 2-carbon acetyl CoA units condense to form ketone bodies (e.g., acetoacetate and β-hydroxybutyrate) that are released into the circulation. During starvation or prolonged low carbohydrate intake, ketone bodies can become an important alternate energy substrate to glucose for the brain and muscle. High dietary intakes of medium-chain fatty acids also result in the generation of ketone bodies. This is explained by the carnitine-independent influx of medium-chain fatty acids into the mitochondria, thus by-passing this regulatory step of fatty acid entry into β-oxidation. Fatty acids of greater than 18 carbon atoms require chain shortening in peroxisomes prior to mitochondrial β-oxidation.

Fatty acids that do not enter into oxidative pathways can be re-esterified into triacylglycerols or other lipids. The major pathway for triacylglycerol synthesis in liver is the 3-glycerophosphate pathway, which shows a high degree of specificity for saturated fatty acids at the *sn*-1(3) position and for unsaturated fatty acids at the *sn*-2 position. In the liver, triacylglycerols can either be stored temporarily or incorporated into triacylglycerol-rich VLDL and released into the plasma. The triacylglycerol fatty acids of VLDL have the same fate as chylomicron triacylglycerol fatty acids. When VLDL triacylglycerols undergo lipolysis, the remaining triacylglycerol-depleted particle is called a VLDL remnant. These remnants are either removed directly by the liver or they are further metabolized in the vascular compartment to form low density lipoproteins (LDL).

Excretion. Fatty acids are generally catabolized entirely by oxidative processes from which the only excretion products are carbon dioxide and water. Small amounts of ketone bodies produced by fatty acid oxidation are excreted in urine. Fatty acids are present in the cells of the skin and intestine, thus small quantities are lost when these cells are sloughed.

Saturated Fatty Acids

Absorption. When saturated fatty acids are ingested along with fats containing appreciable amounts of unsaturated fatty acids, they are absorbed almost completely by the small intestine. In general, the longer the chain length of the fatty acid, the lower will be the efficiency of absorption. However, unsaturated fatty acids are well absorbed regardless of chain length. Studies with human infants have shown the absorption to be 75, 62, 92, and 94 percent of palmitic acid, stearic acid, oleic acid, and linoleic acid, respectively, from vegetable oils (Jensen et al., 1986). The absorption of palmitic acid and stearic acid from human milk is higher than from cow milk and vegetable oils (which are commonly used in infant formulas) because of the specific positioning of these long-chain saturated fatty acids at the *sn*-2 position of milk triacylglycerols (Carnielli et al., 1996a; Jensen, 1999). The intestinal absorption of palmitic acid and stearic acid from vegetable oils was 75 to 78 percent compared with 91 to 97 percent from fats with these fatty acids in the *sn*-2 position (Carnielli et al., 1996a). Still, absorption of stearic acid was over 90 percent complete in healthy adults when contained in triacylglycerols of mixed fatty acids (Bonanome and Grundy, 1989). Long-chain saturated fatty acids released into the lumen through the action of pancreatic lipase are less readily solubilized into mixed micelles than are unsaturated fatty acids; in the alkaline pH of the intestine they can form insoluble soaps with calcium and other divalent

cations and can be excreted (Carnielli et al., 1996a; Lucas et al., 1997; Tomarelli et al., 1968). Following absorption, long-chain saturated fatty acids are re-esterified along with other fatty acids into triacylglycerols and released in chylomicrons. Medium-chain saturated fatty acids (C8:0 and C10:0) are absorbed and transported bound to albumin as free fatty acids in the portal circulation and cleared by the liver. About two-thirds of lauric acid (C12:0) is transported with chylomicron triacylglycerols, whereas the remaining one-third enters the portal circulation as free fatty acids.

Metabolism. Pathways of oxidation of saturated fatty acids are similar to those for other types of fatty acids (see earlier section, "Total Fat"). Unoxidized stearic acid (9 to 14 percent) is rapidly desaturated and converted to the monounsaturated fatty acid, oleic acid (Emken, 1994; Rhee et al., 1997). For this reason, dietary stearic acid has metabolic effects that are closer to those of oleic acid rather than those of other long-chain saturated fatty acids. The saturated fatty acids, in contrast to *cis* mono- or polyunsaturated fatty acids, have a unique property in that they suppress the expression of LDL receptors (Spady et al., 1993). Through this action, dietary saturated fatty acids raise serum LDL cholesterol concentrations (Mustad et al., 1997).

Excretion. Saturated fatty acids, like other fatty acids, are generally completely oxidized to carbon dioxide and water.

cis-*Monounsaturated Fatty Acids*

Absorption. The absorption of *cis*-monounsaturated fatty acids (based on oleic acid data) is in excess of 90 percent in adults and infants (Jensen et al., 1986; Jones et al., 1985). The pathways of *cis*-monounsaturated fat digestion and absorption are similar to those of other fatty acids (see earlier section, "Total Fat").

Metabolism. Oleic acid, the major monounsaturated fatty acid in the body, is derived mainly from the diet. Small amounts also come from desaturation of stearic acid. Stable isotope tracer methods have shown that approximately 9 to 14 percent of dietary stearic acid is converted to oleic acid in vivo (Emken, 1994; Rhee et al., 1997). Based on the amount of stearic acid in the average diet (approximately 3 percent of energy), desaturation of dietary stearic acid is not a main source of oleic acid in the body. Oleic acid is oxidized, as are all other fatty acids, by β-oxidation. However, there is some evidence that oxidation of chylomicron-derived oleic acid is significantly greater than for palmitic acid (Schmidt et al.,

1999). The metabolic implications of the differential rates of oxidation of saturated, monounsaturated, and *cis* *n*-6 and *n*-3 fatty acids are not clear.

Excretion. Because oleic acid is highly absorbed, little is excreted. As for other fatty acids, the oxidation of monounsaturated fatty acids results in production of carbon dioxide and water.

n-*6 Polyunsaturated Fatty Acids*

Absorption. The digestion and absorption of *n*-6 fatty acids is efficient and occurs via the same pathways as that of other long-chain fatty acids (see earlier section, "Total Fat").

Metabolism. Both saturated and *n*-9 monounsaturated fatty acids can be synthesized from the carbon moieties of carbohydrate and protein. Mammalian cells do not have the enzymatic ability to insert a *cis* double bond at the *n*-6 position of a fatty acid chain, thus *n*-6 fatty acids are essential nutrients. The parent fatty acid of the *n*-6 series is linoleic acid. Studies using isotopically labeled linoleic acid have shown that adults and newborn infants can desaturate and elongate linoleic acid to form arachidonic acid (Emken et al., 1998, 1999; Salem et al., 1996; Sauerwald et al., 1997). The elongation of linoleic acid involves the sequential addition of two carbon units and desaturation involves insertion of a methylene-interrupted double bond towards the carboxyl terminus, thus preserving the position of the first *n*-6 double bond. These longer-chain, more polyunsaturated *n*-6 fatty acids are found primarily in membrane phospholipids, and since they can be formed only in animal cells, arachidonic acid is present in the diet only in animal tissue lipids.

Recent studies using stable isotopically labeled fatty acids to investigate the effect of gestational age and intrauterine growth on essential fatty acid desaturation and elongation have shown that the conversion of linoleic to arachidonic acid occurs as early as 26 weeks of gestation, and is in fact more active at earlier gestational ages (Uauy et al., 2000a). In addition to its role as a precursor to dihomo-γ-linolenic acid and arachidonic acid, linoleic acid has a specific role in acylceramides, which are important in maintaining the epidermal water barrier (Hansen and Jensen, 1985).

The 18 and 20 carbon *n*-9, *n*-6, and *n*-3 fatty acids compete for a common Δ6 and Δ5 desaturase. In vitro studies have shown the Δ6 desaturase enzymes preference occurs in the order 18:3*n*-3 > 18:2*n*-6 > 18:1*n*-9 (Brenner, 1974; Castuma et al., 1977). The formation of arachidonic acid and *n*-3 fatty acid metabolites also appears to be inhibited by the products of the reaction and by high amounts of substrate. Thus, high intakes of *n*-3 fatty acids or

arachidonic and linoleic acids will reduce the efficiency of conversion of linoleic acid to arachidonic acid and α-linolenic acid to its products (Emken et al., 1994, 1998, 1999). For example, Emken and coworkers (1994) reported that an intake of 30 g/d of linoleic acid resulted in a 40 to 54 percent lower conversion of stable isotopically labeled linoleic and α-linolenic acid to their metabolites compared to an intake of 15 g/d in healthy men. High dietary intakes of *n*-3 fatty acids result in reduced tissue arachidonic acid concentrations and synthesis of arachidonic acid-derived eicosanoids, with consequent effects on the balance of *n*-6 and *n*-3 fatty acid-derived eicosanoids that are produced. The reduction in arachidonic acid-derived eicosanoids due to high *n*-3 fatty acid intake involves effects on pathways of eicosanoid formation, in addition to reducing concentrations of precursor arachidonic acid availability.

Both the rate of oxidation to carbon dioxide and water and the acylation into different lipids differ among fatty acids of different chain length and unsaturation. Arachidonic acid is primarily found in tissue phospholipids, rather than in triacylglycerols or cholesterol esters. Retroconversion of adrenic acid to arachidonic acid occurs through cleavage of a 2-carbon unit from the carboxyl end of the fatty acid and may be important in maintaining adequate tissue concentrations of arachidonic acid. Besides being elongated to longer-chain fatty acids, arachidonic acid is the precursor to a number of eicosanoids (prostaglandins, thromboxanes, and leukotienes) that are involved in platelet aggregation, hemodynamics, and coronary vascular tone, which can have an effect on the onset of atherogenesis and coronary infarction (Kinsella et al., 1990).

Excretion. *n*-6 Fatty acids are almost completely absorbed and are either incorporated into tissue lipids, utilized in eicosanoid synthesis, or oxidized to carbon dioxide and water. Small amounts are lost during sloughing of cells from skin and other epithelial membranes.

n-*3 Polyunsaturated Fatty Acids*

Absorption. The digestion and absorption of *n*-3 fatty acids is similar to that of other long-chain fatty acids.

Metabolism. Humans are unable to insert a double bond at the *n*-3 position (*cis* 15) of a fatty acid of 18 carbons in length, and thus require a dietary source of *n*-3 fatty acids. The *n*-3 fatty acids cannot be formed from saturated, *n*-9 monounsaturated, or *n*-6 polyunsaturated fatty acids. The parent fatty acid of the *n*-3 series is α-linolenic acid, which can be further metabolized by elongation and desaturation to longer-chain, more highly

unsaturated metabolites using the same pathway and enzymes as those used for the *n*-6 fatty acids. α-Linolenic acid is desaturated by Δ6 desaturase, elongated, and then desaturated by Δ5 desaturase to form EPA, which is the precursor for series 3 eicosanoids and series 5 leukotrienes. The pathway leading from EPA to more highly unsaturated fatty acids involves the addition of two 2-carbon units, then a second Δ6 desaturation, after which the 24-carbon-chain fatty acid is transported to the peroxisomes and converted to DHA through one step of β-oxidation (Sprecher et al., 1995; Voss et al., 1991). DHA is a component of membrane structural lipids that are enriched in certain phospholipids, such as the ethanolamine phosphoglycerides and phosphatidylserine in nervous tissue, retina, and spermatozoa. α-Linolenic acid is not known to have any specific functions other than to serve as a precursor for synthesis of EPA and DHA.

High dietary intakes of EPA and DHA result in decreased tissue concentrations of arachidonic acid and increased concentrations of EPA and DHA, respectively. This results in changes in the balance of eicosanoids synthesized from the *n*-6 and *n*-3 fatty acids. The ability to convert α-linolenic acid to EPA and DHA differs among mammalian species. Studies using isotopically labeled α-linolenic acid, however, have shown that adults and newborn infants can desaturate and elongate α-linolenic acid to form DHA (Carnielli et al., 1996b; Salem et al., 1996; Sauerwald et al., 1996, 1997; Uauy et al., 2000a; Vermunt et al., 2000). Recent studies with infants have shown that the rates of conversion of α-linolenic acid to DHA appear to be higher in preterm infants and decrease with increasing gestational age (Uauy et al., 2000a). These types of studies have also shown that high intakes of α-linolenic acid result in reduced conversion to DHA (Vermunt et al., 2000).

Whereas the retroconversion of adrenic acid to maintain tissue arachidonic acid requires the removal of only a single 2-carbon unit, the retroconversion of DHA to EPA is more complex and involves the removal of the double bond at the Δ4 position, in addition to a 2-carbon unit. Supplementation with DHA is accompanied by an increase in EPA, which could be explained by retroconversion of DHA to EPA or by inhibition of further metabolism of EPA formed from α-linolenic acid (Brossard et al., 1996; Conquer and Holub, 1996; Nelson et al., 1997; Vidgren et al., 1997).

Excretion. *n*-3 Fatty acids are almost completely absorbed and either oxidized to carbon dioxide and water, incorporated into tissue lipids, or utilized in eicosanoid synthesis. Small amounts of *n*-3 fatty acids are lost during sloughing of skin and other epithelial cells.

Trans *Fatty Acids*

Absorption. As with other fatty acids, the coefficient of absorption of elaidic acid (18:1*t*) is about 95 percent (Emken, 1979). Studies in humans using pure triacylglycerols containing deuterated *cis* and *trans* octadecenoic acid isomers varying in melting point and double bond position suggest that the presence of *trans* double bonds in the fatty acyl chain has no measurable effect on efficiency of absorption (Emken, 1979, 1984).

Transport. *Trans* fatty acids are transported similarly to other dietary fatty acids and are distributed within the cholesteryl ester, triacylglycerol, and phospholipid fractions of lipoproteins (Vidgren et al., 1998). Platelet lipids also contain *trans* fatty acids and their composition reflects *trans* fatty acid intake, as do other tissues (except the brain) (Mensink and Hornstra, 1995).

Metabolism. The *trans* isomers of oleic acid and linoleic acid that are formed during partial hydrogenation of unsaturated vegetable oils have been suggested to have potential adverse effects on fetal and infant growth and development through inhibition of the desaturation of linoleic acid and α-linolenic acid to arachidonic acid and DHA, respectively (Koletzko, 1992; van Houwelingen and Hornstra, 1994). Many animal and in vitro studies, however, have involved much higher amounts of *trans* than all-*cis* polyunsaturated fatty acids (Hwang et al., 1982; Shimp et al., 1982). Other animal studies have suggested that the deleterious effects seen with high intakes of *trans* fatty acid do not occur with amounts comparable to those consumed in a normal human diet containing sufficient amounts of linoleic acid (Bruckner et al., 1982; Zevenbergen et al., 1988).

Available animal and human data indicate that adipose tissue *trans* fatty acid content reflects the content of the diet and that selective accumulation does not occur (Emken, 1984). More recent attention has been focused on validating the use of adipose *trans* fatty acid content as a measure of long-term dietary intake. In a study of Canadian individuals, Chen and colleagues (1995b) reported that adipose tissue *trans* fatty acid patterns, particularly those isomers found in partially hydrogenated vegetable fat, reflected dietary sources. Garland and coworkers (1998) also reported that adipose tissue *trans* fatty acid patterns correlated with intake and noted a stronger relationship with the isomers found in vegetable fat rather than animal fat. The authors cautioned that the later conclusion may have been due to the smaller between-person variability with animal versus vegetable *trans* fatty acid intake. In a letter to the editor regarding this study, Aro and Salminen (1998) suggested that the stronger correlation between adipose tissue *trans* fatty acid isomers found in hydrogenated vegetable fat

rather than animal fat may be attributable to different rates of metabolism of the *trans* isomers. Two groups have used adipose tissue *trans* fatty acid to corroborate dietary *trans* fatty acid intake derived from food frequency questionnaires and found a strong relationship (Lemaitre et al., 1998; London et al., 1991). Despite these observations, it should be noted that adipose tissue *trans* fatty acid profiles can be confounded by the retention of intermediate products of β-oxidation (Emken, 1995).

Excretion. *Trans* fatty acids are completely catabolized to carbon dioxide and water.

Clinical Effects of Inadequate Intakes

Total Fat

Impaired Growth. Dietary fat is a major source of body fuel. If intakes of fat, along with carbohydrate and protein, are inadequate to meet energy needs, the individual will be in negative energy balance. Depending on the severity and duration, this may lead to malnutrition or starvation. In an energy-sufficient diet, carbohydrate can replace fat as a source of energy. In some populations, fat intakes are very low and body weight and health are maintained by high intakes of carbohydrate (Bunker et al., 1996; Falase et al., 1973; Shintani et al., 2001). Clearly, humans have the ability to adapt metabolically to a wide spectrum of fat-to-carbohydrate intake ratios. In the short term, an isocaloric diet can be either very high or very low in fat with no obvious differences in health. The critical question therefore is, Are there optimal fat-to-carbohydrate ratios for long-term health, and if so, what are they? One potential concern over fat restriction is the potential for reduction in total energy intake, which is of particular relevance for infants and children, as well as during pregnancy when there is a relatively high energy requirement for both energy expenditure and for fetal development. Chapter 11 provides a detailed discussion on fat intake and growth.

Increased Risk of Chronic Diseases. Compared to higher fat intakes, low fat, high carbohydrate diets may modify the metabolic profile in ways that are considered to be unfavorable with respect to chronic diseases such as coronary heart disease (CHD) and diabetes (see Chapters 6 and 11). These changes include a reduction in high density lipoprotein cholesterol concentration, an increase in serum triacylglycerol concentration, and higher responses in postprandial glucose and insulin concentrations. This metabolic pattern has been associated with increased risk for CHD and type 2 diabetes

in intervention and prospective studies (see Chapter 11). Although changes in the metabolic profile do occur, strong evidence that low fat diets actually predispose to either CHD or diabetes does not exist. In fact, some populations that consume low fat diets and in which habitual energy intake is relatively high have a low prevalence of these chronic diseases (Falase et al., 1973; Shintani et al., 2001). Similarly, populations with high fat diets (i.e., ≥ 40 percent of energy) and a low prevalence of chronic diseases often include people who engage in heavy physical labor, are lean, and have a low family history of chronic diseases. Conversely, in sedentary populations, such as that of the United States where overweight and obesity are common, high carbohydrate, low fat diets induce changes in lipoprotein and glucose/insulin metabolism in ways that could raise risk for chronic diseases (see Chapter 11). Available prospective studies have not concluded whether low fat, high carbohydrate diets provide a health risk in the North American population.

Chronic nonspecific diarrhea in children has been suggested as a potential adverse effect of low fat diets. It is considered a disorder of intestinal motility that may improve with an increase in dietary fat intake in order to slow gastric emptying and alter intestinal motility (Cohen et al., 1979). Detailed discussion on fat intake and risk of chronic disease is provided in Chapter 11.

n-*6 Polyunsaturated Fatty Acids*

Certain polyunsaturated fatty acids were first identified as being essential in rats fed diets almost completely devoid of fat (Burr and Burr, 1929). Subsequently, studies in infants and children fed skimmed cow milk (Hansen et al., 1958, 1963) and patients receiving parenteral nutrition without an adequate source of essential fatty acids (Collins et al., 1971; Holman et al., 1982; Paulsrud et al., 1972) demonstrated clinical symptoms of a deficiency in humans. Because adipose tissue lipids in free-living, healthy adults contain about 10 percent of total fatty acids as linoleic acid, biochemical and clinical signs of essential fatty acid deficiency do not appear during dietary fat restriction or malabsorption when they are accompanied by an energy deficit. In this situation, release of linoleic acid and small amounts of arachidonic acid from adipose tissue reserves may prevent development of essential fatty acid deficiency. However, during parenteral nutrition with dextrose solutions, insulin concentrations are high and mobilization of adipose tissue is prevented, resulting in development of the characteristic signs of essential fatty acid deficiency. Studies on patients given fat-free parenteral feeding have provided great insight into defining levels at which essential fatty acid deficiency may occur. Without intervention, these patients develop clinical signs of a deficiency

in 2 to 4 weeks (Fleming et al., 1976; Goodgame et al., 1978; Jeppesen et al., 1998; Riella et al., 1975). In rapidly growing infants, feeding with milk containing very low amounts of *n*-6 fatty acids results in characteristic signs of an essential fatty acid deficiency and elevated plasma triene:tetraene ratios (see "*n*-6:*n*-3 Polyunsaturated Fatty Acid Ratio").

When dietary essential fatty acid intake is inadequate or absorption is impaired, tissue concentrations of arachidonic acid decrease, inhibition of the desaturation of oleic acid is reduced, and synthesis of eicosatrienoic acid from oleic acid increases. The characteristic signs of deficiency attributed to the *n*-6 fatty acids are scaly skin rash, increased transepidermal water loss, reduced growth, and elevation of the plasma ratio of eicosatrienoic acid:arachidonic acid (20:3*n*-9:20:4*n*-6) to values greater than 0.4 (Goodgame et al., 1978; Holman, 1960; Jeppesen et al., 2000; Mascioli et al., 1996; O'Neill et al., 1977). Other studies have utilized a ratio of 0.2 as indicative of an essential fatty acid deficiency (Holman et al., 1991; Jeppesen et al., 1998). In addition to the clinical signs mentioned above, essential fatty acid deficiency in special populations has been linked to hematologic disturbances and diminished immune response (Bistrian et al., 1981; Boissonneault and Johnston, 1983). Further discussion on this topic is included in "Findings by Life Stage and Gender Group—*n*-6 Polyunsaturated Fatty Acids."

n-*3 Polyunsaturated Fatty Acids*

Tissue levels of arachidonic acid, as well as the amounts of arachidonic acid and EPA- derived eicosanoids that are formed, have important effects on many physiological processes (e.g., platelet aggregation, vessel wall constriction, and immune cell function) via the biosynthesis of eicosanoids. Thus, the amount of *n*-3 fatty acids and their effects on arachidonic acid metabolism are relevant to many chronic diseases. EPA also appears to have specific effects on fatty acid metabolism, resulting in inhibition of hepatic triacylglycerol synthesis and VLDL secretion (Berge et al., 1999; Wong and Nestel, 1987). DHA, on the other hand, is highly enriched in specific phospholipids of the retina and nonmyelin membranes of the nervous system.

Studies in rodents and nonhuman primates have consistently demonstrated that prolonged feeding with diets containing very low amounts of α-linolenic acid result in reductions of visual acuity thresholds and electroretinogram A and B wave recordings, which were prevented when α-linolenic acid was included in the diet (Anderson et al., 1974; Benolken et al., 1973; Bourre et al., 1989; Neuringer et al., 1984, 1986; Wheeler et al., 1975). A variety of changes in learning behaviors in animals fed α-linolenic acid-deficient diets have also been reported (Innis, 1991). These studies have

involved feeding oils such as safflower oil, which contains less than 0.1 percent α-linolenic acid and is high in linoleic acid, as the sole source of fat for prolonged periods. The reduction in visual function is accompanied by decreased brain and retina DHA with an increase in docosapentaenoic acid (DPA, 22:5*n*-6). The compensatory increase in 22 carbon chain *n*-6 fatty acids results in maintenance of the total amount of *n*-6 and *n*-3 polyunsaturated fatty acids in neural tissue. DPA is formed from linoleic acid by similar desaturation and elongation steps used in the synthesis of DHA from α-linolenic acid. However, α-linolenic acid is clearly handled differently from linoleic acid. For example, rates of β-oxidation of α-linolenic acid are much higher than for linoleic acid (Clouet et al., 1989). This may suggest that immaturity or reduced enzyme activity is unlikely to explain lower DHA in the brain of young animals fed diets with low amounts of α-linolenic acid, and that DHA has specific metabolic functions that cannot be accomplished by DPA despite its structural similarity. Stable isotope studies have shown that infants can convert linoleic acid to arachidonic acid and α-linolenic acid to DHA (Carnielli et al., 1996b; Salem et al., 1996; Sauerwald et al., 1996, 1997; Uauy et al., 2000a), with the rate of conversion apparently higher in infants of younger gestational ages (Uauy et al., 2000a).

Unlike essential fatty acid deficiency (*n*-6 and *n*-3 fatty acids), plasma eicosatrienoic acid (20:3*n*-9) remains within normal ranges and skin atrophy and scaly dermatitis are absent when the diet is deficient in only *n*-3 fatty acids. Tissue concentrations of 22-carbon chain *n*-6 fatty acids increase, and DHA concentration decreases with a prolonged dietary deficiency of *n*-3 fatty acids accompanied by adequate *n*-6 fatty acids. Currently, there are no accepted plasma *n*-3 fatty acid or *n*-3 fatty acid-derived eicosanoid concentrations for indicating impaired neural function or impaired health endpoints. Further discussion on this topic is included in the next section.

EVIDENCE CONSIDERED FOR ESTIMATING THE REQUIREMENTS FOR TOTAL FAT AND FATTY ACIDS

Total Fat

Clinical endpoints of fat intake are trends, rather than defined endpoints, and therefore cannot be used to set an Estimated Average Requirement (EAR). The endpoints that strongly predict the relation of total fat intake to the development of chronic disease have been identified and are discussed in Chapter 11 for estimating Acceptable Macronutrient Distribution Ranges (AMDRs).

Growth

Because the amount of fat in the diet can have an impact on energy intake, a number of studies have been conducted to determine if diets containing less than 30 percent of energy from fat can impair growth of children (Boulton and Magarey, 1995; Foman et al., 1976; Lagström et al., 1999; Lapinleimu et al., 1995; Niinikoski et al., 1997a, 1997b; Obarzanek et al., 1997; Shea et al., 1993; Uauy et al., 2000b; Vobecky et al., 1995). These studies showed no effect of the level of dietary fat on growth when energy intake is adequate. Chapter 11 provides further discussion on this topic.

Fat Balance (Maintenance of Body Weight)

Because fat is an important source of energy, studies have been conducted to ascertain whether dietary fat influences energy expenditure and the amount of fat needed in the diet to achieve fat balance and therefore maintain body weight. These studies demonstrated that the amount of fat in the diet does not affect energy expenditure and thus the amount of energy required to maintain body weight (Hill et al., 1991; Leibel et al., 1992). Chapter 11 provides further discussion on this topic.

Saturated Fatty Acids

Saturated fatty acids are a potential fuel source for the body. In addition, they are important structural fatty acids for cell membranes and other functions and therefore are essential for body functions. These fatty acids, however, can be synthesized as needed for these functions from other fuel sources and have not been associated with any beneficial role in preventing chronic disease. Consequently, saturated fatty acids are not essential in the diet.

cis-*Monounsaturated Fatty Acids*

Monounsaturated fatty acids are a potential fuel source for the body and are a critical structural fatty acid for cell membranes and other functions. Monounsaturated fatty acids undoubtedly are required for many body functions. Nevertheless, monounsaturated fatty acids can be biosynthesized from other fuel sources and therefore are not essential in the diet.

n-*6 Polyunsaturated Fatty Acids*

Clinical signs of essential fatty acid deficiency are generally only found in patients with chronic fat malabsorption on parenteral nutrition and without an enteral or parenteral source of polyunsaturated fat. Early signs of essential fatty acid deficiency include rough and scaly skin, which if left untreated, develops into dermatitis (Jeppesen et al., 1998). In studies of patients with dermatitis who were receiving parenteral nutrition, the ratio of eicosatrienoic acid:arachidonic acid (20:3*n*-9:20:4*n*-6) in plasma was elevated. As described earlier, when present in adequate amounts, linoleic acid is converted to arachidonic acid through a multi-step process involving Δ6 and Δ5 desaturases (see Figure 8-1); however, in the absence of linoleic acid, Δ6 and Δ5 desaturases convert oleic acid to eicosatrienoic acid. The increase in eicosatrienoic acid concentration, which occurs in the absence of *n*-6 fatty acids or the combined absence of *n*-6 and *n*-3 fatty acids, led Holman (1960) to define a plasma triene:tetraene ratio of greater than 0.4 as evidence of essential fatty acid deficiency. More recently, a lower threshold of greater than 0.2 has been suggested (Holman et al., 1979; Jeppesen et al., 1998; Mascioli et al., 1996) because the average ratio was found to be 0.1 ± 0.08 (standard deviation) in populations of normal *n*-6 fatty acid status. Optimal plasma or tissue lipid concentrations of linoleic acid, arachidonic acid, and other *n*-6 fatty acids or the ratios of certain *n*-6:*n*-3 fatty acids have not been established.

Because the *n*-6 fatty acid intake is generally well above the levels needed to maintain a triene:tetraene ratio below 0.2 (even for very low fat diets), data on *n*-6 fatty acid requirements from traditional metabolic feeding studies are not available. Instead, studies with patients on total parenteral nutrition (TPN) solutions that contained very low amounts or were completely devoid of *n*-6 fatty acids have been used. In these studies, after developing an essential fatty acid deficiency, patients were treated with linoleic acid. Several case reports, small studies of two or three patients in which varying feeding designs were employed, or larger studies of patients with *n*-6 fatty acid deficiency caused by TPN have been documented (Barr et al., 1981; Collins et al., 1971; Goodgame et al., 1978; Jeppesen et al., 1998; Mascioli et al., 1979; Meng, 1983; Richardson and Sgoutas, 1975; Riella et al., 1975; Siguel et al., 1986; Wene et al., 1975; Wong and Deitel, 1981). These studies observed symptoms such as rash, scaly skin, and ectopic dermititis; reduced serum tetraene concentrations, increased serum triene concentration; and a triene:tetraene ratio greater than 0.4 after 2 to 4 weeks of TPN. Because of the lack of data on the *n*-6 fatty acid requirement in healthy individuals, an EAR cannot be set based on correction of a deficiency.

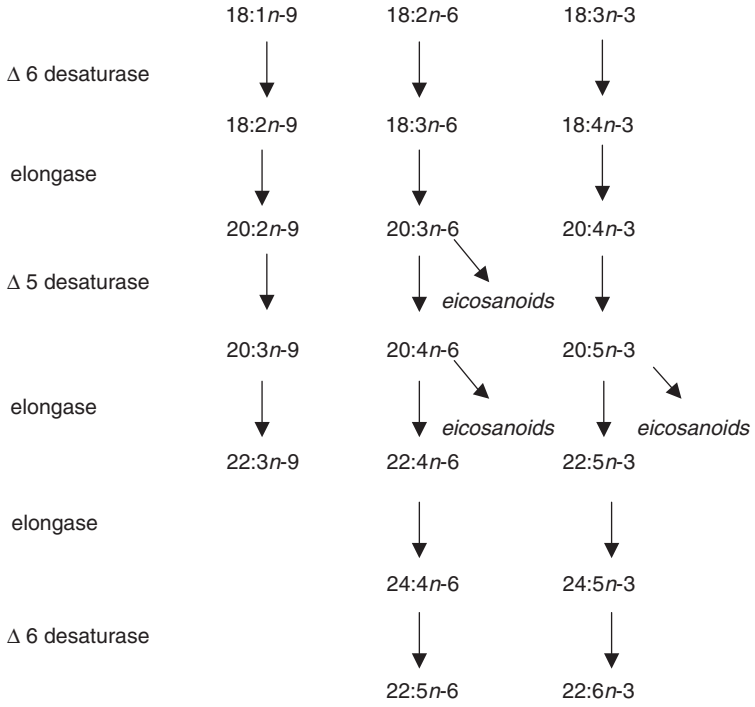

FIGURE 8-1 Biosynthesis of long-chain fatty acids.

n-*3 Polyunsaturated Fatty Acids*

n-*3 Polyunsaturated Fatty Acid Deficiency*

Some evidence for the essentiality of *n*-3 fatty acids in humans can be drawn from case reports of patients receiving parenteral nutrition with intravenous lipids containing an emulsion of safflower oil, which is very low in α-linolenic acid and high in linoleic acid. Biochemical changes of *n*-3 fatty acid deficiency include a decrease in plasma and tissue docosahexaenoic acid (DHA) concentrations. There is no accepted cut-off concentration of plasma or tissue DHA concentrations below which functions ascribed to *n*-3 fatty acids, such as visual or neural function, are impaired. Similarly, there are no accepted normal ranges for eicosapentaenoic acid (EPA) with respect to synthesis of EPA-derived eicosanoids or regulation of arachidonic acid metabolism and its eicosanoid metabolites, nor are there accepted clinical functional endpoints such as immune response.

Dietary or intravenous supplementation with oils containing α-linolenic acid, such as soybean oil, has been shown to increase red blood cell and plasma phospholipid DHA concentration in hospitalized patients with a long history of dietary *n*-3 fatty acid restriction (Bjerve et al., 1987a, 1987b; Holman et al., 1982). Sensory neuropathy and visual problems in a young girl given parenteral nutrition with an intravenous lipid emulsion containing only a small amount of α-linolenic acid were corrected when the emulsion was changed to one containing generous amounts of α-linolenic acid (Holman et al., 1982). Nine patients with an *n*-3 fatty acid deficiency had scaly and hemorrhagic dermatitis, hemorrhagic folliculitis of the scalp, impaired wound healing, and growth retardation (Bjerve, 1989). The possibility of other nutrient deficiencies, such as vitamin E and selenium, has been raised (Anderson and Connor, 1989; Meng, 1983). A series of papers have described low tissue *n*-3 fatty acid concentrations in nursing home patients fed by gastric tube for several years with a powdered diet formulation that provided about 0.5 to 0.6 percent of energy (0.65 to 0.86 g) as linoleic acid, and 0.02 percent of energy (30 to 50 mg) as α-linolenic acid (Bjerve et al., 1987a, 1987b). Skin lesions were resolved following supplementation with cod liver oil and soybean oil or ethyl linolenate (Bjerve et al., 1987a, 1987b). Concurrent deficiency of both *n*-6 and *n*-3 fatty acids in these patients, as in studies of patients supported by lipid-free parenteral nutrition, limits interpretation of the specific problems caused by inadequate intakes of *n*-3 fatty acids. Supplementation with cod liver oil and soybean oil, or feeding with a formula providing linoleic acid and α-linolenic acid or ethyl α-linolenic acid for 14 days, increased red blood cell arachidonic acid and DHA concentrations and gave some resolution of skin signs (Bjerve et al., 1987a, 1987b). Because of the lack of data on the *n*-3 fatty acid requirement in healthy individuals, an EAR cannot be set based on correction of a deficiency.

Growth and Neural Development

The membrane lipids of brain gray matter and the retina contain very high concentrations of DHA, particularly in the amino phospholipids phosphatidylethanolamine and phosphatidylserine. In these tissues, the concentration of DHA can exceed 50 percent of the fatty acids resulting in the presence of di-DHA phospholipid species. During *n*-3 fatty acid deficiency, DHA is tenaciously retained, thus most animal studies investigating the importance of *n*-3 fatty acids have used rats deprived of *n*-3 fatty acids for two or more generations. Small amounts of DHA are also present in cell membranes throughout the body. In these tissues, the phospholipid *sn*-1 chain is usually a saturated fatty acid (e.g., 16:0) and DHA is found on the *sn*-2 position. The developing brain accumulates large amounts of DHA

during pre- and postnatal development and this accumulation continues throughout the first two years after birth (Martinez, 1992). Evidence from autopsy analysis indicates that accumulation of DHA in the retina is complete by term birth (Martinez et al., 1988). Due to the accumulation of DHA during brain growth, the developing brain is more susceptible to *n*-3 fatty acid deficiency than the mature brain. However, the presence of DHA within the membrane hydrophobic interior can influence membrane order (fluidity), thickness, domain size, hydration, and permeability and activity of associated proteins and ion channels. Unesterified DHA also regulates the expression of a variety of genes and influences cell signaling mechanisms (Salem et al., 2001; Sinclair et al., 2000). Animal studies have shown that feeding a diet very low in α-linolenic acid results in reduced brain and retina DHA concentration, which is accompanied by reduced visual function and behavior in learning tasks (Benolken et al., 1973; Bourre et al., 1989; Neuringer et al., 1984; Wheeler et al., 1975). The decrease in DHA concentration in the brain and retina is compensated for by an increase in the *n*-6 fatty acid docosapentaenoic acid, and this leads to maintenance of the total polyunsaturated fatty acid content of the membrane. Reduced growth or changes in food intake have not been noted in the extensive number of studies in animals, including nonhuman primates fed for extended periods on otherwise adequate diets lacking *n*-3 fatty acids.

The essential role of α-linolenic acid appears to be its role as precursor for synthesis of EPA and DHA. Thus, the dietary *n*-3 fatty acid requirement involves the activity of the desaturase enzymes and factors that influence the desaturation of α-linolenic acid in addition to the amount of the *n*-3 fatty acid. The questions of whether term gestation infants can form DHA, or if DHA is required in the infant diet, has been studied extensively. Activity of Δ6 and Δ5 desaturases has been demonstrated in human fetal tissue from as early as 17 to 18 weeks of gestation (Chambaz et al., 1985; Rodriguez et al., 1998), and stable isotope studies have confirmed that preterm and term infants are able to convert α-linolenic acid to DHA (Carnielli et al., 1996b; Salem et al., 1996; Sauerwald et al., 1996, 1997; Uauy et al., 2000a). Furthermore, the ability to convert α-linolenic acid appears to be greater in premature infants than in older term infants (Uauy et al., 2000a), although variability among infants is large. Current information from stable isotope tracer studies does not provide quantitative whole body or organ data on the conversion of α-linolenic acid to DHA, whether the rate of conversion can meet the needs of the developing brain for DHA, or the effect of varying linoleic and α-linolenic acid intakes and ratios on conversion. Experimental studies suggest that the eye and certain brain cells, such as astrocytes, are able to synthesize DHA from α-linolenic acid (Moore et al., 1991; Wetzel et al., 1991). The contribution of synthesis of DHA in the brain and retina to the accumulation of

DHA in these organs is not known. In vivo studies, however, have shown that the brain does take up DHA from plasma (de la Presa Owens and Innis, 1999; Greiner et al., 1997).

A large number of clinical trials have been completed comparing growth, as well as measures of visual, motor, and mental development, in term infants fed formula with no DHA or with addition of DHA to approximate the amount in human milk. Some have included arachidonic acid or γ-linolenic acid (18:3*n*-6), the Δ6 desaturase product of linoleic acid. The results of these trials are summarized in Table 8-1. Several aspects of design are important in evaluating these studies. These include a prospective, double-blind design with a sufficient number of infants randomized to control for the multiple genetic, environmental, and dietary factors that influence infant development and to detect meaningful treatment effects (Gore, 1999; Morley, 1998); the amount and balance of linoleic and α-linolenic acid; the duration of supplementation; the age at testing and tests used; and the physiological significance of any statistical differences found. None of the studies in Table 8-1 reported differences in growth among infants fed formulas with DHA added.

Recent large, randomized trials did not find differences in visual evoked potential, visual acuity, or tests of mental and psychomotor development through at least the first 18 months in term infants fed formulas supplemented with DHA or DHA plus arachidonic acid (Auestad et al., 1997, 2001; Lucas et al., 1999; Scott et al., 1998). These studies used formulas with at least 1.1 percent α-linolenic acid and had linoleic:α-linolenic acid ratios close to 10:1. In the study by Scott and coworkers (1998), indices of early vocabulary development were lower in infants fed formula with DHA, but not in those fed formulas lacking DHA and arachidonic acid or containing both DHA and arachidonic acid. Birch and coworkers (1998, 2000) reported better visual evoked potential, but not visual acuity, and higher Bayley mental developmental indices scores in infants fed formulas with DHA or DHA plus arachidonic acid than in infants fed standard formula. Carlson and coworkers (1996a) on the other hand, found higher visual acuity at 2 months, but not at 4, 6, 9, or 12 months, in infants fed formula with DHA and arachidonic acid. Early studies by Makrides and colleagues (1995) reported better visual evoked potential acuity in infants fed formula with 0.36 percent DHA than infants given no dietary DHA. However, this group did not confirm this finding in subsequent studies with formulas containing 0.34 or 0.35 percent DHA (Makrides et al., 2000b). In addition, greater problem-solving ability has been reported among infants fed formula with DHA and arachidonic acid than in infants fed standard formula (Willatts et al., 1998).

The effect of low *n*-6:*n*-3 ratios (high *n*-3 fatty acids) on arachidonic acid metabolism is also of concern in growing infants. Several studies in

premature infants have reported an association between feeding *n*-3 long-chain fatty acids in the absence of arachidonic acid and reduced growth (Carlson et al., 1992, 1993, 1996b; Ryan et al., 1999). Scott and coworkers (1998) reported lower indices of language development in term infants fed formula with DHA, although not in infants fed formula with both DHA and arachidonic acid or with no DHA and arachidonic acid. Human milk from women in the United States and Canada following usual diets contains both arachidonic acid and DHA, usually in the range of 1:1 to 2:1. No evidence of reduced growth or outcome on developmental tests have been reported for infants fed formulas with both arachidonic acid and DHA in amounts similar to that contained in human milk. Infants fed formula with a ratio of linoleic:α-linolenic acid of 4.8:1 and no arachidonic acid had lower growth, as well as lower plasma arachidonic acid status, than infants fed a formula with a ratio of 44:1 (Jensen et al., 1997), and no differences in growth were found between infants fed formulas containing linoleic:α-linolenic acid ratios of 9.7:1 and 18.2:1. Additionally, no differences in growth were found among infants fed formulas with 1.7 or 3.3 percent α-linolenic acid with linoleic:α-linolenic acid ratios of 10:1 or 5:1, respectively (Makrides et al., 2000a).

In conclusion, randomized clinical studies on growth or neural development with term infants fed formulas currently yield conflicting results on the requirements for *n*-3 fatty acids in young infants, but do raise concern over supplementation with long-chain *n*-3 fatty acids without arachidonic acid. For these reasons, growth and neural development could not be used to set an EAR.

Trans *Fatty Acids and Conjugated Linoleic Acid*

Small amounts of *trans* fatty acids and conjugated linoleic acid are present in all diets. They can serve as a source of fuel energy for the body. However, there are no known requirements for *trans* fatty acids and conjugated linoleic acid for specific body functions.

FACTORS AFFECTING THE REQUIREMENTS

Fat Absorption and Aging

Aging in humans has been associated with a decrease in liver size and hepatic blood flow, slightly decreased serum albumin concentrations, and normal routine liver chemistries (Russell, 1992). Pancreatic secretion after initial stimulation with either secretin or pancreozymin is not diminished with age (Bartoš and Groh, 1969). Similarly, 72-hour fecal fat excretion in response to a dietary fat challenge in young (19 to 44 years of age) and old

TABLE 8-1 Randomized Studies of *n*-3 Fatty Acids and Neural and Visual Development in Full-Term, Formula-Fed Infants

Reference	Study Population[a]	Test/Age[b]	Fatty Acid[c]
Agostoni et al., 1995	*n* = 29 formula *n* = 29 formula + LC-PUFA	Brunet-Lézine psychomotor development test 4 mo	18:2*n*-6 18:3*n*-3 18:3*n*-6 (GLA) 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Makrides et al., 1995	*n* = 14 formula *n* = 12 formula + LC-PUFA	VEP acuity 16, 30 wk	18:2*n*-6 18:3*n*-3 18:3*n*-6 (GLA) 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Carlson et al., 1996a	*n* = 20 formula *n* = 19 formula + DHA + AA	Visual acuity 2, 4, 6, 9, 12 mo	18:2*n*-6 18:3*n*-3 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Agostoni et al., 1997	*n* = 30 formula *n* = 26 formula + LC-PUFA	DQ 24 mo	18:2*n*-6 18:3*n*-3 18:3*n*-6 (GLA) 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Auestad et al., 1997	*n* = 45 formula *n* = 43 formula + DHA *n* = 46 formula + DHA + AA	Sweep VEP 2, 4, 6, 9, 12 mo Visual acuity 2, 4, 6, 9, 12 mo	18:2*n*-6 18:3*n*-3 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Jensen et al., 1997	*n* = 20 each group	VER 4 mo	18:2*n*-6 18:3*n*-3 18:2*n*-6:18:3*n*-3 ratio
Birch et al., 1998	*n* = 21 formula *n* = 20 formula + DHA *n* = 19 formula + DHA + AA	Sweep VEP acuity 6, 17, 26, 52 wk Visual acuity 6, 17, 26, 52 wk	18:2*n*-6 18:3*n*-3 20:4*n*-6 (AA) 22:6*n*-3 (DHA)

Fatty Acid Content (% of fatty acids)				Results
Formula	Formula + LC-PUFA			Infants consuming formula supplemented with LC-PUFA scored significantly higher than standard formula group
11.1	10.8			
0.70	0.73			
—	0.30			
—	0.44			
—	0.30			
Formula	Formula + LC-PUFA			VEP acuity better in infants fed supplemented formula than in infants fed standard formula
16.79	17.44			
1.58	1.52			
0.05	0.27			
—	0.01			
	0.36			
Formula	Formula + DHA + AA			Infants fed formula supplemented with DHA + AA had higher visual acuity than infants fed standard formula at 2 mo, but not at 4, 6, 9, or 12 mo
21.9	21.8			
2.2	2.0			
—	0.43			
—	0.10			
Formula	Formula + LC-PUFA			No differences in DQ values
11.1	10.8			
0.70	0.73			
—	0.30			
—	0.44			
—	0.30			
Formula	Formula + DHA	Formula + DHA + AA		No differences in VEP or visual acuity
21.9	20.7	21.7		
2.2	1.9	1.9		
—	—	0.43		
—	0.23	0.12		
Formula #1	#2	#3	#4	No differences in VER
17.6	17.3	16.5	15.6	Infants fed formula with a ratio of 4.8 weighed less than infants fed formula with a ratio of 44
0.4	0.95	1.7	3.2	
44.0	18.2	9.7	4.8	
Formula	Formula + DHA	Formula + DHA + AA		Sweep VEP acuity better in infants fed supplemented formulas than in infants fed standard formula at 6, 17, and 52 wk, but not 26 wk
14.6	15.1	14.9		
1.49	1.54	1.53		
—	0.02	0.72		Visual acuity not different between groups
—	0.35	0.36		

continued

TABLE 8-1 Continued

Reference	Study Population[a]	Test/Age[b]	Fatty Acid[c]
Jørgensen et al., 1998	*n* = 11 formula *n* = 12 formula + DHA *n* = 14 formula + DHA + GLA	Sweep VEP acuity 4 mo	18:2*n*-6 18:3*n*-3 18:3*n*-6 (GLA) 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Scott et al., 1998	*n* = 42–45 formula *n* = 33–43 formula + DHA *n* = 38–46 formula + DHA + AA	Bayley scales of infant development 12 mo MacArthur communicative development 14 mo	18:2*n*-6 18:3*n*-3 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Lucas et al., 1999	*n* = 125 formula *n* = 125 formula + LC-PUFA	Bayley scales of infant development 18 mo	18:2*n*-6 18:3*n*-3 20:4*n*-6 (AA) 22:6*n*-3 (DHA)
Makrides et al., 2000a	*n* = 30 10:1 formula *n* = 28 5:1 formula	VEP acuity 16, 34 wk	18:2*n*-6 18:3*n*-3
Makrides et al., 2000b	*n* = 21 formula *n* = 23 formula + DHA *n* = 24 formula + DHA + AA	VEP acuity 16, 34 wk Bayley scales of infant development 12, 24 mo	18:2*n*-6 18:3*n*-3 20:4*n*-6 (AA) 22:6*n*-3 (DHA)

[a] LC-PUFA = long chain polyunsaturated fatty acids.
[b] VEP = visual evoked potential, DQ = developmental quotient, VER = visual evoked response.

(70 to 91 years of age) individuals suggests little change in the capacity to absorb fat (Arora et al., 1989). The ratio of mean surface area to volume of jejunal mucosa has been reported not to differ between young and old individuals (Corazza et al., 1986). Total gastrointestinal transit time appears to be similar between young and elderly individuals (Brauer et al.,

Fatty Acid Content (% of fatty acids)			Results
Formula	Formula + DHA	Formula + DHA + GLA	No differences in VEP acuity
12.01	11.95	12.67	
1.20	1.20	1.17	
—	—	0.54	
—	0.06	0.06	
—	0.32	0.32	
Formula	Formula + DHA	Formula + DHA + AA	No differences in mental and psychomotor development
21.9	20.7	21.7	Vocabulary production and comprehension lower in the formula + DHA group
2.2	1.9	1.9	
—	—	0.43	
—	0.23	0.12	
Formula	Formula + LC-PUFA		No differences in mental and psychomotor development
12.4	15.9		
1.1	1.4		
—	0.30		
—	0.32		
10:1 Formula	5:1 Formula		No differences in VEP acuity
16.9	16.6		
1.7	3.3		
Formula	Formula + DHA	Formula + DHA + AA	No differences in VEP acuity or Bayley scales of mental and psychomotor development
16.8	16.8	16.6	
1.5	1.2	1.0	
—	—	0.34	
—	0.35	0.34	

[c] GLA = γ-linolenic acid, AA = arachidonic acid, DHA = docosahexaenoic acid.

1981). Documented changes with age may be confounded by the inclusion of a subgroup with clinical disorders (e.g., atrophic gastritis). The presence of bile salt-splitting bacteria normally present in the small intestine of humans is of potential significance to fat absorption. No evidence of bacterial overgrowth has been reported in older individuals (Arora et

al., 1989). In addition, increases in fat malabsorption have not been demonstrated in normal elderly compared to younger individuals (Russell, 1992).

Exercise

Imposed physical activity decreased the magnitude of weight gain in nonobese volunteers given access to high fat diets (60 percent of energy) (Murgatroyd et al., 1999). In the exercise group, energy and fat balances (fat intake + fat synthesis – fat utilization) were not different from zero. Thus, high fat diets may cause positive fat balance, and therefore weight gain, only under sedentary conditions. These results are consistent with epidemiological evidence that show interactions between dietary fat, physical activity, and weight gain (Sherwood et al., 2000). Higher total fat diets can probably be consumed safely by active individuals while maintaining body weight. Although in longitudinal studies of weight gain, where dietary fat predicts weight gain independent of physical activity, it is important to note that physical activity may account for a greater percentage of the variance in weight gain than does dietary fat (Hill et al., 1989). Another endpoint that merits consideration is physical performance. High fat diets (69 percent of energy) do not appear to compromise endurance in trained athletes (Goedecke et al., 1999); however, athletes may not be able to train as effectively on short-term (less than 6 days) intakes of a high fat diet as on a high carbohydrate diet (Helge, 2000). This effect on training was not observed following long-term adaptation of high fat diets.

Genetic Factors

Studies of the general population may underestimate the importance of dietary fat in the development of obesity in subsets of individuals. Some data indicate that genetic predisposition may modify the relationship between diet and obesity (Heitmann et al., 1995). Additionally, some individuals with relatively high metabolic rates appear to be able to consume high fat diets (44 percent of energy) without obesity (Cooling and Blundell, 1998). Intervention studies have shown that those individuals susceptible to weight gain and obesity appear to have an impaired ability to increase fat oxidation when challenged with high fat meals and diets (Astrup et al., 1994; Raben et al., 1994). Animal studies show that there are important gene and dietary fat interactions that influence the tendency to gain excessive weight on a high fat diet (West and York, 1998). Once these genes are identified, further studies in humans will be feasible.

Alcohol

Alcohol is metabolized to acetylcoenzyme A in the liver and can enter all normal pathways for acetate metabolism, including the synthesis of fatty acids. The formation of nicotinamide adenine dinucleotide, resulting from ethanol oxidation, serves as a cofactor for fatty acid biosynthesis (Eisenstein, 1982). Similar to carbohydrate, alcohol consumption creates a shift in postprandial substrate utilization to reduce the oxidation of fatty acids (Schutz, 2000). Significant intake of alcohol (23 percent of energy) can depress fatty acid oxidation to a level equivalent to storing as much as 74 percent as fat (Murgatroyd et al., 1996). If the energy derived from alcohol is not utilized, the excess is stored as fat (Suter et al., 1992).

Interaction of n*-6 and* n*-3 Fatty Acid Metabolism*

The *n*-6 and *n*-3 unsaturated fatty acids are believed to be desaturated and elongated using the same series of desaturase and elongase enzymes (see Figure 8-1). The rate-limiting steps are the desaturases, rather than the elongase, enzymes. In vitro, the Δ6 desaturase shows clear substrate preference in the following order: α-linolenic acid > linoleic acid > oleic acid (Brenner, 1974). In addition, the formation of docosahexaenoic acid (DHA) from tetracosapentenoic acid (24:5*n*-3) involves a Δ6 desaturation to 24:6*n*-3 and then β-oxidation to yield 22:6*n*-3 (DHA) (Sprecher, 1992). It is not known if these are the Δ6 desaturases that are responsible for metabolism of linoleic acid and α-linolenic acid or a different enzyme (Cho et al., 1999). Many studies, primarily in laboratory animals, have provided evidence that the balance of linoleic and α-linolenic acid is important in determining the amounts of arachidonic acid, eicosapentaenoic acid (EPA), and DHA in tissue lipids. An inappropriate ratio may involve too high an intake of either linoleic acid or α-linolenic acid, too little of one fatty acid, or a combination leading to an imbalance between the two series. The provision of preformed carbon chain *n*-6 and *n*-3 fatty acids results in rapid incorporation into tissue lipids. Thus, the linoleic:α-linolenic acid ratio is likely to be of most importance for diets that are very low in or devoid of arachidonic acid, EPA, and DHA. The importance of the dietary linoleic:α-linolenic acid ratio for diets rich in arachidonic acid, EPA, and DHA is not known. Arachidonic acid is important for normal growth in rats (Mohrhauer and Holman, 1963). Later in life, risk of certain diseases may be altered by arachidonic acid and arachidonic acid-derived eicosanoids. Consequently, the desirable range of *n*-6:*n*-3 fatty acids may differ with life stage.

The regulation of *n*-6 and *n*-3 fatty acid metabolism is complex as the conversion of linoleic acid to arachidonic acid is inhibited by EPA and

DHA in humans, as well as arachidonic acid, α-linolenic acid, and linoleic acid itself (Chen and Nilsson, 1993; Emken et al., 1994, 1998, 1999; Sauerwald et al., 1996). Similarly, stable isotope studies have shown that increased intakes of α-linolenic acid result in decreased conversion of linoleic acid to its metabolites, and the amounts metabolized to longer-chain metabolites is inversely related to the amount oxidized (Vermunt et al., 2000). Unfortunately, very few studies are available on the rates of formation of arachidonic acid and DHA from their precursors in humans fed diets differing in linoleic acid and α-linolenic acid content, and with or without controlled amounts of arachidonic acid, EPA, and DHA.

Arachidonic acid is a precursor to a number of eicsanoids (e.g., thromboxane A_2, prostacylcin, and leukotriene B_4). These eicosanoids have been shown to have beneficial and adverse effects in the onset of platelet aggregation, hemodynamics, and coronary vascular tone. EPA has been shown to compete with the biosynthesis of *n*-6 eicosanoids and is the precursor of several *n*-3 eicosanoids (e.g., thromboxane A_3, prostaglandin I_3, and leukotriene B_5), resulting in a less thrombotic and atherogenic state (Kinsella et al., 1990).

n-*6*:n-*3 Polyunsaturated Fatty Acid Ratio*

Jensen and coworkers (1997) reported that infants fed formulas containing a linoleic acid:α-linolenic acid ratio of 4.8:1 had lower arachidonic acid concentrations and impaired growth compared to infants fed formulas containing ratios of 9.7:1 or higher. More recent, large clinical trials with infants fed formulas providing linoleic acid:α-linolenic acid ratios of 5:1 to 10:1 found no evidence of reduced growth or other problems that could be attributed to decreased arachidonic acid concentrations (Auestad et al., 1997, 2001; Makrides et al., 2000a). Clark and coworkers (1992) concluded that intake ratios less than 4:1 were likely to result in fatty acid profiles markedly different from those from infants fed human milk. Based on the limited studies, the linoleic acid:α-linolenic acid or total *n*-3:*n*-6 fatty acids ratios of 5:1 to 10:1, 5:1 to 15:1, and 6:1 to 16:1 have been recommended for infant formulas (Aggett et al., 1991; ISSFAL, 1994; LSRO, 1998).

In adult rats it has been determined that a linoleic acid:α-linolenic acid ratio of 8:1 was optimal in maintaining normal-tissue fatty acid concentrations (Bourre et al., 1996). Increasing the intake of linoleic acid from 15 to 30 g/d, with an increase in the linoleic:α-linolenic acid ratio from 8:1 to 30:1, resulted in a 40 to 54 percent decreased conversion of linoleic acid and α-linolenic acid to their metabolites in healthy men (Emken et al., 1994). Clinical studies with patients supported by total parenteral nutrition found resolution of signs of deficiency when a

parenteral lipid containing a linoleic acid:α-linolenic acid ratio of 6:1 was provided (Holman et al., 1982).

Clinical and epidemiological studies have addressed the *n*-6:*n*-3 fatty acid ratio, focusing on beneficial effects on risk of certain diseases associated with higher intakes of the *n*-3 fatty acids EPA and DHA, as reviewed in Chapter 11. The specific importance of the ratio in these studies cannot be assessed because the decreased ratio is secondary to an increased intake of fish or EPA and DHA from supplements. For example, low rates of heart disease in Japan, compared with the United States, have been attributed in part to a total *n*-6:*n*-3 fatty acid ratio of 4:1 (Lands et al., 1990), with about 5 percent energy as linoleic acid, 0.6 percent energy from α-linolenic acid, and 2 percent energy from EPA+DHA in Japan, compared with intakes of 6 percent energy from linoleic acid, 0.7 percent energy from α-linolenic acid, and less than 0.1 percent energy from EPA+DHA in the United States (Lands et al., 1992). Similarly, an inverse association between the dietary total *n*-6:*n*-3 fatty acid ratio and cardiovascular disease, cancer, and all-cause mortality (Dolecek and Grandits, 1991), as well as between fish intake and coronary heart disease mortality (Kromhout et al., 1985; Shekelle et al., 1985), have been reported. In other studies, however, no differences were found in coronary heart disease risk factors when a diet containing a total *n*-6:*n*-3 ratio of 4:1 compared to 1:1 was consumed (Ezaki et al., 1999), or in thrombotic conditions with a diet containing a total *n*-6:*n*-3 ratio of 3.3:1 compared with 10:1 (Nelson et al., 1991). Hu and coworkers (1999b) observed a weak relationship between the *n*-6:*n*-3 ratio and fatal ischemic heart disease since both α-linolenic acid and linoleic acid were inversely related to risk. Based on the limited studies in animals, children, and adults, a reasonable linoleic:α-linolenic acid ratio of 5:1 to 10:1 has been recommended for adults (FAO/WHO, 1994).

Impact of Trans *Fatty Acids on* n-*6 and* n-*3 Metabolism*

The *trans* isomers of oleic acid and linoleic acid, which are present in hydrogenated vegetable oils and meats, have been suggested to have adverse effects on growth and development through inhibition of the desaturation of linoleic acid and α-linolenic acid to arachidonic acid and DHA, respectively (Sugano and Ikeda, 1996). Desaturation and elongation of *trans* linoleic and α-linolenic acid isomers containing a double bond at the *cis*-12 and *cis*-15 position, respectively, with formation of 20 and 22 carbon chain metabolites that could be incorporated into mem-brane lipids, have also been suggested. In vitro studies and studies with animals fed diets high in *trans* fatty acids have found evidence of reduced essential *n*-6 and *n*-3 fatty acid desaturation (Cook, 1981; Rosenthal and Doloresco, 1984). An inverse association between total *trans* fatty acids and arachidonic

acid and DHA concentrations in plasma cholesteryl esters, and between plasma cholesteryl esters, elaidic acid (18:1*trans*), and birth weight of premature infants has been reported (Koletzko, 1992). Studies in term infants found no relation between *trans* fatty acids and length of gestation, birth weight, or birth length (Elias and Innis, 2001). Similarly, an inverse association between plasma phospholipid *trans* fatty acids and arachidonic acid has been found for children aged 1 to 15 years (Decsi and Koletzko, 1995). The industrial hydrogenation of vegetable oils results in destruction of *cis* essential *n*-6 and *n*-3 fatty acids and the formation of *trans* fatty acids (Valenzuela and Morgado, 1999). It is not clear if differences in dietary intakes of *n*-6 and *n*-3 fatty acids, rather than inhibition of linoleic acid and α-linolenic acid desaturation by *trans* fatty acids, explains the statistical inverse associations between *trans* and *n*-6 and *n*-3 fatty acids reported in some studies (Craig-Schmidt, 2001). Based on the much greater affinity of the Δ6 desaturase for *cis n*-6 and *n*-3 fatty acids than monounsaturated fatty acids (Brenner, 1974; Castuma et al., 1977), and on experimental work that shows that inhibition of the Δ6 desaturation of linoleic acid is not of concern with linoleic acid intakes above about 2 percent of energy (Zevenbergen et al., 1988), it seems unlikely that inhibition of essential fatty acid metabolism by *trans* fatty acids is of concern for practical human diets.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Total Fat
Infants Ages 0 Through 12 Months

Method Used to Set the Adequate Intake

No functional criteria of fat have been demonstrated that reflects a response to dietary intake in infants. Thus, the recommended intakes of total fat are based on an Adequate Intake (AI) that reflects the observed mean fat intake of infants principally fed human milk.

Ages 0 Through 6 Months. Fat is the major single source of energy in the diet of infants exclusively fed human milk. The high intake of fat and the energy density that it provides to the diet are important in providing the energy needed for rapid growth during early infancy. Thus, the recommended intake of total fat for infants 0 through 6 months of age is based on an AI that reflects the observed mean fat intake of infants fed human milk. Table 8-2 shows the concentration and proportion of energy from fat provided by mature human milk from women delivering at term gestation. Assuming an intake of 0.78 L/d of human milk by infants exclusively fed

human milk (Chapter 1) and a mean milk fat content of 40 g/L, the AI for fat is 31 g/d. This AI assumes that the energy requirements of the young infant are being met. The mean energy content of mature human milk is 650 kcal/L (Chapter 5), thus dietary fat represents 55 percent of total energy intake for infants 0 through 6 months of age. Fomon and coworkers (1976) reported that the length and weight of infants were not different when fed formula and strained food providing 29 or 57 percent of energy from fat. Thus, an intake of 55 percent energy most likely exceeds the minimum percent needed for optimal growth of healthy infants.

Ages 7 Through 12 Months. The proportion of energy from dietary fat decreases during the second 6 months of age when complementary foods, specifically infant cereals, vegetables, and fruits, are added to the diet of the infant. The average concentration of fat in milk is approximately 40 g/L during the second 6 months of lactation (Table 8-2). The infant consumes about 0.6 L/d of human milk during the second 6 months (Chapter 1), with additional energy and nutrients provided by complementary foods, thus achieving total energy and essential nutrient needs of the infant 7 through 12 months of age.

The AI for the older infants is set based on the average intake of fat ingested from human milk and complementary foods (Chapter 1). Data from the Continuing Survey of Food Intakes by Individuals (CFSII) indicate that the average intake of fat from complementary foods by older infants is approximately 5.7 g/d. Therefore, the average fat intake from human milk and complementary foods would be 30 g/d ([0.6 L/d × 40 g/L] + 5.7) after rounding. The average energy intake from human milk is 390 kcal/d (0.6 L/d × 650 kcal/L) and from complementary foods is 281 kcal/d (CFSII), or a total energy intake of 671 kcal/d. Therefore, for infants 7 though 12 months of age, 40 percent of energy from fat is consumed from human milk and complementary foods.

Total Fat AI Summary, Ages 0 Through 12 Months

AI for Infants

0–6 months	**31 g/d of fat**
7–12 months	**30 g/d of fat**

Special Considerations

Conventional milk-based infant formulas contain approximately 48 percent of energy intake as fat (LSRO, 1998). The most common sources of fat in infant formulas are soybean oil, safflower oil, sunflower oil, coconut oil, and palm oil.

TABLE 8-2 Total Fat Content in Term Human Milk of Women in the United States and Canada

Reference	Study Population/ Stage of Lactation[a]	Total Fat Content (g/L)	Total Fat Content (% of total energy)	Total Energy[b] (kcal/L)
Anderson et al., 1983	9 women			
	3 d pp	18 ± 6	31.3	510 ± 90
	7 d pp	31 ± 10	43.6	630 ± 98
	14 d pp	37 ± 10	49.0	670 ± 100
Bitman et al., 1983	8–41 women			
	3 d pp	20.4 ± 3.2		
	7 d pp	28.9 ± 3.1		
	21 d pp	34.5 ± 3.7		
	42 d pp	31.9 ± 4.3		
	84 d pp	48.7 ± 6.2		
Dewey and Lönnerdal, 1983	13–18 women			
	1 mo pp	49.2 ± 10.5	55.9	781 ± 100
	2 mo pp	45.8 ± 9.7	54.0	753 ± 92
	3 mo pp	45.8 ± 16.5	55.2	736 ± 148
	4 mo pp	46.2 ± 18.6	52.1	787 ± 173
	5 mo pp	43.6 ± 16.7	51.8	747 ± 148
	6 mo pp	43.0 ± 19.6	51.0	748 ± 183
Butte et al., 1984	45 women			
	1 mo pp		47.8	
	2 mo pp		47.8	
	3 mo pp		45.7	
	4 mo pp		47.6	
Dewey et al., 1984	119 samples			
	4–6 mo pp	44.1 ± 18.5	60.2[c]	
	7–11 mo pp	34.5 ± 15.3	47.1[c]	
	12–20 mo pp	48.4 ± 1.19	66.0[c]	
Ferris et al., 1988	12 women			
	2 wk pp	39.8 ± 9.9	45.2	781 ± 125
	6 wk pp	44.1 ± 11.7	51.9	753 ± 77
	12 wk pp	48.7 ± 11.9	54.5	792 ± 93
	16 wk pp	55.0 ± 10.9	58.8	829 ± 122
Innis and Kuhnlein, 1988	12 Vancouver women	31 ± 3		

TABLE 8-2 Continued

Reference	Study Population/ Stage of Lactation[a]	Total Fat Content (g/L)	Total Fat Content (% of total energy)	Total Energy[b] (kcal/L)
Nommsen et al., 1991	46–70 women			
	3 mo pp	36.2 ± 7.0	46.1	697 ± 67
	6 mo pp	37.7 ± 9.6	47.3	707 ± 92
	9 mo pp	38.1 ± 8.0	47.7	709 ± 74
	12 mo pp	37.0 ± 11.3	46.7	706 ± 110
Chen et al., 1995a	198 samples			
	3–4 wk pp	31.58 ± 9.37		

[a] pp = postpartum.
[b] Calculated using 8.87 kcal/g of fat.
[c] Percent of energy determined from mean energy content of all milk samples during 7–20 mo pp (650 kcal/L).

Children and Adolescents Ages 1 Through 18 Years

A number of studies have been conducted to ascertain whether a certain amount of fat is needed in the diet to provide normal growth in children. These data generally conclude that there is no effect of fat intake on growth when consumed at levels as low as 21 percent of energy and provided that the energy intake is adequate (Boulton and Magarey, 1995; Fomon et al., 1976; Lagström et al., 1999; Lapinleimu et al., 1995; Niinikoski et al., 1997a, 1997b; Obarzanek et al., 1997; Shea et al., 1993) (see Chapter 11). There is insufficient evidence to identify a defined intake level of fat to prevent obesity or chronic diseases. Based on this lack of evidence and the lack of an effect of fat intake on growth, neither an AI nor an Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) are set for children and adolescents.

Adults Ages 19 Years and Older

The amount of total energy as fat in the diet can vary from 10 to 50 percent without differing effects on short-term health (Jéquier, 1999). When men and women were fed isocaloric diets containing 20, 40, or 60 percent fat, there was no difference in total daily energy expenditure (Hill et al., 1991). Similar observations were reported for individuals who consumed diets containing 10, 40, or 70 percent fat (Leibel et al., 1992) and men fed 9 to 79 percent fat (Shetty et al., 1994). In addition, a number

of studies have reported on the impact of or the relationship between low and high fat diets and the indicators for and risk of chronic diseases (e.g., coronary heart disease, diabetes, and obesity) (see Chapter 11). There are insufficient data, however, to identify a defined intake level for fat based on maintaining fat balance or on the prevention of chronic diseases. Therefore, neither an AI nor an EAR and RDA are set.

Saturated Fatty Acids

There is no evidence to indicate that saturated fatty acids are essential in the diet or have a beneficial role in the prevention of chronic diseases. Therefore, neither an AI nor an EAR and RDA are set.

cis n-*9 Monounsaturated Fatty Acids*

There is no evidence to indicate that monounsaturated fatty acids are essential in the diet, and monounsaturated fatty acids have no known independent role in preventing chronic diseases. Therefore, neither an AI nor an EAR and RDA are set.

n-*6 Polyunsaturated Fatty Acids*
Infants Ages 0 Through 12 Months

Method Used to Set the AI

A series of papers reported skin lesions and poor growth in infants fed skimmed cow milk, which is very low in *n*-6 fatty acids (Hansen et al., 1958, 1963). Cuthbertson (1976) concluded that less than 50 mg/100 kcal of linoleic acid (0.45 percent energy) can provide normal health and well-being during infancy. Studies on the essential fatty acid status of older individuals have established that about 2 percent energy from *n*-6 polyunsaturated fatty acids (linoleic acid) will prevent abnormal elevation of the triene:tetraene ratio (20:3*n*-9:20:4*n*-6) and clinical signs of essential fatty acid deficiency during parenteral nutrition (Barr et al., 1981). Interpretation, however, is complicated because linoleic acid in the soybean oil emulsion used to provide *n*-6 fatty acids can also be expected to inhibit synthesis of eicosatrienoic acid (20:3*n*-9) (Brenner, 1974), and thus reduce the triene:tetraene ratio. Furthermore, children are expected to require higher amounts of *n*-6 fatty acids than adults in order to support deposition of *n*-6 fatty acids in cell membranes of growing tissues. This suggests that a margin of safety is prudent.

Ages 0 Through 6 Months. An AI can be set based on the average amount of *n*-6 polyunsaturated fatty acids provided by human milk. Table 8-2 provides the fat and energy content of human milk. Human milk contains 5.6 g/L (14 percent *n*-6 fatty acid in milk × 40 g/L) of *n*-6 polyunsaturated fatty acids (Table 8-3).

Based on an average intake of 0.78 L/d of human milk (Chapter 1), the AI is 4.4 g/d (0.78 L/d × 5.6 g/L). The energy content of human milk is approximately 650 kcal/L (Chapter 5) and therefore provides 507 kcal/d (650 kcal/L × 0.78 L/d). Thus, *n*-6 polyunsaturated fatty acids contribute approximately 8 percent of daily energy intake. The various *n*-6 fatty acids that are naturally present in human milk can contribute to this AI.

Ages 7 Through 12 Months. The period from 7 through 12 months of age is a time of major transition in the diet, from infants exclusively fed human milk or infant formulas that provide large amounts of dietary fat to a diet containing a variety of foods in addition to milk or formula. The infant consumes about 0.6 L/d of human milk during the second 6 months of life (Chapter 1), with additional energy and nutrients provided by complementary foods, thus achieving total energy and essential nutrient needs. The AI for older infants is set based on the average intake of *n*-6 polyunsaturated fatty acids ingested from human milk and complementary foods (Chapter 1). Data from CFSII indicates that the average intake of *n*-6 polyunsaturated fatty acids from complementary foods by older infants is approximately 1.2 g/d. Therefore, the AI for *n*-6 polyunsaturated fatty acids is 4.6 g/d ([0.6 L/d × 5.6 g/L] + 1.2) after rounding. The average fat energy coming from human milk is 390 kcal/d (0.6 L/d × 650 kcal/L), and from complementary foods is 281 kcal/d (CFSII), for a total energy intake of 671 kcal/d. Therefore, 6 percent of energy from *n*-6 polyunsaturated fat is consumed via human milk and complementary foods.

n-*6 Polyunsaturated Fatty Acids AI Summary, Ages 0 Through 12 Months*

AI for Infants

0–6 months	**4.4 g/d of *n*-6 polyunsaturated fatty acids**
7–12 months	**4.6 g/d of *n*-6 polyunsaturated fatty acids**

Special Considerations

The polyunsaturated vegetables oils (e.g., safflower oil and soybean oil) used in the manufacture of infant formulas contain abundant amounts (45 to 70 percent of total fatty acids) of linoleic acid. The minimum permissible amount of linoleic acid found in infant formulas is 2.7 percent of

TABLE 8-3 *n*-6 Polyunsaturated Fatty Acid Content in Term Human Milk of Women in the United States and Canada

			Content in Human Milk	
Reference	*n*	*n*-6 Fatty Acid	% of Total Fatty Acids	% of Total Energy[a]
Putnam et al., 1982	9	18:2	15.8 ± 0.61	8.62
		20:2	0.4 ± 0.03	0.22
		20:3	0.4 ± 0.03	0.22
		20:4	0.6 ± 0.03	0.33
		22:4	0.2 ± 0.02	0.11
		22:5	0.1 ± 0.02	0.05
		Total	17.50	9.55
Bitman et al., 1983	6	18:2	15.58 ± 1.99	8.50
		20:2	0.18 ± 0.20	0.10
		20:3	0.53 ± 0.15	0.29
		20:4	0.60 ± 0.29	0.33
		22:4	0.07 ± 0.16	0.04
		22:5	0.03 ± 0.08	0.02
		Total	16.99	9.28
Harris et al., 1984	8	18:2	15.3 ± 3.3	8.35
		20:3	0.3 ± 0.1	0.16
		20:4	0.4 ± 0.1	0.22
		Total	16.0	8.73
Finley et al., 1985	172	18:2	16.49 ± 4.80	9.00
		20:2	0.38 ± 0.15	0.21
		20:3	0.28 ± 0.09	0.15
		20:4	0.29 ± 0.08	0.16
		Total	17.44	9.52
Innis and Kuhnlein, 1988	12	18:2	12.7 ± 1.8	6.93
		20:2	0.4 ± 0.1	0.22
		20:4	0.7 ± 0.0	0.38
		22:5	0.2 ± 0.1	0.11
		Total	14.0	7.64
Chen et al., 1995a	198	18:2	10.47 ± 2.62	5.72
		18:3	0.08 ± 0.06	0.04
		20:2	0.17 ± 0.37	0.09
		20:3	0.26 ± 0.09	0.14
		20:4	0.35 ± 0.11	0.19
		22:4	0.04 ± 0.05	0.02
		22:5	0.01 ± 0.02	0.01
		Total	11.38	6.21

TABLE 8-3 Continued

Reference	*n*	*n*-6 Fatty Acid	Content in Human Milk: % of Total Fatty Acids	Content in Human Milk: % of Total Energy[a]
Innis and King, 1999	103	18:2	12.1 ± 0.35	6.60
		18:3	0.1 ± 0.00	0.05
		20:2	0.3 ± 0.01	0.16
		20:3	0.3 ± 0.01	0.16
		20:4	0.4 ± 0.01	0.22
		22:4	0.1 ± 0.00	0.05
		Total	13.3	7.24

[a] Calculated using the following values: 40 g of fat/L of milk, 8.87 kcal/g of fat, 650 kcal/L of milk.

energy (Infant Formula. Nutrient Specifications. 21 C.F.R. §107.100, 1985); however, formulas provide higher amounts than this level.

Children and Adolescents Ages 1 Through 18 Years

Method Used to Set the AI

No specific information is available on the amount of linoleic acid required to correct the symptoms of an *n*-6 polyunsaturated fatty acid deficiency. In the absence of this information, an AI is set based on the median intake of linoleic acid consumed in the United States where the presence of an *n*-6 fatty acid deficiency is basically nonexistent in the free-living population (Appendix Table E-9), and rounding.

Linoleic Acid AI Summary, Ages 1 Through 18 Years

AI for Children

1–3 years	**7 g/d of linoleic acid**
4–8 years	**10 g/d of linoleic acid**

AI for Boys

9–13 years	**12 g/d of linoleic acid**
14–18 years	**16 g/d of linoleic acid**

AI for Girls

9–13 years	**10 g/d of linoleic acid**
14–18 years	**11 g/d of linoleic acid**

Adults Ages 19 Years and Older

Method Used to Set the AI

Various studies on adult patients receiving total parenteral nutrition have shown that linoleic acid intakes of as little as 7.4 to 8 g/d reverses the symptoms of deficiency (Barr et al., 1981; Collins et al., 1971; Goodgame et al., 1978; Jeppesen et al., 1998; Wong and Deitel, 1981). There is inadequate information, however, to set an EAR for healthy individuals. In the absence of this information, an AI is set based on the median intake of linoleic acid in the United States where the presence of an *n*-6 fatty acid deficiency is basically nonexistent in the free-living population (Appendix Table E-9). The highest median intakes have been used, each for men and women 19 to 50 years of age. Energy expenditure increases fat oxidation (Calles-Escandon et al., 1996) and linoleic acid is readily used for energy (Cunnane et al., 2001). Therefore, the AI for older men and women (greater than 50 years of age), whose energy expenditure is less than younger adults, is based on the highest median intake within this age range and rounding.

Linoleic Acid AI Summary, Ages 19 Years and Older

AI for Men

19–30 years	**17 g/d of linoleic acid**
31–50 years	**17 g/d of linoleic acid**
51–70 years	**14 g/d of linoleic acid**
> 70 years	**14 g/d of linoleic acid**

AI for Women

19–30 years	**12 g/d of linoleic acid**
31–50 years	**12 g/d of linoleic acid**
51–70 years	**11 g/d of linoleic acid**
> 70 years	**11 g/d of linoleic acid**

Pregnancy

Method Used to Set the AI

The demand for *n*-6 fatty acids for incorporation into placental tissue and the developing fetus during gestation must be met by *n*-6 fatty acids from maternal tissues or through dietary intake. Longitudinal studies have reported a decrease in plasma arachidonic acid concentration in pregnant women (Ghebremeskel et al., 2000; Sanjurjo et al., 1993). Lower arachidonic acid concentrations have also been reported for red blood cell phospholipids of pregnant women compared with nonpregnant women (Ghebremeskel et al., 2000). It is not clear that this reflects an increased need for *n*-6 fatty acids that was not met in the women in these studies, or whether changes in maternal *n*-6 fatty acid concentrations are normal physiological responses explained by the changes in endocrine status, lipoprotein and lipid metabolism, or nutrient transfer to the fetus. There is no evidence that maternal dietary intervention with *n*-6 fatty acids has any effect on fetal or infant growth and development in women meeting the requirements for *n*-6 fatty acids.

Because of a lack of evidence for determining the requirement during pregnancy, the AI is set based on the median linoleic acid intake of pregnant women in the United States where a deficiency is basically nonexistent in noninstitutionalized populations (Appendix Table E-9), and rounding.

Linoleic Acid AI Summary, Pregnancy

AI for Pregnant Women

14–18 years	**13 g/d of linoleic acid**
19–30 years	**13 g/d of linoleic acid**
31–50 years	**13 g/d of linoleic acid**

Lactation

Method Used to Set the AI

As stated above, there is no evidence that maternal dietary intervention with *n*-6 fatty acids has any effect on infant growth and development in women meeting the requirements for *n*-6 fatty acids. Because of a lack of evidence for determining the requirement during lactation, the AI is set based on the median linoleic acid intake of lactating women in the United States where a deficiency is basically nonexistent in noninstitutionalized populations (Appendix Table E-9), and rounding.

Linoleic Acid AI Summary, Lactation

AI for Lactation	
14–18 years	**13 g/d of linoleic acid**
19–30 years	**13 g/d of linoleic acid**
31–50 years	**13 g/d of linoleic acid**

n-*3 Polyunsaturated Fatty Acids Infants Ages 0 Through 12 Months*

Method Used to Set the AI

Human milk contains α-linolenic acid (18:3), eicosapentaenoic acid (EPA, 20:5), and docosahexaenoic acid (DHA, 22:6) (Table 8-4), but the amounts present are highly variable and depend on the amounts present in the mother's diet. Concentrations of about 0.7 to 1.4 percent DHA have been reported for women who eat large amounts of fish and other marine foods (Innis and Kuhnlein, 1988; Kneebone et al., 1985). Blood concentrations of DHA appear to show little metabolic regulation and increase with increasing DHA intake in breast-fed infants (Gibson et al., 1997; Innis and King, 1999; Sanders and Reddy, 1992) or formula-fed infants (Auestad et al., 1997; Carlson et al., 1996a; Innis et al., 1996; Makrides et al., 1995), as they do in adults. Numerous studies have shown that infants fed formulas with no DHA have lower plasma and red blood cell DHA concentrations than infants fed human milk or formulas with DHA (Auestad et al., 1997; Carlson et al., 1986, 1996a; Innis et al., 1996; Makrides et al., 1995; Ponder et al., 1992; Putnam et al., 1982). Similarly, the plasma and red blood cell DHA concentrations are lower in infants breast-fed by mothers with vegetarian rather than omnivorous diets (Sanders and Reddy, 1992). Evidence of DHA depletion based on functional endpoints has not been reported for populations or subgroups that have diets containing no DHA but with adequate α-linolenic acid.

Several autopsy studies have reported lower DHA concentrations in the brains of infants fed formulas that contain no DHA compared with infants fed human milk (Byard et al., 1995; Farquharson, 1994; Farquharson et al., 1992, 1995; Jamieson et al., 1994, 1999; Makrides et al., 1994). In addition, brain DHA accumulation continues in both breast-fed and formula-fed infants for at least 40 weeks of life, but the accumulation is at a greatly reduced rate in formula-fed infants (Makrides et al., 1996). Although many infant formulas contain similar amounts of α-linolenic acid as human milk, the dietary supply of only α-linolenic acid and no DHA in formulas may be inadequate to supply the infant brain with DHA (Farquharson,

TABLE 8-4 *n*-3 Polyunsaturated Fatty Acid Content in Term Human Milk of Women in the United States and Canada

			Content in Human Milk	
Reference	*n*	*n*-3 Fatty Acid	% of Total Fatty Acids	% of Total Energy[a]
Putnam et al., 1982	9	18:3	0.8 ± 0.09	0.44
		20:5	0.1 ± 0.03	0.05
		22:5	0.1 ± 0.01	0.05
		22:6	0.1 ± 0.01	0.05
		Total	1.1	0.59
Bitman et al., 1983	6	18:3	1.03 ± 0.21	0.56
		20:5	trace	trace
		22:5	0.11 ± 0.15	0.06
		22:6	0.23 ± 0.14	0.13
		Total	1.37	0.75
Harris et al., 1984	8	18:3	0.8 ± 0.5	0.44
		20:5	trace	trace
		22:5	trace	trace
		22:6	0.1 ± 0.1	0.05
		Total	0.9	0.49
Finley et al., 1985	172	18:3	1.56 ± 0.43	0.85
		22:6	0.06 ± 0.004	0.03
		Total	1.62	0.88
Innis and Kuhnlein, 1988	12	18:3	0.6 ± 0.2	0.33
		20:5	0.2 ± 0.2	0.11
		22:5	0.4 ± 0.1	0.22
		22:6	0.4 ± 0.1	0.22
		Total	1.6	0.88
Chen et al., 1995a	198	18:3	1.16 ± 0.37	0.63
		20:4	0.06 ± 0.06	0.03
		20:5	0.05 ± 0.05	0.03
		22:5	0.08 ± 0.06	0.04
		22:6	0.14 ± 0.10	0.08
		Total	1.49	0.81
Innis and King, 1999	103	18:3	1.4 ± 0.07	0.76
		20:5	0.1 ± 0.01	0.05
		22:5	0.2 ± 0.02	0.11
		22:6	0.2 ± 0.03	0.11
		Total	1.9	1.03

[a] Calculated using the following values: 40 g of fat/L of milk, 8.87 kcal/g of fat, 650 kcal/L of milk.

1994). Animal studies have shown that dietary DHA is incorporated into brain tissue to a greater extent than is DHA that is biosynthesized from α-linolenic acid (Abedin et al., 1999; Sinclair, 1975). Furthermore, administration of dietary α-linolenic acid was not effective in restoring brain DHA concentrations in chicks deficient in *n*-3 fatty acids (Anderson et al., 1990). Therefore, the DHA content of the brain may depend more heavily upon the dietary supply of DHA rather than its precursor, α-linolenic acid. Randomized clinical studies on growth or neural development with term infants fed formulas currently yield conflicting results on the requirement for *n*-3 fatty acids in young infants (see "Evidence Considered for Estimating the Requirement for Total Fat and Fatty Acids").

Ages 0 Through 6 Months. *n*-3 Polyunsaturated fatty acids provide DHA that is important for the developing brain and retina. Human milk is assumed to meet the *n*-3 fatty acid requirements of the infants fed human milk. Therefore, an AI for *n*-3 fatty acids is based on the amount of *n*-3 fatty acids, total fat, and energy provided by human milk. Table 8-2 shows the fat and energy content of human milk. Human milk contains approximately 0.63 g/L (1.58 percent *n*-3 fatty acids × 40 g/L total fat) of *n*-3 polyunsaturated fatty acids (Table 8-4). The AI is based on the average amount of milk consumed by the infant (0.78 L/d) and the *n*-3 fatty acid concentration in human milk. Therefore, the AI is set at 0.5 g/d (0.78 L/d × 0.63 g/L), after rounding, which provides approximately 4.5 kcal/d. Because human milk provides 650 kcal/L (Chapter 5) or 507 kcal/d (650 kcal/L × 0.78 L/d), an AI of 0.5 g/d of *n*-3 polyunsaturated fatty acids represents approximately 1 percent (4.5 ÷ 507) energy intake, after rounding. The various *n*-3 fatty acids that are naturally present in human milk can contribute to this AI.

Ages 7 Through 12 Months. While the energy requirement relative to body weight decreases in the second 6 months of life (see Chapter 5), autopsy analyses suggest that brain DHA accretion continues at a similar rate from 0 through 24 months of age (Martinez, 1992). The AI for older infants is set based on the average intake of *n*-3 fatty acids ingested from human milk and complementary foods (Chapter 1). Data from CFSII indicate that the average intake of *n*-3 fatty acids from complementary foods by older infants is approximately 0.11 g/d. Therefore, the AI is 0.5 g/d [0.6 L/d × 0.63 g/L] + 0.11), after rounding, which represents approximately 4.5 kcal/d. The average energy intake from human milk is 390 kcal/d (0.6 L/d × 650 kcal/L), and from complementary foods is 281 kcal/d (CFSII), for a total energy intake of 671 kcal/d. Therefore, approximately 0.67 percent (4.5 kcal/d ÷ 671 kcal/d) of energy is consumed as *n*-3 polyunsaturated fatty acids from human milk and complementary foods.

n-*3 Polyunsaturated Fatty Acid AI Summary, Ages 0 Through 12 Months*

AI for Infants	
0–6 months	**0.50 g/d of *n*-3 polyunsaturated fatty acids**
7–12 months	**0.50 g/d of *n*-3 polyunsaturated fatty acids**

Special Considerations

Vegetable oils that provide α-linolenic acid are used in the manufacture of infant formulas. The U.S. Code of Federal Regulations does not currently specify minimum or maximum levels of α-linolenic acid for infant formulas. At the present time, DHA is not directly added to infant formulas. Information from clinical trials with term infants fed formulas with DHA are inconsistent, and associations between lower growth and delays on some developmental tests have been noted in preterm and term infants fed formulas containing DHA, but not arachidonic acid. Definitive evidence that this is due to the absence of arachidonic acid or explained by antagonism between DHA and *n*-6 fatty acids is not available. DHA is added to infant formula ingredients in the form of oils from fish oils, egg total lipids, egg phospholipids, and oil from single cell microorganisms.

Children and Adolescents Ages 1 Through 18 Years

Method Used to Set the AI

One case study of a 6-year-old girl on total parenteral nutrition (TPN) reported that the TPN solution, which was low in α-linolenic acid and provided approximately 0.08 g/d, resulted in episodes of numbness, weakness, blurred vision, and the inability to walk (Holman et al., 1982). Analysis of the girl's plasma fatty acids confirmed a low *n*-3 fatty acid concentration. It was determined that 1.625 g/d of α-linolenic acid reversed the abnormal neurological symptoms. Bjerve and coworkers (1988) reported low plasma *n*-3 fatty acid concentrations and poor growth in a child fed approximately 0.54 g/d of α-linolenic acid via a gastric tube. Growth was somewhat improved by the addition of 0.56 g/d of α-linolenic acid.

Because of a lack of evidence for determining the requirement for *n*-3 fatty acids during childhood, an AI is set based on the median intake of α-linolenic acid in the United States where a deficiency is basically nonexistent in noninstitutionalized populations (Appendix Table E-11), and rounding. Small amounts of EPA and DHA can contribute toward reversing an *n*-3 fatty acid deficiency (Bjerve, 1989; Bjerve et al., 1987a, 1987b, 1989) and can therefore contribute toward the AI for α-linolenic acid.

EPA and DHA contribute approximately 10 percent of the total *n*-3 fatty acid intake and therefore this percent contributes toward the AI for α-linolenic acid (Appendix Tables E-10, E-12, and E-14).

α-Linolenic Acid AI Summary, Ages 1 Through 18 Years

AI for Children

1–3 years	**0.7 g/d of α-linolenic acid**
4–8 years	**0.9 g/d of α-linolenic acid**

AI for Boys

9–13 years	**1.2 g/d of α-linolenic acid**
14–18 years	**1.6 g/d of α-linolenic acid**

AI for Girls

9–13 years	**1.0 g/d of α-linolenic acid**
14–18 years	**1.1 g/d of α-linolenic acid**

Adults Ages 19 Years and Older

Method Used to Set the AI

Several studies involving adult patients who were fed by gastric tube showed that an *n*-3 fatty acid (α-linolenic acid) deficiency could occur with intakes ranging from 0.015 to 0.095 g/d of α-linolenic acid (Bjerve, 1989; Bjerve et al., 1987a, 1987b, 1989), whereas intakes of as low as 0.3 g/d prevented the symptoms of a deficiency (Bjerve et al., 1987a). There were insufficient data, however, to set an EAR for free-living healthy adults.

Because of a lack of evidence for determining the requirement for *n*-3 fatty acids, an AI is set based on the highest median intake of α-linolenic acid by adults in the United States where a deficiency is basically nonexistent in noninstitutionalized populations (Appendix Table E-11), and rounding. Small amounts of EPA and DHA can contribute toward reversing an *n*-3 fatty acid deficiency (Bjerve, 1989; Bjerve et al., 1987a, 1987b, 1989). EPA and DHA contribute approximately 10 percent of the total *n*-3 fatty acid intake and therefore this percent contributes toward the AI for α-linolenic acid (Appendix Tables E-10, E-12, and E-14).

α-Linolenic Acid AI Summary, Ages 19 Years and Older

AI for Men	
19–30 years	**1.6 g/d of α-linolenic acid**
31–50 years	**1.6 g/d of α-linolenic acid**
51–70 years	**1.6 g/d of α-linolenic acid**
> 70 years	**1.6 g/d of α-linolenic acid**
AI for Women	
19–30 years	**1.1 g/d of α-linolenic acid**
31–50 years	**1.1 g/d of α-linolenic acid**
51–70 years	**1.1 g/d of α-linolenic acid**
> 70 years	**1.1 g/d of α-linolenic acid**

Pregnancy and Lactation

Method Used to Set the AI

The demand for *n*-3 polyunsaturated fatty acids for incorporation into placental tissue and for the developing fetus during gestation, as well as for secretion of *n*-3 polyunsaturated fatty acids in milk during lactation, must be met by *n*-3 fatty acids from maternal tissues or through dietary intake. Several studies have reported lower plasma and red blood cell lipid DHA concentrations in pregnant and lactating women compared with nonpregnant, nonlactating women (Ghebremeskel et al., 2000; Holman et al., 1991). It is not clear that this reflects declining DHA status due to inadequate *n*-3 fatty acid intakes in the women in these studies. An alternative explanation is that changes in maternal DHA concentrations are normal physiological responses to the changes in endocrine status, lipoprotein and lipid metabolism, or nutrient transfer that accompany pregnancy and lactation. However, supplementation with fish oil during pregnancy does increase DHA in both the mother and the newborn infant, and supplementation with fish oil during lactation increases the concentration of DHA in the mother's milk and in the infant's blood (Connor et al., 1996; Henderson et al., 1992; van Houwelingen et al., 1995). Dietary fatty acids are almost completely absorbed, and an increase in blood DHA concentration following the increase in intake with fish oil supplementation is to be expected. Evidence is not available to show that increasing intakes of DHA in pregnant and lactating women consuming diets that meet requirements for *n*-6 and *n*-3 fatty acids have any physiologically significant benefit to the infant. Population comparative studies have found higher birthweights and longer gestation for women in the Faroe Islands than in Denmark (Olsen et al., 1989). This has been attributed to a higher intake of EPA from fish

and other marine foods, leading to *n*-3 fatty acid-induced inhibition of the *n*-6 fatty acid-derived eicosanoids that are important in cervical ripening and initiation of parturition. Subsequent intervention studies indicate that 10.8 g of supplemental *n*-3 fatty acids from fish oil is associated with an increase in gestation of about 4 days (Olsen et al., 1992).

Because of a lack of evidence for determining the requirement for *n*-3 fatty acids during pregnancy and lactation, an AI is set based on the median intake of α-linolenic acid in the United States where a deficiency is basically nonexistent in noninstitutionalized populations (Appendix Table E-11), and rounding. Small amounts of EPA and DHA can contribute toward reversing an *n*-3 fatty acid deficiency (Bjerve, 1989; Bjerve et al., 1987a, 1987b, 1989), and can therefore contribute toward the AI for α-linolenic acid.

α-Linolenic Acid AI Summary, Pregnancy and Lactation

AI for Pregnancy

14–18 years	**1.4 g/d of α-linolenic acid**
19–30 years	**1.4 g/d of α-linolenic acid**
31–50 years	**1.4 g/d of α-linolenic acid**

AI for Lactation

14–18 years	**1.3 g/d of α-linolenic acid**
19–30 years	**1.3 g/d of α-linolenic acid**
31–50 years	**1.3 g/d of α-linolenic acid**

Special Considerations

The ratio of linoleic acid:α-linolenic acid in the diet is important because linoleic acid and α-linolenic acid compete for the same desaturase enzymes. Thus, a high ratio of linoleic acid:α-linolenic acid can inhibit the conversion of α-linolenic acid to DHA, while a low ratio will inhibit the desaturation of linoleic acid to arachidonic acid. The linoleic acid:α-linolenic acid ratio, however, is likely to be of greatest importance in diets that are very low or devoid of arachidonic acid, EPA, and DHA.

The available data, although limited, suggest that linoleic:α-linolenic acid ratios below 5:1 may be associated with impaired growth in infants (Jensen et al., 1997). Although a ratio of 30:1 has been shown to reduce further metabolism of α-linolenic acid, sufficient dose–response data are not available to set an upper range for this ratio with confidence. Assuming an intake of *n*-6 fatty acids of 5 percent energy, with this being mostly linoleic acid, the α-linolenic acid intake at a 5:1 ratio would be 1 percent of energy.

Trans *Fatty Acids*

There are no data available to indicate a health benefit from consuming *trans* fatty acids. Therefore, neither an AI nor an EAR and RDA are established for *trans* fatty acids.

INTAKES OF TOTAL FAT AND FATTY ACIDS

Total Fat

Food Sources

Both animal- and plant-derived food products contain fat. The principal foods that contribute to fat intake are butter, margarine, vegetable oils, visible fat on meat and poultry products, whole milk, egg yolks, nuts, and baked goods (e.g., cookies, doughnuts, and cakes). Over 95 percent of total fat intake is in the form of triacylglycerols. As discussed below, the type of fat present in these food products varies.

Dietary Intake

Intake data from the Continuing Survey of Food Intakes of Individuals (CFSII) (1994–1996, 1998) showed that the median total fat intake ranged from 65 to 100 g/d for men and 48 to 63 g/d for women (Appendix Table E-5). These intake ranges represent approximately 32 to 34 percent of total energy (Appendix Table E-6). During 1990 to 1997, median intakes of fat ranged from 32 to 34 percent and 30 to 33 percent of energy in Canadian men and women, respectively (Appendix Table F-3).

A longitudinal study in the United States found that dietary fat represented 48, 41, 35, and 30 percent of total energy intakes at 3, 6, 12, and 24 months of age, respectively (Butte, 2000). The Third National Health and Nutrition Examination Survey (NHANES) estimated that children 2 to 19 years of age consumed an average of 34 percent of total energy as fat, with little difference across the individual age groups (Troiano et al., 2000). Comparison of data collected across the three NHANES studies conducted since the early 1970s shows that children and adolescents across all race, gender, and age groups have decreased their total fat intake. Mean age-adjusted fat intakes have declined from 36 to 37 percent to 33 to 34 percent of total energy (Troiano et al., 2000). About 23 percent of children 2 to 5 years old, 16 percent of children 6 to 11 years old, and 15 percent of adolescents 12 to 19 years old had dietary fat intakes equal to or less than 30 percent of total energy intakes.

Saturated Fatty Acids

Food Sources

Sources of saturated fatty acids tend to be foods of animal sources, including whole milk, cream, butter, cheese, and fatty meats such as pork and beef (USDA/HHS, 2000). Certain oils, however, such as coconut, palm, and palm kernel oil, also contain relatively high amounts of saturated fatty acids. Saturated fatty acids provide approximately 20 to 25 percent of energy in human milk (Table 8-5).

Dietary Intake

Based on intake data from CFSII (1994–1996, 1998), median saturated fatty acid intake ranged from approximately 21 to 34 g/d for men and 15 to 21 g/d for women (Appendix Table E-7). Data from NHANES III indicated that saturated fatty acids provided 11 to 12 percent of energy in adult diets and ranged from 12.2 to 13.9 percent of energy for children and adolescents (CDC, 1994). NHANES III reported that 9 percent of children 2 to 11 years old and 7 percent of those 12 to 19 years old had saturated fatty acid intakes of less than 10 percent of total energy (Troiano et al., 2000). During 1990 to 1997, median intakes of saturated fatty acids ranged from approximately 10 to 12 percent of energy for Canadian men and women (Appendix Table F-4).

Cis-*Monounsaturated Fatty Acids*

Food Sources

About 50 percent of monounsaturated fatty acids are provided by animal products, primarily meat fat (Jonnalagadda et al., 1995). Oils that contain monounsaturated fatty acids include canola and olive oils. Monounsaturated fatty acids provide approximately 20 percent of energy in human milk (Table 8-6).

Dietary Intake

Based on intake data from CFSII (1994–1996, 1998), median monounsaturated fatty acid intake ranged from approximately 25 to 39 g/d for men and 18 to 24 g/d for women (Appendix Table E-8). Data from the 1987–1988 Nationwide Food Consumption Survey indicated that mean intakes of monounsaturated fatty acids were 13.6 to 14.3 percent of energy (Ganji and Betts, 1995).

TABLE 8-5 Saturated Fatty Acid Content in Term Human Milk of Women in the United States and Canada

			Content in Human Milk	
Reference	*n*	Saturated Fatty Acid	% of Total Fatty Acids	% of Total Energy[a]
Putnam et al., 1982	9	8:0	0.3	0.16
		10:0	1.4	0.76
		12:0	6.2	3.38
		14:0	7.6	4.15
		16:0	20.5 ± 0.70	11.19
		18:0	9.0 ± 0.46	4.91
		20:0	0.3 ± 0.02	0.16
		21:0	0.1 ± 0.02	0.05
		24:0	0.5 ± 0.01	0.27
		Total	45.9	25.03
Bitman et al., 1983	6	10:0	0.97 ± 0.28	0.53
		12:0	4.46 ± 1.17	2.43
		14:0	5.68 ± 1.36	3.10
		15:0	0.31 ± 0.07	0.17
		16:0	22.20 ± 2.28	12.12
		17:0	0.49 ± 0.36	0.27
		18:0	7.68 ± 1.85	4.19
		20:0	0.32 ± 0.11	0.17
		21:0	0.17 ± 0.12	0.09
		Total	42.28	23.07
Harris et al., 1984	8	10:0	trace	trace
		12:0	4.2 ± 1.3	2.29
		14:0	5.9 ± 0.7	3.22
		16:0	22.8 ± 1.6	12.45
		18:0	8.2 ± 1.2	4.48
		Total	41.1	22.44
Finley et al., 1985	172	8:0	0.16 ± 0.11	0.09
		10:0	1.10 ± 0.30	0.60
		12:0	5.56 ± 1.68	3.03
		14:0	8.01 ± 2.46	4.37
		16:0	23.28 ± 3.35	12.71
		18:0	8.06 ± 1.58	4.40
		Total	46.17	25.20
Innis and Kuhnlein, 1988	12	10:0	1.2 ± 0.2	0.66
		12:0	5.2 ± 0.7	2.84
		14:0	6.7 ± 0.5	3.66
		16:0	22.1 ± 2.7	12.06
		18:0	8.2 ± 0.8	4.48
		Total	43.4	23.70

continued

TABLE 8-5 Continued

Reference	*n*	Saturated Fatty Acid	Content in Human Milk: % of Total Fatty Acids	Content in Human Milk: % of Total Energy[a]
Chen et al., 1995a	198	10:0	1.39 ± 0.59	0.76
		12:0	5.68 ± 2.01	3.10
		14:0	6.10 ± 1.73	3.33
		15:0	0.37 ± 0.12	0.20
		16:0	18.30 ± 2.25	9.99
		17:0	0.32 ± 0.08	0.17
		18:0	6.15 ± 0.97	3.36
		20:0	0.15 ± 0.09	0.08
		Total	38.46	20.99
Innis and King, 1999	103	10:0	0.6 ± 0.03	0.33
		12:0	4.1 ± 0.15	2.24
		14:0	6.1 ± 0.21	3.33
		16:0	19.4 ± 0.28	10.59
		18:0	7.2 ± 0.15	3.93
		20:0	0.2 ± 0.00	0.11
		22:0	0.1 ± 0.00	0.05
		24:0	0.1 ± 0.00	0.05
		Total	37.8	20.63

[a] Calculated using the following values: 40 g of fat/L of milk, 8.87 kcal/g of fat, 650 kcal/L of milk.

n-*6 Polyunsaturated Fatty Acids*

Food Sources

Sources of *n*-6 polyunsaturated fatty acids include nuts, seeds, certain vegetables, and vegetable oils such as soybean oil, safflower oil, and corn oil. Certain oils, such as blackcurrant seed oil and evening primrose oil, are high in γ-linolenic acid (18:3*n*-6), which is an intermediate in the conversion of linoleic acid to arachidonic acid. Arachidonic acid is formed from linoleic acid in animal cells, but not plant cells, and is present in the diet in small amounts in meat, poultry, and eggs. Arachidonic acid is not present in plant-derived fats and oils.

TABLE 8-6 Monounsaturated Fatty Acid Content in Term Human Milk of Women in the United States and Canada

			Content in Human Milk	
Reference	*n*	Monounsaturated Fatty Acid	% of Total Fatty Acids	% of Total Energy[a]
Putnam et al., 1982	9	18:1	37.6 ± 0.75	20.52
		20:1	0.9 ± 0.07	0.49
		22:1	0.1 ± 0.02	0.05
		Total	38.6	21.06
Bitman et al., 1983	6	16:1	3.83 ± 0.39	2.09
		18:1	35.51 ± 2.73	19.38
		Total	39.34	21.47
Harris et al., 1984	8	16:1	2.5 ± 0.6	1.36
		18:1	32.6 ± 3.3	17.79
		20:1	0.5 ± 0.1	0.27
		Total	35.6	19.42
Finley et al., 1985	172	16:1	3.02 ± 0.77	1.65
		18:1	31.72 ± 3.81	17.31
		Total	34.74	18.96
Innis and Kuhnlein, 1988	12	16:1	3.3 ± 0.6	1.80
		18:1	36.3 ± 2.7	19.81
		20:1	0.7 ± 0.3	0.38
		22:1	0.2 ± 0.1	0.11
		Total	40.5	22.10
Chen et al., 1995a	198	14:1	0.28 ± 0.08	0.15
		16:1	2.68 ± 0.69	1.46
		17:1	0.21 ± 0.06	0.11
		18:1	36.09 ± 3.51	19.70
		20:1	0.53 ± 0.22	0.29
		22:1	0.02 ± 0.03	0.01
		Total	39.81	21.72
Innis and King, 1999	103	14:1	0.2 ± 0.01	0.11
		16:1	2.5 ± 0.08	1.36
		18:1	35.7 ± 0.41	19.49
		20:1	0.6 ± 0.05	0.33
		22:1	0.2 ± 0.02	0.11
		24:1	0.1 ± 0.01	0.05
		Total	39.3	21.45

[a] Calculated using the following values: 40 g of fat/L of milk, 8.87 kcal/g of fat, 650 kcal/L of milk.

Dietary Intake

Based on intake data from CFSII (1994–1996, 1998), median *n*-6 polyunsaturated fatty acid (linoleic acid) intake ranged from approximately 12 to 17 g/d for men and 9 to 11 g/d for women (Appendix Table E-9).

Polyunsaturated fatty acids have been reported to contribute approximately 5 to 7 percent of total energy intake in diets of adults (Allison et al., 1999; Fischer et al., 1985). Most (approximately 85 to 90 percent) *n*-6 polyunsaturated fatty acids are consumed in the form of linoleic acid. Other *n*-6 polyunsaturated fatty acids, such as arachidonic acid and γ-linolenic acid, are present in small amounts in the diet.

n-*3 Polyunsaturated Fatty Acids*

Food Sources

The major sources of *n*-3 fatty acids include certain vegetable oils and fish (Kris-Etherton et al., 2000). Vegetable oils such as soybean and flaxseed oils contain high amounts of α-linolenic acid. Fish oils provide a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and fatty fish are the major dietary sources of EPA and DHA. Smaller amounts are also present in meat and eggs.

Dietary Intake

Based on intake data from CFSII (1994–1996, 1998), the total *n*-3 fatty intake for men and women ranged from approximately 1.3 to 1.8 g/d and 1.0 to 1.2 g/d, respectively (Appendix Table E-10). These findings are similar to that reported by Kris-Etherton and coworkers (2000), who also reported that the average intake of *n*-3 polyunsaturated fatty acids was approximately 0.7 percent of energy. The median intake of α-linolenic acid ranged from approximately 1.2 to 1.6 g/d for men and 0.9 to 1.1 g/d for women (Appendix Table E-11). For all adults, the median intakes of EPA and DHA ranged from 0.004 to 0.007 and 0.052 to 0.093 g/d, respectively (Appendix Tables E-12 and E-14). The median intake of DHA ranged from 0.066 to 0.093 g/d for men and 0.052 to 0.069 g/d for women (Appendix Table E-14). Docosapentaenoic acid provided only 0.001 to 0.005 g/d (Appendix Table E-13).

Trans *Fatty Acids*

Food Sources

Reports listing the *trans* fatty acid level in selected food items are available from the United States (Enig et al., 1990; Litin and Sacks, 1993; Michels and Sacks, 1995), Canada (Ratnayake et al., 1993), and Europe (Aro et al., 1998a, 1998b, 1998c; Michels and Sacks, 1995; van Erp-baart et al., 1998; van Poppel et al., 1998). More recently, a comprehensive U.S. database was compiled by the U.S. Department of Agriculture (ARS, 2001) that included a description of the methodology used to formulate the nutrient values (Schakel et al., 1997). *Trans* fatty acids are present in foods containing traditional stick margarine (3.04 g *trans* fatty acids/serving) and vegetable shortenings (2.54 g/serving) that have been subjected to hydrogenation, as well as in milk (0.22 g/serving), butter (0.40 g/serving) and meats (0.01 to 0.21 g/serving) (Emken, 1995). Therefore, foods that are contributors of *trans* fatty acids include pastries, fried foods (e.g., doughnuts and french fries), dairy products, and meats. Human milk contains approximately 1 to 5 percent of total energy as *trans* fatty acids (Table 8-7) and similarly, infant formulas contain approximately 1 to 3 percent (Ratnayake et al., 1997).

Dietary Intake

Estimating the amount of *trans* fatty acids in the food supply has been hampered by the lack of an accurate and comprehensive database from which to derive the data and the trend towards the reformulation of products over the past decade to reduce levels. This latter issue complicates analysis of historical food intake data. Additionally, the variability in the *trans* fatty acid content of foods within a food category is extensive and can introduce substantial error when the calculations are based on food frequency questionnaires that heavily rely on the grouping of similar foods (Innis et al., 1999). *trans* Fatty acid intake is not currently collected in U.S. national surveys.

Early reports suggested a wide range of *trans* fatty acid intakes, from 2.6 to 12.8 g/d (Emken, 1995). The lower estimated intakes tended to be derived from food frequency data, whereas the higher estimated intakes tended to be derived from food availability data. More recent data from food frequency questionnaires collected in the United States suggest average *trans* fatty acid intakes of 1.5 to 2.2 percent of energy (Ascherio et al., 1994; Hu et al., 1997), or 5.2 percent of total dietary fat (Lemaitre et al., 1998). Intakes of about 1 to 2 percent of energy have been reported for women in Canada, although the range of intakes was wide (Elias and Innis,

TABLE 8-7 *Trans* Fatty Acid Content in Term Human Milk of Women in the United States and Canada

Reference	Study Population/Stage of Lactation[a]	*Trans* Fatty Acid	Content in Human Milk: % of Total Fatty Acids	Content in Human Milk: % of Total Energy[b]
Gibson and Kneebone, 1981	120 women, 40–45 d pp	16:1	trace	trace
		18:1	~ 10	~ 5.46
Chappell et al., 1985	7 women, 1–37 d pp	18:1(9)	2.6 ± 0.4	1.42
		18:1(7)	0.1 ± 0.03	0.05
		18:1(5)	0.1 ± 0.04	0.05
		18:2(6) c,t+t,c[c]	0.1 ± 0.4	0.05
		Total	2.9	1.57
Chen et al., 1995a	198 samples, 3–4 wk pp	Total *trans*	7.19 ± 3.03	3.92
Innis and King, 1999	103 women, 2 mo pp	Total *trans*	7.1 ± 0.32	3.88

[a] pp = postpartum.
[b] Calculated using the following values: 40 g of fat/L of milk, 8.87 kcal/g of fat, 650 kcal/L of milk.
[c] c,t+t,c = *cis, trans* and *trans, cis.*

2001, 2002). Most recently, *trans* fatty acid intake was estimated from existing CFSII data (Allison et al., 1999). The mean *trans* fatty acid intake for the U.S. population aged 3 years and older was 2.6 percent of total energy intake.

Conjugated Linoleic Acid

Food Sources

The average concentration of conjugated linoleic acid (CLA) in dairy products and ruminant meats is approximately 5 mg of CLA/g of fat (Chin et al., 1992). Although numerous CLA isomers have been reported to be found in meat, milk, and dairy products (Ha et al., 1989), the *cis*-9,*trans*-11 isomer is the predominant form of CLA present in these foods (Ma et al., 1999). The conjugated linoleic acid content of milk can vary depending on a number of factors, such as animal feed diet, pasture grazing, supple-

ment use, and number of lactations (MacDonald, 2000). Ma and coworkers (1999) reported values of 1.8 mg of CLA/g of fat for skim milk, 3.4 mg/g for whole milk, 4.3 mg/g for 1 percent milk, 5.0 mg/g for 2 percent milk, and 5.5 mg/g for half-and-half cream. In addition, values ranged from 2.7 to 6.2 mg of CLA/g of fat for various cheeses and 1.2 to 3.2 mg of CLA/g of fat for different types of raw and cooked beef products.

Dietary Intake

Recent analysis of duplicate food portions indicates CLA intake in the United States is in the range of 151 to 212 mg/d (Ritzenthaler et al., 2001). The average intake of *cis*-9,*trans*-11 octadecadienoic acid in a small group of Canadians was recently estimated to be about 95 mg/d (Ens et al., 2001). Based on the CLA content in the Health Canada National Nutritious Food Basket 1998 for purchased quantities, *cis*-9,*trans*-11 CLA intake for men and women was 332 and 295 mg/d, respectively. These values assume that all food purchased is actually eaten. From food records it is clear that the pattern of CLA intake is highly variable among individuals and from day-to-day for individuals themselves. Estimates from information on foods purchased, however, are higher than estimates from reported food intake data; therefore, the two data sets are not comparable.

ADVERSE EFFECTS OF OVERCONSUMPTION

Total Fat

A Tolerable Upper Intake Level (UL) was not set for total fat because of the lack of a defined intake level at which an adverse effect, such as obesity, can occur (see Chapter 11). An Acceptable Macronutrient Distribution Range (AMDR) for fat intake, however, has been estimated based on adverse effects from consuming low fat and high fat diets (Chapter 11).

Saturated Fatty Acids

Hazard Identification

Elevated LDL Cholesterol Concentration and Risk of CHD. Several hundred studies have been conducted to assess the effect of saturated fatty acids on serum cholesterol concentration. In general, the higher the intake of saturated fatty acids, the higher the serum total (Figure 8-2) and low density lipoprotein (LDL) cholesterol concentrations (Figure 8-3). Regression analyses of such studies have suggested that for each 1 percent increase

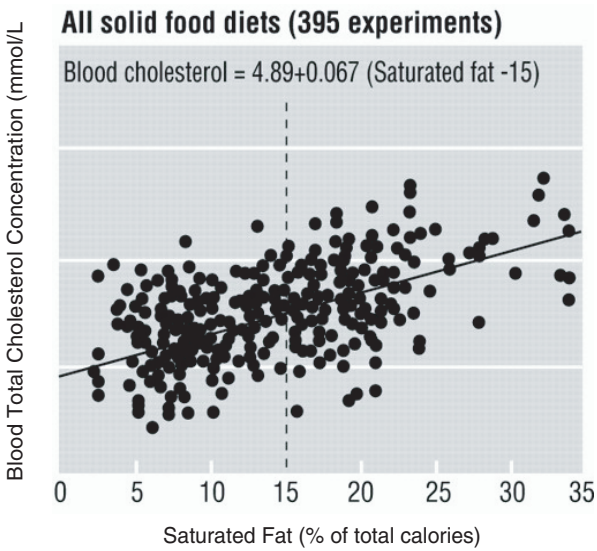

FIGURE 8-2 Relationship between blood total cholesterol concentrations and saturated fatty acid intake. Reprinted, with permission, from Clarke et al. (1997). Copyright 1997 by the *British Medical Journal*.

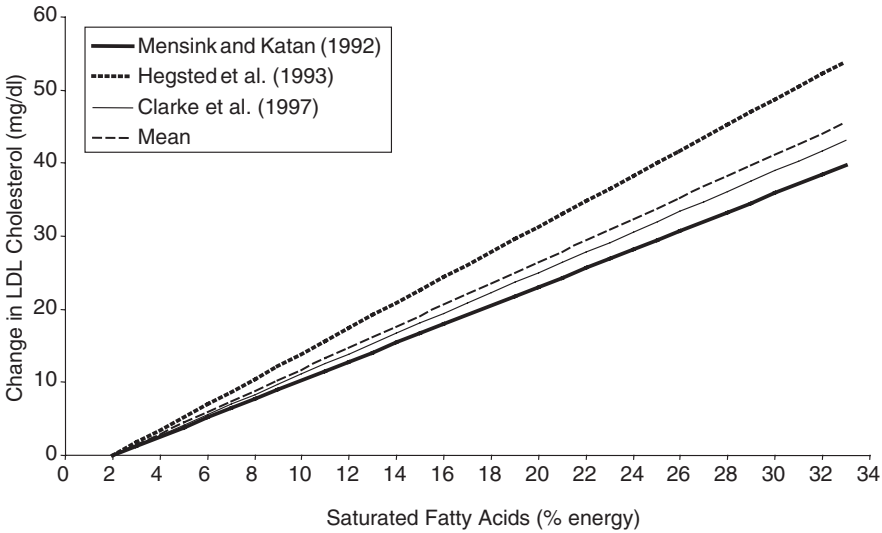

FIGURE 8-3 Calculated changes in serum low density lipoprotein cholesterol concentration in response to percent change in dietary saturated fatty acids. Three regression equations were used to establish the response curves. The range in saturated fatty acid intake was 2.2 to 33 percent of energy.

in energy from saturated fatty acids, serum LDL cholesterol concentration increases by 0.033 mmol/L (Mensink and Katan, 1992), 0.036 mmol/L (Clarke et al., 1997), or 0.045 mmol/L (Hegsted et al., 1993). Although all fats will increase serum high density lipoprotein (HDL) cholesterol concentration relative to carbohydrate, the increase attributable to saturated fats is greater than that observed for monounsaturated and polyunsaturated fatty acids. Serum HDL cholesterol concentration increases by 0.011 to 0.013 mmol/L for each 1 percent increase in saturated fat (Clarke et al., 1997; Hegsted et al., 1993; Mensink and Katan, 1992).

Similar to that observed for saturated fatty acid intake and LDL cholesterol concentration, there is a positive linear relationship between serum total and LDL cholesterol concentrations and risk of coronary heart disease (CHD) or mortality from CHD (Jousilahti et al., 1998; Neaton and Wentworth, 1992; Sorkin et al., 1992; Stamler et al., 1986; Weijenberg et al., 1996). Results from the Zutphen Elderly Study estimated that the relative risk of CHD mortality was 1.4 with a corresponding increase of 1 mmol/L of total serum cholesterol concentration (Weijenberg et al., 1996). It has been estimated that a 10 percent reduction in serum cholesterol concentration would reduce CHD mortality by 20 percent (Jousilahti et al., 1998).

A number of epidemiological studies have reported an association between saturated fatty acid intake and risk of CHD. The majority of these studies have reported a positive relationship between saturated fatty acid intake and risk of CHD and CHD mortality (Goldbourt et al., 1993; Hu et al., 1997, 1999a, 1999c; Keys et al., 1980; McGee et al., 1984). Ascherio and coworkers (1996) concluded that the association between saturated fatty acid intake and risk of CHD was not strong; however, saturated fat and the predicted effects on blood cholesterol concentrations did affect risk. No association between saturated fatty acid intake and coronary deaths was observed in the Zutphen Study or the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Kromhout and de Lezenne Coulander, 1984; Pietinen et al., 1997).

Although all saturated fatty acids were originally considered to be associated with increased adverse health outcomes, including increased blood cholesterol concentrations, it later became apparent that saturated fatty acids differ in their metabolic effects (e.g., potency in raising blood cholesterol concentrations). In general, stearic acid has been shown to have a neutral effect on total and LDL cholesterol concentrations (Bonanome and Grundy, 1988; Denke, 1994; Hegsted et al., 1965; Keys et al., 1965; Yu et al., 1995; Zock and Katan, 1992). While palmitic, lauric, and myristic acids increase cholesterol concentrations (Mensink et al., 1994), stearic acid is more similar to oleic acid in its neutral effect (Kris-Etherton et al., 1993). Furthermore, a stearic acid-rich diet has been shown to improve

thrombogenic and atherogenic risk factor profiles (Kelly et al., 2001). However, it is impractical at the current time to make recommendations for saturated fatty acids on the basis of individual fatty acids.

Mortality. A number of studies have demonstrated a positive association between serum cholesterol concentration and the incidence of mortality (Conti et al., 1983; Corti et al., 1997; Haheim et al., 1993; Klag et al., 1993; Martin et al., 1986). Some studies, however, have reported an increased risk of non-CHD mortality, especially cancer, with low serum cholesterol concentration, suggesting a "U" or "J" shaped curve (Agner and Hansen, 1983; Frank et al., 1992; Kagan et al., 1981). The Poland and United States Collaborative Study on Cardiovascular Epidemiology showed an increased risk for cancer with low serum cholesterol concentrations in Poland, but not in the United States (Rywik et al., 1999). It was concluded that various nutritional and non-nutritional factors (obesity, smoking, alcohol use) were confounding factors, resulting in the differences observed between the two countries. As a specific example, body fat was shown to have a "U" shaped relation to mortality (Yao et al., 1991).

Obesity. A number of studies have attempted to ascertain the relationship between saturated fatty acid intake and body mass index, and these results are mixed. Saturated fatty acid intake was shown to be positively associated with body mass index or percent of body fat (Doucet et al., 1998; Gazzaniga and Burns, 1993; Larson et al., 1996; Ward et al., 1994). In contrast, no relationship was observed for saturated fatty acid intake and body weight (González et al., 2000; Ludwig et al., 1999; Miller et al., 1994).

Impaired Glucose Tolerance and Risk of Diabetes. Epidemiological studies have been conducted to ascertain the association between the intake of saturated fatty acids and the risk of diabetes. A number of these studies found no relationship (Colditz et al., 1992; Costa et al., 2000; Salmerón et al., 2001; Sevak et al., 1994; Virtanen et al., 2000). Several large epidemiological studies, however, showed increased risk of diabetes with increased intake of saturated fatty acids (Feskens et al., 1995; Hu et al., 2001; Marshall et al., 1997; Parker et al., 1993). The Normative Aging Study found that a diet high in saturated fatty acids was an independent predictor for both fasting and postprandial insulin concentration (Parker et al., 1993). A reduction in saturated fatty acid intake from 13.9 to 7.8 percent of energy was associated with an 18 percent decrease in fasting insulin and a 25 percent decrease in postprandial insulin concentrations.

Findings from short-term intervention studies tend to suggest a lack of adverse effect of saturated fatty acids on risk indicators for diabetes in

healthy individuals. Postprandial glucose and insulin concentrations were not significantly different in men who ingested three different levels of saturated fatty acids (Roche et al., 1998). Fasching and coworkers (1996) reported no difference in insulin secretion or sensitivity in men who consumed a 33 percent saturated, monounsaturated, or polyunsaturated fatty acid diet. There was no difference in postprandial glucose or insulin concentration when healthy adults were fed butter or olive oil (Thomsen et al., 1999). Louheranta and colleagues (1998) found no difference in glucose tolerance and insulin sensitivity in healthy women fed either a high oleic or stearic acid diet. In contrast, results of the KANWU study indicate that consumption of high levels (18 percent of energy) of saturated fats can significantly impair insulin sensitivity (Vessby et al., 2001).

Summary

Intakes above an identified UL indicate a potential risk of an adverse health effects. There is a positive linear trend between total saturated fatty acid intake and total and LDL cholesterol concentration and increased risk of CHD. A UL is not set for saturated fatty acids because any incremental increase in saturated fatty acid intake increases CHD risk. It is neither possible nor advisable to achieve 0 percent of energy from saturated fatty acids in typical whole-food diets. This is because all fat and oil sources are mixtures of fatty acids, and consuming 0 percent of energy would require extraordinary changes in patterns of dietary intake, such as the inclusion of fats and oils devoid of saturated fatty acids, which are presently unavailable. Such extraordinary adjustments may introduce undesirable effects (e.g., inadequate intakes of protein and certain micronutrients) and unknown and unquantifiable health risks. It is possible to consume a diet low in saturated fatty acids by following the dietary guidance provided in Chapter 11.

Cis-*Monounsaturated Fatty Acids*

Hazard Identification

Cardiovascular Disease. Within the range of usual intake, there are no clearly established adverse effects of *n*-9 monounsaturated fatty acids in humans. There is some preliminary evidence that a meal providing 50 g of fat from olive oil reduced brachial artery flow-mediated vasodilation by 31 percent in 10 healthy, normolipidemic individuals versus canola oil or salmon (Vogel et al., 2000). In addition, there is evidence from nonhuman primates that a diet rich in *n*-9 monounsaturated fatty acids promotes

atherosclerosis just as much as a diet containing isocaloric amounts of saturated or polyunsaturated fatty acids (Rudel et al., 1997). Dietary monounsaturated fatty acids induce atherogenesis due to greater hepatic lipid concentrations (i.e., triacylglycerol, free cholesterol, and cholesteryl ester), as well as the high degree of cholesteryl oleate enrichment in plasma cholesteryl esters. Overconsumption of energy related to a high *n*-9 monounsaturated fatty acid and high fat diet is another potential risk associated with excess consumption of monounsaturated fatty acids. *n*-9 Monounsaturated fatty acid intake may result in an increase in energy intake from saturated fatty acids due to the simultaneous occurrence of saturated and *n*-9 monounsaturated fatty acids in animal fats.

The *n*-7 monounsaturated fatty acid, palmitoleic acid, behaves like saturated fatty acids in raising LDL cholesterol concentration (Nestel et al., 1994). Watts and coworkers (1996) reported a positive correlation between palmitoleic acid and progression of CHD.

Cancer. While most epidemiological studies indicate that monounsaturated fatty acid intake is not associated with increased risk of most cancers (Holmes et al., 1999; Hursting et al., 1990; van Dam et al., 2000; van den Brandt et al., 1993), a few studies have observed a positive association. There is some epidemiological evidence for a positive association between oleic acid intake and breast cancer risk in women with no history of benign breast disease (Velie et al., 2000). In addition, one study reported that women with a family history of colorectal cancer who consumed a diet high in mono- and polyunsaturated fatty acids were at greater risk of colon cancer than women without a family history (Slattery et al., 1997). Giovannucci and coworkers (1993) reported a positive association between monounsaturated fatty acid intake and risk of advanced prostate cancer, while two studies observed increased risk of lung cancer (De Stefani et al., 1997; Veierød et al., 1997).

Summary

Based on the lack of adequate data on adverse effects of monounsaturated fatty acids, a UL is not set.

n-*6 Polyunsaturated Fatty Acids*

A UL is not set for *n*-6 polyunsaturated fatty acids because of the lack of a defined intake level at which an adverse effect can occur (see Chapter 11). An AMDR for *n*-6 polyunsaturated fatty acids, however, is estimated based on adverse effects from consuming a diet low or high in *n*-6 polyunsaturated fatty acids (Chapter 11).

n-*3 Polyunsaturated Fatty Acids*

Because the longer-chain *n*-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are biologically more potent than their precursor, α-linolenic acid, much of the work on the adverse effects of this group of fatty acids has been on DHA and EPA.

Hazard Identification

Immune Function. Numerous studies have shown suppression of various aspects of human immune function in vitro or ex vivo in peripheral blood mononuclear cells, or in isolated neutrophils or monocytes in individuals provided *n*-3 polyunsaturated fatty acids as a supplement or as an experimental diet compared with baseline values before the intervention (Table 8-8). The minimum dose observed for such an effect was 0.9 g/d of EPA and 0.6 g/d of DHA given as fish oil for 6 to 8 weeks to healthy adults (Cooper et al., 1993). The level of EPA that caused some type of immunosuppression ranged from 0.9 to 9.4 g/d when fed for 3 to 24 weeks. The level of DHA that caused immunosuppression ranged from 0.6 to 6.0 g/d (Table 8-8).

The data in single treatment studies comparing baseline versus post-supplementation immune function indicate that *n*-3 polyunsaturated fatty acids, especially EPA and DHA at levels 7 to 15 times greater than typical current U.S. intakes, diminish the potential of the immune system to attack pathogens (Kelley et al., 1998, 1999; Lee et al., 1985; Schmidt et al., 1989). This diminished ability, however, is also associated with suppression of inflammatory responses, suggesting benefits for individuals suffering from autoimmune diseases such as rheumatoid arthritis. It seems that the same doses of *n*-3 fatty acids that may be beneficial in chronic disease prevention are doses that are also immunosuppressive.

Several studies using a design of comparison across treatment groups (Blok et al., 1997; Kelley et al., 1998; Mølvig et al., 1991; Yaqoob et al., 2000), rather than comparison within individuals with a baseline, have shown a lack of several potential adverse effects of EPA and DHA supplementation on human immune cell functions. In one key study, 58 healthy men were given daily supplements of 0, 3, 6, or 9 g/d of a fish-oil supplement (EPA intake of 0, 0.81, 1.62, or 2.43 g/d and DHA intake of 0, 0.16, 0.33, or 0.49 g/d) for 1 year (Blok et al., 1997). Ex vivo endotoxin-stimulated production of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, or IL-1Ra (IL-1 receptor antagonist) did not differ among treatments up to 6 months after the fish-oil supplementation was stopped. These data support a lack of long-term adverse effect of fish-oil supplementation on cytokine activity.

TABLE 8-8 Effects of *n*-3 Fatty Acid Intake on Immune Function

Reference	Study Design	*n*-3 Fatty Acid Dose (Daily)[a]
Lee et al., 1985	7 men 6 wk	MaxEPA (3.2 g EPA, 2.2 g DHA)
Endres et al., 1989	9 men 6 wk	MaxEPA (2.75 g EPA, 1.85 g DHA)
Schmidt et al., 1989	12 men 6 wk	Cod liver oil (2.5 g EPA)
Kelley et al., 1991	10 men 56-d crossover	Basal diet Flaxseed oil-supplemented diet (20 g 18:3*n*-3)
Meydani et al., 1991	6 young women, 6 older women 12 wk	ProMega (1.68 g EPA, 0.72 g DHA)
Mølvig et al., 1991	8 men 9 men 8 men 7 wk	Placebo oil Fish oil (1 g EPA, 0.5 g DHA) Fish oil (2 g EPA, 1 g DHA)
Thompson et al., 1991	6 men, 6 women 4-wk crossover	MaxEPA (2.16 g EPA) 12 g olive oil
Virella et al., 1991	4 men fed fish oil, 2 men fed olive oil 6 wk	Fish oil (2.4 g EPA)
Yamashita et al., 1991	3 adults 1 d	3 g EPA, infused
Cooper et al., 1993	8 men and women 6–8 wk	Fish oil (0.9 g EPA, 0.6 g DHA)
Endres et al., 1993	9 men 6 wk	MaxEPA (2.75 g EPA, 1.85 g DHA)
Meydani et al., 1993	7 women, 3 men 24 wk after 6 wk on typical U.S. diet (baseline)	Low fat, high fish diet (1.23 g EPA + DHA)
Sperling et al., 1993	5 women and 3 men with rheumatoid arthritis 10 wk	SuperEPA (9.4 g EPA, 5.0 g DHA)

Results[b]
Depressed neutrophil LTB_4, 6-*trans*-LTB_4, 5-HETE, and endothelial adherence, monocyte LTB_4 and 5-HETE, neutrophil chemotaxis
Depressed PBMC IL-1β, IL-1α, TNF, PGE_2, and neutrophil chemotaxis
Depressed neutrophil migration, monocyte cell density (marker of monocyte migration)
Depressed PBMC proliferation in response to T-cell mitogen but not to B-cell mitogen with flaxseed oil-supplemented diet
Depressed PBMC IL-1β and IL-6 (greater in older women), TNF and IL-2 (older women only)
Depressed PBMC proliferation, IL-1β in PBMCs and monocytes with *n*-3 fatty acids PBMC secretion of IL-1β, TNF-α, PGE_2 or LTB_4 not affected by *n*-3 fatty acids
Depressed neutrophil chemiluminescence (marker of neutrophil function) with MaxEPA diet
Depressed PBMC IL-2
Depressed NK cell activity of PBMCs
Typhoid vaccine injection site less inflamed, postvaccination tachycardia inhibited, depressed blood IL-1 and IL-6 concentrations
Depressed PBMC IL-2 and proliferation
Depressed PBMC IL-1β, TNF, IL-6, PGE_2, CD_{4+} lymphocytes, and lymphocyte proliferation, delayed-type hypersensitivity
Depressed neutrophil chemotaxis, inositol tris-phosphate formation, and LTB_4, monocyte LTB_4

continued

TABLE 8-8 Continued

Reference	Study Design	*n*-3 Fatty Acid Dose (Daily)[a]
Gallai et al., 1995	20 patients with relapsing/remitting multiple sclerosis and 15 controls 6 mo	Fish oil (3.06 g EPA, 1.86 g DHA)
Caughey et al., 1996	30 men 4-wk diet + 4-wk diet with fish oil	Flaxseed oil-enriched diet and fish oil (EPA 1.62 g, DHA 1.08 g) Sunflower oil diet and fish oil (EPA 1.62 g, DHA 1.08 g)
Hughes et al., 1996	3 men, 3 women 3 wk	EPA Forte (0.93 g EPA, 0.63 g DHA)
Blok et al., 1997	58 men 1 y	0, 3, 6, or 9 g fish oil (0, 0.81, 1.62, or 2.43 g EPA; 0, 0.16, 0.33, or 0.49 g DHA)
Kelley et al., 1998	4 men 7 men 120 d	Basal diet DHA-enriched oil (6 g DHA)
Kelley et al., 1999	4 men 7 men 120 d	Basal diet DHA-enriched oil (6 g DHA)
Yaqoob et al., 2000	5 men, 3 women 7 men, 1 woman 3 other groups of 8 fed other oils, but all comparable to placebo 12-wk parallel	Placebo oil (3:1 coconut and soybean oils) Fish oil (2.1 g EPA, 1.1 g DHA)

[a] EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.
[b] LTB_4 = leukotriene B_4, 5-HETE = 5-hydroxyeicosatetraenoic acid, PBMC = peripheral blood mononuclear cell, IL = interleukin, TNF = tumor necrosis factor, PGE_2 = prosta-

In studies using multitreatment parallel designs, potential adverse effects of *n*-3 fatty acids on immune function that were observed include decreased expression of monocyte major histocompatibility complex antigens and cell surface adhesion proteins (Hughes et al., 1996), decreased peripheral blood mononuclear cell (PBMC) proliferation and IL-1β in

Results[b]
Depressed PBMC IL-1β, TNF-α, IL-2 and IFN-γ, PGE_2, and LTB_4, serum-soluble IL-2 receptors
Depressed PBMC TNF-α, IL-1β, TxB_2, and PGE_2 with flaxseed oil-enriched diet Greater decreases in PBMC TNF-α, IL-1β, and TxB_2 in both groups after fish-oil supplementation
Depressed monocyte surface proteins: HLA-DR, HLA-DP, HLA-DQ, ICAM-1, LFA-1
No effect on whole blood IL-1β, TNF-α, or IL-1 receptor antagonist
Decreased white blood cells PBMC proliferation and delayed-type hypersensitivity not different between groups
Depressed PBMC IL-1β and TNF-α production, in vitro PBMC PGE_2 and LTB_4 secretion
No effect of fish oil on PBMC NK cell activity, proliferation, types of blood lymphocytes, IL-1α, IL-1β, TNF-α, IL-2, IL-10, and IFN-γ

glandin E_2, NK cell = natural killer cell, IFN-γ = interferon-γ, TxB_2 = thromboxane B_2, HLA = human leukocytes antigen, ICAM = intercellular adhesion molecule, LFA = leukocyte function-associated antigen.

PBMCs and monocytes (Mølvig et al., 1991), decreased PBMC IL-2 (Virella et al., 1991), decreased but still clinically normal neutrophils (Kelley et al., 1998), and decreased tachycardia and inflammation after typhoid vaccine (Cooper et al., 1993).

All of the single treatment studies comparing individuals fed *n*-3 polyunsaturated fatty acids before and after supplementation showed immunosuppressive effects. Differences in study design (single treatment versus multitreatment parallel designs) seem to be quite significant in determining whether *n*-3 fatty acid supplementation exerts immunosuppression or not. There is no clear basis to prefer one type of study design to the other. For example, the difference in results between Caughey and colleagues (1996) (a baseline comparison study) and Blok and colleagues (1997) (a group comparison study) is not accounted for by greater variability in measurements by the latter group. The standard deviation for whole blood TNF-α was no more than 5 percent of the mean in the study by Blok and coworkers (1997), and the standard deviation for mononuclear cell TNF-α was 25 to 45 percent of the mean in the study by Caughey and coworkers (1996). In another study using intertreatment comparisons of control versus men given fish oil for 7 weeks, secretions of IL-1β and TNF-α were not suppressed by fish-oil feeding, but lysates of peripheral blood mononuclear cells from people given fish oil contained less IL-1β and TNF-α than did cells from controls (Mølvig et al., 1991). Therefore, the study by Mølvig and colleagues (1991) showed some concurrence with that of Blok and colleagues (1997) and Caughey and colleagues (1996).

Another alternative is to extrapolate from animal studies using model species that are known to have similar immune system components and responsiveness compared to humans. Detailed characterization of appropriateness of animal models for extrapolation to humans with respect to immunosuppression has not been done. A few animal studies have shown the effects of dietary *n*-3 fatty acids on response to infection (Chang et al., 1992; Fritsche et al., 1997). At this time, there are not sufficient data to support establishing an UL for EPA and DHA based on infection responsiveness.

Bleeding and Increased Risk of Hemorrhagic Stroke. One of a number of factors that has been suggested to link *n*-3 polyunsaturated fatty acid intake with reduced risk of CHD is reduced platelet aggregation, and therefore prolonged bleeding time. The platelet count can decline by as much as 35 percent; however, the count does not usually fall below the lower limit of normal (Goodnight et al., 1981). Although prolonged bleeding times have been shown to be beneficial in preventing heart disease, bleeding times can become prolonged enough to result in excessive bleeding and bruising. Intervention studies that have examined the effects of *n*-3 fatty acids on bleeding time are mixed. A number of short-term studies (4 to 11 weeks) have shown significant increased bleeding time with taking EPA/DHA supplements ranging from 2 to 15 g/d (Cobiac et al., 1991; De

Caterina et al., 1990; Levinson et al., 1990; Lorenz et al., 1983; Mortensen et al., 1983; Sanders et al., 1981; Schmidt et al., 1990, 1992; Smith et al., 1989; Thorngren and Gustafson, 1981; Wojenski et al., 1991; Zucker et al., 1988), whereas other studies using similar intake levels resulted in no difference (Blonk et al., 1990; Freese and Mutanen, 1997; Rogers et al., 1987). Analysis of these studies collectively indicated no dose–response for EPA and DHA intake and the percent increase in bleeding time. Schmidt and coworkers (1992) reported increased bleeding times when 3.1 g/d of EPA and DHA were given for 6 weeks and 9 months. None of the above studies reported excessive bleeding times, bleeding episodes, or bruising.

Dietary feeding studies that provided approximately 2 percent of energy as EPA and DHA from salmon did not result in increased bleeding time compared to a stabilization diet that contained only 0.3 percent of energy as EPA and DHA (Nelson et al., 1991). Excessive cutaneous bleeding time and reduced in vitro platelet aggregability have been reported in Greenland Eskimos (Dyerberg and Bang, 1979; Dyerberg et al., 1978) who ingest on average 6.5 g/d (3.8 percent of energy) of EPA and DHA derived mainly from seal (Bang et al., 1980). A tendency to bleed from the nose and urinary tract was observed among the Greenland Eskimos (Bang and Dyerberg, 1980). One study comparing perirenal adipose tissue fatty acid profiles with incidence of hemorrhagic stroke in human autopsy cases from Greenland showed that the amounts of EPA and DHA in the adipose tissue of 4 hemorrhagic stroke victims was greater than in 26 control cases with no cerebral pathology (Pedersen et al., 1999). Furthermore, ecological studies have suggested an increased risk of hemorrhagic stroke among Greenland Eskimos (Kristensen, 1983; Kromann and Green, 1980). A recent prospective study in the United States showed no association between intake of *n*-3 fatty acids and risk of hemorrhagic stroke (Iso et al., 2001). The median intake levels for the quintiles of *n*-3 polyunsaturated fat intake, however, ranged from only 0.077 to 0.481 g/d, which reflects the relatively low intake level of *n*-3 fatty acids in the Unites States.

Oxidative Damage. Long-chain polyunsaturated fatty acids, particularly DHA and EPA, are vulnerable to lipid peroxidation, resulting in oxidative damage of various tissues. Numerous feeding studies using laboratory animals have demonstrated increased lipid peroxidation and oxidative damage of erythrocytes, liver, and kidney membranes and bone marrow DNA with consumption of DHA (Ando et al., 1998; Song and Miyazawa, 2001; Umegaki et al., 2001; Yasuda et al., 1999). The oxidative damage was shown to be reduced or prevented with the coconsumption of vitamin E (Ando et al., 1998; Leibovitz et al., 1990; Yasuda et al., 1999).

Summary

While there is evidence to suggest that high intakes of *n*-3 polyunsaturated fatty acids, particularly EPA and DHA, may impair immune response and result in excessively prolonged bleeding times, it is not possible to establish a UL. Studies on immune function were done in vitro and it is difficult, if not impossible, to know how well these artificial conditions simulate human immune cell response in vivo. Data on EPA and DHA intakes and bleeding times are mixed and a dose–response effect was not observed. Although excessively prolonged bleeding times and increased incidence of bleeding have been observed in Eskimos, whose diets are rich in EPA and DHA, information is lacking to conclude that EPA and DHA were the sole basis for these observations. At the 99th percentile of intake, the highest intakes of dietary EPA and DHA were 0.662 and 0.651 g/d, respectively, in men 71 years of age and older (Appendix Tables E-12 and E-14). This EPA + DHA intake (1.31 g/d) is much lower than that for Greenland Eskimos (6.5 g/d). EPA and DHA are available as dietary supplements, and until more information is available on the adverse effects of EPA and DHA, these supplements should be taken with caution.

Special Considerations

A few special populations have been reported to exhibit adverse effects from consuming *n*-3 polyunsaturated fatty acids. Despite the favorable effects of *n*-3 fatty acids on glucose homeostasis, caution has been suggested for the use of n-3 fatty acids in those individuals who already exhibit glucose intolerance or diabetic conditions (Glauber et al., 1988; Kasim et al., 1988) that require increased doses of hypoglycemic agents (Friday et al., 1989; Stacpoole et al., 1989; Zambon et al., 1992). Increased episodes of nose bleeds have been observed in individuals with familial hypercholesterolemia during fish-oil supplementation (Clarke et al., 1990). Anticoagulants, such as aspirin, warfarin, and coumadin, will prolong bleeding times and the simultaneous ingestion of n-3 fatty acids by individuals may excessively prolong bleeding times (Thorngren and Gustafson, 1981). Therefore, the subpopulations described above should take supplements containing EPA and DHA with caution.

Trans *Fatty Acids*

Hazard Identification

Total and LDL Cholesterol Concentrations. Prior to 1980 there was generally little concern about the trend toward increased consumption of

hydrogenated fat in the U.S. diet, especially when the hydrogenated fats displaced fats relatively high in saturated fatty acids (Denke, 1995). During the early 1980s studies showed a hypercholesterolemic effect of *trans* fatty acids in rabbits (Kritchevsky, 1982; Ruttenberg et al., 1983). Renewed interest in the topic of hydrogenated fat in human diets, or more precisely *trans* fatty acid intake, started in the early 1990s. The availability of a methodology to distinguish the responses of individual lipoprotein classes to dietary modification expanded the depth to which the topic could be readdressed.

A report from the Netherlands suggested that a diet enriched with elaidic acid (a subfraction of 18:1 *trans*) compared to one enriched with oleic acid (18:1 *cis*) increased total and LDL cholesterol concentrations and decreased HDL cholesterol concentrations, hence resulting in a less favorable total cholesterol:HDL cholesterol ratio (Mensink and Katan, 1990). Consumption of a diet enriched with saturated fatty acids resulted in LDL cholesterol concentrations similar to those observed after individuals consumed the diet high in elaidic acid, but HDL cholesterol concentrations were similar to those observed after individuals consumed the diet high in oleic acid. A number of similar studies have been published since then and have reported that hydrogenated fat/*trans* fatty acid consumption increases LDL cholesterol concentrations (Aro et al., 1997; Judd et al., 1994, 1998; Louheranta et al., 1999; Müller et al., 1998; Sundram et al., 1997) (Tables 8-9, 8-10, and 8-11). Recent data have demonstrated a dose-dependent relationship between *trans* fatty acid intake and the LDL:HDL ratio and when combining a number of studies, the magnitude of this effect is greater for *trans* fatty acids compared with saturated fatty acids (Figure 8-4) (Ascherio et al., 1999).

Similar to the metabolic clinical trial data, studies in free-living individuals asked to substitute hydrogenated fat for other fat in their habitual diet resulted in higher concentrations of total and LDL cholesterol (Table 8-11) (Nestel et al., 1992b; Noakes and Clifton, 1998; Seppänen-Laakso et al., 1993).

No studies have been conducted to evaluate the effect of *trans* fatty acids that are present in meats and dairy products on LDL concentrations. The relative effect of *trans* fatty acids in meat and dairy products on LDL cholesterol concentration would be small compared to hydrogenated oils because of the lower levels that are present, and because any rise in concentration would most likely be due to the abundance of saturated fatty acids.

HDL Cholesterol Concentrations. The data related to the impact of hydrogenated fat/*trans* fatty acids compared with unhydrogenated oil/*cis* fatty acids on HDL cholesterol concentrations are less consistent than for LDL cholesterol concentrations (Tables 8-9, 8-10, and 8-11). As reported

TABLE 8-9 Dietary *Trans* Fatty Acids (TFA) and Blood Lipid Concentration: Controlled Feeding Trials

Reference	Study Population	Diet[a]
Mensink and Katan, 1990; Mensink et al., 1992	79 men and women, avg 25–26 y	3-wk crossover, 40% fat 10% 18:1 10% SF 10% TFA
Zock and Katan, 1992	56 healthy men and women	3 wk crossover, 41% fat 18:2 18:0 TFA
Judd et al., 1994	58 men and women	6-wk crossover, 40% fat 18:1 SFA moderate TFA high TFA
Aro et al., 1997	80 healthy men and women, 20–52 y	5-wk intervention, 33% fat 18:0 TFA
Sundram et al., 1997	27 men and women, 19–39 y	4-wk crossover, 31% fat 18:1 16:0 12:0 + 14:0 TFA
Louheranta et al., 1999	14 healthy women, avg 23 y	4-wk crossover, 37% fat 18:1 TFA
Judd et al., 2002	50 men	5-wk crossover, 39% fat 18:1 18:0 TFA/18:0 TFA

[a] SF = saturated fat, SFA = saturated fatty acids.
[b] LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, Lp(a) = lipoprotein(a).

	Blood Lipid Concentrations[b]		
TFA (% of energy)	LDL-C (mmol/L)	HDL-C (mmol/L)	Lp(a) (mg/L)
0	2.67[c]	1.42[c]	32[c]
1.8	3.14[d]	1.42[c]	26[d]
10.9	3.04[e]	1.25[d]	45[e]
0.1	2.83[c]	1.47[c]	
0.3	3.00[d]	1.41[d]	
7.7	3.07[d]	1.37[d]	
0.7	3.34[c]	1.42[c]	
0.7	3.64[d]	1.40[c,d]	
3.8	3.54[e]	1.47[e]	
6.6	3.60[d,e]	1.38[d]	
0.4	2.89[c]	1.42[c]	270[c]
8.7	3.13[d]	1.22[d]	308[d]
0	3.17	1.25	128.3
0	3.15	1.26	122.0
0	3.57	1.18	134.3
6.9	3.81	1.05	153.3
0	2.53	1.37	225 (units/L)
5.1	2.64	1.31	220 (units/L)
0	2.95[c]		
0	3.10[d]		
4	3.32[e]		
8	3.36[e]		

[c,d,e] Within each study, LDL-C, HDL-C, or Lp(a) concentrations that are significantly different between treatment groups have a different superscript.

TABLE 8-10 Hydrogenated Fat Intake and Blood Lipid Concentrations: Controlled Feeding Trials

Reference	Study Population	Diet[a]
Lichtenstein et al., 1993	14 men and women, 44–78 y	32-d crossover, 30% fat Baseline Corn oil Corn oil margarine
Almendingen et al., 1995	31 men, 21–46 y	3-wk crossover, 33–36% fat Butter PHFO PHSO
Judd et al., 1998b	46 men and women, 28–65 y	5-wk crossover, 34% fat PUFA-M Butter TFA-M
Müller et al., 1998	16 healthy females, 19–30 y	14-d crossover, 31–32% fat Vegetable oil PHFO
Lichtenstein et al., 1999	36 men and women, > 50 y	35-d crossover, 30% fat Soybean oil Semiliquid margarine Butter Soft margarine Shortening Stick margarine

[a] PHFO = partially hydrogenated fish oil, PHSO = partially hydrogenated soybean oil, PUFA-M = margarine containing polyunsaturated fatty acids, TFA-M = margarine containing *trans* fatty acids.
[b] TFA = *trans* fatty acids.

for LDL cholesterol concentrations, the effect of hydrogenated fat/*trans* fatty acids on HDL cholesterol concentrations, if present, is likely to be dose-dependent (Judd et al., 1994). The preponderance of the data suggests that hydrogenated fat/*trans* fatty acids, relative to saturated fatty acids, result in lower HDL cholesterol concentrations (Ascherio et al., 1999; Zock and Mensink, 1996; Zock et al., 1995). Because of the potentially

	Blood Lipid Concentrations[c]		
TFA[b] (% of energy)	LDL-C (mmol/L)	HDL-C (mmol/L)	Lp(a) (mg/L)
0.77	3.96[d]	1.24[d]	140[d]
0.44	3.23[e]	1.14[e]	160[d]
4.16	3.49[e]	1.11[e]	130[d]
0.9	3.81[d]	1.05[d]	194[d]
8.0	3.94[d,f]	0.98[e]	234[e]
8.5	3.58[e]	1.05[d]	238[e]
2.4	3.21[d]	1.24[d]	197[d]
2.7	3.44[e]	1.27[d]	186[e]
3.9	3.27[f]	1.24[d]	202[d]
1.1	2.63[d]	1.32[d]	212[d]
1.7	2.87[e]	1.28[d]	225[d]
0.55	3.98[d]	1.11[d,e]	230
0.91	4.01[d,e]	1.11[d,e]	230
1.25	4.58[f]	1.16[e]	220
3.30	4.11[d,e]	1.11[d,e]	240
4.15	4.24[e]	1.11[d,e]	240
6.72	4.34[e]	1.01[d]	240

[c] LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, Lp(a) = lipoprotein(a).
[d,e,f] Within each study, LDL-C, HDL-C, or Lp(a) concentrations that are significantly different between treatment groups have a different superscript.

differential effects of hydrogenated fat/*trans* fatty acids on LDL and HDL cholesterol concentrations, concern has been raised regarding their effect on the total cholesterol or LDL cholesterol:HDL cholesterol ratio (Ascherio et al., 1999). However, with respect to dietary fat recommendations, the strategy to improve the total cholesterol or LDL cholesterol:HDL

TABLE 8-11 Dietary *Trans* Fatty Acids (TFA), Hydrogenated Fat, and Blood Lipid Concentrations: Free-Living Trials

Reference	Study Population	Diet[a]
Nestel et al., 1992a	26 mildly hypercholesterolemic men, 27–57 y	4-wk crossover, 42% fat Control 1 Control 2 Blend 1 Blend 2
Nestel et al., 1992b	27 mildly hypercholesterolemic men, 30–63 y	3-wk crossover, 36–37% fat Control 18:1 TFA 16:0
Seppänen-Laakso et al., 1993	57 men and women, middle-aged	12-wk crossover to 1 of 2 diets, 39–43% fat Margarine Rapeseed Olive oil
Wood et al., 1993a	38 healthy men, 30–60 y	6-wk crossover, 38% fat Butter Butter-sunflower Butter-olive Hard margarine Soft margarine
Wood et al., 1993b	29 healthy men, 30–60 y	6-wk crossover, 37% fat Butter Crude palm Margarine Refined palm Refined palm+sunflower Sunflower oil
Chisholm et al., 1996	49 hypercholesterolemic men and women, avg 47 y	6-wk crossover, 26–27% fat Butter Margarine

	Blood Lipid Concentrations[c]		
TFA (% of energy)	LDL-C (mmol/L)	HDL-C (mmol/L)	Lp(a) (units/L)
3.8	4.13[c]	1.11[c]	
3.7	4.03[c,d]	1.15[c]	
6.7	3.92[d,e]	1.10[c]	
6.6	3.83[e]	1.11[c]	
< 1	4.22[c]	0.98[c]	235[c]
1.4	3.90[d]	0.98[c]	236[c]
5.7	4.27[c]	0.98[c]	296[d]
< 1	4.16[c]	1.09[d]	249[e]
	Change from baseline	Change from baseline	
2.9	–0.20	+0.05	
0	–0.30	–0.01	
0	–0.32	0.00	
2.1	3.78[c]	1.22[c]	
1.0	3.49[d]	1.19[c]	
1.0	3.59[d]	1.22[c]	
11.1	3.47[d]	1.16[c]	
0	3.26[e]	1.16[c]	
0.2	3.52[c]	1.03[c]	
0	3.36[c]	1.03[c]	
3.0	3.36[c]	1.00[c]	
0	3.41[c]	1.06[d]	
0	3.41[c]	1.03[c]	
0	3.23[d]	1.00[c]	
1.4	4.21[c]	1.26[c]	223[c]
3.6	3.82[d]	1.24[c]	249[c]

continued

TABLE 8-11 Continued

Reference	Study Population	Diet[a]
Noakes and Clifton, 1998	38 mildly hyperlipidemic men and women	3-wk crossover, 2 groups, 31–35% fat Canola + TFA TFA-free canola Butter PUFA + TFA TFA-free PUFA Butter

[a] PUFA = polyunsaturated fatty acids.
[b] LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, Lp(a) = lipoprotein(a).

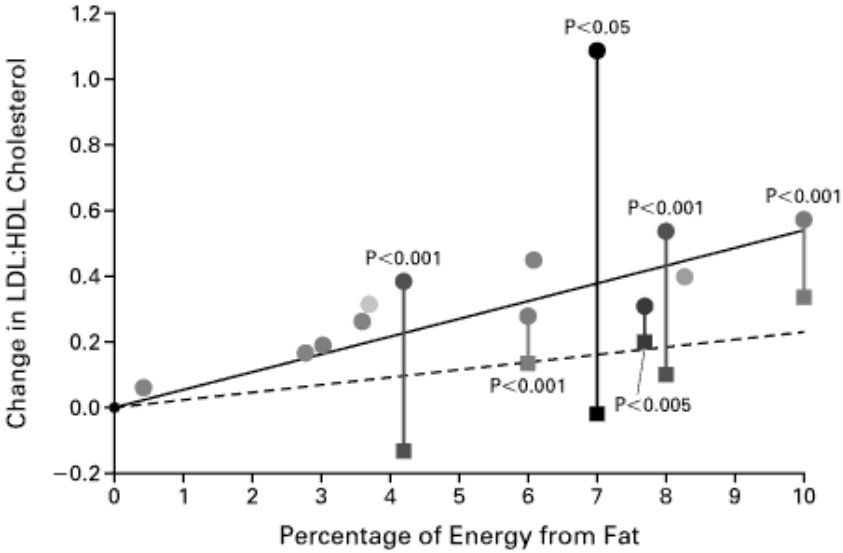

FIGURE 8-4 Change in the low density lipoprotein (LDL):high density lipoprotein (HDL) cholesterol concentration with increasing energy intake from saturated and *trans* fatty acids. Solid line represents the best-fit regression for *trans* fatty acids. Dotted line represents the best-fit regression for saturated fatty acids. Reprinted, with permission, from Ascherio et al. (1999). Copyright 1999 by the Massachusetts Medical Society.

		Blood Lipid Concentrations[c]		
	TFA (% of energy)	LDL-C (mmol/L)	HDL-C (mmol/L)	Lp(a) (units/L)
	3.3	3.64[c]	1.19[c]	
	0	3.61[c]	1.28[c]	
	1.1	4.14[d]	1.20[c]	
	3.6	4.23[c]	1.17[c]	
	0	3.98[d]	1.23[c]	
	1.2	4.70[e]	1.27[c]	

[c,d,e] Within each study, LDL-C, HDL-C, or Lp(a) concentrations that are significantly different between treatment groups have a different superscript.

cholesterol ratio would not be different from that to decrease LDL cholesterol concentrations.

Lp(a) Concentrations. Lipoprotein(a) (Lp(a)) concentrations in plasma have been associated with increased risk for developing cardiovascular and cerebrovascular disease, possibly via inhibition of plasminogen activity (Lippi and Guidi, 1999; Nielsen, 1999; Wild et al., 1997). Lp(a) is a lipoprotein particle similar to LDL with respect to its cholesterol and apolipoprotein B100 content, but it also contains an additional apolipoprotein termed apo(a) (Lippi and Guidi, 1999; Nielsen, 1999). Lp(a) concentrations have been reported by some investigators to be increased after the consumption of diets enriched in hydrogenated fat/*trans* fatty acids (Tables 8-9, 8-10, and 8-11) (Almendingen et al., 1995; Aro et al., 1997; Lichtenstein et al., 1999; Mensink et al., 1992; Nestel et al., 1992b; Sundram et al., 1997), but not by all (Chisholm et al., 1996; Judd et al., 1998; Lichtenstein et al., 1993; Louheranta et al., 1999; Müller et al., 1998). The magnitude of the mean increases in Lp(a) concentrations reported to date that is associated with *trans* fatty acid intake for the most part would not be predicted to have a physiologically significant effect on cardiovascular disease risk. However, an unresolved issue at this time is the potential effect of relatively high levels of *trans* fatty acids in individuals with initially high concentrations of Lp(a).

Hemostatic Factors. The effect of *trans* fatty acids on hemostatic factors has been assessed by a number of investigators (Almendingen et al., 1996; Mutanen and Aro, 1997; Sanders et al., 2000; Turpeinen et al., 1998; Wood et al., 1993b) (Table 8-12). In general, these researchers have concluded that hydrogenated fat/*trans* fatty acids had little effect on a variety of hemostatic variables. Similarly, Müller and colleagues (1998) reported that hemostatic variables were unaffected by the substitution of a vegetable oil-based margarine relatively high in saturated fatty acids when compared with a hydrogenated fish oil-based margarine.

Susceptibility of LDL to Oxidation. Hydrogenated fat/*trans* fatty acids have consistently been reported to have little effect on the susceptibility of LDL to oxidation (Cuchel et al., 1996; Halvorsen et al., 1996; Nestel et al., 1992b; Sørensen et al., 1998) (Table 8-12).

Blood Pressure. A few reports addressed the issue of *trans* fatty acid intake and blood pressure (Mensink et al., 1991; Zock et al., 1993) (Table 8-12). The authors concluded that consumption of diets high in saturated, monounsaturated, or *trans* fatty acids resulted in similar diastolic and systolic blood pressures.

CHD. Similar to saturated fatty acids, there is a positive linear trend between *trans* fatty acid intake and LDL cholesterol concentrations (Judd et al., 1994; Lichtenstein et al., 1999; Zock and Katan, 1992). Some evidence also suggests that *trans* fatty acids result in lower HDL cholesterol concentrations (Table 8-13). Hence, the net result is a higher total cholesterol or LDL cholesterol:HDL cholesterol ratio (Judd et al., 1994; Lichtenstein et al., 1999; Zock and Katan, 1992). This finding, combined with data from prospective cohort studies (Ascherio et al., 1996; Gillman et al., 1997; Hu et al., 1997; Pietinen et al., 1997; Willett et al., 1993) (Table 8-13), has lead to the concern that dietary *trans* fatty acids are more deleterious with respect to CHD than saturated fatty acids (Ascherio et al., 1999).

Summary

Similar to saturated fatty acids, there is a positive linear trend between *trans* fatty acid intake and LDL cholesterol concentration, and therefore increased risk of CHD. A UL is not set for *trans* fatty acids because any incremental increase in *trans* fatty acid intake increases CHD risk. Because *trans* fatty acids are unavoidable in ordinary, nonvegan diets, consuming 0 percent of energy would require significant changes in patterns of dietary intake. Such adjustments may introduce undesirable effects (e.g., elimination of commercially prepared foods and dairy products and meats that

contain *trans* fatty acids may result in inadequate intakes of protein and certain micronutrients) and unknown and unquantifiable health risks. It is possible to consume a diet low in *trans* fatty acids by following the dietary guidance provided in Chapter 11.

RESEARCH RECOMMENDATIONS

Total Fat

- Studies are needed that examine the effects of alterations in the level of total fat in the context of a low saturated fatty acid diet on blood lipid concentrations and glucose-insulin homeostasis in individuals with defined metabolic syndromes, such as type 1 and type 2 diabetes.
- Randomized and blinded long-term (greater than 1 year) studies are needed on the effect of dietary fat versus carbohydrate on body fatness.

Saturated Fatty Acids

- Further examination of intakes at which significant risk of chronic diseases can occur is needed.
- Data that examine the indicators for and risk of chronic disease at low levels of saturated fatty acid intake are necessary.

Cis-*Monounsaturated Fatty Acids*

- Information is needed to assess energy balance in free-living individuals who have implemented a diet high in monounsaturated fatty acids versus a diet lower in monounsaturated fatty acids (and higher in carbohydrate).
- Additional information is needed on the effects of alterations in the level of monounsaturated fatty acid in the context of a low saturated fatty acid diet on blood lipid concentrations and glucose–insulin homeostasis in individuals with defined metabolic syndromes, such as type 1 and type 2 diabetes.
- Studies are needed to evaluate cardiovascular disease risk status and risk of other chronic diseases in individuals consuming a high monounsaturated fatty acid diet versus a diet lower in monounsaturated fatty acids (and higher in carbohydrate).
- An evaluation of the nutritional adequacy and nutrient profile of free-living individuals following a self-selected high monounsaturated fatty acid diet is necessary.
- Studies that assess the effects of a high monounsaturated fatty acid diet on endothelial function and atherogenesis are needed.

TABLE 8-12 *Trans* Fatty Acid (TFA) Intake and Blood Clotting, Low Density Lipoprotein (LDL) Oxidation, and Blood Pressure

Reference	Study Population	Diet[a]	TFA (% of energy)
Clotting			
Wood et al., 1993b	29 men, 30–60 y	6-wk crossover, 37% fat	
		Butter	0.2
		Crude palm oil	0
		Margarine	3.0
		Refined palm oil	0
		Refined palm+sunflower	0
		Sunflower oil	0
Almendingen et al., 1996	31 men, avg 27 y	3-wk crossover, 33–36% fat	
		PHSO	8.5
		PHFO	8.0
		Butter	0.9
Mutanen and Aro, 1997	80 men and women, 20–52 y	5-wk crossover to 1 of 2 diets, 33–34% fat	
		High 18:0	0.4
		High TFA	8.7
Turpeinen et al., 1998	80 men and women, 20–52 y	5-wk crossover to 1 of 2 diets, 32–34% fat	
		18:0	0.4
		TFA	8.7
Sanders et al., 2000	16 men and women, 18–32 y	1 test-meal crossover, 7% or 65% fat	
		18:1	0.1
		18:1 trans	24.7
		18:0	0
		16:0	0.2
		MCT	0
		Low fat	0
Oxidation			
Cuchel et al., 1996	14 men and women, 44–78 y	32-d crossover, 30% fat	
		Corn oil	0.44
		Corn oil+margarine	4.16

Results[b]		Comments
TxB_2 (pg/mL)	6-keto-$PGF_{1\alpha}$ (pg/mL)	
35	89	
41	94	
40	86	
40	87	
36	100	
62	95	
Fibrinogen (g/L)	PAI-1 activity (units/mL)	For PHSO, greater PAI-1 activity than PHFO or butter
3.0	13.5	Increased fibrinogen with butter diet
2.9	10.7	No significant difference in factor VII, fibrinogen peptide A, β-thromboglobulin, or tissue plasminogen activator
3.1	8.8	
Fibrinogen (g/L)		No marked difference in factor VII coagulation activity, tissue type plasminogen activity, or PAI-1 activity
3.62		
3.61		
		No difference in TxB_2 production or ADP-induced platelet aggregation in vitro
		Significant increase in collagen-induced aggregation with 18:0 diet
$FVII_c$ (% standard)	$FVII_a$ (ng/mL)	No significant differences in factor VII coagulation activity; factor VII-activated concentrations were significantly higher with 18:1, 18:1 trans, 18:0, and 16:0 diets
124	2.7	
122	1.9	
114	1.9	
112	2.1	
112	1.5	
99	1.4	
		No difference in susceptibility to LDL oxidation

continued

TABLE 8-12 Continued

Reference	Study Population	Diet[a]	TFA (% of energy)
Halvorsen et al., 1996	29 men, 21–46 y	19-d crossover, 33–36% fat	
		Butter	0.9
		PHSO	8.5
		PHFO	8.0
Sørensen et al., 1998	47 men, 29–60 y	4 wk, consumed 30 g/d of 1 of 2 margarines	mol % of fat
		Sunflower oil	0.79
		Fish oil, enriched	0.98
Blood pressure			
Mensink et al., 1991	59 men and women, 19–57 y, normo-tensive	3-wk crossover, 39–40% fat	
		18:1	0
		TFA	10.9
		SFA	1.8
Zock et al., 1993	55 men and women, 19–49 y	3-wk crossover, 40–43% fat	
		18:2	0.1
		18:0	0.3
		TFA	7.7

[a] PHSO = partially hydrogenated soybean oil, PHFO = partially hydrogenated fish oil, MCT = medium-chain triacylglycerol, SFA = saturated fatty acid.

n-*6 Polyunsaturated Fatty Acids*

- In metabolic and large observational studies, comparison should be made of the benefits of α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) across a range of *n*-6 polyunsaturated fatty acid intakes.
- Using good biomarkers for low density lipoprotein oxidation and cancer susceptibility, assessments are needed of the potential adverse effects of diets at levels of *n*-6 polyunsaturated fatty acids greater than 10 percent of energy.
- Studies that assess the effects of a high *n*-6 polyunsaturated fatty acid diet on markers of endothelial function and inflammation are needed.

Results[b]		Comments
Dienes (nmol/mg LDL)	Formation rate (nmol/mg LDL × min)	No significant differences in conjugated dienes, lipid peroxides, uptake by macrophages, or electrophoretic mobility of LDL
1,020	10	
1,034	10	TFA does not alter susceptibility to LDL oxidation
1,107	10	
Dienes (nmol/g)	Oxidation rate (nmol/mg × min)	Fish oil consumption compared with sunflower oil margarine had no effect on LDL size and led to minor changes in LDL oxidation resistance
445	10.4	
468	10.2	
		No effect of TFA intake on blood pressure
SBP (mmHg)	DBP (mmHg)	
113	66	
112	67	
112	67	
		No effect of TFA intake on blood pressure
SBP (mmHg)	SBP (mmHg)	
114	68	
113	70	
113	69	

[b] TxB_2 = thromboxane B_2, 6-keto-$PGF_{1\alpha}$ = 6-keto-prostaglandin $F_{1\alpha}$, PAI-1 = plasminogen activator inhibitor type 1, $FVII_c$ = factor VII coagulant activity, $FVII_a$ = factor VII activated, SBP = systolic blood pressure, DBP = diastolic blood pressure.

- Further research is needed to address the potentially important relationships between the amount of *n*-3 and *n*-6 fatty acids and glucose tolerance suggested by studies of fatty acid composition in affected individuals.

n-*3 Polyunsaturated Fatty Acids*

- Randomized clinical trials are needed of EPA+DHA, EPA, and DHA to evaluate their impact on cancer (i.e., colon, breast, prostate). The use of biomarkers for cancer susceptibility may expedite such studies.

TABLE 8-13 Dietary *Trans* Fatty Acids (TFA): Epidemiological Studies

Reference	Study Design[a]	Dietary and Other Information
Lipoprotein concentration		
Siguel and Lerman, 1993	47 CAD cases 56 controls Case-control	No dietary intake information
Coronary heart disease (CHD)		
Hudgins et al., 1991	76 men, 23–78 y Cross-sectional	No dietary intake information
Troisi et al., 1992	748 men, 43–85 y Cross-sectional	Food frequency questionnaire, multivariate analysis
Willett et al., 1993	Women, 431 CHD cases Cohort, 8-y follow-up	Food frequency questionnaire, multivariate analysis
Ascherio et al., 1994	239 MI cases 282 controls Case-control	Food frequency questionnaire, multivariate analysis
Kromhout et al., 1995	12,763 men, 40–59 y Cohort, 25-y follow-up	Weighed food record
Ascherio et al., 1996	43,757 men, 40–75 y Cohort, 6-y follow-up	Food frequency questionnaire, multivariate analysis

Results[b]			Comments[c]
Plasma	Case	Control	TFA negatively associated with HDL
TFA (%)	1.38	1.11	TFA positively associated with LDL and TAG
HDL (mmol/L)	0.88	1.34	
LDL (mmol/L)	3.78	2.97	
TAG (mmol/L)	1.78	0.97	
Total TFA in adipose tissue was 4.4% of total fatty acids			Total TFA content in adipose tissue was not significantly related to risk factors of CHD (e.g., age, BMI, LDL, cholesterol, blood pressure)
TFA intake was directly related to total ($r = 0.07$, $P = 0.04$) and LDL ($r = 0.09$, $P = 0.01$) cholesterol			An increased TFA intake from 2.1 to 4.9 g/d increased the risk of MI by 27%
TFA intake (% energy)	RR of CHD		Positive association with TFA intake and risk of CHD
1.3	1.0		
1.8	1.4		
2.2	1.25		
2.6	1.55		
3.2	1.8		
TFA intake (g/d)	RR of MI		Positive association of TFA intake and risk of myocardial infarction
1.69	1.0		
2.48	0.73		
3.35	1.24		
4.52	1.63		
6.51	2.28		
Correlation between 18:1*trans* intake and CHD mortality is 0.78 ($p < 0.001$)			
TFA intake (g/d)	RR of MI		TFA intake directly associated with risk of MI
1.5	1.0		
2.2	1.20		
2.7	1.24		
3.3	1.27		
4.3	1.40		

continued

TABLE 8-13 Continued

Reference	Study Design[a]	Dietary and Other Information
Gillman et al., 1997	Men, 45–64 y 267 CHD cases Cohort, 21-y follow-up	24-h recall, multivariate analysis
Hu et al., 1997	Women, 34–59 y 939 MI cases Cohort, 14-y follow-up	Food frequency questionnaire, multivariate analysis
Pietinen et al., 1997	Smoking men, 50–69 y 1,399 coronary events 635 coronary deaths Cohort, 6.1-y follow-up	Food frequency questionnaire, multivariate analysis
Tavani et al., 1997	Women, 18–74 y 429 MI cases 866 controls Case-control	Questionnaire on selected indicator foods, multivariate analysis
Cancer		
Kohlmeier et al., 1997	Women, 50–74 y 291 breast cancer cases 407 controls Case-control	No diet information

Results[b]			Comments[c]
Margarine intake (tsp/d)	No. of events (/1,000) Period 1	Period 2	RR for CHD for each increment of 1 tsp/d was 0.99 for follow-up period 1 and 1.12 for period 2
0	77	65	Modest risk of CHD with increasing margarine intake
1–4	42	35	
≥ 5	18	30	
TFA intake (% energy)	RR of MI		RR for 2% increment in energy from TFA intake was 1.93
1.3	1.0		
1.7	1.07		
2.0	1.10		
2.4	1.13		
2.9	1.27		
TFA intake (g)	RR of major coronary event		Positive association between TFA intake and risk of coronary death
1.0	1.00		
1.7	1.10		
2.0	0.97		
2.7	1.07		
6.2	1.14		
TFA intake (g)	RR of coronary death		
1.0	1.00		
1.7	1.05		
2.0	1.12		
2.7	0.90		
6.2	1.39		
Margarine intakes	RR of MI		The association with margarine could explain about 6% of MI in this population
No or low	1.0		
Medium or high	1.5		
Adipose TFA concentration	OR of breast cancer		Risk for breast cancer is based on the relative concentration of TFA and PUFA
TFA	1.46		
TFA within lowest PUFA tertile	3.65		
TFA within highest PUFA tertile	0.97		

continued

TABLE 8-13 Continued

Reference	Study Design[a]	Dietary and Other Information
Tuyns et al., 1988	35–75 y 453 colon cancer cases 365 rectal cancer cases 2,851 controls Case-control	Dietary history

[a] CAD = coronary artery disease, CHD = coronary heart disease, MI = myocardial infarction.
[b] HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol, TAG = triacylglycerol, RR = relative risk, OR = odds ratio, PUFA = polyunsaturated fatty acid.

- Randomized clinical trials on the use of EPA+DHA, EPA, and DHA in treatment of inflammatory disorders (e.g., Crohn's disease, arthritis, psoriasis, asthma) and infections are needed.
- Studies of EPA+DHA, EPA, and DHA supplementation in the elderly to prevent degenerative diseases of the central nervous system and retina, such as dementia, age-related macular degeneration, and night blindness are needed.

Trans *Fatty Acids*

- A comprehensive database needs to be developed for the *trans* fatty acid content of the United States food supply; this database could then be used to determine the *trans* fatty acid intakes in different age and socioeconomic groups.
- An assessment of major sources of *trans* fatty acids currently in the marketplace is needed, along with development of alternatives similar to that done for foods high in saturated fatty acids.
- Studies that distinguish *trans* fatty acid isomers from plants and animals with respect to the relative impact on blood lipid and lipoprotein concentrations are needed.
- In light of the wide variability of *trans* fatty acid intakes within food categories, the development of a biochemical marker for *trans* fatty acid intake, independent of self-reported intake data, is needed.

Results[b]	Comments[c]
	There was no increased risk of either cancers with increased consumption of margarine

[c] BMI = body mass index.

REFERENCES

Abedin L, Lien EL, Vingrys AJ, Sinclair AJ. 1999. The effects of dietary α-linolenic acid compared with docosahexaenoic acid on brain, retina, liver, and heart in the guinea pig. *Lipids* 34:475–482.

Adlof RO, Duval S, Emken EA.! Ç00. Biosynthesis of conjugated linoleic acid in humans. *Lipids* 35:131–135.

Aggett PJ, Haschke F, Heine W, Hernell O, Koletzko B, Launiala K, Rey J, Rubino A, Schöch G, Senterre J, Tormo R. 1991. Comment on the content and composition of lipids in infant formulas. *Acta Paediatr Scand* 80:887–896.

Agner E, Hansen PF. 1983. Fasting serum cholesterol and triglycerides in a ten-year prospective study in old age. *Acta Med Scand* 214:33–41.

Agostoni C, Trojan S, Bellù R, Riva E, Giovannini M. 1995. Neurodevelopment quotient of healthy term infants at 4 months and feeding practice: The role of long-chain polyunsaturated fatty acids. *Pediatr Res* 38:262–266.

Agostoni C, Trojan S, Bellù R, Riva E, Bruzzese MG, Giovannini M. 1997. Developmental quotient at 24 months and fatty acid composition of diet in early infancy: A follow up study. *Arch Dis Child* 76:421–424.

Allison DB, Egan SK, Barraj LM, Caughman C, Infante M, Heimbach JT. 1999. Estimated intakes of *trans* fatty and other fatty acids in the US population. *J Am Diet Assoc* 99:166–174.

Almendingen K, Jordal O, Kierulf P, Sandstad B, Pedersen JI. 1995. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp[a] in men. *J Lipid Res* 36:1370–1384.

Almendingen K, Seljeflot I, Sandstad B, Pedersen JI. 1996. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on hemostatic variables in men. *Arterioscler Thromb Vasc Biol* 16:375–380.

Anderson DM, Williams FH, Merkatz RB, Schulman PK, Kerr DS, Pittard WB. 1983. Length of gestation and nutritional composition of human milk. *Am J Clin Nutr* 37:810–814.

Anderson GJ, Connor WE. 1989. On the demonstration of ω-3 essential-fatty-acid deficiency in humans. *Am J Clin Nutr* 49:585–587.

Anderson GJ, Connor WE, Corliss JD. 1990. Docosahexaenoic acid is the preferred dietary *n*-3 fatty acid for the development of the brain and retina. *Pediatr Res* 27:89–97.

Anderson RE, Benolken RM, Dudley PA, Landis DJ, Wheeler TG. 1974. Polyunsaturated fatty acids of photoreceptor membranes. *Exp Eye Res* 18:205–213.

Ando K, Nagata K, Beppu M, Kikugawa T, Kawabata T, Hasegawa K, Suzuki M. 1998. Effect of *n*-3 fatty acid supplementation on lipid peroxidation and protein aggregation in rat erythrocyte membranes. *Lipids* 33:505–512.

Aro A, Salminen I. 1998. Difference between animal and vegetable *trans* fatty acids. *Am J Clin Nutr* 68:918–919.

Aro A, Jauhiainen M, Partanen R, Salminen I, Mutanen M. 1997. Stearic acid, *trans* fatty acids, and dairy fat: Effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. *Am J Clin Nutr* 65:1419–1426.

Aro A, Amaral E, Kesteloot H, Rimestad A, Thamm M, van Poppel G. 1998a. *Trans* fatty acids in French fries, soups, and snacks from 14 European countries: The TRANSFAIR Study. *J Food Comp Anal* 11:170–177.

Aro A, Antoine JM, Pizzoferrato L, Reykdal O, van Poppel G. 1998b. *Trans* fatty acids in dairy and meat products from 14 European countries: The TRANSFAIR Study. *J Food Comp Anal* 11:150–160.

Aro A, Van Amelsvoort J, Becker W, van Erp-Baart M-A, Kafatos A, Leth T, van Poppel G. 1998c. *Trans* fatty acids in dietary fats and oils from 14 European countries: The TRANSFAIR Study. *J Food Comp Anal* 11:137–149.

Arora S, Kassarjian Z, Krasinski SD, Croffey B, Kaplan MM, Russell RM. 1989. Effect of age on tests of intestinal and hepatic function in healthy humans. *Gastroenterology* 96:1560–1565.

ARS (Agricultural Research Service). 2001. *USDA Nutrient Database for Standard Reference, Release 14*. Online. U.S. Department of Agriculture. Available at http://www.nal.usda.gov/fnic/foodcomp/Data/SR14/sr14.html. Accessed November 13, 2001.

Ascherio A, Hennekens CH, Buring JE, Master C, Stampfer MJ, Willett WC. 1994. *Trans*-fatty acids intake and risk of myocardial infarction. *Circulation* 89:94–101.

Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. 1996. Dietary fat and risk of coronary heart disease in men: Cohort follow up study in the United States. *Br Med J* 313:84–90.

Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. 1999. Trans fatty acids and coronary heart disease. *N Engl J Med* 340:1994–1998.

Astrup A, Buemann B, Christensen NJ, Toubro S. 1994. Failure to increase lipid oxidation in response to increasing dietary fat content in formerly obese women. *Am J Physiol* 266:E592–E599.

Auestad N, Montalto MB, Hall RT, Fitzgerald KM, Wheeler RE, Connor WE, Neuringer M, Connor SL, Taylor JA, Hartmann EE. 1997. Visual acuity, erythrocyte fatty acid composition, and growth in term infants fed formulas with long chain polyunsaturated fatty acids for one year. *Pediatr Res* 41:1–10.

Auestad N, Halter R, Hall RT, Blatter M, Bogle ML, Burks W, Erickson JR, Fitzgerald KM, Dobson V, Innis SM, Singer LT, Montalto MB, Jacobs JR, Qiu W, Bornstein MH. 2001. Growth and development in term infants fed long-chain polyunsaturated fatty acids: A double-masked, randomized, parallel, prospective, multivariate study. *Pediatrics* 108:372–381.

Bang HO, Dyerberg J. 1980. The bleeding tendency in Greenland Eskimos. *Dan Med Bull* 27:202–205.

Bang HO, Dyerberg J, Sinclair HM. 1980. The composition of the Eskimo food in north western Greenland. *Am J Clin Nutr* 33:2657–2661.

Barr LH, Dunn GD, Brennan MF. 1981. Essential fatty acid deficiency during total parenteral nutrition. *Ann Surg* 193:304–311.

Bartoš V, Groh J. 1969. The effect of repeated stimulation of the pancreas on the pancreatic secretion in young and aged men. *Gerontol Clin* 11:56–62.

Benolken RM, Anderson RE, Wheeler TG. 1973. Membrane fatty acids associated with the electrical response in visual excitation. *Science* 182:1253–1254.

Berge RK, Madsen L, Vaagenes H, Tronstad KJ, Göttlicher M, Rustan AC. 1999. In contrast with docosahexaenoic acid, eicosapentaenoic acid and hypolipidaemic derivatives decrease hepatic synthesis and secretion of triacylglycerol by decreased diacylglycerol acyltransferase activity and stimulation of fatty acid oxidation. *Biochem J* 343:191–197.

Bessesen DH, Rupp CL, Eckel RH. 1995. Trafficking of dietary fat in lean rats. *Obes Res* 3:191–203.

Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C. 1998. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. *Pediatr Res* 44:201–209.

Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG. 2000. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev Med Child Neurol* 42:174–181.

Bistrian BR, Bothe A, Blackburn GL, DeFriez AI. 1981. Low plasma cortisol and hematologic abnormalities associated with essential fatty acid deficiency in man. *J Parenter Enteral Nutr* 5:141–144.

Bitman J, Wood DL, Hamosh M, Hamosh P, Mehta NR. 1983. Comparison of the lipid composition of breast milk from mothers of term and preterm infants. *Am J Clin Nutr* 38:300–312.

Bjerve KS. 1989. *n*-3 Fatty acid deficiency in man. *J Intern Med* 225:171–175.

Bjerve KS, Mostad IL, Thoresen L. 1987a. Alpha-linolenic acid deficiency in patients on long-term gastric-tube feeding: Estimation of linolenic acid and long-chain unsaturated *n*-3 fatty acid requirement in man. *Am J Clin Nutr* 45:66–77.

Bjerve KS, Thoresen L, Mostad IL, Alme K. 1987b. Alpha-linolenic acid deficiency in man: Effect of essential fatty acids on fatty acid composition. *Adv Prostaglandin Thromboxane Leukot Res* 17:862–865.

Bjerve KS, Thoresen L, Børsting S. 1988. Linseed and cod liver oil induce rapid growth in a 7-year-old girl with *n*-3 fatty acid deficiency. *J Parenter Enteral Nutr* 12:521–525.

Bjerve KS, Fischer S, Wammer F, Egeland T. 1989. α-Linolenic acid and long-chain ω-3 fatty acid supplementation in three patients with ω-3 fatty acid deficiency: Effect on lymphocyte function, plasma and red cell lipids, and prostanoid formation. *Am J Clin Nutr* 49:290–300.

Blok WL, Deslypere J-P, Demacker PNM, van der Ven-Jongekrijg J, Hectors MPC, van der Meer JWM, Katan MB. 1997. Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. *Eur J Clin Invest* 27:1003–1008.

Blonk MC, Bilo HJG, Nauta JJP, Popp-Snijders C, Mulder C, Donker AJM. 1990. Dose-response effects of fish-oil supplementation in healthy volunteers. *Am J Clin Nutr* 52:120–127.

Boissonneault GA, Johnston PV. 1983. Essential fatty acid deficiency, prostaglandin synthesis and humoral immunity in Lewis rats. *J Nutr* 113:1187–1194.

Bonanome A, Grundy SM. 1988. Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels. *N Engl J Med* 318:1244–1248.

Bonanome A, Grundy SM. 1989. Intestinal absorption of stearic acid after consumption of high fat meals in humans. *J Nutr* 119:1556–1560.

Boulton TJC, Magarey AM. 1995. Effects of differences in dietary fat on growth, energy and nutrient intake from infancy to eight years of age. *Acta Paediatr* 84:146–150.

Bourre J-M, Francois M, Youyou A, Dumont O, Piciotti M, Pascal G, Durand G. 1989. The effects of dietary α-linolenic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats. *J Nutr* 119:1880–1892.

Bourre J-M, Dumont O, Durand G. 1996. Does an increase in dietary linoleic acid modify tissue concentrations of cervonic acid and consequently alter alpha-linolenic requirements? Minimal requirement of linoleic acid in adult rats. *Biochem Mol Biol Int* 39:607–619.

Brauer PM, Slavin JL, Marlett JA. 1981. Apparent digestibility of neutral detergent fiber in elderly and young adults. *Am J Clin Nutr* 34:1061–1070.

Brenner RR. 1974. The oxidative desaturation of unsaturated fatty acids in animals. *Mol Cell Biochem* 3:41–52.

Brossard N, Croset M, Pachiaudi C, Riou JP, Tayot JL, Lagarde M. 1996. Retroconversion and metabolism of [^{13}C]22:6*n*-3 in humans and rats after intake of a single dose of [^{13}C]22:6*n*-3-triacylglycerols. *Am J Clin Nutr* 64:577–586.

Bruckner G, Shimp J, Goswami S, Mai J, Kinsella JE. 1982. Dietary trilinoelaidate: Effects on metabolic parameters related to EFA metabolism in rats. *J Nutr* 112:126–135.

Bunker CH, Ukoli FA, Okoro FI, Olomu AB, Kriska AM, Huston SL, Markovic N, Kuller LH. 1996. Correlates of serum lipids in a lean black population. *Atherosclerosis* 123:215–225.

Burr GO, Burr MM. 1929. A new deficiency disease produced by the rigid exclusion of fat from the diet. *J Biol Chem* 82:345–367.

Butte NF. 2000. Fat intake of children in relation to energy requirements. *Am J Clin Nutr* 72:1246S–1252S.

Butte NF, Garza C, Smith EO, Nichols BL. 1984. Human milk intake and growth in exclusively breast-fed infants. *J Pediatr* 104:187–195.

Byard RW, Makrides M, Need M, Neumann MA, Gibson RA. 1995. Sudden infant death syndrome: Effect of breast and formula feeding on frontal cortex and brainstem lipid composition. *J Paediatr Child Health* 31:14–16.

Calles-Escandon J, Goran MI, O'Connell M, Nair KS, Danforth E. 1996. Exercise increases fat oxidation at rest unrelated to changes in energy balance or lipolysis. *Am J Physiol* 270:E1009–E1014.

Carlson SE, Rhodes PG, Ferguson MG. 1986. Docosahexaenoic acid status of preterm infants at birth and following feeding with human milk or formula. *Am J Clin Nutr* 44:798–804.

Carlson SE, Cooke RJ, Werkman SH, Tolley EA. 1992. First year growth of preterm infants fed standard compared to marine oil *n*-3 supplemented formula. *Lipids* 27:901–907.

Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. 1993. Arachidonic acid status correlates with first year growth in preterm infants. *Proc Natl Acad Sci USA* 90:1073–1077.

Carlson SE, Ford AJ, Werkman SH, Peeples JM, Koo WWK. 1996a. Visual acuity and fatty acid status of term infants fed human milk and formulas with and without docosahexaenoate and arachidonate from egg yolk lecithin. *Pediatr Res* 39:882–888.

Carlson SE, Werkman SH, Tolley EA. 1996b. Effect of long-chain *n*-3 fatty acid supplementation on visual acuity and growth of preterm infants with and without bronchopulmonary dysplasia. *Am J Clin Nutr* 63:687–697.

Carnielli VP, Luijendijk IHT, Van Goudoever JB, Sulkers EJ, Boerlage AA, Degenhart HJ, Sauer PJJ. 1996a. Structural position and amount of palmitic acid in infant formulas: Effects on fat, fatty acid, and mineral balance. *J Pediatr Gastroenterol Nutr* 23:553–560.

Carnielli VP, Wattimena DJL, Luijendijk IHT, Boerlage A, Degenhart HJ, Sauer PJJ. 1996b. The very low birth weight premature infant is capable of synthesizing arachidonic and docosahexaenoic acids from linoleic and linolenic acids. *Pediatr Res* 40:169–174.

Castuma JC, Brenner RR, Kunau W. 1977. Specificity of Δ6 desaturase—Effect of chain length and number of double bonds. *Adv Exp Med Biol* 83:127–134.

Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. 1996. The effect on human tumor necrosis factor α and interleukin 1β production of diets enriched in *n*-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr* 63:116–122.

CDC (Centers for Disease Control and Prevention). 1994. Daily dietary fat and total food-energy intakes—Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. *Morb Mortal Wkly Rep* 43:116–117, 123–125.

Chambaz J, Ravel D, Manier M-C, Pepin D, Mulliez N, Bereziat G. 1985. Essential fatty acids interconversion in the human fetal liver. *Biol Neonate* 47:136–140.

Chang HR, Dulloo AG, Vladoianu IR, Piguet PF, Arsenijevic D, Girardier L, Pechère JC. 1992. Fish oil decreases natural resistance of mice to infection with *Salmonella typhimurium*. *Metabolism* 41:1–2.

Chappell JE, Clandinin MT, Kearney-Volpe C. 1985. Trans fatty acids in human milk lipids: Influence of maternal diet and weight loss. *Am J Clin Nutr* 42:49–56.

Chen Q, Nilsson Å. 1993. Desaturation and chain elongation of *n*-3 and *n*-6 polyunsaturated fatty acids in the human CaCo-2 cell line. *Biochim Biophys Acta* 1166:193–201.

Chen ZY, Pelletier G, Hollywood R, Ratnayake WMN. 1995a. *Trans* fatty acid isomers in Canadian human milk. *Lipids* 30:15–21.

Chen ZY, Ratnayake WMN, Fortier L, Ross R, Cunnane SC. 1995b. Similar distribution of *trans* fatty acid isomers in partially hydrogenated vegetable oils and adipose tissue of Canadians. *Can J Physiol Pharmacol* 73:718–723.

Chin SF, Liu W, Storkson JM, Ha YL, Pariza MW. 1992. Dietary sources of conjugated dienoic isomers of linoleic acid, a newly recognized class of anticarcinogens. *J Food Comp Anal* 5:185–197.

Chin SF, Storkson JM, Liu W, Albright KJ, Pariza MW. 1994. Conjugated linoleic acid (9,11- and 10,12-octadecadienoic acid) is produced in conventional but not germ-free rats fed linoleic acid. *J Nutr* 124:694–701.

Chisholm A, Mann J, Sutherland W, Duncan A, Skeaff M, Frampton C. 1996. Effect on lipoprotein profile of replacing butter with margarine in a low fat diet: Randomised crossover study with hypercholesterolaemic subjects. *Br Med J* 312:931–934.

Cho HP, Nakamura MT, Clarke SD. 1999. Cloning, expression, and nutritional requirements of the mammalian Δ-6 desaturase. *J Biol Chem* 274:471–477.

Clark KJ, Makrides M, Neumann MA, Gibson RA. 1992. Determination of the optimal ratio of linoleic acid to α-linolenic acid in infant formulas. *J Pediatr* 120:S151–S158.

Clarke JTR, Cullen-Dean G, Regelink E, Chan L, Rose V. 1990. Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. *J Pediatr* 116:139–141.

Clarke R, Frost C, Collins R, Appleby P, Peto R. 1997. Dietary lipids and blood cholesterol: Quantitative meta-analysis of metabolic ward studies. *Br Med J* 314:112–117.

Clouet P, Niot I, Bézard J. 1989. Pathway of α-linolenic acid through the mitochondrial outer membrane in the rat liver and influence on the rate of oxidation. Comparison with linoleic and oleic acids. *Biochem J* 263:867–873.

Cobiac L, Clifton PM, Abbey M, Belling GB, Nestel PJ. 1991. Lipid, lipoprotein, and hemostatic effects of fish vs. fish-oil *n*-3 fatty acids in mildly hyperlipidemic males. *Am J Clin Nutr* 53:1210–1216.

Cohen SA, Hendricks KM, Eastham EJ, Mathis RK, Walker WA. 1979. Chronic nonspecific diarrhea. A complication of dietary fat restriction. *Am J Dis Child* 133:490–492.

Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. 1992. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023.

Collins FD, Sinclair AJ, Royle JP, Coats DA, Maynard AT, Leonard RF. 1971. Plasma lipids in human linoleic acid deficiency. *Nutr Metab* 13:150–167.

Connor WE, Lowensohn R, Hatcher L. 1996. Increased docosahexaenoic acid levels in human newborn infants by administration of sardines and fish oil during pregnancy. *Lipids* 31:S183–S187.

Conquer JA, Holub BJ. 1996. Supplementation with an algae source of docosahexaenoic acid increases (*n*-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. *J Nutr* 126:3032–3039.

Conti S, Farchi G, Menotti A. 1983. Coronary risk factors and excess mortality from all causes and specific causes. *Int J Epidemiol* 12:301–307.

Cook HW. 1981. The influence of *trans*-acids on desaturation and elongation of fatty acids in developing brain. *Lipids* 16:920–926.

Cooling J, Blundell J. 1998. Differences in energy expenditure and substrate oxidation between habitual high fat and low fat consumers (phenotypes). *Int J Obes Relat Metab* 22:612–618.

Cooper AL, Gibbons L, Horan MA, Little RA, Rothwell NJ. 1993. Effect of dietary fish oil supplementation on fever and cytokine production in human volunteers. *Clin Nutr* 12:321–328.

Corazza GR, Frazzoni M, Gatto MR, Gasbarrini G. 1986. Ageing and small-bowel mucosa: A morphometric study. *Gerontology* 32:60–65.

Corti MC, Guralnik JM, Salive ME, Harris T, Ferrucci L, Glynn RJ, Havlik RJ. 1997. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Ann Intern Med* 126:753–760.

Costa MB, Ferreira SRG, Franco LJ, Gimeno SGA, Iunes M, Japanese-Brazilian Diabetes Study Group. 2000. Dietary patterns in a high-risk population for glucose intolerance. *J Epidemiol* 10:111–117.

Craig-Schmidt MC. 2001. Isomeric fatty acids: Evaluating status and implications for maternal and child health. *Lipids* 36:997–1006.

Cuchel M, Schwab US, Jones PJH, Vogel S, Lammi-Keefe C, Li Z, Ordovas J, McNamara JR, Schaefer EJ, Lichtenstein AH. 1996. Impact of hydrogenated fat consumption on endogenous cholesterol synthesis and susceptibility of low-density lipoprotein to oxidation in moderately hypercholesterolemic individuals. *Metabolism* 45:241–247.

Cunnane SC, Ross R, Bannister JL, Jenkins DJA. 2001. β-Oxidation of linoleate in obese men undergoing weight loss. *Am J Clin Nutr* 73:709–714.

Cuthbertson WFJ. 1976. Essential fatty acid requirements in infancy. *Am J Clin Nutr* 29:559–568.

De Caterina R, Giannessi D, Mazzone A, Berini W, Lazzerini G, Maffei S, Cerri M, Salvatore L, Weksler B. 1990. Vascular prostacyclin is increased in patients ingesting ω-3 polyunsaturated fatty acids before coronary artery bypass graft surgery. *Circulation* 82:428–438.

Decsi T, Koletzko B. 1995. Do trans fatty acids impair linoleic acid metabolism in children? *Ann Nutr Metab* 39:36–41.

de la Presa Owens S, Innis SM. 1999. Docosahexaenoic and arachidonic acid prevent a decrease in dopaminergic and serotoninergic neurotransmitters in frontal cortex caused by a linoleic and α-linolenic acid deficient diet in formula-fed piglets. *J Nutr* 129:2088–2093.

Denke MA. 1994. Effects of cocoa butter on serum lipids in humans: Historical highlights. *Am J Clin Nutr* 60:1014S–1016S.

Denke MA. 1995. Serum lipid concentrations in humans. *Am J Clin Nutr* 62:693S–700S.

De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Carzoglio JC, Ronco A. 1997. Dietary fat and lung cancer: A case-control study in Uruguay. *Cancer Causes Control* 8:913–921.

Dewey KG, Lönnerdal B. 1983. Milk and nutrient intake of breast-fed infants from 1 to 6 months: Relation to growth and fatness. *J Pediatr Gastroenterol Nutr* 2:497–506.

Dewey KG, Finley DA, Lönnerdal B. 1984. Breast milk volume and composition during late lactation. *J Pediatr Gastroenterol Nutr* 3:713–720.

Dolecek TA, Grandits G. 1991. Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *World Rev Nutr Diet* 66:205–216.

Doucet E, Alméras N, White MD, Després J-P, Bouchard C, Tremblay A. 1998. Dietary fat composition and human adiposity. *Eur J Clin Nutr* 52:2–6.

Dyerberg J, Bang HO. 1979. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. *Lancet* 2:433–435.

Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. 1978. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? *Lancet* 2:117–119.

Eisenstein AB. 1982. Nutritional and metabolic effects of alcohol. *J Am Diet Assoc* 81:247–251.

Elias SL, Innis SM. 2001. Infant plasma *trans*, *n*-6, and *n*-3 fatty acids and conjugated linoleic acids are related to maternal plasma fatty acids, length of gestation, and birth weight and length. *Am J Clin Nutr* 73:807–814.

Elias SL, Innis SM. 2002. Bakery foods are the major dietary source of *trans*-fatty acids among pregnant women with diets providing 30 percent energy from fat. *J Am Diet Assoc* 102:46–51.

Emken EA. 1979. Utilization and effects of isomeric fatty acids in humans. In: Emken EA, Dutton HJ, eds. *Geometrical and Positional Fatty Acid Isomers.* Champaign, IL: American Oil Chemists' Society. Pp. 99–129.

Emken EA. 1984. Nutrition and biochemistry of *trans* and positional fatty acid isomers in hydrogenated oils. *Annu Rev Nutr* 4:339–376.

Emken EA. 1994. Metabolism of dietary stearic acid relative to other fatty acids in human subjects. *Am J Clin Nutr* 60:1023S–1028S.

Emken EA. 1995. Physiochemical properties, intake, and metabolism. *Am J Clin Nutr* 62:659S–669S.

Emken EA, Adlof RO, Gulley RM. 1994. Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. *Biochim Biophys Acta* 1213:277–288.

Emken EA, Adlof RO, Duval SM, Nelson GJ. 1998. Effect of dietary arachidonic acid on metabolism of deuterated linoleic acid by adult male subjects. *Lipids* 33:471–480.

Emken EA, Adlof RO, Duval SM, Nelson GJ. 1999. Effect of dietary docosahexaenoic acid on desaturation and uptake *in vivo* of isotope-labeled oleic, linoleic, and linolenic acids by male subjects. *Lipids* 34:785–791.

Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JWM, Cannon JG, Rogers TS, Klempner MS, Weber PC, Schaefer EJ, Wolff SM, Dinarello CA. 1989. The effect of dietary supplementation with *n*-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* 320:265–271.

Endres S, Meydani SN, Ghorbani R, Schindler R, Dinarello CA. 1993. Dietary supplementation with *n*-3 fatty acids suppresses interleukin-2 production and mononuclear cell proliferation. *J Leukoc Biol* 54:599–603.

Enig MG, Atal S, Keeney M, Sampugna J. 1990. Isomeric *trans* fatty acids in the U.S. diet. *J Am Coll Nutr* 5:471–486.

Ens JG, Ma DW, Cole KS, Field CJ, Clandinin MT. 2001. An assessment of *c*9,*t*11 linoleic acid intake in a small group of young Canadians. *Nutr Res* 21:955–960.

Ezaki O, Takahashi M, Shigematsu T, Shimamura K, Kimura J, Ezaki H, Gotoh T. 1999. Long-term effects of dietary α-linolenic acid from perilla oil on serum fatty acids composition and on the risk factors of coronary heart disease in Japanese elderly subjects. *J Nutr Sci Vitaminol* 45:759–772.

Falase AO, Cole TO, Osuntokun BO. 1973. Myocardial infarction in Nigerians. *Trop Geogr Med* 25:147–150.

FAO/WHO (Food and Agricultural Organization/World Health Organization). 1994. General conclusions and recommendations of the consultation. In: *Fats and Oils in Human Nutrition.* Rome: FAO. Pp. 3–7.

Farquharson J. 1994. Infant cerebral cortex and dietary fatty acids. *Eur J Clin Nutr* 48:S24–S26.

Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. 1992. Infant cerebral cortex phospholipid fatty-acid composition and diet. *Lancet* 340:810–813.

Farquharson J, Jamieson EC, Abbasi KA, Patrick WJA, Logan RW, Cockburn F. 1995. Effect of diet on the fatty acid composition of the major phospholipids of infant cerebral cortex. *Arch Dis Child* 72:198–203.

Fasching P, Ratheiser K, Schneeweiss B, Rohac M, Nowotny P, Waldhausl W. 1996. No effect of short-term dietary supplementation of saturated and poly- and monounsaturated fatty acids on insulin secretion and sensitivity in healthy men. *Ann Nutr Metab* 40:116–122.

Fellner V, Sauer FD, Kramer JKG. 1999. Effect of ionophores on conjugated linoleic acid in ruminal cultures and in the milk of dairy cows. In: Yurawecz MP, Mossoba MM, Kramer JKG, Pariza MW, Nelson GJ, eds. *Advances in Conjugated Linoleic Acid Research,* Vol. 1. Champaign, IL: AOCS Press. Pp. 209–214.

Ferris AM, Dotts MA, Clark RM, Ezrin M, Jensen RG. 1988. Macronutrients in human milk at 2, 12, and 16 weeks postpartum. *J Am Diet Assoc* 88:694–697.

Feskens EJM, Virtanen SM, Räsänen L, Tuomilehto J, Stengard J, Pekkanen J, Nissinen A, Kromhout D. 1995. Dietary factors determining diabetes and impaired glucose tolerance: A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes Care* 18:1104–1112.

Finley DA, Lönnerdal B, Dewey KG, Grivetti LE. 1985. Breast milk composition: Fat content and fatty acid composition in vegetarians and non-vegetarians. *Am J Clin Nutr* 41:787–800.

Fischer DR, Morgan KJ, Zabik ME. 1985. Cholesterol, saturated fatty acids, polyunsaturated fatty acids, sodium, and potassium intakes of the United States population. *J Am Coll Nutr* 4:207–224.

Fleming CR, Smith LM, Hodges RE. 1976. Essential fatty acid deficiency in adults receiving total parenteral nutrition. *Am J Clin Nutr* 29:976–983.

Fomon SJ, Thomas LN, Filer LJ, Anderson TA, Nelson SE. 1976. Influence of fat and carbohydrate content of diet on food intake and growth of male infants. *Acta Paediatr Scand* 65:136–144.

Frank JW, Reed DM, Grove JS, Benfante R. 1992. Will lowering population levels of serum cholesterol affect total mortality? Expectations from the Honolulu Heart Program. *J Clin Epidemiol* 45:333–346.

Freese R, Mutanen M. 1997. α-Linolenic acid and marine long-chain *n*-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. *Am J Clin Nutr* 66:591–598.

Friday KE, Childs MT, Tsunehara CH, Fujimoto WY, Bierman EL, Ensinck JW. 1989. Elevated plasma glucose and lowered triglyceride levels from omega-3 fatty acid supplementation in type II diabetes. *Diabetes Care* 12:276–281.

Fritsche KL, Shahbazian LM, Feng C, Berg JN. 1997. Dietary fish oil reduces survival and impairs bacterial clearance in C3H/Hen mice challenged with *Listeria monocytogenes*. *Clin Sci* 92:95–101.

Gallai V, Sarchielli P, Trequattrini A, Franceschini M, Floridi A, Firenze C, Alberti A, Di Benedetto D, Stragliotto E. 1995. Cytokine secretion and eicosanoid production in the peripheral blood mononuclear cells of MS patients undergoing dietary supplementation with *n*-3 polyunsaturated fatty acids. *J Neuroimmunol* 56:143–153.

Ganji V, Betts N. 1995. Fat, cholesterol, fiber and sodium intakes of US population: Evaluation of diets reported in 1987–88 Nationwide Food Consumption Survey. *Eur J Clin Nutr* 49:915–920.

Garland M, Sacks FM, Colditz GA, Rimm EB, Sampson LA, Willett WC, Hunter DJ. 1998. The relation between dietary intake and adipose tissue composition of selected fatty acids in US women. *Am J Clin Nutr* 67:25–30.

Gazzaniga JM, Burns TL. 1993. Relationship between diet composition and body fatness, with adjustment for resting energy expenditure and physical activity, in preadolescent children. *Am J Clin Nutr* 58:21–28.

Ghebremeskel K, Min Y, Crawford MA, Nam J-H, Kim A, Koo J-N, Suzuki H. 2000. Blood fatty acid composition of pregnant and nonpregnant Korean women: Red cells may act as a reservoir of arachidonic acid and docosahexaenoic acid for utilization by the developing fetus. *Lipids* 35:567–574.

Gibson RA, Kneebone GM. 1981. Fatty acid composition of human colostrum and mature breast milk. *Am J Clin Nutr* 34:252–257.

Gibson RA, Neumann MA, Makrides M. 1997. Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. *Eur J Clin Nutr* 51:578–584.

Gillman MW, Cupples LA, Gagnon D, Millen BE, Ellison RC, Castelli WP. 1997. Margarine intake and subsequent coronary heart disease in men. *Epidemiology* 8:144–149.

Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. 1993. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 85:1571–1579.

Glauber H, Wallace P, Griver K, Brechtel G. 1988. Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 108:663–668.

Goedecke JH, Christie C, Wilson G, Dennis SC, Noakes TD, Hopkins WG, Lambert EV. 1999. Metabolic adaptations to a high-fat diet in endurance cyclists. *Metabolism* 48:1509–1517.

Goldbourt U, Yaari S, Medalie JH. 1993. Factors predictive of long-term coronary heart disease mortality among 10,059 male Israeli civil servants and municipal employees. A 23-year mortality follow-up in the Israeli Ischemic Heart Disease Study. *Cardiology* 82:100–121.

González CA, Pera G, Quirós JR, Lasheras C, Tormo MJ, Rodriguez M, Navarro C, Martinez C, Dorronsoro M, Chirlaque MD, Beguiristain JM, Barricarte A, Amiano P, Agudo A. 2000. Types of fat intake and body mass index in a Mediterranean country. *Public Health Nutr* 3:329–336.

Goodgame JT, Lowry SF, Brennan MF. 1978. Essential fatty acid deficiency in total parenteral nutrition: Time course of development and suggestions for therapy. *Surgery* 84:271–277.

Goodnight SH, Harris WS, Connor WE. 1981. The effects of dietary ω3 fatty acids on platelet composition and function in man: A prospective, controlled study. *Blood* 58:880–885.

Gore SM. 1999. Statistical considerations in infant nutrition trials. *Lipids* 34:185–197.

Greiner RCS, Winter J, Nathanielsz PW, Brenna JT. 1997. Brain docosahexaenoate accretion in fetal baboons: Bioequivalence of dietary α-linolenic and docosahexaenoic acids. *Pediatr Res* 42:826–834.

Griinari JM, Bauman DE. 1999. Biosynthesis of conjugated linoleic acid and its incorporation into meat and milk ruminants. In: Yurawecz MP, Mossoba MM, Kramer JKG, Pariza MW, Nelson GJ, eds. *Advances in Conjugated Linoleic Acid Research,* Vol. 1. Champaign, IL: AOCS Press. Pp. 180–200.

Griinari JM, Corl BA, Lacy SH, Chouinard PY, Nurmela KVV, Bauman DE. 2000. Conjugated linoleic acid is synthesized endogenously in lactating cows by Δ^9-desaturase. *J Nutr* 130:2285–2291.

Ha YL, Grimm NK, Pariza MW. 1989. Newly recognized anticarcinogenic fatty acids: Identification and quantification in natural and processed cheeses. *J Agric Food Chem* 37:75–81.

Haheim LL, Holme I, Hjermann I, Leren P. 1993. The predictability of risk factors with respect to incidence and mortality of myocardial infarction and total mortality. A 12-year follow-up of the Oslo Study, Norway. *J Intern Med* 234:17–24.

Halvorsen B, Almendingen K, Nenseter MS, Pedersen JI, Christiansen EN. 1996. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil and butter on the susceptibility of low density lipoprotein to oxidative modification in men. *Eur J Clin Nutr* 50:364–370.

Hansen AE, Haggard ME, Boelsche AN, Adam DJD, Wiese HF. 1958. Essential fatty acids in infant nutrition. III. Clinical manifestations of linoleic acid deficiency. *J Nutr* 66:565–576.

Hansen AE, Wiese HF, Boelsche AN, Haggard ME, Adam DJD, Davis H. 1963. Role of linoleic acid in infant nutrition. Clinical and chemical study of 428 infants fed on milk mixtures varying in kind and amount of fat. *Pediatrics* 31:171–192.

Hansen HS, Jensen B. 1985. Essential function of linoleic acid esterified in acylglucosylceramide and acylceramide in maintaining the epidermal water permeability barrier. Evidence from feeding studies with oleate, linoleate, arachidonate, columbinate and α-linolenate. *Biochim Biophys Acta* 834:357–363.

Harris WS, Connor WE, Lindsey S. 1984. Will dietary ω-3 fatty acids change the composition of human milk? *Am J Clin Nutr* 40:780–785.

Hegsted DM, McGandy RB, Myers ML, Stare FJ. 1965. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr* 17:281–295.

Hegsted DM, Ausman LM, Johnson JA, Dallal GE. 1993. Dietary fat and serum lipids: An evaluation of the experimental data. *Am J Clin Nutr* 57:875–883.

Heitmann BL, Lissner L, Sørensen TIA, Bengtsson C. 1995. Dietary fat intake and weight gain in women genetically predisposed for obesity. *Am J Clin Nutr* 61:1213–1217.

Helge JW. 2000. Adaptation to a fat-rich diet. Effects on endurance performance in humans. *Sports Med* 30:347–357.

Henderson RA, Jensen RG, Lammi-Keefe CJ, Ferris AM, Dardick KR. 1992. Effect of fish oil on the fatty acid composition of human milk and maternal and infant erythrocytes. *Lipids* 27:863–869.

Hill JO, Schlundt DG, Sbrocco T, Sharp T, Pope-Cordle J, Stetson B, Kaler M, Heim C. 1989. Evaluation of an alternating-calorie diet with and without exercise in the treatment of obesity. *Am J Clin Nutr* 50:248–254.

Hill JO, Peters JC, Reed GW, Schlundt DG, Sharp T, Greene HL. 1991. Nutrient balance in humans: Effects of diet composition. *Am J Clin Nutr* 54:10–17.

Holman RT. 1960. The ratio of trienoic:tetraenoic acids in tissue lipids as a measure of essential fatty acid requirement. *J Nutr* 70:405–410.

Holman RT, Smythe L, Johnson S. 1979. Effect of sex and age on fatty acid composition of human serum lipids. *Am J Clin Nutr* 32:2390–2399.

Holman RT, Johnson SB, Hatch TF. 1982. A case of human linolenic acid deficiency involving neurological abnormalities. *Am J Clin Nutr* 35:617–623.

Holman RT, Johnson SB, Ogburn PL. 1991. Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation. *Proc Natl Acad Sci USA* 88:4835–4839.

Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, Hankinson SE, Speizer FE, Rosner B, Willett WC. 1999. Association of dietary intake of fat and fatty acids with risk of breast cancer. *J Am Med Assoc* 281:914–920.

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. 1997. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 337:1491–1499.

Hu FB, Stampfer MJ, Manson JE, Ascherio A, Colditz GA, Speizer FE, Hennekens CH, Willett WC. 1999a. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *Am J Clin Nutr* 70:1001–1008.

Hu FB, Stampfer MJ, Manson JE, Rimm EB, Wolk A, Colditz GA, Hennekens CH, Willett WC. 1999b. Dietary intake of α-linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr* 69:890–897.

Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. 1999c. Dietary fat and coronary heart disease: A comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* 149:531–540.

Hu FB, van Dam RM, Liu S. 2001. Diet and risk of type II diabetes: The role of types of fat and carbohydrate. *Diabetologia* 44:805–817.

Hudgins LC, Hirsch J, Emken EA. 1991. Correlation of isomeric fatty acids in human adipose tissue with clinical risk factors for cardiovascular disease. *Am J Clin Nutr* 53:474–482.

Hughes DA, Pinder AC, Piper Z, Johnson IT, Lund EK. 1996. Fish oil supplementation inhibits the expression of major histocompatibility complex class II molecules and adhesion molecules on human monocytes. *Am J Clin Nutr* 63:267–272.

Hursting SD, Thornquist M, Henderson MM. 1990. Types of dietary fat and the incidence of cancer at five sites. *Prev Med* 19:242–253.

Hwang DH, Chanmugam P, Anding R. 1982. Effects of dietary 9-*trans*,12-*trans* linoleate on arachidonic acid metabolism in rat platelets. *Lipids* 17:307–313.

Innis SM. 1991. Essential fatty acids in growth and development. *Prog Lipid Res* 30:39–103.

Innis SM, King DJ. 1999. *Trans* fatty acids in human milk are inversely associated with concentrations of essential *all-cis n*-6 and *n*-3 fatty acids and determine *trans*, but not *n*-6 and *n*-3, fatty acids in plasma lipids of breast-fed infants. *Am J Clin Nutr* 70:383–390.

Innis SM, Kuhnlein HV. 1988. Long-chain *n*-3 fatty acids in breast milk of Inuit women consuming traditional foods. *Early Hum Dev* 18:185–189.

Innis SM, Auestad N, Siegman JS. 1996. Blood lipid docosahexaenoic and arachidonic acid in term gestation infants fed formulas with high docosahexaenoic acid, low eicosapentaenoic acid fish oil. *Lipids* 31:617–625.

Innis SM, Green TJ, Halsey TK. 1999. Variability in the *trans* fatty acid content of foods within a food category: Implications for estimation of dietary trans fatty acid intakes. *J Am Coll Nutr* 18:255–260.

Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Hennekens CH, Willett WC. 2001. Intake of fish and omega-3 fatty acids and risk of stroke in women. *J Am Med Assoc* 285:304–312.

ISSFAL (International Society for the Study of Fatty Acids and Lipids). 1994. *Recommendations for the Essential Fatty Acid Requirement for Infant Formulas.* Online. Available at http://www.issfal.org.uk/infantnutr.htm. Accessed July 2, 2001.

Jamieson EC, Abbasi KA, Cockburn F, Farquharson J, Logan RW, Patrick WA. 1994. Effect of diet on term infant cerebral cortex fatty acid composition. *World Rev Nutr Diet* 75:139–141.

Jamieson EC, Farquharson J, Logan RW, Howatson AG, Patrick WJA, Weaver LT, Cockburn F. 1999. Infant cerebral gray and white matter fatty acids in relation to age and diet. *Lipids* 34:1065–1071.

Jensen C, Buist NRM, Wilson T. 1986. Absorption of individual fatty acids from long chain or medium chain triglycerides in very small infants. *Am J Clin Nutr* 43:745–751.

Jensen CL, Prager TC, Fraley JK, Chen H, Anderson RE, Heird WC. 1997. Effect of dietary linoleic/alpha-linolenic acid ratio on growth and visual function of term infants. *J Pediatr* 131:200–209.

Jensen RG. 1999. Lipids in human milk. *Lipids* 34:1243–1271.

Jeppesen PB, Høy C-E, Mortensen PB. 1998. Essential fatty acid deficiency in patients receiving home parenteral nutrition. *Am J Clin Nutr* 68:126–133.

Jeppesen PB, Hoy CE, Mortensen PB. 2000. Deficiencies of essential fatty acids, vitamin A and E and changes in plasma lipoproteins in patients with reduced fat absorption or intestinal failure. *Eur J Clin Nutr* 54:632–642.

Jéquier E. 1999. Response to and range of acceptable fat intake in adults. *Eur J Clin Nutr* 53:S84–S93.

Jones PJH, Kubow S. 1999. Lipids, sterols, and their metabolites. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease,* 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 67–94.

Jones PJH, Pencharz PB, Clandinin MT. 1985. Whole body oxidation of dietary fatty acids: Implications for energy utilization. *Am J Clin Nutr* 42:769–777.

Jonnalagadda SS, Egan SK, Heimbach JT, Harris SS, Kris-Etherton PM. 1995. Fatty acid consumption pattern of Americans: 1987–1988 USDA Nationwide Food Consumption Survey. *Nutr Res* 15:1767–1781.

Jørgensen MG, Hølmer G, Lund P, Hernell O, Michaelsen KM. 1998. Effect of formula supplemented with docosahexaenoic acid and γ-linolenic acid on fatty acid status and visual acuity in term infants. *J Pediatr Gastroenterol Nutr* 26:412–421.

Jousilahti P, Vartiainen E, Pekkanen J, Tuomilehto J, Sundvall J, Puska P. 1998. Serum cholesterol distribution and coronary heart disease risk. Observations and predictions among middle-aged population in eastern Finland. *Circulation* 97:1087–1094.

Judd JT, Clevidence BA, Muesing RA, Wittes J, Sunkin ME, Podczasy JJ. 1994. Dietary *trans* fatty acids: Effects on plasma lipids and lipoproteins of healthy men and women. *Am J Clin Nutr* 59:861–868.

Judd JT, Baer DJ, Clevidence BA, Muesing RA, Chen SC, Weststrate JA, Meijer GW, Wittes J, Lichtenstein AH, Vilella-Bach M, Schaefer EJ. 1998. Effects of margarine compared with those of butter on blood lipid profiles related to cardiovascular disease risk factors in normolipemic adults fed controlled diets. *Am J Clin Nutr* 68:768–777.

Judd JT, Baer DJ, Clevidence BA, Kris-Etherton P, Muesing RA, Iwane M. 2002. Dietary *cis* and *trans* monounsaturated and saturated FA and plasma lipids and lipoproteins in men. *Lipids* 37:123–131.

Jump DB, Clarke SD. 1999. Regulation of gene expression by dietary fat. *Annu Rev Nutr* 19:63–90.

Kagan A, McGee DL, Yano K, Rhoads GG, Nomura A. 1981. Serum cholesterol and mortality in a Japanese-American population: The Honolulu Heart Program. *Am J Epidemiol* 114:11–20.

Kasim SE, Stern B, Khilnani S, McLin P, Baciorowski S, Jen K-LC. 1988. Effects of omega-3 fish oils on lipid metabolism, glycemic control, and blood pressure in type II diabetic patients. *J Clin Endocrinol Metab* 67:1–5.

Kelley DS, Branch LB, Love JE, Taylor PC, Rivera YM, Iacono JM. 1991. Dietary αlinolenic acid and immunocompetence in humans. *Am J Clin Nutr* 53:40–46.

Kelley DS, Taylor PC, Nelson GJ, Mackey BE. 1998. Dietary docosahexaenoic acid and immunocompetence in young healthy men. *Lipids* 33:559–566.

Kelley DS, Taylor PC, Nelson GJ, Schmidt PC, Ferretti A, Erickson KL, Yu R, Chandra RK, Mackey BE. 1999. Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men. *Lipids* 34:317–324.

Kelly FD, Sinclair AJ, Mann NJ, Turner AH, Abedin L, Li D. 2001. A stearic acid-rich diet improves thrombogenic and atherogenic risk factor profiles in healthy males. *Eur J Clin Nutr* 55:88–96.

Keys A, Anderson JT, Grande F. 1965. Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet. *Metabolism* 14:776–787.

Keys A, Aravanis C, Blackburn H, Buzina R, Djordevic´ BS, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, Menotti A, Mohacˇek I, Nedeljkovic´ S, Puddu V, Punsar S, Taylor HL, van Buchem FSP. 1980. *Seven Countries. A Multivariate Analysis of Death and Coronary Heart Disease.* Cambridge, MA: Harvard University Press.

Kinsella JE, Lokesh B, Stone RA. 1990. Dietary *n*-3 polyunsaturated fatty acids and amelioration of cardiovascular disease: Possible mechanisms. *Am J Clin Nutr* 52:1–28.

Klag MJ, Ford DE, Mead LA, He J, Whelton PK, Liang KY, Levine DM. 1993. Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med* 328:313–318.

Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, Lehmann JM. 1997. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ. *Proc Natl Acad USA* 94:4318–4323.

Kneebone GM, Kneebone R, Gibson R. 1985. Fatty acid composition of breast milk from three racial groups from Penang, Malaysia. *Am J Clin Nutr* 41:765–769.

Kohlmeier L, Simonsen N, van't Veer P, Strain JJ, Martin-Moreno JM, Margolin B, Huttunen JK, Fernández-Crehuet Navajas J, Martin BC, Thamm M, Kardinaal AFM, Kok FJ. 1997. Adipose tissue *trans* fatty acids and breast cancer in the European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer. *Cancer Epidemiol Biomarkers Prev* 6:705–710.

Koletzko B. 1992. *Trans* fatty acids may impair biosynthesis of long-chain polyunsaturates and growth in man. *Acta Paediatr* 81:302–306.

Kris-Etherton PM, Derr J, Mitchell DC, Mustad VA, Russell ME, McDonnell ET, Salabsky D, Pearson TA. 1993. The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: I. Effects of whole food diets high in cocoa butter, olive oil, soybean oil, dairy butter, and milk chocolate on the plasma lipids of young men. *Metabolism* 42:121–129.

Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, Hargrove RL, Zhao G, Etherton TD. 2000. Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr* 71:179S–188S.

Kristensen MØ. 1983. Increased incidence of bleeding intracranial aneurysms in Greenlandic Eskimos. *Acta Neurochir* 67:37–43.

Kritchevsky D. 1982. Trans fatty acid effects in experimental atherosclerosis. *Fed Proc* 41:2813–2817.

Kritchevsky D, Tepper SA, Wright S, Tso P, Czarnecki SK. 2000. Influence of conjugated linoleic acid (CLA) on establishment and progression of atherosclerosis in rabbits. *J Am Coll Nutr* 19:472S–477S.

Kromann N, Green A. 1980. Epidemiological studies in the Upernavik district, Greenland. Incidence of some chronic diseases 1950–1974. *Acta Med Scand* 208:401–406.

Kromhout D, de Lezenne Coulander C. 1984. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men. *Am J Epidemiol* 119:733–741.

Kromhout D, Bosschieter EB, de Lezenne Coulander C. 1985. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 312:1205–1209.

Kromhout D, Menotti A, Bloemberg B, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Giampaoli S, Jansen A, Karvonen M, Katan M, Nissinen A, Nedeljkovic S, Pekkanen J, Pekkarinen M, Punsar S, Räsänen L, Simic B, Toshima H. 1995. Dietary saturated and *trans* fatty acids and cholesterol and 25-year mortality from coronary heart disease: The Seven Countries Study. *Prev Med* 24:308–315.

Lagström H, Seppänen R, Jokinen E, Niinikoski H, Rönnemaa T, Viikari J, Simell O. 1999. Influence of dietary fat on the nutrient intake and growth of children from 1 to 5 y of age: The Special Turku Coronary Risk Factor Intervention Project. *Am J Clin Nutr* 69:516–523.

Lands WEM, Hamazaki T, Yamazaki K, Okuyama H, Sakai K, Goto Y, Hubbard VS. 1990. Changing dietary patterns. *Am J Clin Nutr* 51:991–993.

Lands WEM, Libelt B, Morris A, Kramer NC, Prewitt TE, Bowen P, Schmeisser D, Davidson MH, Burns JH. 1992. Maintenance of lower proportions of (*n*-6) eicosanoid precursors in phospholipids of human plasma in response to added dietary (*n*-3) fatty acids. *Biochim Biophys Acta* 1180:147–162.

Lapinleimu H, Viikari J, Jokinen E, Salo P, Routi T, Leino A, Rönnemaa R, Seppänen R, Välimäki I, Simell O. 1995. Prospective randomised trial in 1062 infants of diet low in saturated fat and cholesterol. *Lancet* 345:471–476.

Larson DE, Hunter GR, Williams MJ, Kekes-Szabo T, Nyikos I, Goran MI. 1996. Dietary fat in relation to body fat and intraabdominal adipose tissue: A cross-sectional analysis. *Am J Clin Nutr* 64:677–684.

Latruffe N, Vamecq J. 1997. Peroxisome proliferators and peroxisome proliferator activated receptors (PPARs) as regulators of lipid metabolism. *Biochimie* 79:81–94.

Lee TH, Hoover RL, Williams JD, Sperling RI, Ravalese JD, Spur BW, Robinson DR, Corey EJ, Lewis RA, Austen KF. 1985. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med* 312:1217–1224.

Leibel RL, Hirsch J, Appel BE, Checani GC. 1992. Energy intake required to maintain body weight is not affected by wide variation in diet composition. *Am J Clin Nutr* 55:350–355.

Leibovitz BE, Hu ML, Tappel AL. 1990. Lipid peroxidation in rat tissue slices: Effect of dietary vitamin E, corn oil-lard and mehaden oil. *Lipids* 25:125–129.

Lemaitre RN, King IB, Patterson RE, Psaty BM, Kestin M, Heckbert SR. 1998. Assessment of *trans*-fatty acid intake with a food frequency questionnaire and validation with adipose tissue levels of *trans*-fatty acids. *Am J Epidemiol* 148:1085–1093.

Levinson PD, Iosiphidis AH, Saritelli AL, Herbert PN, Steiner M. 1990. Effects of *n*-3 fatty acids in essential hypertension. *Am J Hypertens* 3:754–760.

Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ. 1993. Hydrogenation impairs the hypolipidemic effect of corn oil in humans. Hydrogenation, *trans* fatty acids, and plasma lipids. *Arterioscler Thromb* 13:154–161.

Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ. 1999. Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels. *N Engl J Med* 340:1933–1940.

Lippi G, Guidi G. 1999. Biochemical risk factors and patient's outcome: The case of lipoprotein(a). *Clin Chim Acta* 280:59–71.

Litin L, Sacks F. 1993. *Trans*-fatty-acid content of common foods. *N Engl J Med* 329:1969–1970.

London SJ, Sacks FM, Caesar J, Stampfer MJ, Siguel E, Willett WC. 1991. Fatty acid composition of subcutaneous adipose tissue and diet in postmenopausal US women. *Am J Clin Nutr* 54:340–345.

Lorenz R, Spengler U, Fischer S, Duhm J, Weber PC. 1983. Platelet function, thromboxane formation and blood pressure control during supplementation of the Western diet with cod liver oil. *Circulation* 67:504–511.

Louheranta AM, Turpeinen AK, Schwab US, Vidgren HM, Parviainen MT, Uusitupa MIJ. 1998. A high-steric acid diet does not impair glucose tolerance and insulin sensitivity in healthy women. *Metabolism* 47:529–534.

Louheranta AM, Turpeinen AK, Vidgren HM, Schwab US, Uusitupa MIJ. 1999. A high-*trans* fatty acid diet and insulin sensitivity in young healthy women. *Metabolism* 48:870–875.

LSRO (Life Sciences Research Office). 1998. Fat. In: Raiten DJ, Talbot JM, Waters JH, eds. *Assessment of Nutrient Requirements for Infant Formulas*. Bethesda, MD: LSRO. Pp. 19–46.

Lucas A, Quinlan P, Abrams S, Ryan S, Meah S, Lucas PJ. 1997. Randomised controlled trial of a synthetic triglyceride milk formula for preterm infants. *Arch Dis Child* 77:F178–F184.

Lucas A, Stafford M, Morley R, Abbott R, Stephenson T, MacFadyen U, Elias-Jones A, Clements H. 1999. Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: A randomised trial. *Lancet* 354:1948–1954.

Ludwig DS, Pereira MA, Kroenke CH, Hilner JE, Van Horn L, Slattery ML, Jacobs DR. 1999. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *J Am Med Assoc* 282:1539–1546.

Ma DWL, Wierzbicki AA, Field CJ, Clandinin MT. 1999. Conjugated linoleic acid in Canadian dairy and beef products. *J Agric Food Chem* 47:1956–1960.

MacDonald HB. 2000. Conjugated linoleic acid and disease prevention: A review of current knowledge. *J Am Coll Nutr* 19:111S–118S.

Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. 1994. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. *Am J Clin Nutr* 60:189–194.

Makrides M, Neumann M, Simmer K, Pater J, Gibson R. 1995. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? *Lancet* 345:1463–1468.

Makrides M, Neumann MA, Gibson RA. 1996. Is dietary docosahexaenoic acid essential for term infants? *Lipids* 31:115–119.

Makrides M, Neumann MA, Jeffrey B, Lien EL, Gibson RA. 2000a. A randomized trial of different ratios of linoleic to α-linolenic acid in the diet of term infants: Effects on visual function and growth. *Am J Clin Nutr* 71:120–129.

Makrides M, Neumann MA, Simmer K, Gibson RA. 2000b. A critical appraisal of the role of dietary long-chain polyunsaturated fatty acids on neural indices of term infants: A randomized controlled trial. *Pediatrics* 105:32–38.

Marshall JA, Bessesen DH, Hamman RF. 1997. High saturated fat and low starch and fibre are associated with hyperinsulinemia in a non-diabetic population: The San Luis Valley Diabetes Study. *Diabetologia* 40:430–438.

Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. 1986. Serum cholesterol, blood pressure, and mortality: Implications from a cohort of 361,662 men. *Lancet* 2:933–936.

Martinez M. 1992. Tissue levels of polyunsaturated fatty acids during early human development. *J Pediatr* 120:S129–S138.

Martinez M, Ballabriga A, Gil-Gibernau JJ. 1988. Lipids of the developing human retina: I. Total fatty acids, plasmalogens, and fatty acid composition of ethanolamine and choline phosphoglycerides. *J Neurosci Res* 20:484–490.

Mascioli EA, Smith MF, Trerice MS, Meng HC, Blackburn GL. 1979. Effect of total parenteral nutrition with cycling on essential fatty acid deficiency. *J Parenter Enteral Nutr* 3:171–173.

Mascioli EA, Lopes SM, Champagne C, Driscoll DF. 1996. Essential fatty acid deficiency and home total parenteral nutrition patients. *Nutrition* 12:245–249.

McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. 1984. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. *Am J Epidemiol* 119:667–676.

Meng HC. 1983. A case of human linolenic acid deficiency involving neurological abnormalities. *Am J Clin Nutr* 37:157–159.

Mensink RP, Hornstra G. 1995. The proportion of *trans* monounsaturated fatty acids in serum triacylglycerols or platelet phospholipids as an objective indicator of their short-term intake in healthy men. *Br J Nutr* 73:605–612.

Mensink RP, Katan MB. 1990. Effect of dietary *trans* fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med* 323:439–445.

Mensink RP, Katan MB. 1992. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler Thromb* 12:911–919.

Mensink RP, de Louw MHJ, Katan MB. 1991. Effects of dietary *trans* fatty acids on blood pressure in normotensive subjects. *Eur J Clin Nutr* 45:375–382.

Mensink RP, Zock PL, Katan MB, Hornstra G. 1992. Effect of dietary *cis* and *trans* fatty acids on serum lipoprotein[a] levels in humans. *J Lipid Res* 33:1493–1501.

Mensink RP, Temme EH, Hornstra G. 1994. Dietary saturated and *trans* fatty acids and lipoprotein metabolism. *Ann Med* 26:461–464.

Meydani SN, Endres S, Woods MM, Goldin BR, Soo C, Morrill-Labrode A, Dinarello CA, Gorbach SL. 1991. Oral (*n*-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: Comparison between young and older women. *J Nutr* 121:547–555.

Meydani SN, Lichtenstein AH, Cornwall S, Meydani M, Goldin BR, Rasmussen H, Dinarello CA, Schaefer EJ. 1993. Immunologic effects of National Cholesterol Education Panel Step-2 Diets with and without fish-derived *n*-3 fatty acid enrichment. *J Clin Invest* 92:105–113.

Michels K, Sacks F. 1995. Trans fatty acids in European margarines. *N Engl J Med* 332:541–542.

Miller WC, Niederpruem MG, Wallace JP, Lindeman AK. 1994. Dietary fat, sugar, and fiber predict body fat content. *J Am Diet Assoc* 94:612–615.

Mohrhauer H, Holman RT. 1963. The effect of dose level of essential fatty acids upon fatty acid composition of the rat liver. *J Lipid Res* 4:151–159.

Mølvig J, Pociot F, Worsaae H, Wogensen LD, Baek L, Christensen P, Mandrup-Poulsen T, Andersen K, Madsen P, Dyerberg J, Nerup J. 1991. Dietary supplementation with ω-3-polyunsaturated fatty acids decreases mononuclear cell proliferation and interleukin-1β content but not monokine secretion in healthy and insulin-dependent diabetic individuals. *Scand J Immunol* 34:399–410.

Moore SA, Yoder E, Murphy S, Dutton GR, Spector AA. 1991. Astrocytes, not neurons, produce docosahexaenoic acid (22:6ω-3) and arachidonic acid (20:4ω-6). *J Neurochem* 56:518–524.

Morley R. 1998. Nutrition and cognitive development. *Nutrition* 14:752–754.

Mortensen JZ, Schmidt EB, Nielsen AH, Dyerberg J. 1983. The effect of *n*-6 and *n*-3 fatty acids on hemostasis, blood lipids and blood pressure. *Thromb Haemostas* 50:543–546.

Müller H, Jordal O, Seljeflot I, Kierulf P, Kirkhus B, Ledsaak O, Pedersen JI. 1998. Effect on plasma lipids and lipoproteins of replacing partially hydrogenated fish oil with vegetable fat in margarine. *Br J Nutr* 80:243–251.

Murgatroyd PR, Van De Ven MLHM, Goldberg GR, Prentice AM. 1996. Alcohol and the regulation of energy balance: Overnight effects on diet-induced thermogenesis and fuel storage. *Br J Nutr* 75:33–45.

Murgatroyd PR, Goldberg GR, Leahy FE, Gilsenan MB, Prentice AM. 1999. Effects of inactivity and diet composition on human energy balance. *Int J Obes Relat Metab Disord* 23:1269–1275.

Mustad VA, Etherton TD, Cooper AD, Mastro AM, Pearson TA, Jonnalagadda SS, Kris-Etherton PM. 1997. Reducing saturated fat intake is associated with increased levels of LDL receptors on mononuclear cells in healthy men and women. *J Lipid Res* 38:459–468.

Mutanen M, Aro A. 1997. Coagulation and fibrinolysis factors in healthy subjects consuming high stearic or *trans* fatty acid diets. *Thromb Haemost* 77:99–104.

Neaton JD, Wentworth D. 1992. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. *Arch Intern Med* 152:56–64.

Nelson GJ, Schmidt PC, Corash L. 1991. The effect of a salmon diet on blood clotting, platelet aggregation and fatty acids in normal adult men. *Lipids* 26:87–96.

Nelson GJ, Schmidt PC, Bartolini GL, Kelley DS, Kyle D. 1997. The effect of dietary docosahexaenoic acid on plasma lipoproteins and tissue fatty acid composition in humans. *Lipids* 32:1137–1146.

Nestel PJ, Noakes M, Belling GB, McArthur R, Clifton PM, Abbey M. 1992a. Plasma cholesterol-lowering potential of edible-oil blends suitable for commercial use. *Am J Clin Nutr* 55:46–50.

Nestel PJ, Noakes M, Belling B, McArthur R, Clifton P, Janus E, Abbey M. 1992b. Plasma lipoprotein lipid and Lp[a] changes with substitution of elaidic acid for oleic acid in the diet. *J Lipid Res* 33:1029–1036.

Nestel P, Clifton P, Noakes M. 1994. Effects of increasing dietary palmitoleic acid compared with palmitic and oleic acids on plasma lipids of hypercholesterolemic men. *J Lipid Res* 35:656–662.

Neuringer M, Connor WE, Van Petten C, Barstad L. 1984. Dietary omega-3 fatty acid deficiency and visual loss in infant rhesus monkeys. *J Clin Invest* 73:272–276.

Neuringer M, Connor WE, Lin DS, Barstad L, Luck S. 1986. Biochemical and functional effects of prenatal and postnatal ω3 fatty acid deficiency on retina and brain in rhesus monkeys. *Proc Natl Acad Sci USA* 83:4021–4025.

Nielsen LB. 1999. Atherogenecity of lipoprotein(a) and oxidized low density lipoprotein: Insight from in vivo studies of arterial wall influx, degradation and efflux. *Atherosclerosis* 143:229–243.

Niinikoski H, Lapinleimu H, Viikari J, Rönnemaa T, Jokinen E, Seppänen R, Terho P, Tuominen J, Välimäki I, Simell O. 1997a. Growth until 3 years of age in a prospective, randomized trial of a diet with reduced saturated fat and cholesterol. *Pediatrics* 99:687–694.

Niinikoski H, Viikari J, Rönnemaa T, Helenius H, Jokinen E, Lapinleimu H, Routi T, Lagström H, Seppänen R, Välimäki I, Simell O. 1997b. Regulation of growth of 7- to 36-month-old children by energy and fat intake in the prospective, randomized STRIP baby trial. *Pediatrics* 100:810–816.

Noakes M, Clifton PM. 1998. Oil blends containing partially hydrogenated or interesterified fats: Differential effects on plasma lipids. *Am J Clin Nutr* 68:242–247.

Noble RC, Moore JH, Harfoot CG. 1974. Observations on the pattern of biohydrogenation of esterified and unesterified linoleic acid in the rumen. *Br J Nutr* 31:99–108.

Nommsen LA, Lovelady CA, Heinig MJ, Lönnerdal B, Dewey KG. 1991. Determinants of energy, protein, lipid, and lactose concentrations in human milk during the first 12 mo of lactation: The DARLING Study. *Am J Clin Nutr* 53:457–465.

Obarzanek E, Hunsberger SA, Van Horn L, Hartmuller VV, Barton BA, Stevens VJ, Kwiterovich PO, Franklin FA, Kimm SYS, Lasser NL, Simons-Morton DG, Lauer RM. 1997. Safety of a fat-reduced diet: The Dietary Intervention Study in Children (DISC). *Pediatrics* 100:51–59.

Olsen SF, Hansen HS, Jensen B, Sørensen TIA. 1989. Pregnancy duration and the ratio of long-chain *n*-3 fatty acids to arachidonic acid in erythrocytes from Faroese women. *J Intern Med* 225:185–189.

Olsen SF, Sørensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, Grant A. 1992. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. *Lancet* 339:1003–1007.

O'Neill JA, Caldwell MD, Meng HC. 1977. Essential fatty acid deficiency in surgical patients. *Ann Surg* 185:535–542.

Ou J, Tu H, Luk A, DeBose-Boyd RA, Bashmakov Y, Goldstein JL, Brown MS. 2001. Unsaturated fatty acids inhibit transcription of the sterol regulatory element-binding protein-1c (SREBP-1c) gene by antagonizing ligand-dependent activation of the LXR. *Proc Natl Acad Sci USA* 98:6027–6032.

Pan DA, Lillioja S, Kriketos AD, Milner MR, Baur LA, Bogardus C, Jenkins AB, Storlien LH. 1997. Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes* 46:983–988.

Pariza MW, Park Y, Cook ME. 2001. The biologically active isomers of conjugated linoleic acid. *Prog Lipid Res* 40:283–298.

Parker DR, Weiss ST, Troisi R, Cassano PA, Vokonas PS, Landsberg L. 1993. Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations: The Normative Aging Study. *Am J Clin Nutr* 58:129–136.

Paulsrud JR, Pensler L, Whitten CF, Stewart S, Holman RT. 1972. Essential fatty acid deficiency in infants induced by fat-free intravenous feeding. *Am J Clin Nutr* 25:897–904.

Pedersen HS, Mulvad G, Seidelin KN, Malcom GT, Boudreau DA. 1999. *n*-3 Fatty acids as a risk factor for haemorrhagic stroke. *Lancet* 353:812–813.

Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. 1997. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol* 145:876–887.

Ponder DL, Innis SM, Benson JD, Siegman JS. 1992. Docosahexaenoic acid status of term infants fed breast milk or infant formula containing soy oil or corn oil. *Pediatr Res* 32:683–688.

Putnam JC, Carlson SE, DeVoe PW, Barness LA. 1982. The effect of variations in dietary fatty acids on the fatty acid composition of erythrocyte phosphatidylcholine and phosphatidylethanolamine in human infants. *Am J Clin Nutr* 36:106–114.

Raben A, Andersen HB, Christensen NJ, Madsen J, Holst JJ, Astrup A. 1994. Evidence for an abnormal postprandial response to a high-fat meal in women predisposed to obesity. *Am J Physiol* 267:E549–E559.

Ratnayake WMN, Hollywood R, O'Grady E, Pelletier G. 1993. Fatty acids in some common food items in Canada. *J Am Coll Nutr* 12:651–660.

Ratnayake WM, Chardigny JM, Wolff RL, Bayard CC, Sebedio JL, Martine L. 1997. Essential fatty acids and their *trans* geometrical isomers in powdered and liquid infant formulas sold in Canada. *J Pediatr Gastroenterol* 25:400–407.

Rhee SK, Kayani AJ, Ciszek A, Brenna JT. 1997. Desaturation and interconversion of dietary stearic and palmitic acids in human plasma and lipoproteins. *Am J Clin Nutr* 65:451–458.

Richardson TJ, Sgoutas D. 1975. Essential fatty acid deficiency in four adult patients during total parenteral nutrition. *Am J Clin Nutr* 28:258–263.

Riella MC, Broviac JW, Wells M, Scribner BH. 1975. Essential fatty acid deficiency in human adults during total parenteral nutrition. *Ann Intern Med* 83:786–789.

Ritzenthaler KL, McGuire MK, Falen R, Shultz TD, Dasgupta N, McGuire MA. 2001. Estimation of conjugated linoleic acid intake by written dietary assessment methodologies underestimates actual intake evaluated by food duplicate methodology. *J Nutr* 131:1548–1554.

Roche HM, Zampelas A, Jackson KG, Williams CM, Gibney MJ. 1998. The effect of test meal monounsaturated fatty acid:saturated fatty acid ratio on postprandial lipid metabolism. *Br J Nutr* 79:419–424.

Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, Shulman GI. 1996. Mechanism of free fatty acid-induced insulin resistance in humans. *J Clin Invest* 97:2859–2865.

Rodriguez A, Sarda P, Nessmann C, Boulot P, Poisson J-P, Leger CL, Descomps B. 1998. Fatty acid desaturase activities and polyunsaturated fatty acid composition in human fetal liver between the seventeenth and thirty-sixth gestational weeks. *Am J Obstet Gynecol* 179:1063–1070.

Rogers S, James KS, Butland BK, Etherington MD, O'Brien JR, Jones JG. 1987. Effects of a fish oil supplement on serum lipids, blood pressure, bleeding time, haemostatic and rheological variables. A double blind randomised controlled trial in healthy volunteers. *Atherosclerosis* 63:137–143.

Rosenthal MD, Doloresco MA. 1984. The effects of *trans* fatty acids on fatty acyl Δ5 desaturation by human skin fibroblasts. *Lipids* 19:869–874.

Rudel LL, Haines J, Sawyer JK, Shah R, Wilson MS, Carr TP. 1997. Hepatic origin of cholesteryl oleate in coronary artery atherosclerosis in African green monkeys. *J Clin Invest* 100:74–83.

Russell RM. 1992. Changes in gastrointestinal function attributed to aging. *Am J Clin Nutr* 55:1203S–1207S.

Ruttenberg H, Davidson LM, Little NA, Klurfeld DM, Kritchevsky D. 1983. Influence of *trans* unsaturated fats on experimental atherosclerosis in rabbits. *J Nutr* 113:835–844.

Ryan AS, Montalto MB, Groh-Wargo S, Mimouni F, Sentipal-Walerius J, Doyle J, Siegman JS, Thomas AJ. 1999. Effect of DHA-containing formula on growth of preterm infants to 59 weeks postmenstrual age. *Am J Hum Biol* 11:457–467.

Rywik SL, Manolio TA, Pajak A, Piotrowski W, Davids CE, Broda GB, Kawalec E. 1999. Association of lipids and lipoprotein level with total mortality and mortality caused by cardiovascular and cancer diseases (Poland and United States collaborative study on cardiovascular epidemiology). *Am J Cardiol* 84:540–548.

Salem N, Wegher B, Mena P, Uauy R. 1996. Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. *Proc Natl Acad Sci USA* 93:49–54.

Salem N, Litman B, Kim H-Y, Gawrisch K. 2001. Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids* 36:945–959.

Salmerón J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. 2001. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr* 73:1019–1026.

Sanders TAB, Reddy S. 1992. The influence of a vegetarian diet on the fatty acid composition of human milk and the essential fatty acid status of the infant. *J Pediatr* 120:S71–S77.

Sanders TAB, Vickers M, Haines AP. 1981. Effect of blood lipids and haemostasis of a supplement of cod-liver oil, rich in eicosapentaenoic and docosahexaenoic acids, in healthy young men. *Clin Sci* 61:317–324.

Sanders TAB, de Grassi T, Miller GJ, Morrissey JH. 2000. Influence of fatty acid chain length and *cis/trans* isomerization on postprandial lipemia and factor VII in healthy subjects (postprandial lipids and factor VII). *Atherosclerosis* 149:413–420.

Sanjurjo P, Matorras R, Ingunza N, Alonso M, Rodriguez-Alarcón J, Perteagudo L. 1993. Cross-sectional study of percentual changes in total plasmatic fatty acids during pregnancy. *Horm Metab Res* 25:590–592.

Santora JE, Palmquist DL, Roehrig KL. 2000. *Trans*-vaccenic acid is desaturated to conjugated linoleic acid in mice. *J Nutr* 130:208–215.

Sauerwald TU, Hachey DL, Jensen CL, Chen H, Anderson RE, Heird WC. 1996. Effect of dietary α-linolenic acid intake on incorporation of docosahexaenoic and arachidonic acids into plasma phospholipids of term infants. *Lipids* 31:S131–S135.

Sauerwald TU, Hachey DL, Jensen CL, Chen H, Anderson RE, Heird WC. 1997. Intermediates in endogenous synthesis of C22:6ω3 and C20:4ω6 by term and preterm infants. *Pediatr Res* 41:183–187.

Schakel SF, Buzzard IM, Gebhardt SE. 1997. Procedures for estimating nutrient values for food composition databases. *J Food Comp Anal* 10:102–114.

Schmidt DE, Allred JB, Kien CL. 1999. Fractional oxidation of chylomicron-derived oleate is greater than that of palmitate in healthy adults fed frequent small meals. *J Lipid Res* 40:2322–2332.

Schmidt EB, Pedersen JO, Ekelund S, Grunnet N, Jersild C, Dyerberg J. 1989. Cod liver oil inhibits neutrophil and monocyte chemotaxis in healthy males. *Atherosclerosis* 77:53–57.

Schmidt EB, Varming K, Ernst E, Madsen P, Dyerberg J. 1990. Dose–response studies on the effect of *n*-3 polyunsaturated fatty acids on lipids and haemostasis. *Thromb Haemost* 63:1–5.

Schmidt EB, Lervang H-H, Varming K, Madsen P, Dyerberg J. 1992. Long-term supplementation with *n*-3 fatty acids. I: Effect on blood lipids, haemostasis and blood pressure. *Scand J Clin Lab Invest* 52:221–228.

Schutz Y. 2000. Role of substrate utilization and thermogenesis on body-weight control with particular reference to alcohol. *Proc Nutr Soc* 59:511–517.

Scott DT, Janowsky JS, Carroll RE, Taylor JA, Auestad N, Montalto MB. 1998. Formula supplementation with long-chain polyunsaturated fatty acids: Are there developmental benefits? *Pediatrics* 102:E59.

Seppänen-Laakso T, Vanhanen H, Laakso I, Kohtamäki H, Viikari J. 1993. Replacement of margarine on bread by rapeseed and olive oils: Effects on plasma fatty acid composition and serum cholesterol. *Ann Nutr Metab* 37:161–174.

Sessler AM, Ntambi JM. 1998. Polyunsaturated fatty acid regulation of gene expression. *J Nutr* 128:923–926.

Sevak L, McKeigue PM, Marmot MG. 1994. Relationship of hyperinsulinemia to dietary intake in South Asian and European men. *Am J Clin Nutr* 59:1069–1074.

Shea S, Basch CE, Stein AD, Contento IR, Irigoyen M, Zybert P. 1993. Is there a relationship between dietary fat and stature or growth in children three to five years of age? *Pediatrics* 92:579–586.

Shekelle RB, Missell L, Paul O, Shyrock AM, Stamler J. 1985. Fish consumption and mortality from coronary heart disease. *N Engl J Med* 313:820.

Sherwood NE, Jeffery RW, French SA, Hannan PJ, Murray DM. 2000. Predictors of weight gain in the Pound of Prevention Study. *Int J Obes Relat Metab Disord* 24:395–403.

Shetty PS, Prentice AM, Goldberg GR, Murgatroyd PR, McKenna APM, Stubbs RJ, Volschenk PA. 1994. Alterations in fuel selection and voluntary food intake in response to isoenergetic manipulation of glycogen stores in humans. *Am J Clin Nutr* 60:534–543.

Shimp JL, Bruckner G, Kinsella JE. 1982. The effects of dietary trilinoelaidin on fatty acid and acyl desaturases in rat liver. *J Nutr* 112:722–735.

Shintani TT, Beckham S, Brown AC, O'Connor HK. 2001. The Hawaii Diet: Ad libitum high carbohydrate, low fat multi-cultural diet for the reduction of chronic disease risk factors: Obesity, hypertension, hypercholesterolemia, and hyperglycemia. *Hawaii Med J* 60:69–73.

Siguel EN, Lerman RH. 1993. *Trans*-fatty acid patterns in patients with angiographically documented coronary artery disease. *Am J Cardiol* 71:916–920.

Siguel EN, Blumberg JB, Caesar J. 1986. Monitoring the optimal infusion of intravenous lipids. *Arch Pathol Lab Med* 110:792–797.

Sinclair AJ. 1975. Incorporation of radioactive polyunsaturated fatty acids into liver and brain of developing rat. *Lipids* 10:175–184.

Sinclair AJ, Murphy KJ, Li D. 2000. Marine lipids: Overview "news insights and lipid composition of Lyprinol™" *Allerg Immunol (Paris)* 32:261–271.

Slattery ML, Potter JD, Duncan DM, Berry TD. 1997. Dietary fats and colon cancer: Assessment of risk associated with specific fatty acids. *Int J Cancer* 73:670–677.

Smith P, Arnesen H, Opstad T, Dahl KH, Eritsland J. 1989. Influence of highly concentrated *n*-3 fatty acids on serum lipids and hemostatic variables in survivors of myocardial infarction receiving either oral anticoagulants or matching placebo. *Thromb Res* 53:467–474.

Song JH, Miyazawa T. 2001. Enhanced level of *n*-3 fatty acid in membrane phospholipids induces lipid peroxidation in rats fed dietary docosahexaenoic acid oil. *Atherosclerosis* 155:9–18.

Sørensen NS, Marckmann P, Høy C-E, van Duyvenvoorde W, Princen HMG. 1998. Effect of fish-oil-enriched margarine on plasma lipids, low-density-lipoprotein particle composition, size, and susceptibility to oxidation. *Am J Clin Nutr* 68:235–241.

Sorkin JD, Andres R, Muller DC, Baldwin HL, Fleg JL. 1992. Cholesterol as a risk factor for coronary heart disease in elderly men. The Baltimore Longitudinal Study of Aging. *Ann Epidemiol* 2:59–67.

Spady DK, Woolett LA, Dietschy JM. 1993. Regulation of plasma LDL-cholesterol levels by dietary cholesterol and fatty acids. *Annu Rev Nutr* 13:355–361.

Sperling RI, Benincaso AI, Knoell CT, Larkin JK, Austen KF, Robinson DR. 1993. Dietary ω-3 polyunsaturated fatty acids inhibit phosphoinositide formation and chemotaxis in neutrophils. *J Clin Invest* 91:651–660.

Sprecher H. 1992. Interconversions between 20- and 22-carbon *n*-3 and *n*-6 fatty acids via 4-desaturase independent pathways. In: Sinclair AJ, Gibson R, eds. *Essential Fatty Acids and Eicosanoids: Invited Papers from the Third International Congress*. Champaign, IL: American Oil Chemists' Society. Pp. 18–22.

Sprecher H, Luthria DL, Mohammed BS, Baykousheva SP. 1995. Reevaluation of the pathways for the biosynthesis of polyunsaturated fatty acids. *J Lipid Res* 36:2471–2477.

Stacpoole PW, Alig J, Ammon L, Crockett SE. 1989. Dose–response effects of dietary marine oil on carbohydrate and lipid metabolism in normal subjects and patients with hypertriglyceridemia. *Metabolism* 38:946–956.

Stamler J, Wentworth D, Neaton JD. 1986. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *J Am Med Assoc* 256:2823–2828.

Sugano M, Ikeda I. 1996. Metabolic interactions between essential and *trans*-fatty acids. *Curr Opin Lipidol* 7:38–42.

Sundram K, Ismail A, Hayes KC, Jeyamalar R, Pathmanathan R. 1997. *Trans* (elaidic) fatty acids adversely affect the lipoprotein profile relative to specific saturated fatty acids in humans. *J Nutr* 127:514S–520S.

Suter PM, Schutz Y, Jequier E. 1992. The effect of ethanol on fat storage in healthy subjects. *N Engl J Med* 326:983–987.

Tavani A, Negri E, D'Avanzo B, La Vecchia C. 1997. Margarine intake and risk of nonfatal acute myocardial infarction in Italian women. *Eur J Clin Nutr* 51:30–32.

Thompson PJ, Misso NLA, Passarelli M, Phillips MJ. 1991. The effect of eicosapentaenoic acid consumption on human neutrophil chemiluminescence. *Lipids* 26:1223–1226.

Thomsen C, Rasmussen O, Lousen T, Holst JJ, Fenselau S, Schrezenmeir J, Hermansen K. 1999. Differential effects of saturated and monounsaturated fatty acids on postprandial lipemia and incretin responses in healthy subjects. *Am J Clin Nutr* 69:1135–1143.

Thorngren M, Gustafson A. 1981. Effects of 11-week increase in dietary eicosapentaenoic acid on bleeding time, lipids, and platelet aggregation. *Lancet* 2:1190–1193.

Tomarelli RM, Meyer BJ, Weaber JR, Bernhart FW. 1968. Effect of positional distribution on the absorption of the fatty acids of human milk and infant formulas. *J Nutr* 95:583–590.

Troiano RP, Briefel RR, Carroll MD, Bialostosky K. 2000. Energy and fat intakes of children and adolescents in the United States: Data from the National Health and Nutrition Examination Surveys. *Am J Clin Nutr* 72:1343S–1353S.

Troisi R, Willett WC, Weiss ST. 1992. *Trans*-fatty acid intake in relation to serum lipid concentrations in adult men. *Am J Clin Nutr* 56:1019–1024.

Turpeinen AM, Wübert J, Aro A, Lorenz R, Mutanen M. 1998. Similar effects of diets rich in stearic acid or *trans*-fatty acids on platelet function and endothelial prostacyclin production in humans. *Arterioscler Thromb Vasc Biol* 18:316–322.

Tuyns AJ, Kaaks R, Haelterman M. 1988. Colorectal cancer and the consumption of foods: A case-control study in Belgium. *Nutr Cancer* 11:189–204.

Uauy R, Mena P, Wegher B, Nieto S, Salem N. 2000a. Long chain polyunsaturated fatty acid formation in neonates: Effect of gestational age and intrauterine growth. *Pediatr Res* 47:127–135.

Uauy R, Mize CE, Castillo-Duran C. 2000b. Fat intake during childhood: Metabolic responses and effects on growth. *Am J Clin Nutr* 72:1354S–1360S.

Umegaki K, Hashimoto M, Yamasaki H, Fujii Y, Yoshimura M, Sugisawa A, Shinozuka K. 2001. Docosahexaenoic acid supplementation-increased oxidative damage in bone marrow DNA in aged rats and its relation to antioxidant vitamins. *Free Radic Res* 34:427–435.

USDA (U.S. Department of Agriculture). 1996. *The Food Guide Pyramid*. Home and Garden Bulletin No. 252. Washington, DC: U.S. Government Printing Office.

USDA/HHS (U.S. Department of Health and Human Services). 2000. *Nutrition and Your Health: Dietary Guidelines for Americans*, 5th ed. Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

Valenzuela A, Morgado N. 1999. *Trans* fatty acid isomers in human health and in the food industry. *Biol Res* 32:273–287.

van Dam RM, Huang Z, Giovannucci E, Rimm EB, Hunter DJ, Colditz GA, Stampfer MJ, Willett WC. 2000. Diet and basal cell carcinoma of the skin in a prospective cohort of men. *Am J Clin Nutr* 71:135–141.

van den Brandt PA, van't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJJ, Sturmans F. 1993. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. *Cancer Res* 53:75–82.

van Erp-baart M-A, Couet C, Cuadrado C, Kafatos A, Stanley J, van Poppel G. 1998. *Trans* fatty acids in bakery products from 14 European countries: The TRANSFAIR Study. *J Food Comp Anal* 11:161–169.

van Houwelingen AC, Hornstra G. 1994. *Trans* fatty acids in early human development. *World Rev Nutr Diet* 75:175–178.

van Houwelingen AC, Sørensen JD, Hornstra G, Simonis MMG, Boris J, Olsen SF, Secher NJ. 1995. Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. *Br J Nutr* 74:723–731.

van Poppel G, van Erp-baart M-A, Leth T, Gevers E, Van Amelsvoort J, Lanzmann-Petithory D, Kafatos A, Aro A. 1998. *Trans* fatty acids in foods in Europe: The TRANSFAIR Study. *J Food Comp Anal* 11:112–136.

Veierød MB, Laake P, Thelle DS. 1997. Dietary fat intake and risk of lung cancer: A prospective study of 51,452 Norwegian men and women. *Eur J Cancer Prev* 6:540–549.

Velie E, Kulldorff M, Schairer C, Block G, Albanes D, Schatzkin A. 2000. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: A prospective cohort study. *J Natl Cancer Inst* 92:833–839.

Verhulst A, Janssen G, Parmentier G, Eyssen H. 1987. Isomerization of polyunsaturated long chain fatty acids by propionibacteria. *Syst Appl Microbiol* 9:12–15.

Vermunt SHF, Mensink RP, Simonis MMG, Hornstra G. 2000. Effects of dietary α-linolenic acid on the conversion and oxidation of ^{13}C-α-linolenic acid. *Lipids* 35:137–142.

Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nälsén C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson I-B, Storlien LH. 2001. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. *Diabetologia* 44:312–319.

Vidgren HM, Ågren JJ, Schwab U, Rissanen T, Hänninen O, Uusitupa MIJ. 1997. Incorporation of *n*-3 fatty acids into plasma lipid fractions, and erythrocyte membranes and platelets during dietary supplementation with fish, fish oil, and docosahexaenoic acid-rich oil among healthy young men. *Lipids* 32:697–705.

Vidgren HM, Louheranta AM, Ågren JJ, Schwab US, Uusitupa MIJ. 1998. Divergent incorporation of dietary *trans* fatty acids in different serum lipid fractions. *Lipids* 33:955–962.

Virella G, Fourspring K, Hyman B, Haskill-Stroud R, Long L, Virella I, La Via M, Gross AJ, Lopes-Virella M. 1991. Immunosuppressive effects of fish oil in normal human volunteers: Correlation with the in vitro effects of eicosapentanoic acid on human lymphocytes. *Clin Immunol Immunopathol* 61:161–176.

Virtanen SM, Feskens EJM, Räsänen L, Fidanza F, Tuomilehto J, Giampaoli S, Nissinen A, Kromhout D. 2000. Comparison of diets of diabetic and non-diabetic elderly men in Finland, The Netherlands and Italy. *Eur J Clin Nutr* 54:181–186.

Vobecky JS, Vobecky J, Normand L. 1995. Risk and benefit of low fat intake in childhood. *Ann Nutr Metab* 39:124–133.

Vogel RA, Corretti MC, Plotnick GD. 2000. The postprandial effect of components of the Mediterranean diet on endothelial function. *J Am Coll Cardiol* 36:1455–1460.

Voss A, Reinhart M, Sankarappa S, Sprecher H. 1991. The metabolism of 7,10,13,16,19-docosapentaenoic acid to 4,7,10,13,16,19-docosahexaenoic acid in rat liver is independent of a 4-desaturase. *J Biol Chem* 266:19995–20000.

Ward KD, Sparrow D, Vokonas PS, Willett WC, Landsberg L, Weiss ST. 1994. The relationships of abdominal obesity, hyperinsulinemia and saturated fat intake to serum lipid levels: The Normative Aging Study. *Int J Obes Relat Metab Disord* 18:137–144.

Watts GF, Jackson P, Burke V, Lewis B. 1996. Dietary fatty acids and progression of coronary artery disease in men. *Am J Clin Nutr* 64:202–209.

Weijenberg MP, Feskens EJM, Kromhout D. 1996. Total and high density lipoprotein cholesterol as risk factors for coronary heart disease in elderly men during 5 years of follow-up. The Zutphen Elderly Study. *Am J Epidemiol* 143:151–158.

Wene JD, Connor WE, DenBesten L. 1975. The development of essential fatty acid deficiency in healthy men fed fat-free diets intravenously and orally. *J Clin Invest* 56:127–134.

West DB, York B. 1998. Dietary fat, genetic predisposition, and obesity: Lessons from animal models. *Am J Clin Nutr* 67:505S–512S.

Wetzel MG, Li J, Alvarez RA, Anderson RE, O'Brien PJ. 1991. Metabolism of linolenic acid and docosahexaenoic acid in rat retinas and rod outer segments. *Exp Eye Res* 53:437–446.

Wheeler TG, Benolken RM, Anderson RE. 1975. Visual membranes: Specificity of fatty acid precursors for the electrical response to illumination. *Science* 188:1312–1314.

Wild SH, Fortmann SP, Marcovina SM. 1997. A prospective case-control study of lipoprotein(a) levels and apo(a) size and risk of coronary heart disease in Stanford Five-City Project participants. *Arterioscler Thromb Vasc Biol* 17:239–245.

Willatts P, Forsyth JS, DiModugno MK, Varma S, Colvin M. 1998. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* 352:688–691.

Willett WC, Stampfer MJ, Mason JE, Colditz GA, Speizer FE, Rosner BA, Sampson LA, Hennekens CH. 1993. Intake of *trans* fatty acids and risk of coronary heart disease among women. *Lancet* 341:581–585.

Wojenski CM, Silver MJ, Walker J. 1991. Eicosapentaenoic acid ethyl ester as an antithrombotic agent: Comparison to an extract of fish oil. *Biochim Biophys Acta* 1081:33–38.

Wong KH, Deitel M. 1981. Studies with a safflower oil emulsion in total parenteral nutrition. *Can Med Assoc J* 125:1328–1334.

Wong S, Nestel PJ. 1987. Eicosapentaenoic acid inhibits the secretion of triacylglycerol and of apoprotein B and the binding of LDL in Hep G2 cells. *Atherosclerosis* 64:139–146.

Wood R, Kubena K, O'Brien B, Tseng S, Martin G. 1993a. Effect of butter, mono- and polyunsaturated fatty acid-enriched butter, *trans* fatty acid margarine, and zero *trans* fatty acid margarine on serum lipids and lipoproteins in healthy men. *J Lipid Res* 34:1–11.

Wood R, Kubena K, Tseng S, Martin G, Crook R. 1993b. Effect of palm oil, margarine, butter, and sunflower oil on the serum lipids and lipoproteins of normocholesterolemic middle-aged men. *J Nutr Biochem* 4:286–297.

Yamashita N, Maruyama M, Yamazaki K, Hamazaki T, Yano S. 1991. Effect of eicosapentaenoic and docosahexaenoic acid on natural killer cell activity in human peripheral blood lymphocytes. *Clin Immunol Immunopathol* 59:335–345.

Yao CH, Slattery ML, Jacobs DR, Folsom AR, Nelson ET. 1991. Anthropometric predictors of coronary heart disease and total mortality: Findings from the US Railroad Study. *Am J Epidemiol* 134:1278–1289.

Yaqoob P, Pala HS, Cortina-Borja M, Newsholme EA, Calder PC. 2000. Encapsulated fish oil enriched in α-tocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. *Eur J Clin Invest* 30:260–274.

Yasuda S, Watanabe S, Kobayashi T, Hata N, Misawa Y, Utsumi H, Okuyama H. 1999. Dietary docosahexaenoic acid enhances ferric nitrilotriacetate-induced oxidative damage in mice but not when additional alpha-tocopherol is supplemented. *Free Radic Res* 30:199–205.

Yu S, Derr J, Etherton TD, Kris-Etherton PM. 1995. Plasma cholesterol-predictive equations demonstrate that stearic acid is neutral and monounsaturated fatty acids are hypocholesterolemic. *Am J Clin Nutr* 61:1129–1139.

Zambon S, Friday KE, Childs MT, Fujimoto WY, Bierman EL, Ensinck JW. 1992. Effect of glyburide and ω3 fatty acid dietary supplements on glucose and lipid metabolism in patients with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 56:447–454.

Zevenbergen JL, Houtsmuller UMT, Gottenbos JJ. 1988. Linoleic acid requirement of rats fed *trans* fatty acids. *Lipids* 23:178–186.

Zock PL, Katan MB. 1992. Hydrogenation alternatives: Effects of *trans* fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res* 33:399–410.

Zock PL, Mensink RP. 1996. Dietary *trans*-fatty acids and serum lipoproteins in humans. *Curr Opin Lipidol* 7:34–37.

Zock PL, Blijlevens RAMT, de Vries JHM, Katan MB. 1993. Effects of stearic acid and *trans* fatty acids versus linoleic acid on blood pressure in normotensive women and men. *Eur J Clin Nutr* 47:437–444.

Zock PL, Katan MB, Mensink RP. 1995. Dietary *trans* fatty acids and lipoprotein cholesterol. *Am J Clin Nutr* 61:617.

Zucker ML, Bilyeu DS, Helmkamp GM, Harris WS, Dujovne CA. 1988. Effects of dietary fish oil on platelet function and plasma lipids in hyperlipoproteinemic and normal subjects. *Atherosclerosis* 73:13–22.

9
Cholesterol

SUMMARY

Cholesterol plays an important role in steroid hormone and bile acid biosynthesis and serves as an integral component of cell membranes. Given the capability of all tissues to synthesize sufficient amounts of cholesterol for their metabolic and structural needs, there is no evidence for a biological requirement for dietary cholesterol. Therefore, neither an Adequate Intake nor a Recommended Dietary Allowance is set for cholesterol.

There is much evidence to indicate a positive linear trend between cholesterol intake and low density lipoprotein cholesterol concentration, and therefore increased risk of coronary heart disease (CHD). A Tolerable Upper Intake Level is not set for cholesterol because any incremental increase in cholesterol intake increases CHD risk. Because cholesterol is unavoidable in ordinary diets, eliminating cholesterol in the diet would require significant changes in patterns of dietary intake. Such significant adjustments may introduce undesirable effects (e.g., inadequate intakes of protein and certain micronutrients) and unknown and unquantifiable health risks. Nonetheless, it is possible to have a diet low in cholesterol while consuming a nutritionally adequate diet. Dietary guidance for minimizing cholesterol intake is provided in Chapter 11.

BACKGROUND INFORMATION

Function

Cholesterol is a sterol that is present in all animal tissues. Tissue cholesterol occurs primarily as free (unesterified) cholesterol, but is also bound covalently to fatty acids as cholesteryl esters and to certain proteins. Free cholesterol is an integral component of cell membranes and serves as a precursor for steroid hormones such as estrogen, testosterone, and aldosterone, as well as bile acids.

Physiology of Absorption and Metabolism

Absorption

After emulsification and bile acid micellar solubilization, dietary cholesterol, as well as cholesterol derived from hepatic secretion and sloughed intestinal epithelium, is absorbed in the proximal jejunum. Cholesteryl esters, comprising 10 to 15 percent of total dietary cholesterol, are hydrolyzed by a specific pancreatic esterase. Cholesterol absorption by enterocytes is believed to occur primarily by passive diffusion across a concentration gradient established by the solubilization of cholesterol in bile acid micelles. However, recent evidence has shown that scavenger receptor class B type I is present in the small intestine brush-border membrane where it facilitates the uptake of micellar cholesterol (Hauser et al., 1998). In addition, as described further below, two recently identified adenosine triphosphate binding-cassette (ABC) proteins (ABCG5 and ABCG8) have been found to form heterodimers that export plant sterols and cholesterol from enterocytes into the gut lumen, thereby decreasing net sterol absorption (Berge et al., 2000). ABC1, a transporter involved in high density lipoprotein–(HDL) mediated cellular cholesterol efflux, may also participate in this process (Repa et al., 2000).

Esterification of cholesterol and subsequent secretion of both esterified and unesterified cholesterol into lymph and plasma in intestinally synthesized chylomicron and HDL particles may also affect net cholesterol uptake by enterocytes. Key components of this process include cholesterol esterification by acylCoA:cholesterol acyltransferase; lipoprotein assembly with the structural protein apoB48 (chylomicrons) and apoAI (HDL), as well as with triacylglycerols and phospholipids; and lipoprotein secretion into lymphatics facilitated by microsomal triacylglycerol transfer protein.

Cholesterol balance studies in humans have indicated a wide variation in efficiency of intestinal cholesterol absorption (from 20 to 80 percent), with most individuals absorbing between 40 and 60 percent of ingested

cholesterol (Ros, 2000). As discussed below, such variability, which is likely due in part to genetic factors, may contribute to interindividual differences in plasma cholesterol response to dietary cholesterol. In addition, cholesterol absorption may be reduced by the cholesterol content of a meal and by decreased intestinal transit time (Ros, 2000). Although fatty acids are required for intestinal micelle formation, there is no strong evidence that fat content (or other dietary constituents such as fiber) has a significant effect on cholesterol absorption.

An average of 250 mg/d of plant sterols (e.g., sitosterol, stigmasterol, and campesterol) are consumed in the diet, but the absorption of such sterols (approximately 5 percent) is considerably lower than that for cholesterol (Ling and Jones, 1995; Salen et al., 1970). They are not known to have important biological effects in humans at the levels consumed in the diet. An exception is sitosterolemia, a rare genetic disorder that is characterized by markedly increased absorption and tissue accumulation of plant sterols and elevated plasma cholesterol levels (Lütjohann et al., 1996; Salen et al., 1992). Recently, patients with this disorder have been shown to have mutations in genes encoding ABCG5 and ABCG8, indicating the importance of these transporters in regulating sterol absorption presumably by promoting the export of nearly all plant sterols, and a portion of cholesterol, from intestinal cells (Berge et al., 2000). Moreover, increased expression of these genes induced by cholesterol feeding may be of importance in limiting cholesterol absorption (Berge et al., 2000). The ability of very high intakes of plant sterols to lower plasma cholesterol concentrations by reducing cholesterol absorption may also involve regulation of this transport process (Miettinen and Gylling, 1999).

Metabolism

Intestinally derived cholesterol is transported in the circulation to other tissues via chylomicrons, and to a lesser extent HDL, mainly in the form of cholesteryl ester. The hydrolysis of chylomicron triacylglycerols in peripheral tissues by lipoprotein lipase and subsequent remodeling by lipid transfer proteins yields a "remnant" particle that is internalized by receptors, primarily in the liver, that recognize apoprotein E and perhaps other constituents. Cholesterol released by intracellular cholesteryl esterase activity can be stored in hepatocytes; re-esterified and secreted into plasma in lipoproteins, primarily very low density lipoproteins (VLDL); oxidized and excreted as bile acids; or directly secreted into the bile. Free and esterified cholesterol circulate in the blood in humans principally in low density lipoproteins (LDL).

Cholesterol homeostasis in hepatocytes is of critical importance for the regulation of plasma LDL cholesterol concentrations (Dietschy et al.,

1993). Increased cellular cholesterol content leads to suppression of synthesis of LDL receptors via a series of steps resulting in interaction of sterol regulatory element-binding protein (SREBP) 1 and 2 transcription factors with a sterol response element in the LDL receptor gene (Brown and Goldstein, 1999). Increased plasma LDL concentrations can result from reduced hepatic LDL uptake, as well as reduced uptake of VLDL and intermediate density lipoproteins, leading to increased metabolic conversion of these particles to LDL (Kita et al., 1982). Metabolic studies in humans have indicated that a high cholesterol diet induces both increased LDL synthesis and reduced receptor-dependent fractional removal rate of LDL particles (Packard et al., 1983).

There are a number of other genes involved in cholesterol and lipoprotein metabolism in which hepatic regulation can be affected by cholesterol availability either directly via SREBPs or indirectly by the action of other transcription factors, such as liver X receptors (Repa and Mangelsdorf, 2000). These genes play a role in cholesterol regulatory pathways, including those involved in cholesterol synthesis that are suppressed by cholesterol (e.g., 3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase) and others involved in bile acid production from cholesterol that are activated by cholesterol (e.g., 7 α-hydroxylase). Thus, increased hepatic cholesterol delivery from diet and other sources results in a complex admixture of metabolic effects that are generally directed at maintaining tissue and plasma cholesterol homeostasis. However, as described below, empirical observations in humans have indicated that increased dietary cholesterol does result in a net increase in plasma LDL cholesterol concentrations, probably as a consequence of reduced hepatic LDL receptor activity.

All cells are capable of synthesizing cholesterol in sufficient amounts for their structural and metabolic needs. However, certain tissues (e.g., adrenal glands and gonads) derive a significant proportion of cholesterol by uptake from plasma lipoproteins. Cholesterol synthesis via a series of intermediates from acetyl CoA is highly regulated. The enzyme HMG CoA reductase catalyzes the rate-limiting step in cholesterol synthesis—the formation of mevalonic acid from HMG CoA. The genes for this enzyme and a number of other proteins involved in cholesterol metabolism, such as the LDL receptor, are regulated by intracellular sterols and other signaling molecules to maintain tissue cholesterol homeostasis, as described above. Endogenous cholesterol synthesis in humans is approximately 12 to 13 mg/kg/d (840 to 910 mg/d for a 70-kg individual) (Di Buono et al., 2000).

Another group of diet-derived sterols with potential biological effects are oxysterols (Vine et al., 1998), which are cholesterol oxidation products that can be found in cholesterol-rich processed foods such as dried egg yolk, although typical levels of oxysterols in the diet are generally low

(van de Bovenkamp et al., 1988). These cholesterol oxidation products can have major effects on cholesterol metabolism and have been shown to be highly atherogenic in animal models (Staprans et al., 2000; Vine et al., 1998). Their role in human nutrition remains to be established.

Overall, body cholesterol homeostasis is highly regulated by balancing intestinal absorption and endogenous synthesis with hepatic excretion of cholesterol and bile acids derived from hepatic cholesterol oxidation.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Given the capability of all tissues to synthesize sufficient cholesterol for their metabolic and structural needs, there is no evidence for a biological requirement for dietary cholesterol. As an example, many Tarahumara Indians of Mexico consume very low amounts of dietary cholesterol and have no reported developmental or health problems that could be attributed to this aspect of their diet (McMurry et al., 1982). Therefore, neither an Adequate Intake (AI) nor an Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) are set for cholesterol.

The question of whether cholesterol in the infant diet plays some essential role on lipid and lipoprotein metabolism that is relevant to growth and development or to the atherosclerotic process in adults has been difficult to resolve. The idea that the early diet might have relevance to later lipid metabolism was first raised by Hahn and Koldovský (1966) in prematurely weaned rat pups and later supported by observations that normal weaning to a high intake of cholesterol resulted in greater resistance to dietary cholesterol in later adulthood (Reiser and Sidelman, 1972; Reiser et al., 1979). This led to the hypothesis that cholesterol in human milk may play some important role in establishing regulation of cholesterol homeostasis. Since human milk typically provides about 100 to 200 mg/L (Table 9-1), whereas infant formulas contain very little cholesterol (10 to 30 mg/L) (Huisman et al., 1996; Wong et al., 1993), it is not surprising that plasma cholesterol concentrations are higher in infants fed human milk than in formula-fed infants. Formula-fed infants also have a higher rate of cholesterol synthesis (Bayley et al., 1998; Cruz et al., 1994; Wong et al., 1993). However, the available evidence suggests that this effect is transient. Differences in cholesterol synthesis and plasma cholesterol concentration are not sustained once complementary feeding is introduced (Darmady et al., 1972; Friedman and Goldberg, 1975; Mize et al., 1995). Also, no clinically significant effects on growth and development due to these differences in plasma cholesterol concentration have been noted between breast-fed and formula-fed infants under 1 year of age. One explanation may be that the developing brain synthesizes the cholesterol required for myelination in situ and does not take up cholesterol from

TABLE 9-1 Cholesterol Content in Term Human Milk of Women in the United States

Reference	*n*	Stage of Lactation	Cholesterol Content (mg/L)
Picciano et al., 1978	18	6–12 wk postpartum (pp)	
		Early morning	157
		Midday	151
		Evening	178
Mellies et al., 1979	33	1 mo pp	201
		2 mo pp	195
		3 mo pp	97
		4 mo pp	220
		5 mo pp	156
		6 mo pp	283
		7 mo pp	289
		8 mo pp	220
		9 mo pp	260
		10 mo pp	210
		11 mo pp	135
		12–13 mo pp	151
Clark et al., 1982	10	2 wk pp	110
		6 wk pp	97
		12 wk pp	103
		16 wk pp	104
Bitman et al., 1983	6	3 wk pp	122
		6 wk pp	112
		12 wk pp	103
Lammi-Keefe et al., 1990	6	8 wk pp	
		0600 h	88
		1000 h	107
		1400 h	111
		1800 h	110
		2200 h	112
Jensen et al., 1995	10	12 wk pp	
		0600–1000 h	140
		1000–1400 h	162
		1400–1800 h	217
		1800–2200 h	220
		2200–0600 h	129
Bayley et al., 1998	14	4 mo pp	120

plasma (Edmond et al., 1991; Haave and Innis, 2001; Jurevics and Morell, 1994).

The effects of early cholesterol intake and weaning on cholesterol metabolism later in life have been studied in a number of different animal species (Hamosh, 1988; Kris-Etherton et al., 1979; Mott et al., 1990) and in short-term studies with infants and children. Studies in baboons fed breast milk or formulas with or without cholesterol and with varying fat compositions found that early cholesterol intake had little effect on serum cholesterol concentrations in young adults up to about 8 years of age (Mott et al., 1990). However, adult baboons that had been breast fed had lower high density lipoprotein (HDL) cholesterol concentrations, higher very low density lipoprotein + low density lipoprotein (LDL):HDL ratios, and more extensive atherosclerotic lesions than those that had been formula fed (Lewis et al., 1988; Mott et al., 1990, 1995). These differences were not explained by variations in the saturated and unsaturated fat content of the formulas and milk. The major metabolic difference associated with the differences in plasma lipoproteins was lower rates of bile acid synthesis and excretion among the baboons that had been breast fed.

The possible relations of early breast and bottle feeding with later cholesterol concentrations and other coronary heart disease risk factors were explored in several short-term studies and larger retrospective epidemiological studies, but these observations are inconsistent (Fall et al., 1992; Kolaček et al., 1993; Leeson et al., 2001; Ravelli et al., 2000).

The relationship between early dietary cholesterol intake from milk or formula and serum cholesterol concentration in infancy and that observed in children and young adults following their usual diets was either absent (Andersen et al., 1979; Friedman and Goldberg, 1975; Glueck et al., 1972; Huttunen et al., 1983), in favor of formula feeding compared to breast feeding during infancy in 7- to 12-year-old children (Hodgson et al., 1976), or in favor of feeding human milk compared to formula feeding in men and women. The disparate findings may be due to confounding factors such as duration of breast feeding, since human-milk feeding for less than 3 months was associated with higher serum cholesterol concentrations in men at 18 to 23 years of age, or the type of formula fed since formula composition, especially quality of fat, which has changed dramatically in the last century (Kolaček et al., 1993). A follow-up study of nearly 6,000 elderly men for whom early feeding methods had been recorded found higher total and LDL cholesterol concentrations and increased risk of coronary heart disease (CHD) mortality in men who had been exclusively fed human milk than in those who had been fed human milk and bottle fed or fed human milk and weaned at 1 year of age. Men who had been exclusively bottle-fed during infancy also had higher total and LDL choles-

terol concentrations and CHD mortality than men who had previously been fed human milk (Fall et al., 1992).

The available data do not warrant a recommendation with respect to dietary cholesterol intake for infants who are not fed human milk. However, further research to identify possible mechanisms whereby early nutritional experiences affect the atherosclerotic process in adults, as well as the sensitive periods in development when this may occur, would be valuable.

INTAKE OF CHOLESTEROL

Food Sources

Cholesterol is present in foods of animal origin. High amounts of cholesterol are present in liver (375 mg/3 oz slice) and egg yolk (250 mg/yolk). Although generally low in total fat, some seafood, including shrimp, lobster, and certain fish, contain moderately high amounts of cholesterol (60 to 100 g/half-cup serving). One cup of whole milk contains approximately 30 mg of cholesterol, whereas the cholesterol contained in 2 percent and skim milk is 15 and 7 mg/cup, respectively. Therefore, products that contain milk (e.g., cheese, ice cream, and cottage cheese) are moderate sources of cholesterol. One tablespoon of butter contains approximately 12 mg of cholesterol, whereas margarine does not contain cholesterol. The majority of cholesterol is consumed from eggs and meat (FASEB, 1995).

Dietary Intake

Based on intake data from the Continuing Survey of Food Intakes by Individuals (1994–1996, 1998), the median cholesterol intake ranged from approximately 250 to 325 mg/d for men and 180 to 205 mg/d for women (Appendix Table E-15).

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Plasma Total, HDL, and LDL Cholesterol Concentrations

Numerous studies in humans have examined the effects of dietary cholesterol on plasma total and lipoprotein cholesterol concentrations (Tables 9-2 and 9-3, Figures 9-1 and 9-2), and empirical formulas have been derived to describe these relationships. Although most studies have

TABLE 9-2 Effects of Adding Dietary Cholesterol to Defined Diets with Strict Control of Dietary Intake on Serum Cholesterol Concentration

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Beveridge et al., 1960	6	13	81
	9	13	140
	9	13	280
	9	13	621
	6	13	1,282
	10	13	2,481
	9	13	4,490
Connor et al., 1961a	2	0	475
	2	0	950
	2	0	1,425
Connor et al., 1961b	3	0	2,400
	1	0	1,650
	1	0	1,900
	1	0	4,800
Steiner et al., 1962	6	0	3,000
Wells and Bronte-Stewart, 1963	3	0	17
	3	0	42
	3	0	67
	3	0	88
	3	0	142
	3	0	267
	3	0	517
	3	0	1,017
	3	0	1,517
	3	0	3,017
Connor et al., 1964	6	0	729
	5	0	725
Erickson et al., 1964	6	0	742
	6	0	742
Hegsted et al., 1965	10	116	570
	10	306	380
	10	116	570

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.06	30	0.08
0.10	30	0.08
1.17	30	0.08
0.43	30	0.08
0.59	30	0.08
1.20	30	0.08
0.87	30	0.08
1.71	40	0.76
1.64	40	0.76
1.99	40	0.76
1.47	40	0.88
2.43	40	0.88
2.97	40	0.88
2.53	40	0.88
1.30	40	0.68
0.44	15	
0.56	15	
0.66	15	
0.80	15	
0.96	15	
1.03	15	
1.18	15	
1.09	15	
1.29	15	
1.23	15	
1.03	40	0.25
0.74	40	1.7
0.61	41	1.6
0.69	41	1.6
0.75	39	5.4
0.29	39	0.05
0.70	39	0.68

continued

TABLE 9-2 Continued

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Keys et al., 1965	22	50	470
	22	50	1,410
	22	50	33
	22	50	1,400
	22	50	1,410
National Diet-Heart Study Research Group,1968	81	126	495
	81	126	495
	57	401	495
	57	154	495
Quintão et al., 1971	4	43	2,441
	1	43	499
	1	44	197
	2	53.5	4,002
Mattson et al., 1972	14	0	297
	14	0	594
	14	0	888
Anderson et al., 1976	12	3	291
	12	3	291
Nestel and Poyser, 1976	4	210	500
	2	257	500
	2	334	532
	1	103	439
Quintão et al., 1977	6	0	3,250
Bronsgeest-Schoute et al., 1979a, 1979b	21	98	567
	21	98	567
	9	124	607
	9	124	607
Lin and Connor, 1980	2	45	1,081
McMurry et al., 1981	12	0	600

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.36	40	
0.70	40	
0.41	40	
0.80	40	1.3
0.75	40	0.08
0.12	30	2.31
0.27	39	0.5
0.32	40	0.08
0.18	40	0.96
0.96	40	0.93
0.88	40	0.93
–0.80	40	0.93
0.13	40	0.93
0.34	39	0.31
0.61	39	0.31
1.05	39	0.31
0.23	35	0.26
0.21	35	4.7
1.56	40	1.9
0.25	40	1.9
0.76	40	1.9
0.67	40	1.9
0.74		
0.32	44	2
0.25	44	2
0.70	34	0.2
0.66	34	0.2
2.45	40	0.8
0.93	40	0.8

continued

TABLE 9-2 Continued

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
McMurry et al., 1982	8	0	905
Nestel et al., 1982	6	200	1,500
Schonfeld et al., 1982	11	300	750
	9	300	1,500
	6	300	750
	6	300	1,500
	6	300	750
	6	300	1,500
Maranhão and Quintdo, 1983	13	40	1,350
Applebaum-Bowden et al., 1984	9	137	897
Beynen and Katan, 1985b	6	114	526
Katan et al., 1986	94	110	500
Zanni et al., 1987	9	130	745
	9	130	745
Johnson and Greenland, 1990	10	200	400
Ginsberg et al., 1994	20	128	155
	20	128	340
	20	128	730
Sundram et al., 1994	17	192	7
	17	192	13
Fielding et al., 1995	20	200	403
	22	200	435
Ginsberg et al., 1995	13	108	169
	13	108	559

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.88	20	0.7
0.42	31	1
0.47	40	0.32
0.72	40	0.32
0.13	40	0.8
0.70	40	0.8
0.05	40	2.5
0.26	40	2.5
1.19	40	0.93
0.28	40	0.82
0.25	42	0.46
0.5	42	0.16
0.58	31	2.1
0.39	31	0.64
0.26	30	1.5
0.14	27	0.89
0.16	27	0.93
0.29	28	0.87
0.06	31	0.21
–0.35	31	0.25
0.50	39	0.81
0.76	36	0.28
0.16	28	0.89
0.41	28	0.86

TABLE 9-3 Effects of Adding Dietary Cholesterol to Self-Selected Diets with Strict Control of Dietary Intake on Serum Cholesterol Concentration

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Slater et al., 1976	25	314	482
Kummerow et al., 1977	21	250	470
Porter et al., 1977	55	301	235
	59	301	235
Flynn et al., 1979	56	260	540
	60	260	540
Mistry et al., 1981	37	522	1,500
	14	480	750
Roberts et al., 1981	16	196	532
Packard et al., 1983	7	180	1,290
Beynen and Katan, 1985a	6	207	1,596
	6	207	1,596
Oh and Miller, 1985	21	474	654
Edington et al., 1987	33	120	188
	135	120	188
McNamara et al., 1987	39	192	628
	36	288	575
Kestin et al., 1989	10	180	686
	15	204	735
Clifton et al., 1990	Normal: 11	185	681
	Hypercholesterolemic diet-insensitive: 22	185	681
	Hypercholesterolemic diet-sensitive: 23	185	681

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
–0.09		
0.05	40	
0.16	38	
0.03	38	
0.49	38	
0.00	38	
0.75	41	
0.62	41	
0.40	40	
1.47	38	0.17
0.48	46	0.5
0.61	46	0.5
0.27	35	0.62
0.13	26	0.8
0.12	35	0.6
0.16	35	1.45
0.13	35	0.27
–0.02	41	0.37
0.04	36	0.85
0.06	29	0.6
0.19	29	0.6
0.36	29	0.6

continued

TABLE 9-3 Continued

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Kern, 1994	8	585	2,393
	8	548	2,462
McCombs et al., 1994	12	213	938
	11	197	888
Clifton et al., 1995	67	151	691
	53	208	939
Sutherland et al., 1997	12	349	250
	14	349	250
Romano et al., 1998	10	200	800
	11	200	800

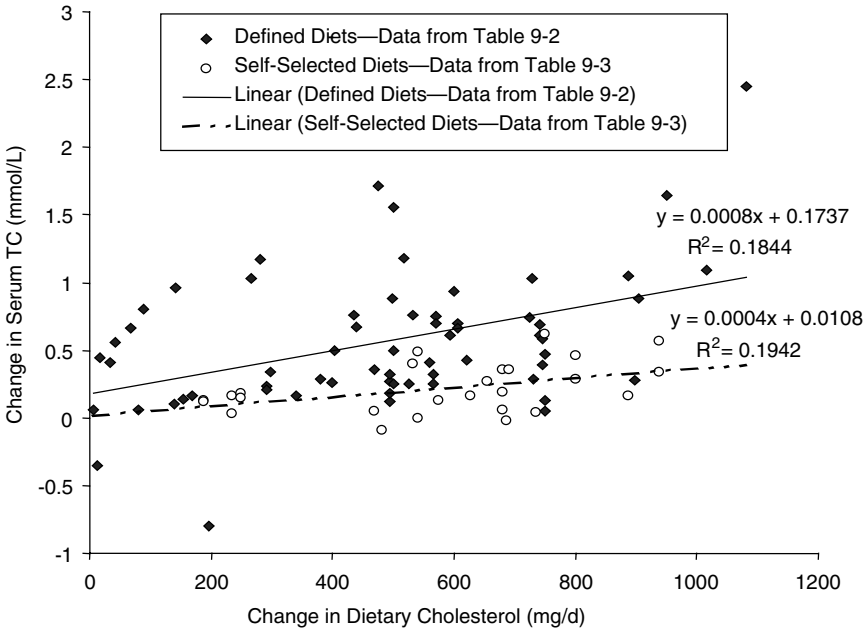

FIGURE 9-1 Relationship between change in dietary cholesterol (0 to 1,000 mg/d) and change in serum total cholesterol (TC) concentration.

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.14	44	0.59
–0.22	44	0.65
0.57	35	0.49
0.16	34	0.54
0.36	35	0.31
0.34	35	0.30
0.18	34	
0.15	34	
0.29	30	
0.46	30	

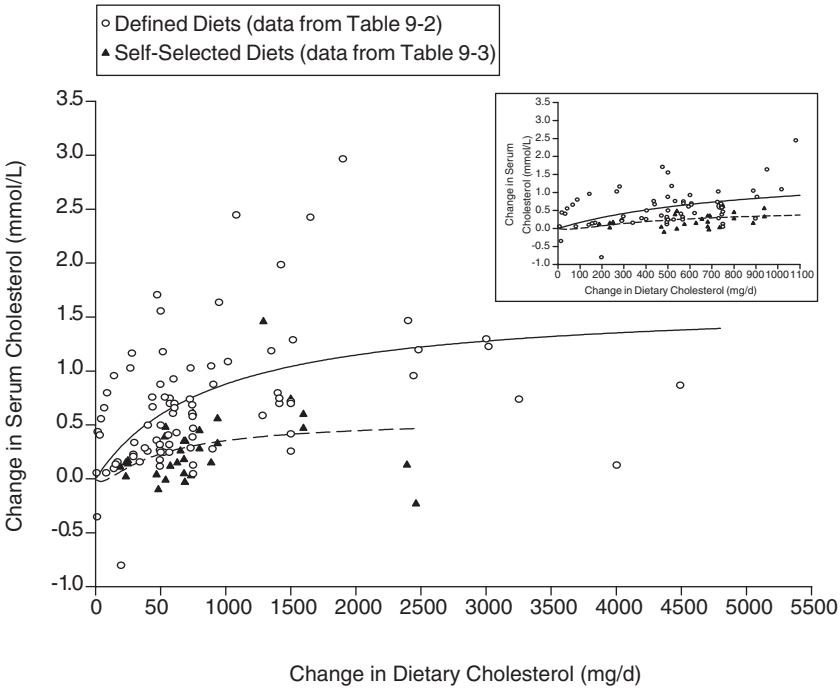

FIGURE 9-2 Relationship between change in dietary cholesterol (0 to 4,500 mg/d) and change in serum cholesterol (TC) concentration.

reported a linear relationship between changes in dietary cholesterol and total serum cholesterol concentration, other studies, including a meta-analysis of 27 controlled metabolic feeding studies of added dietary cholesterol (Hopkins, 1992), have indicated a curvilinear univariate relationship that is quasilinear in the range from 0 to 300 to 400 mg/d of added dietary cholesterol. The range of added dietary cholesterol in the studies was 17 to 4,800 mg/d. The meta-analysis also identified a diminishing increment of serum cholesterol with increasing baseline dietary cholesterol intake. With a baseline cholesterol intake of 0, the estimated increases in serum total cholesterol concentration for intakes from 100 to 400 mg/d of added dietary cholesterol were 0.16 to 0.51 mmol/L, whereas for a baseline cholesterol intake of 300 mg/d, the estimated increases in serum total cholesterol were 0.05 to 0.16 mmol/L (Hopkins, 1992). Another meta-analysis showed that dietary cholesterol raises the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol, therefore adversely affecting the cholesterol profile (Weggemans et al., 2001).

Other predictive formulas for the effect of 100 mg/d of added dietary cholesterol, which did not consider baseline cholesterol intake and are based on compilations of studies with a variety of experimental conditions, have yielded estimates of 0.1 mmol/L (Hegsted, 1986), 0.057 mmol/L (Howell et al., 1997), and 0.065 mmol/L (Clarke et al., 1997), the latter two involving meta-analyses with adjustment for other dietary variables. Furthermore, pooled analyses of the effects of 100 mg/d of added dietary cholesterol on plasma lipoprotein cholesterol concentrations (Clarke et al., 1997) indicated an estimated increase of 0.05 mmol/L in low density lipoprotein (LDL) and 0.01 mmol/L in HDL (ratio of 5 LDL:1 HDL). There is evidence that the increase in HDL is largely accounted for by higher levels of apoE-containing HDL particles (Mahley et al., 1978), but the significance in atherosclerosis protection is not established. Hegsted and coworkers (1993) reported that the majority of the increase in serum total cholesterol concentration with increased cholesterol intake was due to an increase in LDL cholesterol concentration.

The incremental serum cholesterol response to a given amount of dietary cholesterol appears to diminish as baseline serum cholesterol intake increases (Hopkins, 1992). There is also evidence from a number of studies that increases in serum cholesterol concentration due to dietary cholesterol are blunted by diets low in saturated fat, high in polyunsaturated fat, or both (Fielding et al., 1995; National Diet-Heart Study Research Group, 1968; Schonfeld et al., 1982), although this effect has not been observed by others (Kestin et al., 1989; McNamara et al., 1987).

There is considerable evidence for interindividual variation in serum cholesterol response to dietary cholesterol, ranging from 0 to greater than 100 percent (Hopkins, 1992). It has been reported that such responsive-

ness is relatively stable within individuals (Beynen and Katan, 1985b) and appears to be correlated with serum cholesterol response to saturated fatty acids (Katan et al., 1988). Intrinsic differences in intestinal cholesterol absorption (Sehayek et al., 1998), suppression of hepatic cholesterol synthesis by dietary cholesterol (Dietschy et al., 1993; McNamara et al., 1987; Nestel and Poyser, 1976; Quintão et al., 1971), and LDL catabolism (Dietschy et al., 1993; Mistry et al., 1981) may all contribute to the observed variation in dietary cholesterol response.

There is increasing evidence that genetic factors underlie a substantial portion of interindividual variation in response to dietary cholesterol. An instructive case is that of the Tarahumara Indians, who in addition to consuming a diet low in cholesterol, have both low intestinal cholesterol absorption and increased transformation of cholesterol to bile acids (McMurry et al., 1985). However, with an increase in dietary cholesterol from 0 to 905 mg/d, their average plasma cholesterol concentration increased 0.88 mmol/L (from 2.92 to 3.8 mmol/L), the same value predicted by the formula of Hopkins (1992), indicating the likelihood of above-average responsiveness of other aspects of cholesterol or lipoprotein metabolism.

Variations in several genes have been associated with altered responsiveness to dietary cholesterol. The common E4 polymorphism of the apoE gene has been associated with increased cholesterol absorption (Kesäniemi et al., 1987) and with increased plasma LDL cholesterol response to dietary saturated fat and cholesterol in some, but not all studies (Dreon and Krauss, 1997). The recent finding that apoE is of importance in regulating cholesterol absorption and bile acid formation in apoE knockout mice (Sehayek et al., 2000) lends support to a possible role for this gene in modulating dietary cholesterol responsiveness in humans. The A-IV-2 variant allele of the apo A-IV gene has been found to attenuate the plasma cholesterol response to dietary cholesterol (McCombs et al., 1994). Recently, the A-IV-2 allele has been associated with reduced intestinal cholesterol absorption in diets high in polyunsaturated fat but not in diets high in saturated fat (Weinberg et al., 2000). However, this has not been confirmed in other studies (Weggemans et al., 2000). Finally, the recent discovery that defects in the ABCG5 and ABCG8 genes can lead to markedly increased intestinal absorption of both cholesterol and plant sterols (Berge et al., 2000) points to the possibility that more common variants of these genes may contribute to variation in cholesterol absorption and dietary cholesterol response in the general population.

There are numerous other candidate genes that could modulate plasma lipid and lipoprotein response to dietary cholesterol by affecting cholesterol absorption, cellular cholesterol homeostasis, and plasma lipoprotein metabolism. Among the most likely candidates are those regulated

by lipid-responsive nuclear transcription factors, including sterol regulatory element-binding proteins, peroxisome proliferator-activated receptors, and orphan nuclear receptors. Studies in animal models have generated data in support of the possibility that variations among these genes may be of importance in influencing dietary cholesterol response in humans, but to date such human data are lacking. Nevertheless, the existence of marked interindividual variability in dietary cholesterol response among and within various animal models points to the likelihood that some of the mechanisms underlying this variability will also apply to humans.

Cardiovascular Disease and CHD

An association of dietary cholesterol with cardiovascular disease is based on several lines of evidence, including studies in animal models, epidemiological data in humans, and the effects of dietary cholesterol on plasma lipoproteins (Table 9-4). There is compelling evidence that dietary cholesterol can induce atherosclerosis in several animal species, including rabbits, pigs, nonhuman primates, and transgenic mice (Bocan, 1998; McNamara, 2000; Rudel, 1997). However, given the existence of marked inter- and intraspecies differences in cholesterol metabolism and atherogenic mechanisms, it is not possible to extrapolate these data directly to humans.

A number of prospective epidemiological studies have investigated the relationship of dietary cholesterol and other nutrients to the development of coronary heart disease (CHD) (reviewed in Kritchevsky and Kritchevsky, 2000; McNamara, 2000). Significant univariate relationships of cholesterol intake to risk for CHD have been observed in the Seven Countries Study (Kromhout et al., 1995) and the Honolulu Heart Program (McGee et al., 1984). A significant relative risk was also observed in the Western Electric Study, which remained significant after adjustment for a number of covariates, including dietary fat and serum cholesterol concentration (Stamler and Shekelle, 1988). More recently, in a study of 10,802 health-conscious men and women in the United Kingdom, a univariate relationship of cholesterol intake to ischemic heart disease mortality was observed (Mann et al., 1997).

However, a number of other epidemiological studies have not demonstrated a significant independent relationship of dietary cholesterol intake and CHD (Esrey et al., 1996; Kromhout and de Lezenne Coulander, 1984; Pietinen et al., 1997; Posner et al., 1991). In a cohort of 43,757 male health professionals, dietary cholesterol intake was significantly related to age-adjusted risk for myocardial infarction and fatal CHD ($p < 0.003$ and 0.002, respectively) across cholesterol quintiles ranging from median intakes of 189 to 422 mg/d (Ascherio et al., 1996). However, the risk was

attenuated with multivariate analyses ($p < 0.07$ and 0.03), which included other risk factors such as body mass index, smoking habits, alcohol consumption, physical activity, history of hypertension or high blood cholesterol, family history of myocardial infarction, and profession. The risk became insignificant after adjustment for fiber intake, which was reported to be significantly inversely related to CHD risk in this cohort. A similar cohort analysis in a group of 80,082 female nurses showed a positive but nonsignificant relationship between dietary cholesterol and CHD in quintiles of median intakes ranging from 132 to 273 mg/1,000 kcal/d (Hu et al., 1997). In both the male Health Professionals Follow-up Study and the female Nurses' Health Study cohorts, there was no relationship of egg intake to CHD risk with intakes of up to 1 egg/d (Hu et al., 1999). There was, however, a significant increase of CHD risk associated with higher ranges of egg consumption in patients with diabetes. This finding was corroborated in a European study, but after multivariate analysis adjusting for fiber intake, the association was no longer significant (Toeller et al., 1999).

Measures of atherosclerosis using imaging techniques have also been assessed in relation to diet. Angiographically assessed coronary artery disease progression over 39 months in 50 men was weakly related to cholesterol intake in univariate, but not multivariate, analysis (Watts et al., 1994). In 13,148 male and female participants in the Atherosclerosis Risk in Communities Study, carotid artery wall thickness, an index of early atherosclerosis, was significantly related to dietary cholesterol intake by univariate analyses; multivariate analysis was not performed (Tell et al., 1994).

The lack of consistency in observations relating dietary cholesterol intake to clinical cardiovascular disease and CHD endpoints may be due to many factors, including the limited ability to detect such effects (e.g., due to relatively small increases in LDL cholesterol concentration and inaccuracies in dietary intake data) and to the limited ability to distinguish the effects of dietary cholesterol independent of energy intake and other dietary variables that may be positively (e.g., saturated fat intake) or negatively (e.g., fiber intake) associated with dietary cholesterol and heart disease risk. Another uncertainty relates to interpreting the effects of dietary cholesterol on blood cholesterol concentrations. Evidence indicates that increased dietary cholesterol results, on average, in increased blood concentrations of both LDL and HDL cholesterol, and it is possible that the net impact on cardiovascular disease risk depends on the relative changes in these lipoproteins, as well as on other unmeasured mediators of atherogenesis. Finally, the considerable interindividual variation in lipid response to dietary cholesterol may result in differing outcomes in different populations or population subgroups.

TABLE 9-4 Dietary Cholesterol and Coronary Heart Disease (CHD)

Reference	Study Design	Diet Information
Kromhout and de Lezenne Coulander, 1984	Men, 40–59 y 14 cases 857 controls Cohort, 10-y follow-up	Dietary history
McGee et al., 1984	456 cases 6,632 controls Cohort, 10-y follow-up	24-h recall Adjusted for age
Kushi et al., 1985	Men 110 cases 891 controls Cohort, 20-y follow-up	Dietary history Adjusted for age and cohort
McGee et al., 1985	8,006 men Cohort, 10-y follow-up	24-h recall Adjusted for age
Posner et al., 1991	Men 45–55 y Cohort, 16-y follow-up	24-h recall Multivariate analysis
Tzonou et al., 1993	Men and women 329 cases 570 controls Case-control	Dietary history
Tell et al., 1994	Men and women, 45–64 y Cohort	Food frequency questionnaire
Watts et al., 1994	50 men 26 lipid-lowering diet 24 usual care Intervention	Dietary history

Results[a]		Comments
Mean cholesterol intake (mg/1,000 kcal)		No association between cholesterol intake and CHD
Cases	145	
Controls	143	
Mean cholesterol intake (mg/1,000 kcal)		Significant positive association between cholesterol intake and incidence of CHD
Cases	256	
Controls	241	
Mean cholesterol intake (mg/1,000 kcal)		Significantly greater cholesterol intake in CHD deaths
Cases	266	
Controls	248	
Cholesterol intake (mg/1,000 kcal)	Rate of CHD death (per 1,000)	Cholesterol intake as mg/1,000 kcal positively associated with CHD death, but not when intake measured as mg/d
< 125	≈ 8	
125–175	≈ 16	
175–225	≈ 14	
225–275	≈ 12	
275–325	≈ 13	
> 325	≈ 20	
Cholesterol intake (mg/d)	RR of CHD	No association between cholesterol intake and risk of CHD
300	1.0	
529	0.99	
Mean cholesterol intake (mg/d)		No association between cholesterol intake and CHD
	Men / Women	
Cases	345 / 322	
Controls	350 / 292	
		Cholesterol intake was positively associated with carotid artery wall thickness
Mean cholesterol intake (mg/d)		Cholesterol was positively associated with progression of coronary artery disease
Diet	215	
Usual	341	

continued

TABLE 9-4 Continued

Reference	Study Design	Diet Information
Ascherio et al., 1996	Men 40–75 y 734 cases Cohort, 6-y follow-up	Food frequency questionnaire Multivariate analysis (including fiber intake)
Esrey et al., 1996	52 cases, 30–59 y 3,873 controls 40 cases, 60–79 y 581 controls Cohort, 12-y follow-up	24-h recall Multivariate analysis
Hu et al., 1997	80,082 women, 34–59 y Cohort, 14-y follow-up	Food frequency questionnaire Multivariate analysis
Mann et al., 1997	Men and women, 16–79 y Prospective observation	Food frequency questionnaire Adjusted for age, sex, smoking, and social class
Pietinen et al., 1997	Smoking men, 50–69 y Cohort, 6.1-y follow-up	Food frequency questionnaire Multivariate analysis

Results[a]			Comments
Mean cholesterol intake (mg/d)		RR for MI or fatal CHD	No significant association between cholesterol intake and risk for MI or fatal CHD after adjustment for fiber intake
189		1.00	
246		0.86	
290		0.98	
338		0.94	
422		1.03	
Mean cholesterol intake (mg/d)			Cholesterol intake was not significantly associated with CHD mortality
Age (y)	30–59	60–79	
Cases	427	423	
Controls	416	355	
Quintile of cholesterol intake		RR of CHD	A positive but nonsignificant association between cholesterol intake and risk of CHD
1		1.00	
2		1.19	
3		1.14	
4		1.32	
5		1.25	
Tertile of cholesterol intake		IHD death rate ratio	Increased IHD mortality with increased cholesterol intake
1st		100	
2nd		181	
3rd		353	
Median cholesterol intake (mg/d)		RR of coronary death	No association between cholesterol intake and risk of coronary death
390		1.00	
477		0.90	
543		0.81	
621		0.86	
768		0.92	

continued

TABLE 9-4 Continued

Reference	Study Design	Diet Information
Hu et al., 1999	37,851 men, 40–75 y 866 cases Cohort, 8-y follow-up 80,082 women, 34–59 y 939 cases Cohort, 14-y follow-up	Food frequency questionnaire Multivariate analysis
Toeller et al., 1999	Diabetic men and women, 14–61 y Cross-sectional	3-d dietary records Multivariate analysis (including fiber intake)

[a] RR = relative risk, MI = myocardial infarction, IHD = ischemic heart disease, OR = odds ratio, CVD = cardiovascular disease.

Cancer

As shown in Tables 9-5 through 9-8, no consistent significant associations have been established between dietary cholesterol intake and cancer, including lung, breast, colon, and prostate. Several case-control studies have suggested that a high consumption of cholesterol may be associated with an increased risk of lung cancer (Alavanja et al., 1993; Byers et al., 1987; Goodman et al., 1988; Hinds et al., 1983; Jain et al., 1990). This positive association was shown in one cohort study (Shekelle et al., 1991), but not in three others (Heilbrun et al., 1984; Knekt et al., 1991; Wu et al., 1994).

Dose–Response Assessment

The main adverse effect of dietary cholesterol is increased serum LDL cholesterol concentration, which would be predicted to result in increased risk for CHD. Serum HDL concentration also increases, although to a

Results[a]			Comments
Egg intake (eggs/wk)	Mean cholesterol intake (mg/d)	RR of CHD	No significant association between egg consumption (up to 1 egg/d) and risk of CHD
Men			
< 1	237	1.00	
1	266	1.06	
2–4	330	1.12	
5–6	404	0.90	
≥ 7	536	1.08	
Women			
< 1	228	1.00	
1	258	0.82	
2–4	342	0.99	
5–6	436	0.95	
≥ 7	557	0.82	
Cholesterol intake (mg/d)	OR for CVD		No significant association between cholesterol intake and CVD risk after adjusting for fiber intake
15–236	1.00		
236–335	0.80		
335–461	0.86		
462–2,165	0.96		

lesser extent, but the impact of such a diet-induced change in CHD risk is uncertain.

As reviewed above, on average, an increase of 100 mg/d of dietary cholesterol is predicted to result in a 0.05 to 0.1 mmol/L increase in total serum cholesterol, of which approximately 80 percent is in the LDL fraction. This effect of added cholesterol is highly variable among individuals and is considerably attenuated at higher baseline cholesterol intakes. The LDL cholesterol concentration increase would predict approximately a 1 to 2 percent increase in CHD, with possibly offsetting effects of increased HDL cholesterol concentration. Epidemiological studies have limited power to detect effects of such magnitude and thus do not provide a meaningful basis for establishing adverse effects of dietary cholesterol. Therefore, it would seem reasonable to define the lowest-observed-adverse-effect level for dietary cholesterol as the lowest level shown to increase total or LDL cholesterol concentration. However, no studies have examined the effects of very small increments of dietary cholesterol in numbers of subjects sufficiently large enough to permit statistical treatment of the data. An increase

TABLE 9-5 Dietary Cholesterol and Risk of Lung Cancer

Reference	Study Design	Dietary and Other Information
Hinds et al., 1983	Men 188 cases 294 controls Case-control	Dietary history Adjusted for smoking, age, ethnicity, and occupational exposure
Heilbrun et al., 1984	Men 109 cases 7,420 controls Cohort, 15-y follow-up	24-h recall Adjusted for age and smoking
Byers et al., 1987	Men and women 450 cases 902 controls Case-control	Food frequency questionnaire Adjusted for age and smoking
Goodman et al., 1988	Men and women 336 cases 865 controls Case-control	Dietary history Adjusted for age, ethnicity, and pack-years of smoking
Jain et al., 1990	Men and women 839 cases 772 controls Case-control	Dietary history Adjusted for cumulative cigarette smoking
Knekt et al., 1991	Men 117 cases 4,421 controls Cohort, 20-y follow-up	Dietary history Adjusted for age, smoking, and energy intake

Results[a]			Comments
Cholesterol intake (mg/d)	RR of lung cancer		Increased lung cancer risk was positively associated with cholesterol intake
0–143	1.00		
144–285	1.65		
286–500	2.28		
≥ 501	3.50		
Cholesterol intake (mg/d)	RR of lung cancer		No significant association between lung cancer risk and cholesterol intake
0–299	1.00		
300–499	0.71		
500–749	0.99		
≥ 750	0.98		
Quartile of	RR of lung cancer		Weak but nonsignificant association between cholesterol intake and lung cancer risk in men, but not in women
cholesterol intake	Men	Women	
1 (low)	0.7	1.1	
2	0.9	1.7	
3	1.2	1.2	
4 (high)	1.0	1.0	
Mean cholesterol			Significant positive association between lung cancer risk and cholesterol intake in men, but not in women
intake (mg/d)	Men	Women	
Cases	385	249	
Controls	332	245	
Quartile of	OR for lung cancer		
cholesterol intake	Men	Women	
1 (low)	1.0	1.0	
2	2.3	0.6	
3	1.8	1.5	
4 (high)	2.2	0.9	
Cholesterol intake (mg/d)	OR for lung cancer		Significant increase in risk of lung cancer in highest quartile with cholesterol intake > 468 mg/d
< 235	1.00		
235–342	0.87		
343–468	0.99		
> 468	1.58		
Cholesterol intake (mg/d)	RR of lung cancer		Cholesterol intake was not associated with risk of lung cancer
< 441	1.00		
441–609	0.80		
> 609	1.03		

continued

TABLE 9-5 Continued

Reference	Study Design	Dietary and Other Information
Shekelle et al., 1991	Men 57 cases 1,821 controls Cohort, 24-y follow-up	Dietary history Adjusted for age, smoking, β-carotene intake, and percent of calories from fat
Alavanja et al., 1993	Women 429 cases 1,021 controls All nonsmokers Case-control	Food frequency questionnaire, Multivariate analysis
Wu et al., 1994	Women 212 cases Cohort, 6-y follow-up	Food frequency questionnaire Adjusted for age, smoking, occupation, physical activity, and total energy intake
Swanson et al., 1997	Women 587 cases 624 controls Case-control	Food frequency questionnaire Multivariate analysis

[a] RR = relative risk, M = men, W = women, OR = odds ratio.

in serum cholesterol concentration was observed with as little as 17 mg/d of cholesterol added to a cholesterol-free diet, but only three subjects were studied (Wells and Bronte-Stewart, 1963).

Serum cholesterol concentrations increase with increased dietary cholesterol (Figures 9-1 and 9-2), and the relationship of serum cholesterol concentration to CHD risk or mortality increases progressively (Neaton and Wentworth, 1992; Sorkin et al., 1992; Stamler et al., 1986; Weijenberg et al., 1996). Therefore, it is not appropriate to set a Tolerable Upper Intake Level (UL) for dietary cholesterol because increased risk may occur at a very low intake level and at a level that is exceeded by usual diets.

Results[a]		Comments
Cholesterol intake (mg/d)	RR of lung cancer	Cholesterol intake (specific to consumption of eggs) was positively associated with risk of lung cancer
198–604	1.00	
605–794	1.30	
795–1,909	1.94	
Cholesterol intake (mg/d)	OR for lung cancer	No significant association between cholesterol intake and risk of lung cancer
< 120	1.00	
120–162	0.63	
163–214	0.71	
215–302	1.14	
> 302	1.09	
Quartile of cholesterol intake	RR of lung cancer	Cholesterol intake was not associated with risk of lung cancer
1 (low)	1.0	
2	0.6	
3	0.9	
4 (high)	0.9	
Cholesterol intake (mg/1,000 kcal)	RR of lung cancer	Cholesterol intake was not associated with risk of lung cancer
< 102	1.00	
102–126	1.21	
127–148	0.88	
149–176	1.04	
> 176	1.22	

RISK CHARACTERIZATION

Intakes above an identified Tolerable Upper Intake Level (UL) indicate a potential risk of an adverse health effect. There is much evidence to indicate a positive linear trend between cholesterol intake and low density lipoprotein cholesterol concentration, and therefore increased risk of coronary heart disease (CHD). A UL is not set for cholesterol because any incremental increase in cholesterol intake increases CHD risk. Because cholesterol is unavoidable in ordinary, nonvegan diets, eliminating cholesterol in the diet would require significant changes in patterns of dietary intake. Such significant adjustments may introduce undesirable effects (e.g., inadequate intakes of protein and certain micronutrients) and unknown and unquantifiable health risks. Nonetheless, it is possible to

TABLE 9-6 Dietary Cholesterol and Risk of Breast Cancer

Reference	Study Design	Dietary and Other Information
Hirohata et al., 1987	Caucasian women 161 cases 161 hospital controls 161 neighborhood controls Case-control	Dietary history
Jones et al., 1987	Women 99 cases 5,386 controls Cohort, mean 10-y follow-up	24-h recall Multivariate analysis
Willett et al., 1987	Women 601 cases Cohort, 6-y follow-up	Food frequency questionnaire Multivariate analysis
van den Brandt et al., 1993	Women 55–69 y Cohort, 3.3-y follow-up	Food frequency questionnaire Multivariate analysis
Franceschi et al., 1996	Women 2,569 cases 2,588 controls Case-control	Food frequency questionnaire Multivariate analysis

[a] RR = relative risk, OR = odds ratio.

have a diet low in cholesterol while consuming a nutritionally adequate diet. Dietary guidance for minimizing cholesterol intake is provided in Chapter 11.

RESEARCH RECOMMENDATIONS

- Studies are needed to identify possible mechanisms whereby early nutritional experiences, such as dietary cholesterol, affect the atherosclerotic

Results[a]		Comments
Mean cholesterol intake (mg/d)		No significant differences in cholesterol intake between breast cancer cases and controls
Cases 286		
Controls 267–289		
Cholesterol intake (mg/d)	RR of breast cancer	No association between cholesterol intake and risk of breast cancer
< 130	1.00	
130–233	1.33	
233–415	0.79	
> 415	0.70	
Mean cholesterol intake (mg/d)	RR of breast cancer	No association between cholesterol intake and breast cancer
204	1.00	
262	1.06	
325	1.02	
345	1.07	
436	0.91	
Quintile of cholesterol intake	RR of breast cancer	No association between cholesterol intake and risk of breast cancer
1	1.00	
2	0.84	
3	0.85	
4	0.85	
5	1.09	
Cholesterol intake (mg/d)	OR for breast cancer	No association between cholesterol intake and risk of breast cancer
< 224	1.00	
225–281	0.93	
282–335	0.90	
336–414	0.97	
> 414	0.91	

process in adults and the sensitive periods in development when this may occur.

- The molecular mechanisms that regulate absorption of dietary cholesterol need to be determined.
- Specific genetic variants that contribute to wide interindividual variation in low density lipoprotein (LDL) cholesterol response to dietary cholesterol need to be delineated.

TABLE 9-7 Dietary Cholesterol and Risk of Colon Cancer

Reference	Study Design	Dietary and Other Information
Willett et al., 1990	Women Cohort, 6-y follow-up	Food frequency questionnaire Adjusted for age and total energy intake
Sandler et al., 1993	Men and women 236 cases 409 controls Case-control	Food frequency questionnaire Adjusted for age, alcohol intake, body mass index, and calories
Giovannucci et al., 1994	Men 205 cases Cohort, 6-y follow-up	Food frequency questionnaire Adjusted for age and total energy intake
Le Marchand et al., 1997	698 male case-control pairs 494 female case-control pairs Case-control	Food frequency questionnaire Multivariate analysis
Pietinen et al., 1999	Male smokers Cohort, 8-y follow-up	Food frequency questionnaire Multivariate analysis

[a] RR = relative risk, OR = odds ratio.

Results[a]			Comments
Cholesterol intake (mg/d)	RR of colon cancer		Increased risk of colon cancer associated with cholesterol intake > 406 mg/d
< 247	1.00		
247–299	1.09		
300–344	0.75		
345–406	1.07		
> 406	1.39		
Cholesterol intake (mg/d)	OR for colorectal adenomas		No association between cholesterol intake and risk of colorectal adenomas
< 156	1.0		
156–189	0.78		
190–227	0.73		
228–289	0.89		
> 289	0.99		
Quintile/median cholesterol intake (mg/d)	RR of colon cancer		No association between cholesterol intake and risk of colon cancer
1/198	1.0		
2/262	1.27		
3/313	0.99		
4/369	1.07		
5/467	1.07		
Quartile of cholesterol intake from eggs	OR for colorectal cancer		Cholesterol intake (limited to cholesterol from eggs) was positively associated with risk of colorectal cancer
	Men	Women	
1 (low)	1.0	1.0	
2	1.8	1.3	
3	1.8	1.5	
4 (high)	2.0	2.0	
Quartile/median cholesterol intake (mg/d)	RR of colorectal cancer		No association between cholesterol intake and risk of colorectal cancer
1/378	1.0		
2/501	1.2		
3/594	1.1		
4/759	1.0		

TABLE 9-8 Dietary Cholesterol and Risk of Prostate Cancer

Reference	Study Design	Dietary and Other Information
Kolonel et al., 1988	452 cases 899 controls Case-control	Dietary history Adjusted for age and ethnicity
Andersson et al., 1996	522 cases 536 controls Case-control	Food frequency questionnaire Adjusted for age and energy
Key et al., 1997	328 cases 328 controls Case-control	Food frequency questionnaire
Vlajinac et al., 1997	101 cases 202 controls Case-control	Dietary history Adjusted for energy and significant nutrients

[a] OR = odds ratio.

- Other factors (dietary and constitutional) that contribute to the wide interindividual variation in LDL cholesterol response to dietary cholesterol also need to be delineated.
- Studies are needed to better define the relation between dietary cholesterol intakes and LDL cholesterol concentrations over a broad range of cholesterol intakes, from very low to high.
- The relationship between dietary cholesterol intakes and body pools of cholesterol needs to be determined.

REFERENCES

Alavanja MCR, Brown CC, Swanson C, Brownson RC. 1993. Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. *J Natl Cancer Inst* 85:1906–1916.

Andersen GE, Lifschitz C, Friis-Hansen B. 1979. Dietary habits and serum lipids during first 4 years of life. A study of 95 Danish children. *Acta Paediatr Scand* 68:165–170.

Results[a]			Comments
Quartile of cholesterol intake	Age and OR for prostate cancer ≤ 70	≧ 70	Significant positive association between cholesterol intake and risk of prostate cancer, but no clear gradient effect
1 (low)	1.0	1.0	
2	1.2	1.6	
3	1.2	1.7	
4 (high)	1.3	1.6	
Cholesterol intake (mg/d)	OR for prostate cancer		No association between cholesterol intake and risk of prostate cancer
< 241	1.00		
241–301	0.71		
302–390	0.85		
> 390	0.96		
Mean cholesterol intake (mg/d)			No significant difference in cholesterol intake between prostate cancer cases andcontrols
Cases 341			
Controls 351			
Tertile of cholesterol intake	OR for prostate cancer		No significant association between cholesterol intake and risk of prostate cancer
1	1.00		
2	0.97		
3	0.60		

Anderson JT, Grande F, Keys A. 1976. Independence of the effects of cholesterol and degree of saturation of the fat in the diet on serum cholesterol in man. *Am J Clin Nutr* 29:1184–1189.

Andersson S-O, Wolk A, Bergström R, Giovannucci E, Lindgren C, Baron J, Adami H-O. 1996. Energy, nutrient intake and prostate cancer risk: A population-based case-control study in Sweden. *Int J Cancer* 68:716–722.

Applebaum-Bowden D, Haffner SM, Hartsook E, Luk KH, Albers JJ, Hazzard WR. 1984. Down-regulation of the low-density lipoprotein receptor by dietary cholesterol. *Am J Clin Nutr* 39:360–367.

Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. 1996. Dietary fat and risk of coronary heart disease in men: Cohort follow up study in the United States. *Br Med J* 313:84–90.

Bayley TM, Alasmi M, Thorkelson T, Krug-Wispe S, Jones PJH, Bulani JL, Tsang RC. 1998. Influence of formula versus breast milk on cholesterol synthesis rates in four-month-old infants. *Pediatr Res* 44:60–67.

Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH. 2000. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 290:1771–1775.

Beveridge JMR, Connell WF, Mayer GA, Haust HL. 1960. The response of man to dietary cholesterol. *J Nutr* 71:61–65.

Beynen AC, Katan MB. 1985a. Effect of egg yolk feeding on the concentration and composition of serum lipoproteins in man. *Atherosclerosis* 54:157–166.

Beynen AC, Katan MB. 1985b. Reproducibility of the variations between humans in the response of serum cholesterol to cessation of egg consumption. *Atherosclerosis* 57:19–31.

Bitman J, Wood L, Hamosh M, Hamosh P, Mehta NR. 1983. Comparison of the lipid composition of breast milk from mothers of term and preterm infants. *Am J Clin Nutr* 38:300–312.

Bocan TMA. 1998. Animal models of atherosclerosis and interpretation of drug intervention studies. *Curr Pharm Des* 4:37–52.

Bronsgeest-Schoute DC, Hautvast JGAJ, Hermus RJJ. 1979a. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man. I. Effects of dietary cholesterol in a linoleic acid-rich diet. *Am J Clin Nutr* 33:2183–2187.

Bronsgeest-Schoute DC, Hermus RJJ, Dallinga-Thie GM, Hautvast JGAJ. 1979b. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man. II. Effects of dietary cholesterol in a linoleic acid-poor diet. *Am J Clin Nutr* 33:2188–2192.

Brown MS, Goldstein JL. 1999. A proteolytic pathway that controls the cholesterol content of membranes, cells, and blood. *Proc Natl Acad Sci USA* 96:11041–11048.

Byers TE, Graham S, Haughey BP, Marshall JR, Swanson MK. 1987. Diet and lung cancer risk: Findings from the Western New York Diet Study. *Am J Epidemiol* 125:351–363.

Clark RM, Ferris AM, Fey M, Brown PB, Hundrieser KE, Jensen RG. 1982. Changes in the lipids of human milk from 2 to 16 weeks postpartum. *J Pediatr Gastroenterol Nutr* 1:311–315.

Clarke R, Frost C, Collins R, Appleby P, Peto R. 1997. Dietary lipids and blood cholesterol: Quantitative meta-analysis of metabolic ward studies. *Br Med J* 314:112–117.

Clifton PM, Kestin M, Abbey M, Drysdale M, Nestel PJ. 1990. Relationship between sensitivity to dietary fat and dietary cholesterol. *Arteriosclerosis* 10:394–401.

Clifton PM, Abbey M, Noakes M, Beltrame S, Rumbelow N, Nestel PJ. 1995. Body fat distribution is a determinant of the high-density lipoprotein response to dietary fat and cholesterol in women. *Arterioscler Thromb Vasc Biol* 15:1070–1078.

Connor WE, Hodges RE, Bleiler RE. 1961a. Effect of dietary cholesterol upon serum lipids in man. *J Lab Clin Med* 57:331–342.

Connor WE, Hodges RE, Bleiler RE. 1961b. The serum lipids in men receiving high cholesterol and cholesterol-free diets. *J Clin Invest* 40:894–901.

Connor WE, Stone DB, Hodges RE. 1964. The interrelated effects of dietary cholesterol and fat upon human serum lipid levels. *J Clin Invest* 43:1691–1696.

Cruz MLA, Wong WW, Mimouni F, Hachey DL, Setchell KDR, Klein PD, Tsang RC. 1994. Effects of infant nutrition on cholesterol synthesis rates. *Pediatr Res* 35:135–140.

Darmady JM, Fosbrooke AS, Lloyd JK. 1972. Prospective study of serum cholesterol levels during first year of life. *Br Med J* 2:685–688.

Di Buono M, Jones PJH, Beaumier L, Wykes LJ. 2000. Comparison of deuterium incorporation and mass isotopomer distribution analysis for measurement of human cholesterol biosynthesis. *J Lipid Res* 41:1516–1523.

Dietschy JM, Turley SD, Spady DK. 1993. Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans. *J Lipid Res* 34:1637–1659.

Dreon DM, Krauss RM. 1997. Diet-gene interactions in human lipoprotein metabolism. *J Am Coll Nutr* 16:313–324.

Edington J, Geekie M, Carter R, Benfield L, Fisher K, Ball M, Mann J. 1987. Effect of dietary cholesterol on plasma cholesterol concentration in subjects following reduced fat, high fibre diet. *Br Med J* 294:333–336.

Edmond J, Korsak RA, Morrow JW, Torok-Both G, Catlin DH. 1991. Dietary cholesterol and the origin of cholesterol in the brain of developing rats. *J Nutr* 121:1323–1330.

Erickson BA, Coots RH, Mattson FH, Kligman AM. 1964. The effect of partial hydrogenation of dietary fats, of the ratio of polyunsaturated to saturated fatty acids, and of dietary cholesterol upon plasma lipids in man. *J Clin Invest* 43:2017–2025.

Esrey KL, Joseph L, Grover SA. 1996. Relationship between dietary intake and coronary heart disease mortality: Lipid research clinics prevalence follow-up study. *J Clin Epidemiol* 49:211–216.

Fall CHD, Barker DJP, Osmond C, Winter PD, Clark PMS, Hales CN. 1992. Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. *Br Med J* 304:801–805.

FASEB (Federation of American Societies for Experimental Biology). 1995. *Third Report on Nutrition Monitoring in the United States.* Washington, DC: U.S. Government Printing Office.

Fielding CJ, Havel RJ, Todd KM, Yeo KE, Schloetter MC, Weinberg V, Frost PH. 1995. Effects of dietary cholesterol and fat saturation on plasma lipoproteins in an ethnically diverse population of healthy young men. *J Clin Invest* 95:611–618.

Flynn MA, Nolph GB, Flynn TC, Kahrs R, Krause G. 1979. Effect of dietary egg on human serum cholesterol and triglycerides. *Am J Clin Nutr* 32:1051–1057.

Franceschi S, Favero A, Decarli A, Negri E, La Vecchia C, Ferraroni M, Russo A, Salvini S, Amadori D, Conti E, Montella M, Giacosa A. 1996. Intake of macronutrients and risk of breast cancer. *Lancet* 347:1351–1356.

Friedman G, Goldberg SJ. 1975. Concurrent and subsequent serum cholesterols of breast- and formula-fed infants. *Am J Clin Nutr* 28:42–45.

Ginsberg HN, Karmally W, Siddiqui M, Holleran S, Tall AR, Rumsey SC, Deckelbaum RJ, Blaner WS, Ramakrishnan R. 1994. A dose-response study of the effects of dietary cholesterol on fasting and postprandial lipid and lipoprotein metabolism in healthy young men. *Arterioscler Thromb* 14:576–586.

Ginsberg HN, Karmally W, Siddiqui M, Holleran S, Tall AR, Blaner WS, Ramakrishnan R. 1995. Increases in dietary cholesterol are associated with modest increases in both LDL and HDL cholesterol in healthy young women. *Arterioscler Thromb Vasc Biol* 15:169–178.

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. 1994. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54:2390–2397.

Glueck CJ, Tsang R, Balistreri W, Fallat R. 1972. Plasma and dietary cholesterol in infancy: Effects of early low or moderate dietary cholesterol intake on subsequent response to increased dietary cholesterol. *Metabolism* 21:1181–1192.

Goodman MT, Kolonel LN, Yoshizawa CN, Hankin JH. 1988. The effect of dietary cholesterol and fat on the risk of lung cancer in Hawaii. *Am J Epidemiol* 128:1241–1255.

Haave NC, Innis SM. 2001. Cholesterol synthesis and accretion within various tissues of the fetal and neonatal rat. *Metabolism* 50:12–18.

Hahn P, Koldovský O. 1966. *Utilization of Nutrients During Postnatal Development.* New York: Pergamon Press.

Hamosh M. 1988. Does infant nutrition affect adiposity and cholesterol levels in the adult? *J Pediatr Gastroenterol Nutr* 7:10–16.

Hauser H, Dyer JH, Nandy A, Vega MA, Werder M, Bieliauskaite E, Weber FE, Compassi S, Gemperli A, Boffelli D, Wehrli E, Schulthess G, Phillips MC. 1998. Identification of a receptor mediating absorption of dietary cholesterol in the intestine. *Biochemistry* 37:17843–17850.

Hegsted DM. 1986. Serum-cholesterol response to dietary cholesterol: A re-evaluation. *Am J Clin Nutr* 44:299–305.

Hegsted DM, McGandy RB, Myers ML, Stare FJ. 1965. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr* 17:281–295.

Hegsted DM, Ausman LM, Johnson JA, Dallal GE. 1993. Dietary fat and serum lipids: An evaluation of the experimental data. *Am J Clin Nutr* 57:875–883.

Heilbrun LK, Nomura AMY, Stemmermann GN. 1984. Dietary cholesterol and lung cancer risk among Japanese men in Hawaii. *Am J Clin Nutr* 39:375–379.

Hinds MW, Kolonel LN, Lee J, Hankin JH. 1983. Dietary cholesterol and lung cancer risk among men in Hawaii. *Am J Clin Nutr* 37:192–193.

Hirohata T, Nomura AMY, Hankin JH, Kolonel LN, Lee J. 1987. An epidemiological study on the association between diet and breast cancer. *J Natl Cancer Inst* 78:595–600.

Hodgson PA, Ellefson RD, Elveback LR, Harris LE, Nelson RA, Weidman WH. 1976. Comparison of serum cholesterol in children fed high, moderate, or low cholesterol milk diets during neonatal period. *Metabolism* 25:739–746.

Hopkins PN. 1992. Effects of dietary cholesterol on serum cholesterol: A meta-analysis and review. *Am J Clin Nutr* 55:1060–1070.

Howell WH, McNamara DJ, Tosca MA, Smith BT, Gaines JA. 1997. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: A meta-analysis. *Am J Clin Nutr* 65:1747–1764.

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. 1997. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 337:1491–1499.

Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, Rosner BA, Spiegelman D, Speizer FE, Sacks FM, Hennekens CH, Willett WC. 1999. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *J Am Med Assoc* 281:1387–1394.

Huisman M, van Beusekom CM, Lanting CI, Nijeboer HJ, Muskiet FAJ, Boersma ER. 1996. Triglycerides, fatty acids, sterols, mono- and disaccharides and sugar alcohols in human milk and current types of infant formula milk. *Eur J Clin Nutr* 50:255–260.

Huttunen JK, Saarinen UM, Kostiainen E, Siimes MA. 1983. Fat composition of the infant diet does not influence subsequent serum lipid levels in man. *Atherosclerosis* 46:87–94.

Jain M, Burch JD, Howe GR, Risch HA, Miller AB. 1990. Dietary factors and risk of lung cancer: Results from a case-control study, Toronto, 1981–1985. *Int J Cancer* 45:287–293.

Jensen RG, Lammi-Keefe CJ, Ferris AM, Jackson MB, Couch SC, Capacchione CM, Ahn HS, Murtaugh M. 1995. Human milk total lipid and cholesterol are dependent on interval of sampling during 24 hours. *J Pediatr Gastroenterol Nutr* 20:91–94.

Johnson C, Greenland P. 1990. Effects of exercise, dietary cholesterol, and dietary fat on blood lipids. *Arch Intern Med* 150:137–141.

Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, Hoover R, Taylor PR. 1987. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey. I. Epidemiologic follow-up study. *J Natl Cancer Inst* 79:465–471.

Jurevics HA, Morell P. 1994. Sources of cholesterol for kidney and nerve during development. *J Lipid Res* 35:112–120.

Katan MB, Beynen AC, De Vries JHM, Nobels A. 1986. Existence of consistent hypo- and hyperresponders to dietary cholesterol in man. *Am J Epidemiol* 123:221–234.

Katan MB, Berns MAM, Glatz JFC, Knuiman JT, Nobels A, de Vries JHM. 1988. Congruence of individual responsiveness to dietary cholesterol and to saturated fat in humans. *J Lipid Res* 29:883–892.

Kern F. 1994. Effects of dietary cholesterol on cholesterol and bile acid homeostasis in patients with cholesterol gallstones. *J Clin Invest* 93:1186–1194.

Kesäniemi YA, Ehnholm C, Miettinen TA. 1987. Intestinal cholesterol absorption efficiency in man is related to apoprotein E phenotype. *J Clin Invest* 80:578–581.

Kestin M, Clifton PM, Rouse IL, Nestel PJ. 1989. Effect of dietary cholesterol in normolipidemic subjects is not modified by nature and amount of dietary fat. *Am J Clin Nutr* 50:528–532.

Key TJA, Silcocks PB, Davey GK, Appleby PN, Bishop DT. 1997. A case-control study of diet and prostate cancer. *Br J Cancer* 76:678–687.

Keys A, Anderson JT, Grande F. 1965. Serum cholesterol response to changes in the diet. II. The effect of cholesterol in the diet. *Metabolism* 14:759–765.

Kita T, Brown MS, Bilheimer DW, Goldstein JL. 1982. Delayed clearance of very low density and intermediate density lipoproteins with enhanced conversion to low density lipoprotein in WHHL rabbits. *Proc Natl Acad Sci USA* 79:5693–5697.

Kolaček S, Kapetanović T, Zimolo A, Lužar V. 1993. Early determinants of cardiovascular risk factors in adults. A. Plasma lipids. *Acta Paediatr* 82:699–704.

Kolonel LN, Yoshizawa CN, Hankin JH. 1988. Diet and prostatic cancer: A case-control study in Hawaii. *Am J Epidemiol* 127:999–1012.

Knekt P, Seppänen R, Järvinen R, Virtamo J, Hyvönen L, Pukkala E, Teppo L. 1991. Dietary cholesterol, fatty acids, and the risk of lung cancer among men. *Nutr Cancer* 16:267–275.

Kris-Etherton PM, Layman DK, York PV, Frantz ID. 1979. The influence of early nutrition on the serum cholesterol of the adult rat. *J Nutr* 109:1244–1257.

Kritchevsky SB, Kritchevsky D. 2000. Egg consumption and coronary heart disease: An epidemiologic overview. *J Am Coll Nutr* 19:549S–555S.

Kromhout D, de Lezenne Coulander C. 1984. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men. The Zutphen Study. *Am J Epidemiol* 119:733–741.

Kromhout D, Menotti A, Bloemberg B, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Giampaoli S, Jansen A, Karvonen M, Katan M, Nissinen A, Nedeljkovic S, Pekkanen J, Pekkarinen M, Punsar S, Räsänen L, Simic B, Toshima H. 1995. Dietary saturated and *trans* fatty acids and cholesterol and 25-year mortality from coronary heart disease: The Seven Countries Study. *Prev Med* 24:308–315.

Kummerow FA, Kim Y, Hull J, Pollard J, Ilinov P, Dorossiev DL, Valek J. 1977. The influence of egg consumption on the serum cholesterol level in human subjects. *Am J Clin Nutr* 30:664–673.

Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. 1985. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. *N Engl J Med* 312:811–818.

Lammi-Keefe CJ, Ferris AM, Jensen RG. 1990. Changes in human milk at 0600, 1000, 1400, 1800, and 2200 h. *J Pediatr Gastroenterol Nutr* 11:83–88.

Leeson CPM, Kattenhorn M, Deanfield JE, Lucas A. 2001. Duration of breast feeding and arterial distensibility in early adult life: Population based study. *Br Med J* 322:643–647.

Le Marchand L, Wilkens LR, Hankin JH, Kolonel LN, Lyu L-C. 1997. A case-control study of diet and colorectal cancer in a multiethnic population in Hawaii (United States): Lipids and foods of animal origin. *Cancer Causes Control* 8:637–648.

Lewis DS, Mott GE, McMahan CA, Masoro EJ, Carey KD, McGill HC. 1988. Deferred effects of preweaning diet on atherosclerosis in adolescent baboons. *Arteriosclerosis* 8:274–280.

Lin DS, Connor WE. 1980. The long term effects of dietary cholesterol upon the plasma lipids, lipoproteins, cholesterol adsorption, and the sterol balance in man: The demonstration of feedback inhibition of cholesterol biosynthesis and increased bile acid excretion. *J Lipid Res* 21:1042–1052.

Ling WH, Jones PJH. 1995. Dietary phytosterols: A review of metabolism, benefits, and side effects. *Life Sci* 57:195–206.

Lütjohann D, Björkhem I, Ose L. 1996. Phytosterolaemia in a Norwegian family: Diagnosis and characterization of the first Scandinavian case. *Scand J Clin Lab Invest* 56:229–240.

Mahley RW, Innerarity TL, Bersot TP, Lipson A, Margolis S. 1978. Alterations in human high-density lipoproteins, with or without increased plasma-cholesterol, induced by diets high in cholesterol. *Lancet* 2:807–809.

Mann JI, Appleby PN, Key TJ, Thorogood M. 1997. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart* 78:450–455.

Maranhão RC, Quintão ECR. 1983. Long term steroid metabolism balance studies in subjects on cholesterol-free and cholesterol-rich diets: Comparison between normal and hypercholesterolemic individuals. *J Lipid Res* 24:167–173.

Mattson FH, Erickson BA, Kligman AM. 1972. Effect of dietary cholesterol on serum cholesterol in man. *Am J Clin Nutr* 25:589–594.

McCombs RJ, Marcadis DE, Ellis J, Weinberg RB. 1994. Attenuated hypercholesterolemic response to a high-cholesterol diet in subjects heterozygous for the apolipoprotein A-IV-2 allele. *N Engl J Med* 331:706–710.

McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. 1984. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. *Am J Epidemiol* 119:667–676.

McGee D, Reed D, Stemmerman G, Rhoads G, Yano K, Feinleib M. 1985. The relationship of dietary fat and cholesterol to mortality in 10 years: The Honolulu Heart Program. *Int J Epidemiol* 14:97–105.

McMurry MP, Connor WE, Goplerud CP. 1981. The effects of dietary cholesterol upon the hypercholesterolemia of pregnancy. *Metabolism* 30:869–879.

McMurry MP, Connor WE, Cerqueira MT. 1982. Dietary cholesterol and the plasma lipids and lipoproteins in the Tarahumara Indians: A people habituated to a low cholesterol diet after weaning. *Am J Clin Nutr* 35:741–744.

McMurry MP, Connor WE, Lin DS, Cerqueira MT, Connor SL. 1985. The absorption of cholesterol and the sterol balance in the Tarahumara Indians of Mexico fed cholesterol-free and high cholesterol diets. *Am J Clin Nutr* 41:1289–1298.

McNamara DJ. 2000. Dietary cholesterol and atherosclerosis. *Biochim Biophys Acta* 1529:310–320.

McNamara DJ, Kolb R, Parker TS, Batwin H, Samuel P, Brown CD, Ahrens EH. 1987. Heterogeneity of cholesterol homeostasis in man. Response to changes in dietary fat quality and cholesterol quantity. *J Clin Invest* 79:1729–1739.

Mellies MJ, Burton K, Larsen R, Fixler D, Glueck CJ. 1979. Cholesterol, phytosterols, and polyunsaturated/saturated fatty acid ratios during the first 12 months of lactation. *Am J Clin Nutr* 32:2383–2389.

Miettinen TA, Gylling H. 1999. Regulation of cholesterol metabolism by dietary plant sterols. *Curr Opin Lipidol* 10:9–14.

Mistry P, Miller NE, Laker M, Hazzard WR, Lewis B. 1981. Individual variation in the effects of dietary cholesterol on plasma lipoproteins and cellular cholesterol homeostasis in man. Studies of low density lipoprotein receptor activity and 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in blood mononuclear cells. *J Clin Invest* 67:493–502.

Mize CE, Uauy R, Kramer R, Benser M, Allen S, Grundy SM. 1995. Lipoprotein-cholesterol responses in healthy infants fed defined diets from ages 1 to 12 months: Comparison of diets predominant in oleic acid versus linoleic acid, with parallel observations in infants fed a human milk-based diet. *J Lipid Res* 36:1178–1187.

Mott GE, Jackson EM, McMahan CA, McGill HC. 1990. Cholesterol metabolism in adult baboons is influenced by infant diet. *J Nutr* 120:243–251.

Mott GE, Jackson EM, DeLallo L, Lewis DS, McMahan CA. 1995. Differences in cholesterol metabolism in juvenile baboons are programmed by breast-versus formula-feeding. *J Lipid Res* 36:299–307.

National Diet-Heart Study Research Group. 1968. Faribault second study. National Diet-Heart Study final report. *Circulation* 37:I260–I274.

Neaton JD, Wentworth D. 1992. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 152:56–64.

Nestel PJ, Poyser A. 1976. Changes in cholesterol synthesis and excretion when cholesterol intake is increased. *Metabolism* 25:1591–1599.

Nestel P, Tada N, Billington T, Huff M, Fidge N. 1982. Changes in very low density lipoproteins with cholesterol loading in man. *Metabolism* 31:398–405.

Oh SY, Miller LT. 1985. Effect of dietary egg on variability of plasma cholesterol levels and lipoprotein cholesterol. *Am J Clin Nutr* 42:421–431.

Packard CJ, McKinney L, Carr K, Shepherd J. 1983. Cholesterol feeding increases low density lipoprotein synthesis. *J Clin Invest* 72:45–51.

Picciano MF, Guthrie HA, Sheehe DM. 1978. The cholesterol content of human milk. A variable constituent among women and within the same women. *Clin Pediatr* 17:359–362.

Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. 1997. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol* 145:876–887.

Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, Virtamo J. 1999. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 10:387–396.

Porter MW, Yamanaka W, Carlson SD, Flynn MA. 1977. Effect of dietary egg on serum cholesterol and triglyceride of human males. *Am J Clin Nutr* 30:490–495.

Posner BM, Cobb JL, Belanger AJ, Cupples LA, D'Agostino RB, Stokes J. 1991. Dietary lipid predictors of coronary heart disease in men. The Framingham Study. *Arch Intern Med* 151:1181–1187.

Quintão E, Grundy SM, Ahrens EH. 1971. Effects of dietary cholesterol on the regulation of total body cholesterol in man. *J Lipid Res* 12:233–247.

Quintão ECR, Brumer S, Stechhahn K. 1977. Tissue storage and control of cholesterol metabolism in man on high cholesterol diets. *Atherosclerosis* 26:297–310.

Ravelli ACJ, van der Meulen JHP, Osmond C, Barker DJP, Bleker OP. 2000. Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. *Arch Dis Child* 82:248–252.

Reiser R, Sidelman Z. 1972. Control of serum cholesterol homeostasis by cholesterol in the milk of the suckling rat. *J Nutr* 102:1009–1016.

Reiser R, O'Brien BC, Henderson GR, Moore RW. 1979. Studies on a possible function for cholesterol in milk. *Nutr Rept Int* 19:835–849.

Repa JJ, Mangelsdorf DJ. 2000. The role of orphan nuclear receptors in the regulation of cholesterol homeostasis. *Annu Rev Cell Dev Biol* 16:459–481.

Repa JJ, Turley SD, Lobaccaro J-MA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, Mangelsdorf DJ. 2000. Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. *Science* 289:1524–1529.

Roberts SL, McMurry MP, Connor WE. 1981. Does egg feeding (i.e., dietary cholesterol) affect plasma cholesterol levels in humans? The results of a double-blind study. *Am J Clin Nutr* 34:2092–2099.

Romano G, Tilly-Kiesi MK, Patti L, Taskinen M-R, Pacioni D, Cassader M, Riccardi G, Rivellese AA. 1998. Effects of dietary cholesterol on plasma lipoproteins and their subclasses in IDDM patients. *Diabetologia* 41:193–200.

Ros E. 2000. Intestinal absorption of triglyceride and cholesterol. Dietary and pharmacological inhibition to reduce cardiovascular risk. *Atherosclerosis* 151:357–379.

Rudel LL. 1997. Genetic factors influence the atherogenic response of lipoproteins to dietary fat and cholesterol in nonhuman primates. *J Am Coll Nutr* 16:306–312.

Salen G, Ahrens EH, Grundy SM. 1970. Metabolism of β-sitosterol in man. *J Clin Invest* 49:952–967.

Salen G, Shefer S, Nguyen L, Ness GC, Tint GS, Shore V. 1992. Sitosterolemia. *J Lipid Res* 33:945–955

Sandler RS, Lyles CM, Peipins LA, McAuliffe CA, Woosley JT, Kupper LL. 1993. Diet and risk of colorectal adenomas: Macronutrients, cholesterol, and fiber. *J Natl Cancer Inst* 85:884–891.

Schonfeld G, Patsch W, Rudel LL, Nelson C, Epstein M, Olson RE. 1982. Effects of dietary cholesterol and fatty acids on plasma lipoproteins. *J Clin Invest* 69:1072–1080.

Sehayek E, Nath C, Heinemann T, McGee M, Seidman CE, Samuel P, Breslow JL. 1998. U-shape relationship between change in dietary cholesterol absorption and plasma lipoprotein responsiveness and evidence for extreme interindividual variation in dietary cholesterol absorption in humans. *J Lipid Res* 39:2415–2422.

Sehayek E, Shefer S, Nguyen LB, Ono JG, Merkel M, Breslow JL. 2000. Apolipoprotein E regulates dietary cholesterol absorption and biliary cholesterol excretion: Studies in C57BL/6 apolipoprotein E knockout mice. *Proc Natl Acad Sci USA* 97:3433–3437.

Shekelle RB, Rossof AH, Stamler J. 1991. Dietary cholesterol and incidence of lung cancer: The Western Electric Study. *Am J Epidemiol* 134:480–484.

Slater G, Mead J, Dhopeshwarkar G, Robinson S, Alfin-Slater RB. 1976. Plasma cholesterol and triglycerides in men with added eggs in the diet. *Nutr Rep Int* 14:249–260.

Sorkin JD, Andres R, Muller DC, Baldwin HL, Fleg JL. 1992. Cholesterol as a risk factor for coronary heart disease in elderly men. The Baltimore Longitudinal Study of Aging. *Ann Epidemiol* 2:59–67.

Stamler J, Shekelle R. 1988. Dietary cholesterol and human coronary heart disease. The epidemiologic evidence. *Arch Pathol Lab Med* 112:1032–1040.

Stamler J, Wentworth D, Neaton JD. 1986. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *J Am Med Assoc* 256:2823–2828.

Staprans I, Pan X-M, Rapp JH, Grunfeld C, Feingold KR. 2000. Oxidized cholesterol in the diet accelerates the development of atherosclerosis in LDL receptor- and apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 20:708–714.

Steiner A, Howard EJ, Akgun S. 1962. Importance of dietary cholesterol in man. *J Am Med Assoc* 181:186–190.

Sundram K, Hayes KC, Siru OH. 1994. Dietary palmitic acid results in lower serum cholesterol than does a lauric-myristic acid combination in normolipemic humans. *Am J Clin Nutr* 59:841–846.

Sutherland WHF, Ball MJ, Walker H. 1997. The effect of increased egg consumption on plasma cholesteryl ester transfer activity in healthy subjects. *Eur J Clin Nutr* 51:172–176.

Swanson CA, Brown CC, Sinha R, Kulldorff M, Brownson RC, Alavanja MCR. 1997. Dietary fats and lung cancer risk among women: The Missouri Women's Health Study (United States). *Cancer Causes Control* 8:883–893.

Tell GS, Evans GW, Folsom AR, Shimakawa T, Carpenter MA, Heiss G. 1994. Dietary fat intake and carotid artery wall thickness: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol* 139:979–989.

Toeller M, Buyken AE, Heitkamp G, Scherbaum WA, Krans HMJ, Fuller JH. 1999. Associations of fat and cholesterol intake with serum lipid levels and cardiovascular disease: The EURODIAB IDDM Complications Study. *Exp Clin Endocrinol Diabetes* 107:512–521.

Tzonou A, Kalandidi A, Trichopoulou A, Hsieh C-C, Toupadaki N, Willett W, Trichopoulos D. 1993. Diet and coronary heart disease: A case-control study in Athens, Greece. *Epidemiology* 4:511–516.

van de Bovenkamp P, Kosmeijer-Schuil TG, Katan MB. 1988. Quantification of oxysterols in Dutch foods: Egg products and mixed diets. *Lipids* 23:1079–1085.

van den Brandt PA, van't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJJ, Sturmans F. 1993. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. *Cancer Res* 53:75–82.

Vine DF, Mamo JCL, Beilin LJ, Mori TA, Croft KD. 1998. Dietary oxysterols are incorporated in plasma triglyceride-rich lipoproteins, increase their susceptibility to oxidation and increase aortic cholesterol concentration of rabbits. *J Lipid Res* 39:1995–2004.

Vlajinac HD, Marinkovic´ JM, Ilic´ MD, Kocev NI. 1997. Diet and prostate cancer: A case-control study. *Eur J Cancer* 33:101–107.

Watts GF, Jackson P, Mandalia S, Brunt JNH, Lewis ES, Coltart DJ, Lewis B. 1994. Nutrient intake and progression of coronary artery disease. *Am J Cardiol* 73:328–332.

Weggemans RM, Zock PL, Meyboom S, Funke H, Katan MB. 2000. Apolipoprotein A4-1/2 polymorphism and response of serum lipids to dietary cholesterol in humans. *J Lipid Res* 41:1623–1628.

Weggemans RM, Zock PL, Katan MB. 2001. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr* 73:885–891.

Weijenberg MP, Feskens EJM, Kromhout D. 1996. Total and high density lipoprotein cholesterol as risk factors for coronary heart disease in elderly men during 5 years of follow-up. The Zutphen Elderly Study. *Am J Epidemiol* 143:151–158.

Weinberg RB, Geissinger BW, Kasala K, Hockey KJ, Terry JG, Easter L, Crouse JR. 2000. Effect of apolipoprotein A-IV genotype and dietary fat on cholesterol absorption in humans. *J Lipid Res* 41:2035–2041.

Wells VM, Bronte-Stewart B. 1963. Egg yolk and serum-cholesterol levels: Importance of dietary cholesterol intake. *Br Med J* 1:577–581.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. 1987. Dietary fat and the risk of breast cancer. *N Engl J Med* 316:22–28.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. 1990. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 323:1664–1672.

Wong WW, Hachey DL, Insull W, Opekun AR, Klein PD. 1993. Effect of dietary cholesterol on cholesterol synthesis in breast-fed and formula-fed infants. *J Lipid Res* 34:1403–1411.

Wu Y, Zheng W, Sellers TA, Kushi LH, Bostick RM, Potter JD. 1994. Dietary cholesterol, fat, and lung cancer incidence among older women: The Iowa Women's Health Study (United States). *Cancer Causes Control* 5:395–400.

Zanni EE, Zannis VI, Blum CB, Herbert PN, Breslow JL. 1987. Effect of egg cholesterol and dietary fats on plasma lipids, lipoproteins, and apoproteins of normal women consuming natural diets. *J Lipid Res* 28:518–527.

10
Protein and Amino Acids

SUMMARY

Protein is the major structural component of all cells in the body. Proteins also function as enzymes, in membranes, as transport carriers, and as hormones; and their component amino acids serve as precursors for nucleic acids, hormones, vitamins, and other important molecules. The Recommended Dietary Allowance (RDA) for both men and women is 0.80 g of good quality protein/kg body weight/d and is based on careful analyses of available nitrogen balance studies. For amino acids, isotopic tracer methods and linear regression analysis were used whenever possible to determine the requirements. The estimated average requirements for amino acids were used to develop amino acid scoring patterns for various age groups based on the recommended intake of dietary protein. The recommended protein digestibility corrected amino acid scoring pattern (PDCAAS) for proteins for children 1 year of age and older and all other age groups is as follows (in mg/g of protein): isoleucine, 25; leucine, 55; lysine, 51, methionine + cysteine (SAA), 25; phenylalanine + tyrosine, 47; threonine, 27; tryptophan, 7; valine, 32; and histidine, 18. While an upper range for total protein in the diet as a percent of total energy intake was set at no more than 35 percent to decrease risk of chronic disease (see Chapter 11), there were insufficient data to provide dose–response relationships to establish a Tolerable Upper Intake Level (UL) for total protein or for any of the amino acids. However, the absence of a UL means that caution is warranted in using any single amino acid at levels significantly above that normally found in food.

BACKGROUND INFORMATION

Chemistry of Proteins and Amino Acids

Protein

Protein is the major functional and structural component of all the cells of the body; for example, all enzymes, membrane carriers, blood transport molecules, the intracellular matrices, hair, fingernails, serum albumin, keratin, and collagen are proteins, as are many hormones and a large part of membranes. Moreover, the constituent amino acids of protein act as precursors of many coenzymes, hormones, nucleic acids, and other molecules essential for life. Thus an adequate supply of dietary protein is essential to maintain cellular integrity and function, and for health and reproduction.

Proteins in both the diet and body are more complex and variable than the other energy sources, carbohydrates and fats. The defining characteristic of protein is its requisite amino (or imino) nitrogen group. The average content of nitrogen in dietary protein is about 16 percent by weight, so nitrogen metabolism is often considered to be synonymous with protein metabolism. Carbon, oxygen, and hydrogen are also abundant elements in proteins, and there is a smaller proportion of sulfur.

Proteins are macromolecules consisting of long chains of amino acid subunits. The structures for the common L-amino acids found in typical dietary proteins are shown in Figure 10-1. In the protein molecule, the amino acids are joined together by peptide bonds, which result from the elimination of water between the carboxyl group of one amino acid and the α-amino (or imino in the case of proline) group of the next in line. In biological systems, the chains formed might be anything from a few amino acid units (di, tri, or oligopeptide) to thousands of units long (polypeptide), corresponding to molecular weights ranging from hundreds to hundreds of thousands of Daltons. The sequence of amino acids in the chain is known as the primary structure.

A critical feature of proteins is the complexity of their physical structures. Polypeptide chains do not exist as long straight chains, nor do they curl up into random shapes, but instead fold into a definite three-dimensional structure. The chains of amino acids tend to coil into helices (secondary structure) due to hydrogen bonding between side chain residues, and sections of the helices may fold on each other due to hydrophobic interactions between nonpolar side chains and, in some proteins, to disulfide bonds so that the overall molecule might be globular or rod-like (tertiary structure). Their exact shape depends on their function and for some proteins, their interaction with other molecules (quaternary structure).

Name	Abbreviation	Form
Aliphatic side chains		
Glycine	Gly	$H-CH(NH_2)-COOH$
Alanine	Ala	$CH_3-CH(NH_2)-COOH$
Valine[a]	Val	$(CH_3)_2CH-CH(NH_2)-COOH$
Leucine[a]	Leu	$(CH_3)_2CH-CH_2-CH(NH_2)-COOH$
Isoleucine[a]	Ile	$CH_3-CH_2-CH(CH_3)-CH(NH_2)-COOH$
Aromatic side chains		
Phenylalanine	Phe	$C_6H_5-CH_2-CH(NH_2)-COOH$
Tyrosine	Tyr	$HO-C_6H_4-CH_2-CH(NH_2)-COOH$
Tryptophan	Trp	$C_8H_6N-CH_2-CH(NH_2)-COOH$
Hydroxyl groups in side chains		
Serine	Ser	$CH_2(OH)-CH(NH_2)-COOH$
Threonine	Thr	$CH_3-CH(OH)-CH(NH_2)-COOH$
Sulfur-containing side chains		
Cysteine[b]	Cys	$HS-CH_2-CH(NH_2)-COOH$
Methionine	Met	$CH_3-S-CH_2-CH_2-CH(NH_2)-COOH$
Imino Acids		
Proline[c]	Pro	$C_4H_7N-COOH$
Acidic side chains and their amides		
Glutam	Glu	$HOOC-CH_2-CH_2-CH(NH_2)-COOH$
Glutamine	Gln	$H_2N-C(=O)-CH_2-CH_2-CH(NH_2)-COOH$
Aspartic acid	Asp	$HOOC-CH_2-CH(NH_2)-COOH$
Asparagione	Asn	$H_2N-C(=O)-CH_2-CH(NH_2)-COOH$
Basic side chains		
Lysine	Lys	$H_2N-CH_2-CH_2-CH_2-CH_2-CH(NH_2)-COOH$
Arginine	Arg	$H_2N-C(=NH)-NH-CH_2-CH_2-CH_2-CH(NH_2)-COOH$
Histidine	His	$C_3H_3N_2-CH_2-CH(NH_2)-COOH$

Amino acids in italics are classed as nutritionally indispensable to humans.
[a] Leucine, valine, and isoleucine are known as the branched-chain amino acids.
[b] Cysteine is often found as a dimer (cysteine), linked through sulfur atoms (-S-S-) by oxidation.
[c] Proline is, strictly speaking, an imino acid rather than an amino acid.

FIGURE 10-1 L-amino acids of nutritional significance.

Many proteins are composed of several separate peptide chains held together by ionic or covalent links, an example being hemoglobin, in which each active unit consists of two pairs of dissimilar subunits (the α and β chains).

The most important aspect of a protein from a nutritional point of view is its amino acid composition, but the protein's structure may also influence its digestibility. Some proteins, such as keratin, are highly insoluble in water and hence are resistant to digestion, while highly glycosylated proteins, such as the intestinal mucins, are resistant to attack by the proteolytic enzymes of the intestine.

Amino Acids

The amino acids that are incorporated into mammalian protein are α-amino acids, with the exception of proline, which is an α-imino acid. This means that they have a carboxyl group, an amino nitrogen group, and a side chain attached to a central α-carbon (Figure 10-1). Functional differences among the amino acids lie in the structure of their side chains. In addition to differences in size, these side groups carry different charges at physiological pH (e.g., nonpolar, uncharged but polar, negatively charged, positively charged); some groups are hydrophobic (e.g., branched chain and aromatic amino acids) and some hydrophilic (most others).

These side chains have an important bearing on the ways in which the higher orders of protein structure are stabilized and are intimate parts of many other aspects of protein function. Attractions between positive and negative charges pull different parts of the molecule together. Hydrophobic groups tend to cluster together in the center of globular proteins, while hydrophilic groups remain in contact with water on the periphery. The ease with which the sulfhydryl group in cysteine forms a disulfide bond with the sulfhydryl group of another cysteine in a polypeptide chain is an important factor in the stabilization of folded structures within the polypeptide and is a crucial element in the formation of inter-polypeptide bonds. The hydroxyl and amide groups of amino acids provide the sites for the attachment of the complex oligosaccharide side chains that are a feature of many mammalian proteins such as lactase, sucrase, and the mucins. Histidine and amino acids with the carboxyl side chains (glutamic acid and aspartic acid) are critical features in ion-binding proteins, such as the calcium-binding proteins (e.g., troponin C), critical for muscular contraction, and the iron-binding proteins (e.g., hemoglobin) responsible for oxygen transport.

Some amino acids in protein only achieve their final structure after their precursors have been incorporated into the polypeptide. Notable examples of such post-translational modifications are the hydroxyproline

and hydroxylysine residues found in collagen (proline and lysine are converted to these after they have been incorporated into procollagen) and 3-methylhistidine present in actin and myosin. The former hydroxylated amino acids are critical parts of the cross-linking of collagen chains that lead to rigid and stable structures. The role of methylated histidine in contractile protein function is unknown.

Nutritional and Metabolic Classification of Amino Acids

Older views of the nutritional classification of amino acids categorized them into two groups: indispensable (essential) and dispensable (nonessential). The nine indispensable amino acids (Table 10-1) are those that have carbon skeletons that cannot be synthesized to meet body needs from simpler molecules in animals, and therefore must be provided in the diet. Although the classification of the indispensable amino acids and their assignment into a single category has been maintained in this report, the definition of dispensable amino acids has become blurred as more information on the intermediary metabolism and nutritional characteristics of these compounds has accumulated. Laidlaw and Kopple (1987) divided dispensable amino acids into two classes: truly dispensable and conditionally indispensable. Five of the amino acids in Table 10-1 are termed dispensable as they can be synthesized in the body from either other amino

TABLE 10-1 Indispensable, Dispensable, and Conditionally Indispensable Amino Acids in the Human Diet

Indispensable	Dispensable	Conditionally Indispensable[a]	Precursors of Conditionally Indispensable
Histidine[b]	Alanine	Arginine	Glutamine/glutamate, asparate
Isoleucine	Aspartic acid	Cysteine	Methionine, serine
Leucine	Asparagine	Glutamine	Gl utamic acid/ammonia
Lysine	Glutamic acid	Glycine	Serine, choline
Methionine	Serine	Proline	Glutamate
Phenylalanine		Tyrosine	Phenylalanine
Threonine			
Tryptophan			
Valine			

[a] Conditionally indispensable is defined as requiring a dietary source when endogenous synthesis cannot meet metabolic need.
[b] Although histidine is considered indispensable, unlike the other eight indispensable amino acids, it does not fulfill the criteria used in this report of reducing protein deposition and inducing negative nitrogen balance promptly upon removal from the diet.
SOURCE: Laidlaw and Kopple (1987).

acids or other complex nitrogenous metabolites. In addition, six other amino acids, including cysteine and tyrosine, are conditionally indispensable as they are synthesized from other amino acids or their synthesis is limited under special pathophysiological conditions (Chipponi et al., 1982; Harper, 1983; Laidlaw and Kopple, 1987). This is even more of an issue in the neonate where it has been suggested that only alanine, aspartate, glutamate, serine, and probably asparagine are truly dietarily dispensable (Pencharz et al., 1996).

The term conditionally indispensable recognizes the fact that under most normal conditions the body can synthesize these amino acids to meet metabolic needs. However, there may be certain physiological circumstances: prematurity in the young infant where there is an inadequate rate at which cysteine can be produced from methionine; the newborn, where enzymes that are involved in quite complex synthetic pathways may be present in inadequate amounts as in the case of arginine (Brunton et al., 1999), which results in a dietary requirement for this amino acid; or pathological states, such as severe catabolic stress in an adult, where the limited tissue capacity to produce glutamine to meet increased needs and to balance increased catabolic rates makes a dietary source of these amino acids required to achieve body nitrogen homeostasis. The cells of the small intestine become important sites of conditionally indispensable amino acid, synthesis, with some amino acids (e.g., glutamine and arginine) becoming nutritionally indispensable under circumstances of intestinal metabolic dysfunction (Stechmiller et al., 1997). However, the quantitative requirement levels for conditionally indispensable amino acids have not been determined and these, presumably, vary greatly according to the specific condition.

There now appears to be a requirement for preformed α-amino nitrogen in the form of glutamate, alanine, or aspartate, for example (Katagiri and Nakamura, 2002). It was previously thought that, in addition to the indispensable amino acids, simple sources of nitrogen such as urea and diammonium citrate together with carbon sources would be sufficient to maintain nitrogen homeostasis (FAO/WHO, 1965). However, there are now good theoretical reasons to conclude that this is not likely in the human (Katagiri and Nakamura, 2002). The mixture of dispensable and conditionally indispensable amino acids as supplied by food proteins at adequate intakes of total nitrogen will assure that both the nitrogen and specific amino acid needs are met.

Protein and Amino Acid Homeostasis

Maintenance of Body Protein

Body Protein Reserve. The body of a 70-kg man contains about 11 kg of protein. Nearly half of this protein (about 43 percent) is present as skeletal muscle, while other structural tissues such as skin and blood each contain approximately 15 percent of the total protein (Lentner, 1981). The metabolically active visceral tissues (e.g., liver and kidney) contain comparatively small amounts of protein (together about 10 percent of the total). Other organs such as the brain, lung, heart, and bone contribute the remainder. The distribution among the organs varies with developmental age, as the newborn infant has proportionately less muscle and much more brain and visceral tissue than the adult. It is also notable that, despite the very wide variety of enzymes and proteins within a single organism, almost one half of the total protein content of the human is present in just four proteins (myosin, actin, collagen, and hemoglobin). Collagen in particular may comprise 25 percent of the total. Moreover, in induced malnutrition, this proportion can rise to 50 percent because of the substantial loss of noncollagen proteins, whereas collagen itself is retained (Picou et al., 1966).

Even in the adult, when the protein mass of the body has reached a plateau, it can be influenced by a variety of nutritional and pathological factors. Thus, when diets high or low in protein are given, there is a gain or loss of body protein over the first few days, before re-equilibration of protein intake with the rates of oxidation and excretion (Swick and Benevenga, 1977). This phenomenon has led to the concept of a "labile protein reserve," which can be gained or lost from the body as a short-term store for use in emergencies or to take account of day-to-day variations in dietary intake. Studies in animals have suggested that this immediate labile protein store is contained in the liver and visceral tissues, as their protein content decreases very rapidly during starvation or protein depletion (by as much as 40 percent), while skeletal muscle protein drops much more slowly (Swick and Benevenga, 1977). During this situation, protein breakdown becomes a source of indispensable amino acid needs for synthesis of proteins critical to maintaining essential body function (Reeds et al., 1994).

This labile protein reserve in humans is unlikely to account for more than about 1 percent of total body protein (Waterlow, 1969; Young et al., 1968). Thus, the immediately accessible stores of protein (which serve as the source of indispensable amino acids and amino nitrogen) cannot be considered in the same light as the huge energy stores in the form of body fat; the labile protein reserve is similar in weight to the glycogen store. However, it should be recognized that this protein reserve is unlike the fat

and glycogen stores, whose primary roles are for energy use. The protein lost during fasting is functional body protein and thus there is no evidence for a protein reserve that serves only as a store to meet future needs.

There is a wide range of variation in daily dietary protein intake, from the protein requirement and beyond, to which the body is able to adapt over a period of days, after which no further change in body protein content occurs. However, pathological conditions, such as severe disease states, can cause substantial rates of protein loss due to the increased demand for either amino acids or carbon skeletons to meet local energy demands. If these conditions go unchecked for more than a few days, there may be a serious depletion of the body's protein mass, which might eventually become life threatening. Although the evidence from short-term changes in diet suggests that the main loss of protein is from the viscera (de Blaauw et al., 1996), in chronic illness skeletal muscle, which comprises over 40 percent of the protein mass of a healthy individual, becomes the largest single contributor to protein loss (Hansen et al., 2000).

Free Amino Acids. Although the free amino acids dissolved in the body fluids are only a very small proportion of the body's total mass of amino acids, they are very important for the nutritional and metabolic control of the body's proteins.

The content of free and protein-bound amino acids in rat muscle is shown in Table 10-2. It can be seen that their ranges are considerable and that their concentrations in the free pool are in no way related to their concentrations in body proteins. In the human, free phenylalanine comprises less than 2 percent of its total body pool, and corresponds to only about 1.5 hour worth of protein synthesis, or 25 percent of the day's intake of protein (Waterlow et al., 1978). Free glutamate and alanine comprise a larger proportion of their respective body pools, but they could not be considered as reserves for more than a very short time. In human muscle, glutamine has an exceptionally large free pool, containing about 10 to 15 g of nitrogen. After trauma, this pool can become depleted by more than 50 percent (Labow and Souba, 2000); its loss may then make a significant contribution to the total loss of nitrogen.

Although the plasma compartment is most easily sampled, the concentration of most amino acids is higher in tissue intracellular pools. Typically, large neutral amino acids, such as leucine and phenylalanine, are essentially in equilibrium with the plasma. Others, notably glutamine, glutamic acid, and glycine, are 10- to 50-fold more concentrated in the intracellular pool. Dietary variations or pathological conditions can result in substantial changes in the concentrations of the individual free amino acids in both the plasma and tissue pools (Furst, 1989; Waterlow et al., 1978).

TABLE 10-2 Comparison of the Pool Sizes of Free and Protein-Bound Amino Acids in Rat Muscle

	μmol/g Wet Weight		
	Protein	Free	Protein: Free Ratio
Indispensable amino acids			
Histidine	26	0.39	67
Isoleucine	50	0.16	306
Leucine	109	0.20	556
Lysine	58	1.86	31
Methionine	36	0.16	225
Phenylalanine	45	0.07	646
Threonine	60	1.94	31
Valine	83	0.31	272
Dispensable and some conditionally indispensable amino acids			
Alanine	111	2.77	40
Arginine	67	0.25	269
Aspartic acid (+ amide)	110	1.13	97
Glutamic acid (+ amide)	148	9.91	15
Glycine	117	1.94	60
Serine	74	1.96	38
Tyrosine	36	0.14	266

SOURCE: Data of E.B. Fern, quoted by Waterlow et al. (1978).

Pathways of Amino Acid Metabolism

The exchange between body protein and the free amino acid pool is illustrated by the highly simplified scheme shown in Figure 10-2. Here, all the proteins in the tissues and circulation are grouped into one pool. Similarly, there is a second pool, consisting of the free amino acids dissolved in body fluids. The arrows into and out of the protein pool show the continual degradation and resynthesis of these macromolecules (i.e., protein turnover). The other major pathways that involve the free amino acid pool are the supply of amino acids by the gut from the absorbed amino acids derived from dietary proteins, the de novo synthesis in cells (including those of the gut, which are a source of dispensable amino acids), and the loss of amino acids by oxidation, excretion, or conversion to other metabolites. Although this scheme represents protein metabolism in the human as a whole, with minor modifications it can also be used to repre-

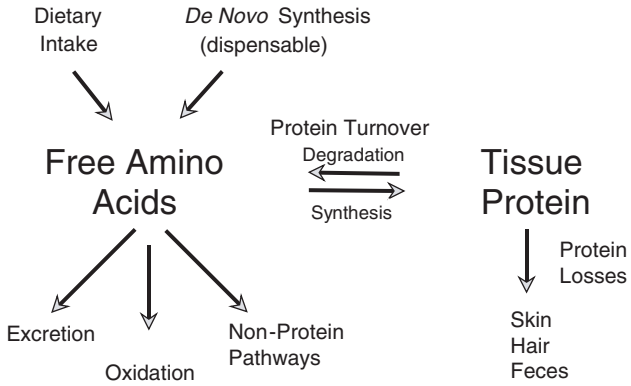

FIGURE 10-2 Exchange between body protein and free amino acid pools.

sent protein metabolism in individual organs, or indeed the metabolism of a single protein.

Amino Acid Utilization for Growth

Dietary protein is not only needed for maintaining protein turnover and the synthesis of physiologically important products of amino acid metabolism but is, of course, laid down as new tissue. Studies in animals show that the composition of amino acids needed for growth is very similar to the composition of body protein (Dewey et al., 1996). It is important to note, however, that the amino acid composition of human milk is not the same as that of body protein (Dewey et al., 1996), and although the present recommendations for the dietary amino acids for infants provided in this report continue to be based on human milk as the standard, recent authors (Dewey et al., 1996) have cautioned that the composition of human milk proteins is not necessarily a definition of the biological amino acid requirements of the growing neonate.

Maintenance Protein Needs

Even when mammals consume no protein, nitrogen continues to be lost. Provided that the energy intake is adequate, these "basal" losses are closely related to body weight and basal metabolic rate (Castaneda et al., 1995b; Scrimshaw et al., 1972). In man, normal growth is very slow and the dietary requirement to support growth is small in relation to maintenance needs except at very young ages. Moreover, the human being is a long-

lived species. It follows that maintenance needs are of particular importance to humans and account for a very large majority of lifetime needs for dietary protein.

It has been known for decades (Said and Hegsted, 1970) that the body's capacity to conserve individual amino acids at low intakes varies, so the pattern of amino acids needed in the diet to match their individual catabolic rates does not correspond precisely with the composition of body protein. For example, the indispensable amino acid requirements for adults may provide a quarter of their minimum total need for amino nitrogen, compared with the need for noncollagen body protein in which approximately half of the amino acids are indispensable (FAO/WHO/UNU, 1985). This implies that there is very effective recycling of indispensable amino acids released continuously from protein degradation back into protein synthesis. Under conditions where the diet is devoid of protein, the efficiency of amino acid recycling is over 90 percent for both indispensable and dispensable amino acids (Neale and Waterlow, 1974). While highly efficient, some amino acids are recycled at different rates than others.

Physiology of Absorption, Metabolism, and Excretion

Protein Digestion and Absorption

After ingestion, proteins are denatured by the acid in the stomach, where they are also cleaved into smaller peptides by the enzyme pepsin, which is activated by the increase in stomach acidity that occurs on feeding. The proteins and peptides then pass into the small intestine, where the peptide bonds are hydrolyzed by a variety of enzymes. These bond-specific enzymes originate in the pancreas and include trypsin, chymotrypsins, elastase, and carboxypeptidases. The resultant mixture of free amino acids and small peptides is then transported into the mucosal cells by a number of carrier systems for specific amino acids and for di- and tri-peptides, each specific for a limited range of peptide substrates. After intracellular hydrolysis of the absorbed peptides, the free amino acids are then secreted into the portal blood by other specific carrier systems in the mucosal cell or are further metabolized within the cell itself. Absorbed amino acids pass into the liver, where a portion of the amino acids are taken up and used; the remainder pass through into the systemic circulation and are utilized by the peripheral tissues.

Although there are good reasons to suppose that dietary protein digestion is incomplete and variable among different diets, recent studies using proteins intrinsically labeled with ^{15}N added to a diet suggest that many common dietary proteins, including proteins from casein, mixed whey, wheat, and legumes, are digested with an efficiency of greater than 90 per-

cent when fed as isolates, concentrates, or flours (Bergner et al., 1990; Gausserès et al., 1997). Thus, a significant portion (at least 50 percent) of fecal nitrogen losses represents the fixation by the colonic and cecal bacteria of nitrogenous substances (urea, ammonia, and protein secretions) that have been secreted into the intestinal lumen.

Some authors have argued that the host-colon nitrogen cycle, by which nitrogenous compounds that diffuse into the gut are converted to ammonia by the microflora and are reabsorbed, is a regulated function and serves as a mechanism of nitrogen conservation (Jackson, 1989). The theoretical basis of this proposition has been partly confirmed by the recent demonstration of the availability to the host of indispensable amino acids synthesized by intestinal microbes (Metges et al., 1999a, 1999b). However, not all investigators have obtained results indicative of regulated nitrogen cycling (Raguso et al., 1999; Young et al., 2000).

Although it seems clear that the efficiency of dietary protein digestion (in the sense of removal of amino acids from the small intestinal lumen) is high, there is now good evidence to show that nutritionally significant quantities of indispensable amino acids are metabolized by the tissues of the splanchnic bed, including the mucosal cells of the intestine (Fuller and Reeds, 1998). Thus, less than 100 percent of the amino acids removed from the intestinal lumen appear in the peripheral circulation, and the quantities that are metabolized by the splanchnic bed vary among the amino acids, with intestinal threonine metabolism being particularly high (Stoll et al., 1998). Currently, there is a lack of systematic information about the relationship between dietary amino acid intake and splanchnic metabolism, although there are indications that there is a nonlinear relationship between amino acid intake and appearance in the peripheral blood (van der Schoor et al., 2001).

Intestinal Protein Losses

Protein secretion into the intestine continues even under conditions of protein-free feeding, and fecal nitrogen losses (i.e., nitrogen lost as bacteria in the feces) may account for 25 percent of the obligatory loss of nitrogen (Fuller and Reeds, 1998). Under this dietary circumstance, the amino acids secreted into the intestine as components of proteolytic enzymes and from sloughed mucosal cells are the only sources of amino acids for the maintenance of the intestinal bacterial biomass. In those studies in which highly digestible protein-containing diets have been given to individuals previously ingesting protein-free diets, fecal nitrogen excretion increased by only a small amount. For highly digestible proteins, it also is likely that when humans consume diets that do not provide an excessive quantity of protein, a high proportion of the fecal nitrogen losses

originate from a combination of gastrointestinal secretions and the partial capture of the significant quantities of secreted urea that are hydrolyzed and subsequently used by the microflora in the large intestine (Jackson, 1989).

The following points support the view that the intestinal route of protein (amino acid) loss is of quantitative significance to maintenance protein needs. First, continued mucosal cell turnover and enzyme and mucin secretion are necessary for maintaining the integrity of the gastrointestinal tract and its normal digestive physiology. Second, animal studies show that the amino acid composition of the proteins leaving the ileum for bacterial fermentation in the colon is quite different from that of body protein (Taverner et al., 1981). In particular, the secretions are relatively rich in dispensable amino acids as well as threonine and cysteine (Dekker et al., 1991; Khatri et al., 1998; Taverner et al., 1981), probably because mucin secretions make a substantial contribution to the endogenous outflow. These two amino acids are of significance in meeting amino acid needs when intake is close to the requirement (Laidlaw and Kopple, 1987).

Other routes of loss of intact amino acids are via the urine and through skin and hair loss. These losses are small by comparison with those described above, but nonetheless may have a significant impact on estimates of requirements, especially in disease states (Matthews, 1999).

Protein Synthesis

Amino acids are selected for protein synthesis by binding with transfer RNA (tRNA) in the cell cytoplasm. The information on the amino acid sequence of each individual protein is contained in the sequence of nucleotides in the messenger RNA (mRNA) molecules, which are synthesized in the nucleus from regions of DNA by the process of transcription. The mRNA molecules then interact with various tRNA molecules attached to specific amino acids in the cytoplasm to synthesize the specific protein by linking together individual amino acids; this process, known as translation, is regulated by amino acids (e.g., leucine) (Jefferson and Kimball, 2001), and hormones. Which specific proteins are expressed in any particular cell and the relative rates at which the different cellular proteins are synthesized, are determined by the relative abundances of the different mRNAs and the availability of specific tRNA-amino acid combinations, and hence by the rate of transcription and the stability of the messages.

From a nutritional and metabolic point of view, it is important to recognize that protein synthesis is a continuing process that takes place in most cells of the body. In a steady state, when neither net growth nor protein loss is occurring, protein synthesis is balanced by an equal amount of protein degradation. The major consequence of inadequate protein

intakes, or diets low or lacking in specific indispensable amino acids relative to other amino acids (often termed limiting amino acids), is a shift in this balance so that rates of synthesis of some body proteins decrease while protein degradation continues, thus providing an endogenous source of those amino acids most in need.

Protein Degradation

The mechanism of intracellular protein degradation, by which protein is hydrolyzed to free amino acids, is more complex and is not as well characterized at the mechanistic level as that of synthesis (Kirschner, 1999). A wide variety of different enzymes that are capable of splitting peptide bonds are present in cells. However, the bulk of cellular proteolysis seems to be shared between two multienzyme systems: the lysosomal and proteasomal systems. The lysosome is a membrane-enclosed vesicle inside the cell that contains a variety of proteolytic enzymes and operates mostly at acid pH. Volumes of the cytoplasm are engulfed (autophagy) and are then subjected to the action of the protease enzymes at high concentration. This system is thought to be relatively unselective in most cases, although it can also degrade specific intracellular proteins (Cuervo and Dice, 1998). The system is highly regulated by hormones such as insulin and glucocorticoids, and by amino acids (Inubushi et al., 1996).

The second system is the ATP-dependent ubiquitin-proteasome system, which is present in the cytoplasm. The first step is to join molecules of ubiquitin, a basic 76-amino acid peptide, to lysine residues in the target protein. Several enzymes are involved in this process, which selectively targets proteins for degradation by a second component, the proteasome. This is a very large complex of proteins, possessing a range of different proteolytic activities. The ubiquitin-proteasome system is highly selective, so can account for the wide range of degradation rates (half-lives ranging from minutes to days) observed for different proteins. It is thought to be particularly responsible for degrading abnormal or damaged proteins, along with regulatory proteins that typically are synthesized and degraded very rapidly (Ciechanover et al., 1991; Goldberg and Rock, 1992; Hershko and Ciechanover, 1998).

Protein Turnover

The process by which all body proteins are being continuously broken down and resynthesized is known as protein turnover. In the adult human body, upward of 250 g/d of protein is synthesized and degraded (Waterlow, 1984). This compares with a median daily adult intake of about 55 to 100 g/d (Appendix Table E-16). The daily amount of protein turned

over is greater in infants and less in the elderly, when compared with young adults on a body-weight basis (Table 10-3). Some tissues are more active in protein turnover than others. Thus the liver and intestine, despite their rather small contribution to the total protein content of the body, are together believed to contribute as much as 50 percent of whole body protein turnover (McNurlan and Garlick, 1980; Waterlow, 1984). Conversely, skeletal muscle is the largest single component of body protein mass (43 percent), but contributes only about 25 percent to total body protein turnover (Reeds and Garlick, 1984; Waterlow, 1984).

At the tissue level, proteins are continually being synthesized and degraded as a sensitive means of regulating the amount of each separate enzyme or structural component. Other proteins may be secreted from the cell after synthesis and subsequently degraded at a distant site. Examples of such proteins are serum albumin synthesized in the liver, antibodies in the B-lymphocytes, digestive enzymes in the pancreas, and peptide hormones formed in the endocrine glands.

Amino Acid Catabolism

Nitrogen Metabolism

About 11 to 15 g of nitrogen are excreted each day in the urine of a healthy adult consuming 70 to 100 g of protein, mostly in the form of urea, with smaller contributions from ammonia, uric acid, creatinine, and some free amino acids (Table 10-4). These are the end products of protein metabolism, with urea and ammonia arising from the partial oxidation of amino acids. Uric acid and creatinine are indirectly derived from amino acids as well.

The removal of nitrogen from the individual amino acids and its conversion to a form that can be excreted by the kidney can be considered as a two-part process. The first step usually takes place by one of two types of

TABLE 10-3 Whole-Body Protein Synthesis in Humans at Different Life Stages

Life Stage	Protein Synthesis (g/kg/d)
Newborn (preterm)	17.4
Infant	6.9
Adult	3.0
Elderly	1.9

SOURCE: Young et al. (1975b).

TABLE 10-4 Approximate Distribution of Nitrogen in Urinary Constituents in Humans Consuming 100 g of Protein per Day (~16 g of Nitrogen)

Compound	Nitrogen (g/d)
Urea	12.8
Ammonia	0.7
Amino acids	0.7
Creatine/Creatinine	0.7
Uric acid	0.3
Hippuric acid	0.1
Total	15.3

SOURCE: Diem (1962).

enzymatic reactions: transamination or deamination. Transamination is a reversible reaction that uses ketoacid intermediates of glucose metabolism (e.g., pyruvate, oxaloacetate, and α-ketoglutarate) as recipients of the amino nitrogen. Most amino acids can take part in these reactions, with the result that their amino nitrogen is transferred to just three amino acids: alanine from pyruvate, aspartate from oxaloacetate, and glutamate from α-ketoglutarate.

Unlike many amino acids, branched-chain amino acid transamination occurs throughout the body, particularly in skeletal muscle. Here the main recipients of amino nitrogen are alanine and glutamine (from pyruvate and glutamate, respectively), which then pass into the circulation. These serve as important carriers of nitrogen from the periphery (skeletal muscle) to the intestine and liver. In the small intestine, glutamine is extracted and metabolized to ammonia, alanine, and citrulline, which are then conveyed to the liver via the portal circulation (Harper et al., 1984).

Nitrogen is also removed from amino acids by deamination reactions, which result in the formation of ammonia. A number of amino acids can be deaminated, either directly (histidine), by dehydration (serine, threonine), by way of the purine nucleotide cycle (aspartate), or by oxidative deamination (glutamate). These latter two processes are important because glutamate and aspartate are recipients of nitrogen by transamination from other amino acids, including alanine. Glutamate is also formed in the specific degradation pathways of arginine and lysine. Thus, nitrogen from any amino acid can be funneled into the two precursors of urea synthesis, ammonia and aspartate.

Urea synthesis takes place in the liver by the cyclic pathway known as the Krebs-Henseleit cycle. Among the essential reactions in this process is

the hydrolysis of the amino acid arginine by the enzyme arginase to yield urea and another amino acid, ornithine, which is not incorporated into body protein. The remaining part of the cycle involves the resynthesis of arginine using nitrogen from ammonia and aspartate. Thus, although arginine is the direct precursor of urea, it is not consumed in the process, as the nitrogen excreted as urea is all derived from ammonia and aspartate.

After synthesis, the urea is carried by the circulation from the liver to the kidney, where it is excreted into the urine. Although the excretion of urea dominates nitrogen excretion as a whole, significant quantities of ammonium ions are also excreted. There are some metabolic pathways, notably the purine nucleotide cycle, whereby purine nitrogen is converted to ammonium ions. It is generally believed that much of the ammonia produced by this cycle in skeletal muscle is transported in the blood as glutamine. Some of this glutamine is metabolized in the kidneys, where the enzyme glutaminase leads to the release of ammonium ions and glutamate. This glutamate, after losing its amino group, is then utilized in the synthesis of glucose in the kidney. The generation of ammonium ions from glutamine has a specific role in acid–base homeostasis, as ammonium ion excretion serves as the main vehicle for the excretion of excess hydrogen ions to prevent acidosis.

Carbon Metabolism

For most amino acids, removal of the amino nitrogen group generates their ketoacid analogues. Many of these are already in a form for entry into the pathways of oxidative metabolism (Figure 10-3). For example, both α-ketoglutarate (from glutamate) and pyruvate (from alanine) are intermediates of the glycolysis-tricarboxylic acid (TCA) pathway of glucose oxidation. All the others have specific degradation systems that give rise to intermediates that can be metabolized in these oxidative pathways. Thus, protein can make a significant contribution to the body's energy supply. This is particularly true in non-growing adults, who on average consume, and therefore oxidize, about 10 to 15 percent of their dietary energy as protein (Appendix Table E-17).

The contribution of protein to energy needs may be significant during periods of energy restriction or following the utilization of the body's limited endogenous carbohydrate stores. Protein oxidation also has been shown to rise considerably in highly traumatized or septic individuals, which results in large amounts of body protein loss; this loss can compromise recovery or even lead to death (see below) (Klein, 1990). It is much less in periods of chronic starvation because of various metabolic adaptations related to ketone utilization, or on protein-restricted diets.

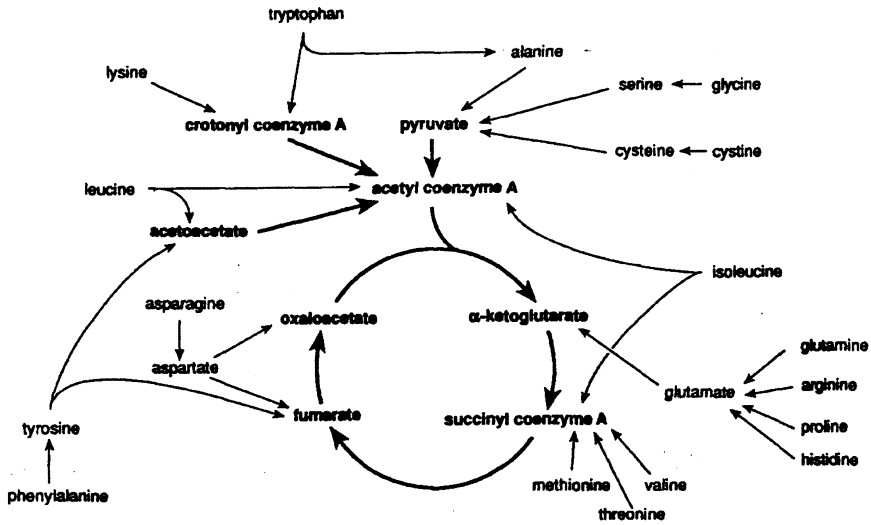

FIGURE 10-3 Metabolism of the carbon skeletons of the amino acid chains (light arrows) and their points of entry into the general pathways of metabolism of glucose and fat (bold arrows).
SOURCE: Garlick and Reeds (1993).

Once the amino acid deamination products enter the TCA cycle (also known as the citric acid cycle or Krebs cycle) or the glycolytic pathway, their carbon skeletons are also available for use in biosynthetic pathways, particularly for glucose and fat. Whether glucose or fat is formed from the carbon skeleton of an amino acid depends on its point of entry into these two pathways. If they enter as acetyl-CoA, then only fat or ketone bodies can be formed. The carbon skeletons of other amino acids can, however, enter the pathways in such a way that their carbons can be used for gluconeogenesis. This is the basis for the classical nutritional description of amino acids as either ketogenic or glucogenic (i.e., able to give rise to either ketones [or fat] or glucose).

Some amino acids produce both products upon degradation and so are considered both ketogenic and glucogenic (Figure 10-3). It has been argued that the majority of hepatic amino acid catabolism is directed in an obligatory fashion to glucose synthesis (Jungas et al., 1992). The synthesis of glucose in the liver from amino acids is dominated by alanine and glutamate, which derive much of their carbon from peripheral metabolism of glucose to lactate and TCA cycle intermediates. Thus, much of gluco-

neogenesis in metabolism is the result of a metabolic cycle of glucose carbon between the peripheral tissues (especially muscle) and the liver and kidney. This cycle also involves the peripheral synthesis of glutamine, an amino acid that is utilized in substantial quantities by the intestinal cells in which it is used for energy and for the synthesis of proline, citrulline, and nucleic acids.

A significant proportion of the glucose synthesized in the liver is due to recapture and recycling via the liver of 3-carbon units in the form of lactate derived from anaerobic glucose breakdown in muscle (the Cori cycle). Hepatic gluconeogenesis also occurs via the glucose–alanine cycle (a direct parallel of the Cori cycle) and the glucose–glutamine cycle. Since the nitrogen donors may be either glucogenic or ketogenic amino acids, these cycles function as mechanisms for transporting nitrogen from the periphery to the liver as well as for glucose production. The cycle involving glutamine transport from the periphery to the gastrointestinal tract is also vital to the synthesis of arginine and proline and is critical to the prevention of the build up of excessive ammonia in the circulation.

Nonprotein Pathways of Amino Acid Nitrogen Utilization

Although in general the utilization of dietary amino acids is dominated by their incorporation into protein and their role in energy metabolism, amino acids are also involved in the synthesis of other nitrogenous compounds important to physiological viability as shown in Table 10-5. Some pathways have the potential for exerting a substantial impact on the utilization of certain amino acids, and may be of potential significance for the requirements for these amino acids. This is particularly true for glycine, which is a precursor for six nitrogenous compounds, as shown in Table 10-5. Its utilization in the synthesis of creatine (muscle function), heme (oxygen transport and oxidative phosphorylation), and glutathione (protective reactions which are limited by the amount of available cysteine) is not only of physiological importance, but can also involve substantial quantities of the amino acid. For example, in the absence of a dietary source of creatine, adults require at least 1.1 g/d of glycine in order to sustain an adequate rate of creatine synthesis (calculated from a creatinine excretion of 1.8 g/d for a 70-kg man [Young et al., 1984] assuming 1 mole of glycine is used to synthesize 1 mole of creatine which gives rise to 1 mole of urinary creatinine). In premature infants, mainly fed human milk, there is evidence that the glycine supply may be a primary nutritional limitation to growth (Jackson, 1991). This so-called dispensable amino acid is then needed in the diet for optimum growth and may be termed "conditionally indispensable."

Similarly, the synthesis of carnitine (involved in intracellular fatty acid transport) could, under some circumstances, become of quantitative sig-

TABLE 10-5 Amino Acid Precursors of Nonprotein Products

Precursor Amino Acids	End Product
Tryptophan	Serotonin
Tryptophan	Nicotinic acid
Tyrosine	Catecholamines
Tyrosine	Thyroid hormones
Tyrosine	Melanin
Lysine	Carnitine
Cysteine	Taurine
Arginine	Nitric oxide
Glycine	Heme
Glycine, arginine, methionine	Creatine
Methionine, glycine, serine	"Methyl group metabolism"
Glycine, taurine	Bile acids
Glutamate, cysteine, glycine	Glutathione
Glutamate, aspartate, glycine	Nucleic acid bases

nificance to lysine requirements. These may be important nutritional considerations in individuals consuming marginal amounts of proteins of plant origin and undoubtedly have an impact on overall amino acid utilization when protein intake is very low.

Clinical Effects of Inadequate Protein Intake

As outlined above, protein is the fundamental component necessary for cellular and organ function. Not only must sufficient protein be provided, but also sufficient nonprotein energy (i.e., carbohydrates, fats) must be available so that the carbon skeletons of amino acids are not used to meet energy needs (Duffy et al., 1981). Similarly, unless amino acids are present in the diet in the right balance (see later section, "Protein Quality"), protein utilization will be affected (Duffy et al., 1981). In the world as a whole, protein-energy malnutrition (PEM) is fairly common in both children and adults (Stephenson et al., 2000), and is associated with the deaths of about 6 million children each year (FAO, 2000). In the industrialized world, PEM is seen predominantly in hospitals (Bistrian, 1990; Willard et al., 1980), is associated with disease (Wilson and Pencharz, 1997), and often found in the elderly (Allison, 1995). Hypoalbuminemic malnutrition has been described in hospitalized adults (Bistrian, 1990) and has also been called adult kwashiorkor (Hill, 1992).

Clearly, protein deficiency has adverse effects on all organs (Corish and Kennedy, 2000). In infants and young children, it has been shown to have harmful effects on the brain and may have longer-term effects on

brain function (Pollitt, 2000). Furthermore, protein deficiency has been shown to have adverse effects on the immune system, resulting in a higher risk of infections (Bistrian, 1990). It also affects gut mucosal function and permeability, which, in turn, affects absorption and makes possible bacterial invasion from the gut, which can result in septicemia (Reynolds et al., 1996). Protein deficiency has also been shown to adversely affect kidney function, where it has adverse effects on both glomerular and tubular function (Benabe and Martinez-Moldonado, 1998).

Total starvation will result in death in initially normal-weight adults in 60 to 70 days (Allison, 1992). For comparison, protein and energy reserves are much smaller in premature infants, and survival of 1,000-g neonates is only about 5 days (Heird et al., 1972).

Clinical Assessment of Protein Nutritional Status

No single parameter is completely reliable to assess protein nutritional status. Borderline inadequate protein intakes in infants and children are reflected in failure to grow as estimated by length or height (Jelliffe, 1966; Pencharz, 1985). However, weight-height relationships can be distorted by edema and ascites (Corish and Kennedy, 2000). Mid-upper arm parameters such as arm muscle circumference have been used to measure protein status (Young et al., 1990). The triceps skinfold is reflective of energy nutritional status while the arm muscle circumference (or diameter) is reflective of protein nutritional status (unless a myopathy or neuropathy is present) (Patrick et al., 1994).

In addition, urinary creatinine excretion has been used as a reflection of muscle mass (Corish and Kennedy, 2000; Forbes, 1987; Young et al., 1990), but it is not very sensitive. The most commonly used methods to clinically evaluate protein status measure serum proteins; the strengths and weaknesses of these indicators are summarized in Table 10-6. In practical terms, acute protein depletion is not clinically important as it is rare, while chronic deficiency is important. Serum proteins as shown in Table 10-6 are useful, especially albumin and transferrin (an iron-binding protein). In a study from Nigeria, low transferrin levels were more predictive of risk of death in children with PEM than were albumin levels (Ramsey et al., 1992). Due to their very short half-lives, prealbumin and retinol binding protein (apart from their dependence on vitamin A status) may reflect more acute protein intake than risk of protein malnutrition (which is a process with an onset of period of 7 to 10 days (Ramsey et al., 1992). Hence, albumin and transferrin remain the best measures of protein malnutrition, but with all of the caveats listed in Table 10-6.

Physical examination related to protein malnutrition focuses attention on the skin and hair as they are rapidly growing protein-containing

TABLE 10-6 Use of Serum Proteins to Assess Protein Nutritional Status

	Half-Life	Clinical Use	Limitations
Albumin	18 d	Severe malnutrition	Affected by protein losing enteropathy, renal loss, burn, and by liver disease
Transferrin	8–9 d	Limited—chronic deficiency	Affected by iron deficiency and by infection
Pre-albumin	2 d	Acute depletion	Affected by vitamin A deficiency
Retinol-binding protein	12 h	Acute depletion	Affected by vitamin A deficiency

SOURCE: Adapted from Young et al. (1990).

tissues. In protein malnutrition, the skin becomes thinner and appears dull; the hair first does not grow, then it may fall out or show color changes (Pencharz, 1985). Over a longer period of time, assessment of changes in lean body mass reflects protein nutritional status. The clinical tools most available to assess lean mass are dual emission x-ray absorptiometry and bioelectrical impedance (Pencharz and Azcue, 1996).

SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR PROTEIN (NITROGEN)

In the framework for Dietary Reference Intakes, as described in Chapter 1 and Appendix B, adequacy of requirements is defined as the lowest daily intake value for a nutrient that will meet the need, as defined by the specified indicator or criterion of adequacy, of apparently healthy individuals. This section reviews some of the possible indicators used or proposed for use in analyses estimating human protein requirements.

Factorial Method

The factorial method is based on estimating the nitrogen (obligatory) losses that occur when a person is fed a diet that meets energy needs but is essentially protein free and, when appropriate, also relies on estimates of the amount of nitrogen that is accreted during periods of growth or lost to mothers during lactation. The major losses of nitrogen under most conditions are in urine and feces, but also include sweat and miscellaneous losses, such as nasal secretions, menstrual losses, or seminal fluid. In this

method, the protein requirement is estimated by interpolating or extrapolating the obligatory losses to the zero balance point in which protein needs (as nitrogen) are assumed to equal the obligatory protein lost as nitrogen (nitrogen equilibrium).

This is where the factorial method has its greatest weakness, since the relationship between protein intake and nitrogen retention is somewhat curvilinear; the efficiency of nitrogen retention becomes less as the zero balance point is approached (Rand and Young, 1999; Young et al., 1973). Additionally, in order to utilize the factorial approach when determining the protein requirement for infants and children, their needs for protein accreted as a result of growth must be added to their maintenance needs.

Nitrogen Balance Method

This classical method has been viewed by many as theoretically the most satisfactory way of determining the protein requirement. Nitrogen balance is the difference between nitrogen intake and the amount excreted in urine, feces, skin, and miscellaneous losses. As discussed below, nitrogen balance remains the only method that has generated sufficient data for the determination of the total protein (nitrogen) requirement. It is assumed that when needs are met or exceeded adults come into nitrogen balance; when intakes are inadequate, negative nitrogen balance results. In determining total protein (nitrogen) needs, high-quality proteins are utilized as test proteins to prevent negative nitrogen balance resulting from the inadequate intake of a limiting indispensable amino acid. A significant literature exists regarding the methods and procedures to use in determining nitrogen balance amount (Manatt and Garcia, 1992; Rand et al., 1981).

Limitations of the Method

The nitrogen balance method does have substantial practical limitations and problems. First, the rate of urea turnover in adults is slow, so several days of adaptation are required for each level of dietary protein tested to attain a new steady state of nitrogen excretion (Meakins and Jackson, 1996; Rand et al., 1976). Second, the execution of accurate nitrogen balance measurements requires very careful attention to all the details of the procedures involved. Since it is easy to overestimate intake and underestimate excretion, falsely positive nitrogen balances may be obtained (Hegsted, 1976). Indeed, an overestimate of nitrogen balance seems consistent throughout the literature because there are many observations of quite considerable apparent retention of nitrogen in adults (Oddoye and Margen, 1979). This observation is biologically implausible because (a) adults

do not normally accrete body protein, and (b) the magnitude of the positive nitrogen balances is inconsistent with stability of body weight. A third limitation of the nitrogen balance method is that since the requirement is defined for the individual, and studies rarely provide exactly the amount of protein necessary to produce zero balance, individuals must be studied at several levels of protein intake in the region of the requirement so that estimates of individual requirements can be interpolated (Rand et al., 1976; Zello et al., 1990). Finally, dermal and miscellaneous losses of nitrogen must be included in the calculation. These are inordinately difficult to measure, and vary with the environmental conditions (e.g., ambient temperature). In fact, the literature indicates marked (at least twofold) differences between studies (Calloway et al., 1971). The inclusion of dermal and miscellaneous nitrogen losses can have a significant effect on estimates of amino acid requirements via nitrogen balance, especially in adults (Calloway et al., 1971; Millward, 1998; Rand and Young, 1999).

Statistical Analysis of Nitrogen Balance Data

In studies with healthy adults in presumably good nutritional status, it is generally assumed that the protein requirement is achieved when an individual is in zero nitrogen balance. To some extent, this assumption poses problems that may lead to underestimates of the true protein requirement. First, there are sufficient observations of paradoxically high positive nitrogen balances in the literature to imply that when individuals are in *measured* body nitrogen equilibrium, they are in fact in a small negative nitrogen balance (Kopple, 1987). The large majority of the studies have concentrated their measurements of protein adequacy at levels of intake below nitrogen balance and as a result, the intercept of protein intake at zero nitrogen balance is lower than the true intercept as the efficiency of protein utilization decreases as zero balance is reached (Young et al., 1973).

The empirical solution is to carry out measurements that span nitrogen equilibrium, ideally by using multiple levels of intake in the same individual and interpolating individual requirement levels. Three different interpolation schemes have been proposed, based on (1) a smooth nonlinear model (Hegsted, 1963; Rand and Young, 1999), (2) a two-phase linear model (also called bilinear or breakpoint) (Kurpad et al., 2001a; Zello et al., 1995), and (3) a linear model (Rand et al., 1976; Rand et al., 2003). Since the physiological response relationship between nitrogen intake and balance is theoretically expected not to be linear, the more complex models (1 and 2 above) would be appropriate bases for arriving at a requirement estimate. However, in order to set the Recommended Dietary Allowance (RDA), it is necessary to determine the variability of the

requirement between individuals, free from the considerable within-individual variability, and both these models require more data points on each individual than are currently available in published studies.

Thus, while it is recognized that the first two models above are more realistic biologically, because of the lack of available data the method adopted for this report is to use linear interpolation to estimate the individual requirements (the intakes predicted to result in zero balance) that in turn are used to estimate the distribution of protein requirements. The bilinear model was used to estimate requirements for some of the amino acids; however, estimates of population variability (between individuals) were derived from the analysis of protein requirements.

SELECTION OF INDICATORS FOR ESTIMATING THE REQUIRMENT FOR INDIVIDUAL AMINO ACIDS

Irrespective of whether a design involving multiple studies in a limited number of individuals or single studies in a larger number of subjects has been used, the uniform approach to the determination of the requirement for an individual indispensable amino acid involves measuring the relationship between the intake of the amino acid (in an otherwise adequate diet) and some predetermined marker of nutritional adequacy. The marker can be one that follows the state of protein metabolism or balance (e.g., nitrogen balance or whole body protein turnover) or the status of the metabolism and utilization of the amino acid under investigation (e.g., its concentration). These approaches give somewhat different information about the requirement for the amino acid. Moreover, each method has peculiar theoretical and practical disadvantages, thus the level of consistency of estimates based on different approaches should be examined. The following approaches have been proposed.

Nitrogen Balance Method

This classical method is discussed earlier in more detail under "Selection of Indicators for Estimating the Requirement for Protein (Nitrogen)." It has been apparent for at least 15 years that the nitrogen balance–derived values for amino acid requirements in adults are lower than values derived by the other methods described below, which provide results similar to each other (Millward et al., 1990; Young, 1987; Young et al., 1989). Many explanations have been put forward for the lower results using nitrogen balance methodology, including the fact that excess nonprotein energy may have been used in many nitrogen balance studies (Garza et al., 1976, 1977a, 1977b, 1978).

Rand and Young (1999) analyzed the data of Jones and coworkers (1956) in which young women were fed up to five different intake levels of lysine. The design of that study allowed for the determination of between-individual variance by studying each individual at several levels of lysine intake. In fact, within the large nitrogen balance and amino acid requirement literature, only one other study (Reynolds et al., 1958) was found in which adults were studied at four or more different intakes of amino acids with constant levels of total nitrogen (Reynolds et al., 1958). These investigators studied four different levels of methionine and cysteine.

With these two data sets, nonlinear regression can be utilized. The reanalysis of the 1956 Jones study produced an estimate of nitrogen equilibrium for lysine of 30 mg/kg/d, which is comparable to the values derived by the other methods described below (Rand and Young, 1999). In addition, most of the classic amino acid work using nitrogen balance (Leverton et al., 1956a, 1956b, 1956c, 1956d; Rose, 1957; Rose et al., 1955a, 1955b, 1955c, 1955d, 1955e, 1955f) did not include dermal and miscellaneous losses, which result in further underestimation of indispensable amino acid requirements.

Unfortunately, for infants and children the only data available are those based on nitrogen balance, and considerable uncertainty about the accuracy of the estimates remains. However, recent factorial estimates are in reasonable agreement with the nitrogen balance estimates (Dewey et al., 1996).

Plasma Amino Acid Response Method

This method was the first that focused on the physiology of the individual amino acid (Longnecker and Hause, 1959; Munro, 1970). The reasoning behind this approach is that when the intake of the test amino acid is below its dietary requirement, then its circulating concentration is not only low, but also is relatively insensitive to changes in intake. As intakes of the target amino acid approach the requirement level by increasing the intake of the limiting amino acid, the plasma level of the amino acid starts to increase progressively (see Figure 10-4). The point at which the "constant" portion of the relationship between intake and plasma concentration intersects the linear portion is considered to be an estimate of the requirement.

A variation on this method involves the examination of the changes in the plasma concentration of the test amino acid as the adult moves from the post absorptive to the fed state post-consumption (Longnecker and Hause, 1961). At intakes below the requirement, the plasma concentration of the test amino acid is expected to fall in the fed state and rise only when the dietary supply of the amino acid is greater than the individual's

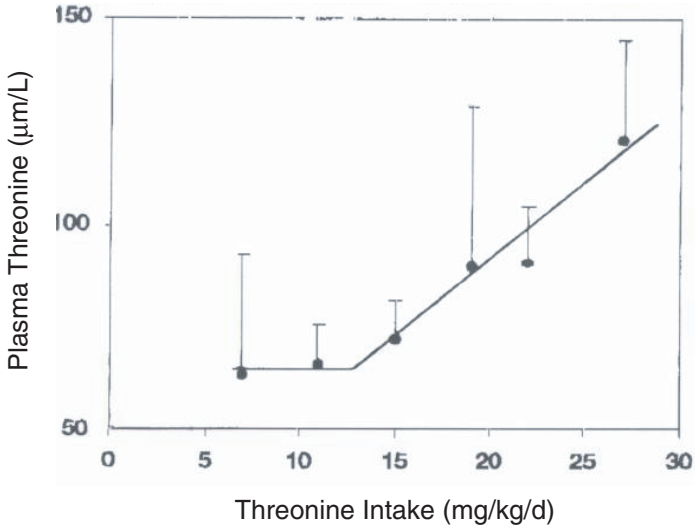

FIGURE 10-4 Plasma threonine levels in the fed state with increasing levels of threonine intake in well-nourished men. Two-phase regression revealed a breakpoint at about 13 mg/kg/d. Taken from Kurpad and Young (2001), with permission.

requirement. The theoretical basis of the approach is sound but the method has disadvantages. The main difficulty is that amino acid metabolism is so complex that factors other than the level of amino acid intake, such as gastric emptying time, can influence its concentration (Munro, 1970). Furthermore, the relationship between the intake of the amino acid and its circulating concentration is not necessarily bilinear, so it is difficult to determine a "breakpoint" (Young et al., 1972). Although in some regards this problem applies also to the oxidation methods discussed below, over the last 20 years these later methods have supplanted plasma amino acid concentration–based approaches.

Direct Amino Acid Oxidation (DAAO) Method

In the 1980s, Young and his coworkers introduced the use of measurements of the carbon oxidation of single indispensable amino acids as indicators of adequacy of the amino acids (Young et al., 1989). This marked a major theoretical advance over the nitrogen balance and plasma amino acid response methods. The theoretical basis of the direct amino acid oxidation (DAAO) method is that the nutritional indispensability of an amino acid is a function of its inability to synthesize its carbon skeleton.

Thus, when the test amino acid is labeled with ^{13}C, the production of breath $^{13}CO_2$ is assumed to be a good measure of the irreversible oxidative loss of the amino acid.

The method has been applied in a similar manner to the plasma amino acid response approach by designing experiments to determine a breakpoint in the relationship between the carbon catabolism of the amino acid (as measured as breath $^{13}CO_2$) and its intake. Thus by analogy to the concentration method, it is assumed that below the requirement the test amino acid is conserved and that there is a low constant oxidation rate, but once the requirement is reached, the oxidation of the test amino acid increases progressively.

Although the DAAO method was an important advance beyond nitrogen balance, it also presented limitations, which have been discussed in depth (Fuller and Garlick, 1994). The most salient problem arises from the reliance on the determination of a breakpoint in the oxidation of the test amino acid. This reliance requires studies at very low intakes of the test amino acid. However, at these low dietary intakes, the intake of the infused labeled amino acid becomes significant in relation to dietary intake. This can lead to errors in the estimation of amino acid oxidation based on the production of labeled CO_2. Thus, values of amino acid oxidation based on the production of $^{13}CO_2$ are likely to be overestimated. The second limitation is that the DAAO method can only be used with full accuracy for those amino acids whose carboxyl group is released directly to the body bicarbonate pools. This limits its use largely to the branched chain amino acids, phenylalanine, and lysine. Other amino acids, such as threonine and tryptophan, pose particular problems (Zhao et al., 1986).

A criticism of this method has been that measurements were only made during a short period during which food was given at regular hourly intervals. This period was therefore not representative of the day as a whole. A later modification of this approach was to infuse the labeled amino acid during a period of fasting followed by a period of hourly meals, thus acknowledging the discontinuous way in which food is normally taken (Young et al., 1987). However, although this was an advance on the earlier approach, assumptions still had to be made to extrapolate the results from the short periods to a full day.

Twenty-four Hour Amino Acid Balance Method

Over the last decade, the DAAO method has been adapted in such a way that it allows the carbon balance of the amino acid under investigation to be determined over a full 24-hour period (El-Khoury et al., 1994a, 1994b). In some respects, the development of the 24-hour amino acid balance method stemmed from the fact that the DAAO method had been

criticized because measurements were made only in the fed state. Thus the 24-hour amino acid balance method was developed to determine the balance of the test amino acid over a 24-hour period that encompassed periods of fasting and feeding. This marked a significant advance in determining amino acid requirements because it moved investigations away from the simple study of nitrogen metabolism and allowed, in principle at least, direct measurements of the quantities of the amino acid lost under different nutritional circumstances.

There also are drawbacks to this method. The first limitation arises from the unresolved questions related to the method's theoretical basis. Although the end point of the method is the measurement of the body's balance of the test amino acid, the base measurement is the proportion of the dose of ^{13}C-amino acid that is excreted as $^{13}CO_2$. In order to convert the measured rate of production of labeled CO_2 to a rate of oxidation of the amino acid, it is necessary to know the isotopic enrichment of the amino acid at the intracellular site of oxidation. This is difficult because amino acid metabolism is compartmentalized and measurements of plasma amino acid labeling likely underestimate true turnover, and hence true oxidative loss, of the amino acid. Although for some amino acids this problem can be circumvented by administering a labeled metabolic product of the amino acid (e.g., α-keto isocaproic acid in studies of leucine metabolism).

The second drawback is practical—measuring the oxidation of the test amino acid over a complete 24-hour period makes the method labor intensive. This probably underlies the fact that to date this method has been applied to only three amino acids: leucine (El-Khoury et al., 1994a, 1994b; Kurpad et al., 2001b), lysine (El-Khoury et al., 2000; Kurpad et al., 2001a), and phenylalanine with and without tyrosine (Basile-Filho et al., 1998), and only a limited number of different levels of amino acid intake have been investigated.

Indicator Amino Acid Oxidation (IAAO) Method

The indicator amino acid oxidation (IAAO) method arose from work on the amino acid requirements of neonatal pigs (Kim et al., 1983). Although the IAAO method is based on measurements of amino acid oxidation, it uses measurements of the carbon catabolism of a nonlimiting amino acid (called the indicator amino acid) as a carbon analogue of nitrogen balance. The reasoning is that when a single indispensable amino acid is provided below its requirement, it acts as the single and primary limitation to the ability to retain other nonlimiting amino acids in body protein. These other amino acids, including the indicator amino acid, are then in nutritional excess and are oxidized (Zello et al., 1995). When the

intake of the test amino acid is zero, then protein synthesis is minimal and oxidation of the indicator is maximal. As the intake of the test amino acid is increased, protein retention increases and the oxidation of the indicator amino acid falls until the requirement level of the test amino acid is reached, after which the oxidation of the indicator amino acid is lower and essentially constant. The data are then analyzed to obtain as estimate of the intersection of the constant and linear portions of the relationship (the breakpoint).

The IAAO method has some advantages over the direct oxidation and carbon balance methods and has been validated in growing piglets by comparing estimates based on growth and body composition (Kim et al., 1983). The first advantage is that the metabolic restrictions of carbon dioxide release apply only to the indicator amino acid. Thus amino acids such as threonine, whose peculiar metabolism makes them problematical in the DAAO method, can be studied. Second, the pool size of the indicator amino acid does not change radically as the intake of the test amino acid is varied. Thus to some extent, potential problems of compartmentation are minimized and, in principle, the method does not require estimates of the turnover of the indicator amino acid.

However, the IAAO method also has several limitations as it has been applied. First, like the DAAO approach, it has only been used in the fed state and the extent to which the fasting-state oxidation of the indicator amino acid is altered by the status of the limiting amino acid has not been determined. Second, the dependence of the result on the amount of total protein given during the isotope infusion has not been established. Third, the choice of the best indicator is still under study so that data obtained with the method are dependent on the assumption of the general applicability of the indicator amino acids (phenylalanine and lysine) that have been used most frequently.

Classical nitrogen balance studies in humans show that it takes 7 to 10 days for urinary nitrogen to equilibrate in adults put on a protein-free diet (Rand et al., 1976). On the other hand, it has been shown that most (about 90 percent) of the adaptation in leucine kinetics is complete in 24 hours (Motil et al., 1994). Zello and coworkers (1990) studied 2- to 8-day adaptation periods to either 4.2 or 14 mg/kg/d of phenylalanine on rates of phenylalanine oxidation at phenylalanine intakes of 5, 7, 10, 14, 21, 28, or 60 mg/kg/d. These investigators were unable to show any effect of prior adaptation to these two different phenylalanine intakes on the rates of phenylalanine oxidation at changing phenylalanine intakes, where the adaptation to the test level was about 4 hours. Clearly, from this study, adaptations in amino acid metabolism appear to take place much more quickly than do adaptations in urinary nitrogen excretion and are (at least for leucine [Motil et al., 1994]) virtually complete within 24 hours.

The most satisfactory statistical models for determining amino acid requirements use regression to define the population mean and variance. For the regression models to work, ranges of intake (particularly at the low end) have to be fed. In practical terms, this has greatly hampered studies in infants, children, and other vulnerable groups. On the other hand, if the individual only needs to be on a low or even zero intake of the test amino acid for a matter of 8 hours, then it becomes feasible to study indispensable amino acids in these and other vulnerable groups.

Such a minimally invasive indicator oxidation model has been developed (Bross et al., 1998) and applied to determine tyrosine requirements in children with phenylketonuria (Bross et al., 2000). In this model the oxidation study is conducted after only 6 hours of adaptation to the level of the test amino acid, which is administered every 30 minutes.

For amino acid oxidation measurements, two-phase linear crossover regression analysis was introduced during the validation of indicator amino acid oxidation in piglets (Kim et al., 1983). Later, this approach was transferred to humans in a direct oxidation study (Zello et al., 1990) and in indicator oxidation studies (Bross et al., 2000; Zello et al., 1993). This technique permits a precise determination of the breakpoint, which is used as the estimate of the requirement for the amino acid Estimated Average Requirement (EAR).

As pointed out above, the drawbacks of the indicator method are the short period of measurement in the fed state only, and the lack of a period of adaptation to the test diets. To avoid these drawbacks, a 24-hour indicator method has been developed (Kurpad et al., 2001a), which takes advantage of the strengths of the indicator approach, as well as the 24-hour period of measurements including feeding and fasting. On theoretical grounds, this method has advantages over other methods for estimating amino acid requirements, and is the chosen method for estimated amino acids requirements where data are available.

FINDINGS BY LIFE STAGE AND GENDER GROUP FOR TOTAL PROTEIN

Infants Ages 0 Through 6 Months

Method Used to Set the Adequate Intake

The recommended intakes of protein are based on an Adequate Intake (AI) that reflects the observed mean protein intake of infants fed principally with human milk.

Human Milk. Human milk is recognized as the optimal source of nutrients for infants throughout at least the first year of life and is recommended as the sole nutritional source for infants during the first 4 to 6 months of life (IOM, 1991). There are no reports of apparently healthy, full-term infants, exclusively fed human milk, who manifest any signs of protein deficiency (Heinig et al., 1993). Therefore, determination of the AI for protein for infants is based on data from infants fed human milk as the principal source of nutrients during the period 0 through 6 months of age. As is described in Chapter 2, the AI is set at the mean value calculated from studies in which the volume of human milk was measured by test weighing, and the average concentration of the protein content in human milk was determined using average values from several reported studies.

The protein content of human milk at various stages of lactation is shown in Table 10-7. In general, protein concentrations decline in the later stages of lactation. Nonprotein nitrogen contributes 20 to 27 percent of total milk nitrogen (Atkinson et al., 1980; Butte et al., 1984a, 1984b; Dewey et al., 1996). These nonprotein nitrogenous components include free amino acids, pyrimidine nucleotides, creatine, and glutathione, but the large majority is urea. Using data from 13 lactating mothers of term infants, Butte and coworkers (1984a) reported that the protein content of human milk was 1.29 g/dL at 2 weeks of lactation, 1.08 g/dL at 4 weeks, 1.01 g/dL at 6 weeks, 0.94 g/dL at 8 weeks, and 0.91 g/dL from 10 to 12 weeks. Similar results of 0.91 g/dL were reported by Lammi-Keefe and coworkers (1990) at 8 weeks of lactation in 6 mothers of term infants. Both of these studies analyzed nitrogen by the Kjeldahl method. However, higher human milk protein content has been reported by Nommsen and coworkers (1991): 1.21 g/dL at 3 months, 1.14 g/dL at 6 months, 1.16 g/dL at 9 months, and 1.24 g/dL at 12 months of lactation. Dewey and coworkers (1984) reported values of approximately 1.25 g/dL at 4 to 11 months of lactation. These latter investigators attribute the higher values to their utilization of the modified Lowry assay for total protein, which tends to result in slightly higher values (Nommsen et al., 1991).

Ages 0 Through 6 Months. The AI for infants 0 through 6 months is based on the estimated average volume of milk intake of 0.78 L/d (Allen et al., 1991; Heinig et al., 1993) for this age group, and an average protein content of human milk of 11.7 g/L. This is the average protein content of human milk during the first six months of lactation from studies (Butte et al., 1984a; Dewey and Lönnerdal, 1983; Dewey et al., 1984; Nommsen et al., 1991) in which the sample size was at least 10 and actual data were provided (see Table 10-7). This value is in the range of protein content reported in other studies (Table 10-7). Multiplying this amount by the estimated average volume of intake of human milk for infants 0 through

6 months, the AI would be 11.7 g/L × 0.78 L/d = 9.1 g/d or 1.52 g/kg/d based on the reference weight of 6 kg for the 2- through 6-month-old infant from Chapter 1 (Table 1-1).

Protein AI Summary, Ages 0 Through 6 Months

AI for Infants	
0–6 months	**1.52 g/kg/d**

Special Considerations

Although protein intakes have been reported to be 66 to 70 percent higher in infants fed formula compared with those fed human milk for up to 12 months of age, there is no evidence that the lower protein intakes in the breast-fed infants were associated with adverse outcomes (Heinig et al., 1993). In fact, despite their lower protein intakes, some studies have demonstrated that infants fed human milk have better immune function and behavioral development than formula-fed infants (IOM, 1991; Lucas et al., 1992; Rogan and Gladen, 1993). As expected, gains in weight and lean body mass are higher in the formula-fed than breast-fed infants, but when controlled for energy intake, protein intake is not associated with weight or length gain within the breast-fed infants (Heinig et al., 1993). Several studies have shown that infants fed formula with a true protein level ([total nitrogen – nonprotein nitrogen] multiplied by 6.25) of 15 g/L have higher urea nitrogen and plasma amino acid levels than those seen in breast-fed infants (Janas et al., 1985, 1987; Järvenpää et al., 1982a, 1982b; Räihä et al., 1986a, 1986b), a true protein intake of 13 g/L of infant formula based on cow milk has been shown to result in a similar plasma amino acid profile in formula-fed infants to that seen in breast-fed infants (Lönnerdal and Chen, 1990).

It is recognized that casein and whey in cow milk is not the same as human casein and whey and that the absorption and digestibility of amino acids from formula is different than that of human milk. The 1985 Joint FAO/WHO/UNU expert group (FAO/WHO/UNU, 1985) recommended a factor of 0.70 for protein in cow milk, finding that it is 70 percent as efficiently utilized as the protein in human milk based on studies in 1-year-old infants. Later Fomon (1991) recommended a conversion estimate of 90 percent for infants receiving infant formula as the only source of dietary protein and suggested that infant formula should contain a minimum of 1.6 g α-amino nitrogen/100 kcal. Thus in determining the level of protein to be included in infant formula based on various possible protein sources, it is important to evaluate the digestibility and comparative protein quality (see "Protein Quality") as indicated above.

TABLE 10-7 Protein Content of Human Milk in the United States and Canada

Reference	Country	*n*	Stage of Lactation	Protein Content in Milk (g/dL)[a]	Comments
Anderson et al., 1981	Canada	10	3–5 d	1.9	Milk protein content was approximated from study figure
			8–11 d	1.7	
			15–18 d	1.5	Nitrogen determined by Kjeldahl analysis
			25–29 d	1.3	
Lemons et al., 1982	United States	7	7 d	1.59 ± 0.08	Nitrogen determined by Kjeldahl analysis
			14 d	1.23 ± 0.09	Protein determined by multiplying milk protein nitrogen by 6.25
			21 d	1.18 ± 0.04	
			28 d	1.10 ± 0.05	
Anderson et al., 1983	United States	9	3 d	2.3 ± 0.6	Nitrogen determined by Kjeldahl analysis
			7 d	1.7 ± 0.2	
			14 d	1.3 ± 0.4	
Dewey and Lönnerdal, 1983	United States	13	1 mo	**1.44 ± 0.20**	Protein analyzed by dye-binding assay
		16	2 mo	**1.33 ± 0.16**	
		18	3 mo	**1.32 ± 0.16**	
		16	4 mo	**1.30 ± 0.24**	
		14	5 mo	**1.25 ± 0.17**	
		15	6 mo	**1.27 ± 0.36**	
Neville et al., 1984	United States	10	33–210 d (median 115 d)	1.41 ± 0.06 (SEM)	Protein analyzed by the Biuret reaction Mid-feed sample

Dewey et al., 1984	United States	40 27	4–6 mo 7–11 mo	**1.26 ± 0.27** *1.24 ± 0.22*	Protein analyzed by a modified Lowry assay
Butte et al., 1984a	United States	13	2 wk 4 wk 6 wk 8 wk 10 wk 12 wk	1.29 ± 0.18 **1.08 ± 0.16** **1.01 ± 0.10** **0.94 ± 0.15** **0.91 ± 0.16** **0.91 ± 0.16**	Nitrogen determined by Kjeldahl analysis Protein determined by multiplying milk protein nitrogen by 6.25
Lönnerdal et al., 1987	United States	3 4 7	1–3 d 7–20 d 32–166 d	2.70 ± 0.18 (SEM) 1.61 ± 0.10 1.02 ± 0.05	Nitrogen determined by Kjeldahl analysis Protein determined by multiplying milk protein nitrogen by 6.25
Lammi-Keefe et al., 1990	United States	6	8 wk	0.91	Nitrogen determined by Kjeldahl analysis Protein determined by multiplying milk protein nitrogen by 6.25
Nommsen et al., 1991	United States	58 45 28 21	3 mo 6 mo 9 mo 12 mo	**1.21 ± 0.15** **1.14 ± 0.15** *1.16 ± 0.18* *1.24 ± 0.15*	Protein analyzed by a modified Lowry assay

[a] Mean ± standard deviation, unless otherwise noted. Values in bold used to estimate average protein content of human milk as 11.7 g/L during months 1 through 6 of lactation. Values in italics used to estimate average protein content of human milk as 12.3 g/L during months 7 through 12 of lactation.

Infants Ages 7 Through 12 Months

Method Used to Estimate Average Intakes

During the second 6 months of life, solid foods become a more important part of the diet of infants and add a significant amount of protein to the diet. Although limited data are available for typical protein intakes from foods by infants fed human milk, mean protein intake from complementary foods for infants aged 7 through 12 months was estimated to be 7.1 g/d for human milk–fed infants based on data from the Third National Health and Nutrition Examination Survey. Heinig and coworkers (1993) reported slightly higher values for nonmilk protein intake during the second 6 months of life. Based on their data, the average volume of human milk consumed during the second 6 months of life would be about 0.6 L/d. Thus, protein intake from human milk with a protein content of about 12.1 g/L at 7 to 12 months of lactation from the data for this age group (Dewey et al., 1984; Nommsen et al., 1991) would be approximately 7.3 g/d (12.1 g/L × 0.6 L/d). It should be noted that this is greater than that derived from the studies of content of milk from earlier lactation periods, primarily due to the use of the Lowry methods by both of these reports and the small number of studies available from this lactation period.

Adding the intake from milk (7.3 g/d) and food (7.1 g/d), the total average protein intake is estimated to be 14.4 g/d or 1.6 g/kg/d based on the reference weight of 9 kg for the 7- through 12-month-old infant from Chapter 1 (Table 1-1).

Method Used to Estimate the Average Requirement

Published data on the relationship between protein (nitrogen) intake and nitrogen balance were utilized to estimate protein requirements by the factorial method for infants 7 through 12 months of age as well as for children and adolescents through 18 years of age. The factorial method includes: (1) estimates of the maintenance requirement, which is determined by regression analysis of the relationship between nitrogen intake and nitrogen balance, (2) measurement of the rates of protein deposition, which are derived from body composition analysis, and (3) estimates of the efficiency of protein utilization, which is derived from the slope of the line relating intake and balance from the available data on infants and children.

Several nitrogen balance studies that involved children in the age range of 9 months to about 14 years were identified and analyzed (Table 10-8). The studies fall into three groups: (1) studies designed to measure "basal" nitrogen loss at very low or zero protein intakes, (2) studies

involving children receiving only one of a variety of protein levels, and (3) studies involving a limited number of individuals but with each individual receiving a range of protein intakes. Included in the analysis were studies in which the children consumed diets containing milk/egg, legume/cereal, and mixed vegetable/animal protein sources. The results, summarized in Table 10-8, were obtained in mostly boys and include a number of different ethnic groups including European, African, Central American, and Chinese.

Miscellaneous Losses. A critical aspect of the analysis is the inclusion of an estimate for integumental and unaccounted losses that were based on direct measurements in children, mostly boys, aged 7 months through 14 years. On the basis of five reports (Howat et al., 1975; Huang et al., 1980; Korslund et al., 1976; Uauy et al., 1981; Viteri and Martinez, 1981), the mean miscellaneous nitrogen losses are estimated to be 6.5 (± 2.3) mg/kg/d with a range of 5 to 9 mg/kg/d. In deriving the protein requirement, this estimate of miscellaneous losses was included as an adjustment to the reported nitrogen balances for the studies included in Table 10-8. The miscellaneous losses from both boys and girls are assumed to be the same since data from girls were limited.

Maintenance Requirement. Individual maintenance protein requirements were estimated by first regressing nitrogen balance on nitrogen intake for the individuals studied at several different intake levels, and then using these individual regression equations to interpolate the intakes that would be expected to produce zero nitrogen balance (adjusting for 6.5 mg/kg/d for miscellaneous losses). Table 10-8 contains seven studies that permit estimation of individual requirements and three studies that were used to estimate pooled requirements. As shown in the table, the average individual maintenance requirement was estimated as the median of the individual nitrogen requirements (108 mg/kg/d). For each study, an estimate was calculated as the median of the individual studies or the study pooled nitrogen requirement for those studies without individual data, and was 110 mg/kg/d . Since data for girls were sparse and could not be separated from that for boys, the protein maintenance requirement for both boys and girls is set at the same level. In addition, the maintenance protein requirement was not adjusted for age, as the requirement per kg of body weight for children 8 years of age and above appeared to be similar to that of younger children ranging in age from 9 months to 5 years (Table 10-8). Supporting this decision are the data of Widdowson and Dickerson (1964), which demonstrated that around 4 years of age, body protein concentration reaches the adult value of 18 to 19 percent of body weight.

TABLE 10-8 Maintenance Protein Requirement for Children Based on Nitrogen Balance Data[a]

Reference	Country	Diet	Age
Huang et al., 1980	China	Milk	9–17 mo
Huang et al., 1980	China	Egg	9–17 mo
Intengan et al., 1981	Philippines	Rice and fish	18–26 mo
Torun and Viteri, 1981	Guatemala	Milk	17–31 mo
Torun et al., 1981	Guatemala	Soy	17–31 mo
Egana et al., 1984	Chile	Milk	34–62 mo
Egana et al., 1984	Chile	Soy	34–62 mo
Intengan, 1984	Philippines	Rice and beans	22–29 mo
Gattas et al., 1990	Chile	Mixed	8–10 y
Gattas et al., 1992	Chile	Mixed	12–14 y
Median of all individual estimates (n = 7 studies)			
Median of all studies (n = 10)			

[a] Entries are medians (mean ± standard deviation).
[b] Multiple data on each individual not available.
[c] Regression estimate of study requirement.

Protein Deposition. Estimates of rates of protein deposition for infants from 9 months through 3 years of age (Butte et al., 2000) and total body protein content from 4 through 18 years of age (Ellis et al., 2000) were utilized to estimate rates of body protein deposition and are shown in Table 10-9. This table contains longitudinal (Butte et al., 2000) and cross-

n	Intercept at 6.5 mg N/kg/d	Slope	Maintenance Requirement Including 6.5 mg N/kg/d
32 points[b] (24 boys)	–77.5[c]	0.69[c]	112[c]
29 points[b] (10 boys)	–81.6[c]	0.71[c]	116[c]
7 boys	–53.6 (–47.4 ± 26.0)	0.52 (0.49 ± 0.10)	102 (91 ± 37)
10 boys	–52.0 (–51.1 ± 22.1)	0.70 (0.71 ± 0.12)	66 (71 ± 28)
10 boys	–55.5 (–52.2 ± 14.5)	0.55 (0.58 ± 0.09)	90 (89 ± 18)
6 boys and girls	–35.4 (–40.1 ± 16.2)	0.52 (0.51 ± 0.08)	76 (79 ± 27)
7 boys and girls	–58.2 (–59.4 ± 9.9)	0.51 (0.49 ± 0.10)	127 (124 ± 19)
5 boys	–98.1 (–121.1 ± 43.7)	0.68 (0.77 ± 0.24)	149 (156 ± 15)
8 boys	–67.3 (–55.4 ± 39.2)	0.54 (0.43 ± 0.29)	126 (126 ± 11)
8 boys (pooled)[b]	–61.4[c]	0.57[c]	107[c]
53	–57.5 (–57.9 ± 32.3)	0.56 (0.57 ± 0.19)	108 (101 ± 35)
	–57.4	0.58	110

sectional (Ellis et al., 2000) data based on a combination of water dilution, whole body potassium, and dual-energy x-ray absorptiometry (DXA) scanning methods used to estimate body composition. To obtain protein deposition rates since the data in young children were longitudinal (Butte et al., 2000), and the data in older children were cross-sectional (Ellis et

TABLE 10-9 Mean Daily Rates of Protein Deposition and Factorial Model Calculations of Mean Requirements for Protein

	Girls		Boys	
Age (y)	Protein Deposition[a] (mg/kg/d)	Mean Requirement[b] (g/kg/d)	Protein Deposition[a] (mg/kg/d)	Mean Requirement[b] (g/kg/d)
0.75	183	1.00	180	1.00
1	150	0.94	150	0.94
1.5	112	0.88	116	0.89
2	91	0.84	96	0.85
3	57	0.78	54	0.78
1–3	103	0.86	104	0.87
4	48	0.77	44	0.76
5	44	0.76	40	0.76
6	48	0.77	42	0.76
7	46	0.76	46	0.76
8	42	0.76	51	0.77
4–8	46	0.77	45	0.77
9	48	0.77	55	0.78
10	36	0.74	51	0.77
11	35	0.75	48	0.77
12	39	0.75	48	0.77
13	29	0.74	41	0.76
9–13	37	0.75	49	0.77
14	23	0.73	38	0.75
15	19	0.72	34	0.74
16	8	0.70	28	0.73
17	0	0.69	19	0.72
18	0	0.69	6	0.70
14–18	10	0.71	25	0.71

[a] Deposition was derived from the data for protein accumulation in children (Butte et al., 2000; Ellis et al., 2000), which were fitted to the following polynomial equations. The gradients at specific ages in the range 4 through 17 years were determined by differentiation of the regression equation. The growth rates given by Butte et al. (2000) were employed for ages 0.75 through 2 years.

Girls protein content = $-0.00027 \times \text{age (y)}^4 + 0.00816 \times \text{age (y)}^3 - 0.0665 \times \text{age (y)}^2 + 0.51819 \times \text{age (y)} + 0.60856$ ($R^2 = 0.9946$).

Boys protein content = $-0.00047 \times \text{age (y)}^4 + 0.01663 \times \text{age (y)}^3 - 0.16613 \times \text{age (y)}^2 + 0.95166 \times \text{age (y)} + 0.36037$ ($R^2 = 0.9966$).

notes continue

al., 2000), the data for body protein content from the two studies were pooled and regressed on age, giving a smooth curve and yielding the polynomial equations that are shown in footnote *a* in Table 10-9. Inclusion of data from the young children (Butte et al., 2000) improved the fit over the range of ages 4 through 18 years, but the fit at the younger ages, near the tail of the curve, was not satisfactory. Hence, the gradients at specific ages in the age range 4 through 18 years were determined by differentiation of the regression equation, whereas for ages 9 months through 2 years, the growth rates given by Butte and coworkers (2000) were employed.

Protein EAR Summary, Ages 7 Through 12 Months

The Estimated Average Requirement (EAR) is estimated by the factorial method by taking the median (110 mg nitrogen/kg/d equivalent to 688 mg protein/kg/d) of the nitrogen intake for nitrogen equilibrium (thus measuring maintenance requirement only) derived from Table 10-8, plus the product of 1.72 (the reciprocal of the slope [0.58] of those data, which estimates the efficiency of protein utilization for growth) and the mean protein deposition (Table 10-9) for boys and for girls. The resulting mean protein requirement is estimated to be 1.0 g/kg/d for boys and for girls.

EAR for Older Infants

7–12 months	**1.0 g/kg/d**

Protein RDA Summary, Ages 7 Through 12 Months

The Recommended Dietary Allowance (RDA) is defined as covering 97.5 percent of the age group. Thus, the EAR must be increased by an amount equal to two times its standard deviation to cover the needs of almost all of this age group. The variation in requirements is based on both the variation in maintenance needs and the variation in the rate of protein deposition (protein for growth).

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[b] Mean requirement = maintenance requirement from Table 10-8 or 10-12 + dietary amount needed from protein deposition by life stage and gender group.

Median requirement for ages 0.75 through 13 years = 688 mg protein/kg/d (110 mg N/kg/d [Table 10-8] × 6.25 mg protein/kg N) + (1.72 [efficiency of protein utilization derived from reciprocal of slope in Table 10-8] × mean protein deposition for life stage and gender group).

Median requirement for ages 14 through 18 years = 656 mg protein/kg/d (105 mg N/kg/d [Table 10-12] × 6.25 mg protein/kg N) + (2.13 [the efficiency of protein utilization derived from reciprocal of slope in Table 10-12 = 0.47] × mean protein deposition).

Due to lack of adequate data on this age group, the variation in maintenance requirement for protein was assumed to be the same in children of all ages as in adults. Thus, the coefficient of variation (CV) for maintenance for this age group is 12 percent, the same as the CV of the protein requirement for adults developed by Rand and coworkers (2003) (see "Adults Ages 19 Through 30 Years"). A coefficient of variation for growth of 43 percent was determined in a study of whole body potassium-40 content in children (Butte et al., 2002). The total variation from both sources combined is calculated from the formula:

$$SD_T = (\sqrt{[CV_M \times \text{maintenance requirement}]^2 + [CV_G \times \text{growth requirement}]^2}),$$

where CV_M is 0.12, the maintenance requirement is 0.688 g protein/kg/d, CV_G is 0.43, and the growth requirement is the rate of protein deposition divided by the efficiency of dietary protein utilization. This yields the following formula:

$$SD_T = (\sqrt{[0.12 \times 0.688 \text{ g protein/kg/d}]^2 + [0.43 \times 1.72 \times Y \text{ g protein/kg/d}^2]}),$$

where Y = 0.182 g/kg/d (average of value for boys and girls from Table 10-9).

The RDA is then calculated as the RDA = EAR + 2 × SD_T, yielding the formula:

$$RDA = EAR + 2 \times (\sqrt{[0.12 \times 0.688 \text{ g protein/kg/d}]^2 + [0.43 \times 1.72 \times 0.182 \text{ g protein/kg/d}]^2})$$

The estimated amount by which to increase the EAR to cover 97.5 percent of older infants is thus the EAR + 2 (0.101 g protein/kg/d) = 1.0 + 0.2 g protein/kg/d for a total of 1.2 g/kg/d of protein. This value is slightly lower than the AI for protein based on mean protein content of human milk and the intake from complementary foods of 1.6 g/kg/d.

RDA for Older Infants

7–12 months 1.2 g/kg/d or 11.0 g/d of protein[1]

[1]Due to a calculation error in the prepublication copy, the value is changed from 1.5 g/kg/d to 1.2 g/kg/d and for the reference infant from 13.5 g/d to 11.0 g/d.

Children Ages 1 Through 13 Years

Protein EAR Summary, Ages 1 Through 13 Years

The Estimated Average Requirement (EAR) is estimated by the factorial method, which adds the amount needed for maintenance based on body weight to the amount estimated to be needed for protein deposition. The mean of the nitrogen intake for nitrogen equilibrium (thus measuring maintenance requirement only) is derived from all of the individual estimates for children and is 110 mg nitrogen/kg/d or 688 mg protein/kg/d (110 × 6.25) (Table 10-8). This is increased by the product of 1.72 (the reciprocal of the slope [0.58] of that data, which estimates the amount of protein utilization) and the efficiency of utilization as estimated by Rand and coworkers (2003) for adults (see "Adults Ages 19 Years and Older"). This is multiplied by the mean protein deposition (Table 10-9) for boys and for girls for each age group. Given the assumptions in this method and the few girls in the studies included in Tables 10-8 and 10-9, the EAR is set at the average for boys and girls in each age group.

EAR for Boys and Girls

1–3 years	**0.87 g/kg/d of protein**[2]
4–8 years	**0.76 g/kg/d of protein**
9–13 years	**0.76 g/kg/d of protein**

Protein RDA Summary, Ages 1 Through 13 Years

Assuming the variation of maintenance requirements for protein and protein deposition requirements vary, then the RDA is set as indicated at the 97.5th percentile, estimated as follows:

$$\text{RDA} = \text{EAR} + 2\ (\sqrt{[0.12 \times 0.688 \text{ g protein/kg/d}]^2 + [0.43 \times 1.72 \times \text{Y g protein/kg/d}]^2}),$$

where Y = 0.104 g for age group 1–3 years, 0.046 g for age group 4–8 years, and 0.043 g for age group 9–13 years. Numbers are rounded to nearest 0.05 g.

Using the reference values for body weight for each age group as shown in Table 1-1, the RDA for protein would be 13 g/d for ages 1–3 years, 19 g/d for 4–8 years, and 34 g/d for 9–13 years.

[2]Due to a calculation error in the prepublication copy, the value is changed from 0.88 g/kg/d to 0.87 g/kg/d.

RDA for Boys and Girls

1–3 years	**1.05 g/kg/d or 13 g/d of protein**[3]
4–8 years	**0.95 g/kg/d or 19 g/d of protein**
9–13 years	**0.95 g/kg/d of 34 g/d of protein**

Adolescents Ages 14 Through 18 Years

Since data were not available to determine the maintenance protein requirement in children older than 14 years of age (Table 10-8), and since the maintenance nitrogen requirement of children (110 mg/kg/d) is similar to that for adults (105 mg/kg/d as shown in Table 10-12), the EAR for adolescents 14 through 18 years of age is based on the adult estimates of maintenance requirements from nitrogen balance studies (Rand et al., 2003), plus an additional amount to cover the needs for growth for this age as determined by the factorial method.

Protein EAR Summary, Ages 14 Through 18 Years

The maintenance requirement of adults of 105 mg nitrogen/kg/d or 656 mg protein/kg/d is added to the product of 2.13 (the reciprocal of the slope [0.47], which is the estimate of the efficiency of protein utilization in adults) (Rand et al., 2003), times the mean protein deposition as adjusted for efficiency of protein utilization (0.43), and calculated for boys or girls 14 through 18 years of age using the polynomial equations given in Table 10-9 to estimate protein deposition.

EAR for Boys

14–18 years	**0.73 g/kg/d of protein**

EAR for Girls

14–18 years	**0.71 g/kg/d of protein**

Protein RDA Summary, Ages 14 Through 18 Years

The RDA for protein for adolescents is set by determining the CV for maintenance and protein deposition. Since the CV of the maintenance requirement could not be calculated from the data shown in Table 10-8, and because of the similarity in maintenance requirements in children (Table 10-8; 110 mg N/kg/d) and adults (105 mg N/kg/d as estimated by

[3]Due to a calculation error in the prepublication copy, the value is changed from 1.10 g/kg/d to 1.05 g/kg/d.

Rand et al., [2003]), the CV in adults (12 percent) was also utilized to determine the variation in maintenance requirements for children and adolescents (see section "Protein RDA Summary, Ages 19–50 Years"). A CV of 43 percent for protein deposition was determined in the study of Butte and coworkers (2000), and this varied little with age and gender. Therefore, this value was used as the CV for growth for all ages.

The RDA is set for older adolescents as indicated at the 97.5th percentile, estimated as follows:

$$\text{RDA} = \text{EAR} + 2\ (\sqrt{[0.12 \times 0.656\ \text{g protein/kg/d}]^2 + [0.43 \times 2.13 \times \text{Y g protein/kg/d}]^2}),$$

where Y = 0.010 g for girls and 0.025 g for boys. Numbers are rounded to nearest 0.05 g.

Using the reference values for body weight shown in Table 1-1, the RDA for protein for girls 14–18 years of age would be 46 g/d, and for boys, 52 g/d.

RDA for Boys	
14–18 years	**0. 85 g/kg/d of protein or 52 g/d of protein**
RDA for Girls	
14–18 years	**0.85 g/kg/d of protein or 46 g/d of protein**

Adults Ages 19 Through 50 Years

Evidence Considered in Estimating the Average Requirement

In adults, protein requirement estimates have depended on one of two main approaches, namely, the factorial method and nitrogen balance response to different levels of intake of defined quality protein intakes. While the nitrogen balance method for estimation of protein requirements has serious shortcomings (see "Nitrogen Balance Method"), this method remains the primary approach for determining the protein requirement in adults, in large part because there is no validated or accepted alternative.

Nitrogen Balance Studies

Over the last 40 years, a number of analyses of available data on adult nitrogen balance studies have been utilized to estimate adult protein requirements; some reports are listed in Table 10-10. A growing body of data has accumulated that allows a more refined approach to such estimates, as improved techniques for measuring nitrogen output and controlling for

TABLE 10-10 Estimates of Adult Protein Requirements Using Nitrogen Balance Data

Reference	Estimates of Adult Protein Requirements for High Quality Protein (includes estimate of variation in requirements) (g/kg/d)		Estimation of Variation in Requirements (%)
	Men	Women	
FAO/WHO, 1965	0.71	0.71	10
FAO/WHO, 1973	0.60	0.60	15
FAO/WHO/UNU, 1985	0.75	0.75	12.5
Rand et al., 2003	0.80	0.80	12

external variables that impact nitrogen utilization have been implemented, and there has been a move toward standardization of study protocols.

The most recent in-depth analysis conducted at the request of the International Dietary Energy Consultative Group in 1996 and then more recently by the Food and Agriculture Organization, World Health Organization, and the United Nations University (FAO/WHO/UNU) included 19 studies conducted across the globe that measured and published nitrogen balance responses for 235 individuals given at least three levels of nitrogen intake for periods of 10 to 14 days (to be included in the analysis, it was required that individual data be available for at least three levels of intake adapted to by consuming the diet for least 10 days, with urinary and fecal nitrogen collection in the final 5 days of the diet period) (Rand et al., 2003). This was considered important so that estimates of individual requirements could be interpolated. In addition, 9 studies of individuals fed a single level of nitrogen intake or that only provided group data for multiple levels of intake (n = 174 individuals) were used to assess the fit of the analyses conducted (Rand et al., 2003). The studies used were classified on the basis of age of the adults (young: 19 through 52 years of age; old: 53 years of age and older); protein source (animal [animal sources provided > 90 percent of the total protein], vegetable [vegetable sources provided > 90 percent of the total protein], or mixed), as well as gender and climatic origin (temperate or tropical area), and corrected for skin and miscellaneous losses when not included in the nitrogen balance data (Rand et al., 2003). (See Appendix M for data on studies used.)

Analyses have also been made estimating endogenous protein loss in healthy adults when consuming protein-free diets adequate in all other respects. Estimates of endogenous loss from some of the various analyses of protein requirements are included in Table 10-11.

Methods Used to Estimate Individual Requirements

Earlier estimates of adult protein requirements (FAO/WHO, 1965) utilized information from endogenous nitrogen losses as the basis for determining protein requirements, assuming maximal utilization at levels near endogenous losses. However, as discussed in earlier sections, the efficiency of utilization of dietary protein declines as nitrogen equilibrium is reached. More recent approaches have averaged nitrogen balance data obtained from various studies where healthy individuals were given high-quality protein sources so that total nitrogen is considered the limiting dietary component rather than a specific indispensable amino acid (FAO/WHO/UNU, 1985).

With additional data it is possible to estimate requirements using regression analysis. Linear regression of nitrogen balance on nitrogen intake was utilized to estimate the nitrogen intake that would produce zero nitrogen balance in the most recent carefully done analysis available (Rand et al., 2003). In adults, it is generally presumed that the protein requirement is achieved when an individual is in zero nitrogen balance. To some extent, this assumption poses problems that may lead to underestimates of the true protein requirement (see "Nitrogen Balance Method").

Although the authors (Rand et al., 2003) acknowledge that it is known that the nitrogen response curve is nonlinear (because at high intakes the efficiency of nitrogen retention decreases), linear interpolation was utilized because the primary data utilized for the regression were gathered at intake levels close to those that were expected to produce zero balance. In this range there is no indication, either visually or statistically, for the utilization of an interpolation scheme other than linear (Rand et al., 2003). It was also recognized that while the use of more complex models would improve the standard error of fit, these models did not statistically improve the fits, in large part because of the small number of data points (3 to 6) for each individual (Rand et al., 2003).

Estimation of the Median Requirement

Utilizing the recent analysis of nitrogen balance data (Rand et al., 2003), the individual requirement estimates were found to be both significantly skewed and kurtotic, being characterized by more than expected very large or very small requirements (see Figure 10-5) (Rand et al., 2003).

TABLE 10-11 Estimates of Endogenous Loss of Nitrogen

Reference	Estimates of Urinary Losses (mg N/kg/d)		Estimates of Fecal Losses (mg N/kg/d)	Integumental Obligatory and Miscellaneous Losses (mg N/kg/d)	Total Endogenous Loss of Nitrogen (mg N/kg/d)
	Men	Women			
FAO/WHO, 1965	46	46	46	46	~ 100
FAO/WHO, 1973				5	
FAO/WHO/UNU, 1985 (n = 11 studies)	34	27	34	27	Men = 54 Women = 47 All = 52
Rand et al., 2003 (n = 14 studies)				5 temperate 11 tropical	Men = 50 Women = 35 All = 47

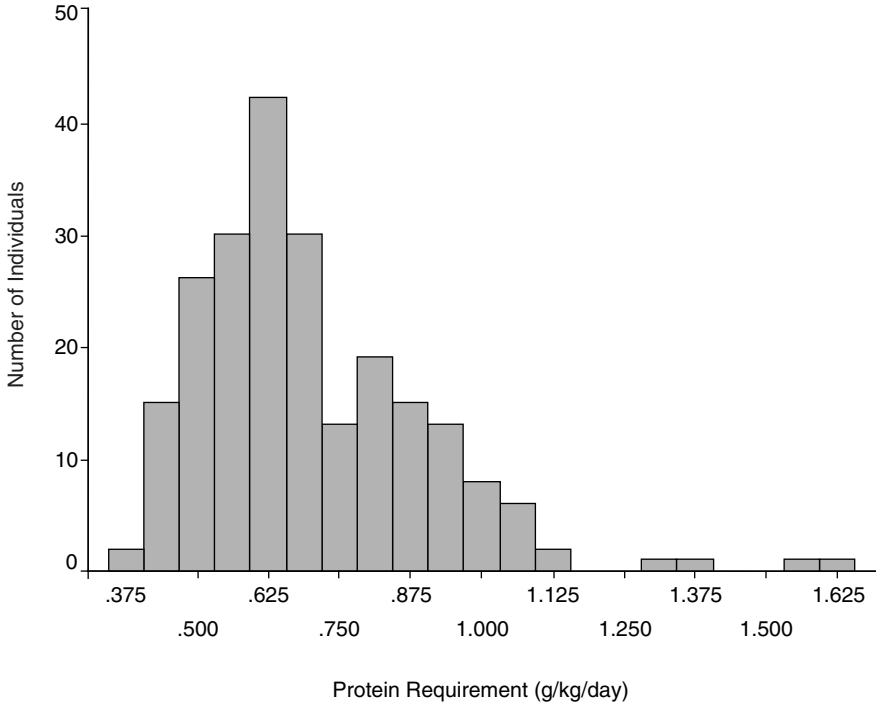

FIGURE 10-5 Distribution of the estimated protein requirements for 225 individuals (Rand et al., 2003) in a trimmed data set showing the skewness of protein requirement.
SOURCE: William Rand, personal communication, 2002.

The median requirement, potentially of use as the EAR, was calculated in two different ways: first as the median of the entire sample of 235 individuals in the primary data set (weighting all individuals the same), and second as the median of the medians of each distinct substudy (weighting each substudy equally) (Rand et al., 2003). In either case, data from all individuals were included in the analysis.

The results of these analyses are included in Table 10-12. Because of the non-normality of the individual data, nonparametric tests were used (Mann-Whitney and Kruskal-Wallis) to compare requirements between the age, gender, diet, and climate subgroups (Table 10-13). Where nonsignificant differences were found, Analysis of Variance was used for power calculations to roughly estimate the differences that could have been found with the data and variability. Separate analyses were conducted for all the

TABLE 10-12 Analyses of Linear Regression Analysis of Nitrogen Requirements in Adults

Data Sets Used	Linear Regression—Median Nitrogen Requirement (mg/kg/d)			Linear Regression—Slope	Intercept at 0 Intake (mg N/kg/d)
	Men	Women	All		
19 Estimation studies (n = 235; men = 181, women = 54)	109	91	105	0.47	–48
95% confidence intervals			(101, 110)	(0.44, 0.50)	(–51, –45)
32 substudies (n = 32 group medians; men = 24, women = 8)	102	102	102	0.49	–47
All individual data (n = 1,593)			103		
Linear regression model (grouped data)			122		
Quadratic regression model (grouped data)			114		
Asymptotic growth exponential (grouped data)			116		
Asymptote			42		
Linear bi-phase			108		
Breakpoint			126		
Asymptote			–7.2		

SOURCE: Rand et al. (2003).

individual requirements and for substudies, both excluding and including secondary estimation data (Rand et al., 2003).

Statistical Analysis of Nitrogen Balance Data to Determine the Protein Requirement

Data Analysis. The relationship between nitrogen balances, corrected for integumental and miscellaneous losses, and nitrogen intake from Rand and coworkers (2003) is shown in Figure 10-6. This figure includes individual data from the linear regression of nitrogen balance in adults examined (Rand et al., 2003). The authors noted that positive nitrogen balance was found in some individuals at nitrogen intakes as low as 60 mg/kg/d, and in other individuals negative balance was noted at nitrogen intakes as high as 200 mg/kg/d. This suggests that at least some of these individuals were not at constant nitrogen balance equilibrium.

In addition, while the nitrogen balance response to increasing nitrogen intake is theoretically expected to be nonlinear, the primary individual data points near the equilibrium balance point demonstrate a linear relationship, which appears to become nonlinear at high intakes. This can be attributed to different study designs in the test data included in Figure 10-6. The data points from only the estimation studies show a linear response over the relatively narrow range of intakes studied, while data points from the test studies also show a response that is not different from linear, although more variable and with a lower slope. Much variability is noted in the response data because the studies differ in methodology, individuals differ from each other, and an individual's response differs from day to day.

Table 10-12, a summary of the nitrogen requirement for all the data points included in the analysis by Rand and coworkers (2003), shows a nitrogen requirement of 105 mg/kg/d or 0.66 g protein/kg/d (105 mg N/kg/d × 6.25), with an approximately 95 percent confidence interval of 101 to 110 mg/kg/d (0.63 to 0.69 g protein/kg/d). When only the individual data points in the primary estimation studies are considered, the nitrogen requirement is 102 mg/kg/d (0.64 g protein/kg/d), and when all of the estimation study data points are considered, the nitrogen requirement is 103 mg/kg/d (0.64 g/kg/d). The median slope of the nitrogen balance response regression was 0.47 mg N/kg/d for all the data points, with a 95 percent confidence interval of 0.44 to 0.50 mg N/kg/d, which is in close agreement with the median slope of the primary estimation studies of 0.49 mg N/kg/d and all estimation studies of 0.47 mg N/kg/d.

Factor Analysis. Since all the data meeting the criteria for the meta-analysis were combined in the regression analysis by the authors (Rand et

TABLE 10-13 Factor Analysis: Estimation of Nitrogen Requirement with Medians and Mann-Whitney or Kruskal-Wallis Testing

Data	Factor	Number of Points	Median Slope	Median Intercept (mg/kg/d)	Median Nitrogen Requirement[a] (mg/kg/d)
Primary estimation studies	All	32	0.49	–47.1	102
Climate	Temperate	22	0.45	–43.0	101
	Tropical	10	0.52	–54.8	111
	P-value		0.10	0.020	0.27
Age	Young	30	0.50	–48.9	102
	Old	2	0.31	–36.7	111
	P-value		0.12	0.23	0.97
Gender	Male	24	0.50	–48.9	102
	Female	8	0.46	–42.0	102
	P-value		0.45	0.27	0.62
Diet	Animal	9	0.50	–48.1	101
	Vegetable	11	0.50	–45.9	104
	Mixed	12	0.48	–49.7	102
	P-value		0.88	0.83	0.72
Other estimation studies	All	45	0.47	–46.0	103
Climate	Temperate	33	0.42	–41.8	101
	Tropical	12	0.51	–54.5	111
	P-value		0.026	0.002	0.29

Age	Young	43	0.48	–47.0	103
	Old	2	0.31	–36.7	111
	P-value		0.18	0.27	0.98
Gender	Male	36	0.48	–47.6	103
	Female	9	0.44	–39.2	103
	P-value		0.47	0.40	0.94
Diet	Animal	17	0.46	–40.6	101
	Vegetable	13	0.50	–45.0	108
	Mixed	15	0.47	–50.5	105
	P-value		0.85	0.40	0.64
All data	All	235	0.47	–48.1	105
Climate	Temperate	154	0.45	–45.3	103
	Tropical	81	0.50	–51.9	113
	P-value		0.20	0.011	0.047
Age	Young	221	0.48	–49.4	104
	Old	14	0.31	–36.7	131
	P-value		0.003	0.025	0.401
Gender	Male	181	0.46	–49.4	109
	Female	54	0.47	–43.1	91
	P-value		0.47	0.20	< 0.001
Diet	Animal	64	0.46	–48.8	104
	Vegetable	77	0.47	–49.4	107
	Mixed	94	0.48	–46.6	104
	P-value		0.62	0.81	0.62

[a] Protein requirement = 6.25 × nitrogen requirement.

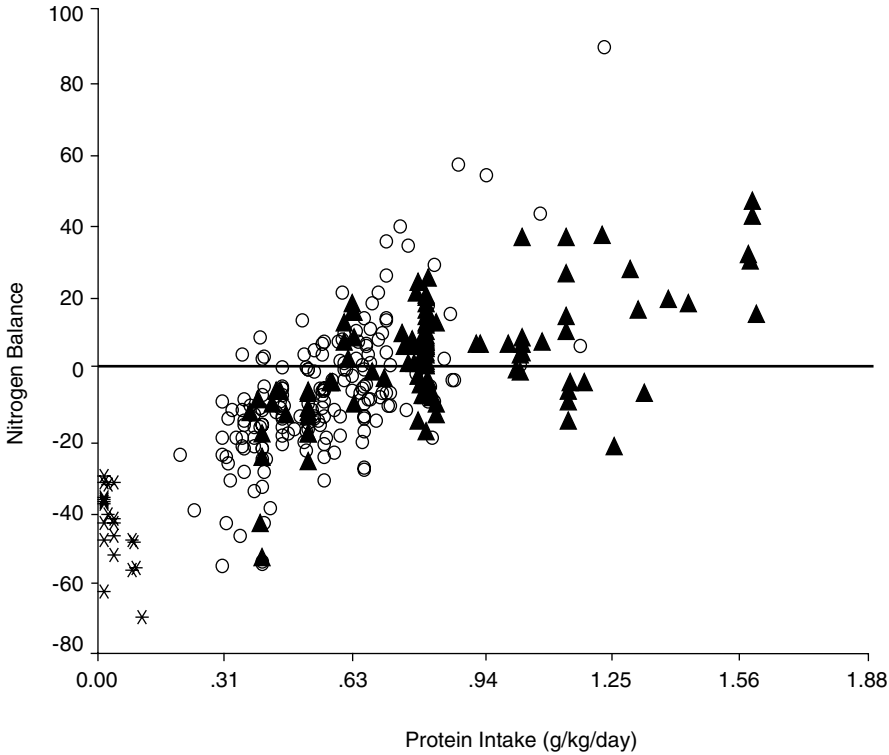

FIGURE 10-6 Relationship between individual nitrogen balances, corrected for integumental and nitrogen losses and nitrogen intake in random selection of data. □ = primary data; ▲ = test data; * = obligatory losses data.
SOURCE: Rand et al. (2003).

al., 2003), a separate analysis was conducted to evaluate the extent to which the four factors thought to have the most influence on protein requirements—climate, age, gender, and dietary protein source—were analyzed. As shown in Table 10-13, expected climate in the country of the study had a significant effect ($p < 0.47$), with differences of the magnitude of about +10 mg N/kg/d (0.06 g protein/kg/d) in tropical climates. The effect of age, as shown in Table 10-13, was a nonsignificant difference of 27 mg N/d (0.17 g protein/d) in the nitrogen requirement between young (19 to 52 years of age) and older (53 years of age and older) individuals per kg of body weight. Although the young individuals had a lower nitrogen requirement than the older individuals, the requirement of young individuals was more variable and more positively skewed than that for the older individuals.

In addition, men had a statistically significant higher median nitrogen requirement by about 18 mg N/kg/d (0.11 g protein/kg/d) than did the women studied, although this difference disappears when medians of the primary estimation studies are compared. Ninety-five percent confidence intervals for these estimates are 104 and 114 mg N/kg/d (0.65 and 0.71 g protein/kg/d) for men and 85 and 104 mg N/kg/d (0.53 and 0.65 g protein/kg/d) for women. Finally, the source of protein (90 percent animal, 90 percent vegetable, or mixed) did not significantly affect the median nitrogen requirement, slope, or intercept. It should be noted that almost all of the studies included as 90 percent vegetable were based on complementary proteins. For further discussion on this aspect of the data analysis and for information on vegetarian diets see later sections on "Protein Quality" and on "Vegetarians."

All of the various estimates of protein requirements (Table 10-10) are confounded by variations in energy intake relative to energy balance and expenditure. It has been estimated that an error of about 10 percent in energy intake as estimated from a diet history or a prediction equation (FAO/WHO/UNU, 1985) would cause the nitrogen balance estimate to be affected by about ± 6 mg/kg/d (Pellett and Young, 1992).

Other Approaches to Determine the Protein Requirement Based on the Recent Meta-Analysis

In addition to the linear statistical approach to determine protein requirements described in detail above, the authors considered three other statistical approaches to the nitrogen balance analysis (Rand et al., 2003). All data from the studies in the meta-analysis were fitted to the following models: linear, quadratic, asymptotic exponential growth and linear biphase (see Table 10-12).

Since the above analyses used all of the available data points without linking the individuals or restricting the range of intakes, the authors made the decision to use nitrogen equilibrium as the criterion and individual linear regressions, using only those individuals in the primary data set to determine the protein requirement (Rand et al., 2003). However, due to the shortcomings of the nitrogen balance method noted earlier, it is recommended that the use of nitrogen balance should no longer be regarded as the "gold standard" for the assessment of the adequacy of protein intake and that alternative means should be sought.

Protein EAR Summary, Ages 19 Through 50 Years

Using the recent meta-analysis of the nitrogen balance studies (Rand et al., 2003), the best estimate of the nitrogen EAR in the healthy adult popu-

lation is determined to be 105 mg N/kg/d, the median requirement for all data (Table 10-13), or 0.66 g/kg/d of protein (105 mg N/kg/d × 6.25). The criterion of adequacy used for the protein EAR is based on the lowest continuing intake of dietary protein that is sufficient to achieve body nitrogen equilibrium (zero balance). While the data as analyzed in the meta analysis (Rand et al., 2003) do not provide any basis for assuming different requirements for climate, age, or source of protein in the diet, it must be recognized that such a lack of statistically significant differences in this data may well be artifacts of the method and the variability in both its determination and in the individuals measured.

Although the data indicate that women have a lower nitrogen requirement than men per kilogram of body weight, this was only statistically significant when all studies were included, but not when the analysis was restricted to the primary data sets. This difference may be due to differences in body composition between men and women, with women and men having on average 28 and 15 percent fat mass, respectively. When controlled for lean body mass, no gender differences in the protein requirements were found. However, in view of the uncertain significance of the difference between the genders, the same protein EAR on a body weight basis for both men and women is chosen. Based on the reference body weights of 70 kg and 57 kg for men and women, respectively, from Table 1-1, the EAR for protein is 47 g/d for men and 38 g/d for women.

EAR for Men	
19–30 years	**0.66 g/kg/d of protein**
31–50 years	**0.66 g/kg/d of protein**
EAR for Women	
19–30 years	**0.66 g/kg/d of protein**
31–50 years	**0.66 g/kg/d of protein**

Protein RDA Summary, Ages 19 Through 50 Years

The RDA for protein is set using the nitrogen balance database and methodology detailed by Rand and colleagues (2003) who demonstrated that the natural logarithm of requirement (in mg nitrogen/kg/day) has a normal distribution with a mean of 4.65 and a standard deviation of 0.12. The 97.5th percentile of the log requirement is then calculated as 4.89 (the mean plus 1.96 times the standard deviation) and the RDA is the exponentiation (exp) of this value, 132 mg nitrogen/kg/d, or equivalently, 0.80 g protein/kg/d (rounding to the nearest 0.1 g). It should be noted that protein requirement having a log normal distribution permits the

estimation the protein intake adequate for any percentile (P) of a healthy population from the equivalent formulae:

$$\exp[0.12 \times z(P) + 4.65] \text{ for nitrogen (mg/kg/d), or}$$
$$\exp[0.12 \times z(P) - 0.425] \text{ for protein (g/kg/d)}$$

In these equations,

(1) "4.65" and "–0.425" are, respectively, the means of the log requirement distributions in mg nitrogen/kg/d and g protein/kg/d [the EAR in mg nitrogen/kg/d = exp(4.65) = 105, while the EAR in g protein/kg/d = exp(–0.425) = 0.65];

(2) "0.12" is the standard deviation of the log of requirement (note that one feature of log normal distributions is that their standard deviation does not change when the units are changed); and

(3) "z(P)" is the value of the standardized normal distribution associated with P.

For example, the intake that is estimated to be adequate for 80 percent of a healthy population is exp [0.12 × z(0.8) – 0.425] = exp [0.12 × 0.84 – 0.425] = exp[–0.324] = 0.72 g protein/kg/d.

Based on the reference body weights of 70 kg for men and 57 kg for women from Table 1-1, the RDA for protein is 56 g/d for men and 46 g/d for women ages 19 through 50 years.

Because the distribution of individual requirements for protein is log normal, and thus skewed, the calculated standard deviation and coefficient of variation of requirement itself does not have the usual intuitive meaning (that the mean plus two standard deviations exceeds all but about 2.5 percent of the population's requirement). However, because this skewing is not extreme, an approximate standard deviation can be calculated as half the distance from the 16th to the 84th percentile of the protein requirement distribution as estimated from the log normal distribution of requirements. This gives a value of 12.5 mg nitrogen/kg/d (CV = 12 percent) which can be used to estimate the RDA's of other age groups and for individual amino acids where fewer data from the following formula: RDA = EAR + 2 CV, or RDA = 1.24 × EAR.

RDA for Men

19–30 years	**0.80 g/kg/d or 56 g/d of protein**
31–50 years	**0.80 g/kg/d or 56 g/d of protein**

RDA for Women

19–30 years	**0.80 g/kg/d or 46 g/d of protein**
31–50 years	**0.80 g/kg/d or 46 g/d of protein**

Adults Ages 51 Years and Older

Evidence Considered in Estimating the Average Requirement

In the meta-analysis described in Table 10-12 and used as the basis to determine adult protein requirements (Rand et al., 2003), there were six studies to assess the protein requirement of individuals aged 51 years and older. These have been analyzed and evaluated in various publications (Campbell and Evans, 1996; Campbell et al., 1994; Millward and Roberts, 1996; Millward et al., 1997). Table 10-14 shows the value for the EAR derived by the original authors, plus the values obtained in the reassessments of the original data by Campbell's group in 1994 and Millward's group in 1997. The variability among the derived values, and the changes due to reassessment, are the result of the many inadequacies in the original data, which are described below.

Only the study of Cheng and coworkers (1978) involved a direct comparison of old with young adults; however, the authors made no assessment of the miscellaneous nitrogen losses and were not able to show any clear difference in the requirement of older and younger adults. In inter-

TABLE 10-14 Nitrogen Balance Studies in Older Individuals

Reference	Study Population	Protein Intake Levels (g/kg/d)
Cheng et al., 1978	7 men, 60–73 y	0.40, 0.80, 1.60
Uauy et al., 1978	7 men, 7 women	0.57, 0.70, 0.85 0.52, 0.65, 0.80
Zanni et al., 1979	6 men, 63–77 y	0.38, 0.44
Gersovitz et al., 1982	7 men, 70–82 y 8 women, 71–99 y	0.80 0.80
Campbell et al., 1994	8 men, 56–68 y 4 women, 66–80 y	0.80, 1.62 0.80, 1.62
Castaneda et al., 1995b	12 women, 66–79 y	0.45, 0.92

[a] Estimates of average requirements derived from studies on elderly adults by the original authors and in subsequent reanalyses by Millward et al. (1997) and Campbell et al. (1994).

preting the data of Cheng's group, it was suggested that the energy intake of the older Chilean men was too high, 40 kcal/kg/d, as it was the same as that given to the younger men, who would be expected to have higher energy expenditures (Campbell et al., 1994).

Dietary energy excess is believed to give rise to erroneously low estimates of protein requirements (Garza et al., 1976, 1977a). However, the energy requirements of the elderly have been shown to be higher than previously believed (Roberts, 1996). Moreover, the urinary creatinine to body weight ratio reported by Cheng and coworkers (1978) was the same in the old (0.023 g/kg/d) as in the young (0.022 g/kg/d) men, suggesting that the two groups were of similar body composition. This is in contrast to studies in the United States where lower creatinine to body weight ratios were observed in the older adults (0.014 to 0.018 g/kg/d) (Campbell et al., 1994; Uauy et al., 1978; Zanni et al., 1979).

The study of nitrogen balance by Zanni and coworkers (1979) suggested that the average amount of protein intake required to maintain nitrogen balance in older adults was very low (0.46 g/kg/d). This study was performed under almost the same conditions as those used with younger adults in an earlier study from the same laboratory (Calloway and

	Average Requirement (g protein/kg/d)[a] as calculated by:		
Energy Intake (kcal/kg/d)[b]	Authors	Campbell et al. (1994)	Millward et al. (1997)
40 (constant)	0.77	0.93	> 0.4
32	0.70–0.85	0.81	≤ 0.57
28 (varied)	0.83	0.81	Uncertain
31 (varied)	0.46	0.65	Uncertain
32 29 (varied)	> 0.8	—	< 0.8
32 29 (varied)	1.0	1.0	< 0.8
32 (varied)	0.78–0.82	—	< 0.92

[b] Energy intake was either held constant for duration of nitrogen balance period, or varied to maintain body weight; varied levels are average intakes of group as reported by authors.

Margen, 1971) and demonstrated that the amount of protein needed by older adults (0.46 g/kg/d) was quite similar per kg of body weight compared to the younger adults (0.42 g/kg/d). Since the two different diets studied were relatively low in protein (0.38 and 0.44 g/kg/d), Millward and coworkers (1997) suggested that these low protein intakes led to an underestimate of the requirement. Moreover, since the adults were on a protein-free diet for 17 days preceding the two low-protein diets (each fed in random order for 15 days), this could have resulted in significant protein depletion, probably leading to a further underestimate of requirement. On the other hand, the study of Uauy and coworkers (1978) employed energy intakes (30 kcal/kg/d) that may have been too low, suggesting that their estimate of requirement (~0.8 g/kg/d) might have been an overestimate (Millward et al., 1997). It can be seen from Table 10-14 that the reanalysis by Campbell and coworkers (1994) led to overall higher estimates of the requirements of older adults than the original authors, whereas the reanalysis by Millward's group (1997) led to lower estimates.

In studies designed to evaluate the adequacy of diets containing 0.8 g/kg/d of protein (the 1973 FAO/WHO recommendation for a safe level of intake of egg or milk protein in adults [FAO/WHO, 1973]), nitrogen balance was measured in adults given single levels of protein for various periods. Gersovitz and coworkers (1982) showed that almost 50 percent of older men and women were in negative nitrogen balance at this level after 30 days. Similar results were obtained by Campbell and coworkers (1994) in individuals given 0.8 g/kg/d of protein for 11 days, whereas Castaneda and coworkers (1995a) found that the majority of older women were in positive nitrogen balance after 3 and 9 weeks on a diet containing 0.92 g/kg/d of protein.

On the basis of these data and reanalysis of the original data from the studies discussed above, it was suggested that the estimated requirement should be increased (Campbell and Evans, 1996), although Millward and coworkers (1997) were not in agreement with this conclusion. More recent data have shown that elderly adults given 0.8 g/kg/d of protein were in nitrogen balance after 2 weeks, and in positive balance after 8 and 14 weeks (Campbell et al., 2001). However, the thigh muscle area was significantly reduced after 14 weeks compared with 2 weeks, although there were no changes in any other measured indices of body protein composition.

In order to address these problems of interpretation of the relevant literature, the meta-analysis evaluated the data from the studies on elderly adults compared with those from the studies used to evaluate the requirement in younger individuals (Rand et al., 2003). All the data from studies of nitrogen balance in the older adults were included in the regression procedure employed to determine the protein requirement of adults 19 to 50 years of age, and no significant effect of age in terms of the amount of protein required per kilogram of body weight was detected (Table 10-13).

Protein EAR Summary, Ages 51 Years and Older

In summary, no significant effect of age on protein requirement in older adults was detected using the linear regression model by Rand and coworkers (2003) when evaluated in terms of amount needed per kg of body weight, recognizing that lean body mass as a percent of body weight and the protein content of the body both decrease with age. Therefore, for older adults, no additional protein allowance based on body weight beyond that of younger adults is warranted.

EAR for Men	
51–70 years	**0.66 g/kg/d of protein**
> 70 years	**0.66 g/kg/d of protein**

EAR for Women	
51–70 years	**0.66 g/kg/d of protein**
> 70 years	**0.66 g/kg/d of protein**

Protein RDA Summary, Ages 51 Years and Older

As with younger adults, because the distribution of individual requirements for protein is not a normal distribution and is skewed, its calculated standard deviation and coefficient of variation do not have the usual intuitive meaning (the mean plus two standard deviations exceeding all but about 2.5 percent of the population's requirement). However, an approximate standard deviation can be calculated as half of the distance from the 16th to the 84th percentiles of the protein requirement distribution as estimated from the log normal distribution of requirements. This gives, for comparative purposes, an approximate standard deviation of 12.5 mg N/kg/d (CV = 12 percent). It can thus be assumed as with younger adults percent that the RDA = EAR + 2 CV for protein and individual amino acids, or RDA = 1.24 × EAR. The calculated RDA is rounded to the nearest 0.05.

RDA for Men	
51–70 years	**0.80 g/kg/d or 56 g/d of protein**
> 70 years	**0.80 g/kg/d or 56 g/d of protein**

RDA for Women	
51–70 years	**0.80 g/kg/d or 46 g/d of protein**
> 70 years	**0.80 g/kg/d or 46 g/d of protein**

Pregnancy

Physiological Adaptations to Protein Metabolism During Pregnancy

Whole body protein turnover, measured by leucine kinetics, is increased in pregnant women at weeks 24 and 35 compared with pregnant women at 13 weeks or with nonpregnant women (Thompson and Halliday, 1992). Similar observations of increased whole body protein turnover during pregnancy have been made using ^{15}N lysine as a tracer (Kalhan and Devapatla, 1999). A significant reduction in urea synthesis has been shown to occur in the first trimester and is sustained throughout pregnancy (Kalhan et al., 1998). There is general agreement that the amount of nitrogen accreted due to a pregnancy involving 12.5 kg of maternal weight gain (which includes a term infant weighing 3.3 kg) is 148 g (equivalent to 925 g protein if using a conversion factor of 6.25) (Hytten and Leitch, 1971; King, 1975). This amount of protein accumulation is predicted by a summation of the protein components of the fetus (440 g), uterus (166 g), expanded maternal blood volume (81 g), placenta (100 g), extracellular fluid (135 g), and amniotic fluid (3 g) (IOM, 1990). There is also evidence from both nitrogen balance studies and whole body potassium counting that there are additional maternal protein-containing tissues that accumulate during pregnancy and are presumed to be in skeletal muscle (Kalhan, 2000; King, 1975; King et al., 1973).

Evidence Considered in Estimating the Average Requirement

Nitrogen and Potassium Balance. King and coworkers (1973) studied 10 adolescent women aged 15 to 19 years during the last trimester of pregnancy. Since all but one of the individuals were more than 4 years beyond menarche, the authors excluded consideration of maternal height growth. Nitrogen retention was linearly related to protein intake when five different nitrogen levels (9.3 to 20.0 g of N/d [58 to 125 g of protein/d]) were fed for 12-day periods, and the slope of the relationship was 0.3 ($r = 0.68$, $p < 0.001$). The average nitrogen retention (corrected for skin and miscellaneous nitrogen losses) was 2.4 g/d.

Nitrogen balance studies in pregnant women that account for skin and miscellaneous losses have shown that nitrogen retention during all periods of pregnancy is double the theoretical factorial gain (Calloway, 1974; King, 1975; King et al., 1973) and as noted previously (see "Nitrogen Balance Methods"), at high nitrogen intakes erroneous positive nitrogen balances have frequently been obtained.

The rate of protein accretion has also been calculated indirectly from the increase in whole body potassium. The average potassium deposition, measured by total body ^{40}potassium counts, was 3.41 mmol/d in the adolescent girls (King et al., 1973), but a review of the literature suggests that this value may be too high. The results of measurements of total body potassium during pregnancy from the study of King's group (1973) and five other reports are shown in Table 10-15, and yield a weighted mean value of 2.48 mmol/d from 120 individuals, most of whom were in their third trimester of pregnancy. To calculate nitrogen deposition, King and coworkers (1973) used the potassium/nitrogen ratio of 2.15 mmol of potassium/g of nitrogen as determined by carcass analysis of 21 whole human infants (Fee and Weil, 1963; Hamilton and Moriarty, 1929; Iob and Swanson, 1934; Widdowson and Dickerson, 1964). Using this ratio, the accumulation of 2.48 mmol/d of potassium is equivalent to a nitrogen deposition of 1.16 g/d (2.48 mmol of potassium/2.15 mmol of potassium/g of nitrogen/d) or 7.2 g protein/d using the factor of 6.25 g of protein/g of nitrogen. This estimates the average amount of protein deposited dur-

TABLE 10-15 Total Body Potassium Content During Pregnancy

Reference	n	Total Body Potassium (mmol/d)	$n \times$ Total Body Potassium (mmol/d)	Average Protein Deposition (g/d)[a]
MacGillivray and Buchanan, 1958	6	3.22	19.3	9.4
King et al., 1973	10	3.41	34.1	9.9
Emerson et al., 1975	5	3.43	17.2	10.0
Pipe et al., 1979	27	1.78	48.1	5.2
Forbes, 1987	50	2.64	132	7.7
Forsum et al., 1988	22	2.13	48.9	6.2
Total	120		297.9	
Mean		2.48[b]		7.2

[a] Protein deposition = Total potassium accumulated (mmol/d) ÷ 2.15 (mmol potassium/g nitrogen) × 6.25.
[b] Mean total body potassium calculated as the sum of column 3 divided by the total number of cases (298 ÷ 120) = 2.48).

ing the third trimester of pregnancy at a total of approximately 670 g of protein.

Calculation of the amount of dietary protein needed for a deposition of 7.2 g of protein/d during the third trimester of pregnancy requires a value for the efficiency of utilization of dietary protein. This was reported as being about 30 percent in a group of adolescent women in the third trimester of pregnancy (King et al., 1973). Closer review of the data indicates that for those six adolescents who demonstrated a positive efficiency at multiple levels of protein intake, the mean of the slope of the positive nitrogen balances was 0.43 ± 0.21 (median = 0.44). Compared with the slope for maintenance of adults of 0.47, which was calculated from a much larger data set (see "Adults Ages 19 Through 50 Years"), it is possible that the paucity of the data for both infants and during pregnancy has obscured the true rate of efficiency of deposition. While other physiological changes occurring in pregnancy appear to enhance nutrient utilization during periods of increased need (e.g., calcium absorption), it would be surprising to find that efficiency of protein utilization during pregnancy is diminished over that of other life stages. However, to ensure adequate intakes, 0.43 was chosen to use based on the six women studied. As calculated in Table 10-16, the average protein deposition was converted to the amount of intake needed to provide this level: 7.2 ÷ 0.43 = 16.7 g of protein/d for accretion during the third trimester.

The protein needed to maintain the new tissue accreted during pregnancy must also be added. The increase of body weight during a full-term pregnancy averages approximately 16 kg, which is the median weight gain of 4,218 women who had good pregnancy outcomes (Carmichael et al., 1997). Weight gain during pregnancy is made up of both additional fat and new lean tissue (including fetus, amniotic fluid, increased plasma volume, etc.), which has been estimated at 91 percent water (van Raaij et al., 1988), compared with the expected 73 percent of water in general nonpregnant lean tissue. The incremental weight gain at the 50th percentile for normal weight individuals with good pregnancy outcomes at the end of the first trimester is 2.2 kg; for the second trimester, 7.3 kg; and for the third trimester, 6.5 kg, which totals 16 kg (Carmichael et al., 1997).

The amount of protein to support additional tissue is calculated in Table 10-16 using a factor of 0.66 g/kg of body weight, the EAR for protein for adults. While it is recognized that pregnancy lean tissue contains a greater amount of water, correction for assumed differences in body composition have not been made given the lack of actual data delineating protein maintenance needs in pregnant women. This results in an average total additional need for protein during the last two trimesters of pregnancy of about 21 g/d over prepregnancy requirements.

TABLE 10-16 Derivation of Protein Requirements During Pregnancy

Trimester	Average Additional Body Weight Gained by the End of Trimester (kg)[a]	Total Weight Gain by End of Trimester	[A] Additional Protein to Maintain Increased Body Weight[b] (g/d)	Average Protein Deposition (additional lean tissue)[c] (g/d)	[B] Protein Deposition Corrected for Conversion Efficiency[d] (g/d)	[A + B] Average Total Additional Protein Required (g/d)[e]	RDA (g/d)[f]
1	Δ2.2	2.2	+1.4	~		~	
2	Δ7.3	9.5	+6.3	3.6	8.4	+14.7	
3	Δ6.5	16.0	+10.6	7.2	16.7	+27.3	
Average over 2nd and 3rd trimesters				5.4	12.6	+21.0	+ 25

[a] Carmichael et al. (1997); average body weight gain by end of trimester; divided by 2 to get approximate increase mid-trimester.
[b] End of trimester increase in body weight × 0.66 g/kg/d, the Estimated Average Requirement (EAR) for maintenance of protein in adults.
[c] From Table 10-15 where protein deposition = total potassium accumulated (mmol/d) ÷ 2.15 (mmol potassium/g nitrogen) × 6.25; and assumption that nitrogen accretion during second trimester is ~ 50% that of third trimester.
[d] Protein deposition ÷ 0.43, slope of regression line of protein intake versus nitrogen balance (recalculated from King et al., 1973).
[e] Average required additional amount needed during pregnancy.
[f] RDA is based on EAR + assumed variation in requirements; amount needed above nonpregnant needs.

Outcome of Food Supplementation Trials. Burke and coworkers (1943) conducted an observational study of 216 mothers giving birth to single infants in Boston and found a significant correlation between average daily protein intake and birth length and birth weight. They concluded that for practical purposes, a protein intake less than 75 g/d was associated with an infant who would be short and light in weight. Studies from the Montreal Diet Dispensary have also shown a relationship between maternal protein-energy intake and birth weight (Higgins, 1976). This study involved 1,736 low-income pregnant women, 20 years of age or more, whose average maternal protein and energy intakes at various stages of pregnancy were 68 g and 2,249 kcal/d during pregnancy, and were increased to an average of 101 g of protein and 2,778 kcal/d by supplementing the mothers with whole milk and eggs during a subsequent pregnancy. Birth weights were significantly higher for siblings with supplemented mothers compared with their older siblings born to the same mothers when they did not receive the supplementary milk and eggs. These data support the value increased intake of foods high in protein and energy during pregnancy and the additional requirements outlined above.

Adolescent Pregnancy. It is well established that both the mother's pre-pregnant weight and weight gain during pregnancy are correlated with the birth weight of the infant (Higgins, 1976; IOM, 1990; Wynn and Wynn, 1979). The problem of adolescent pregnancy is that the mother may still be completing her growth (Frisancho et al., 1983; Hediger et al., 1990; Scholl et al., 1990, 1994). In those pregnancies in which the mother's growth is not yet completed, it appears that there is competition between maternal and fetal growth needs (Hediger et al., 1990; Scholl et al., 1990, 1994).

The Montreal Diet Dispensary studied the effect of supplementing 1,203 low-income pregnant adolescents with whole milk and eggs and compared them with 1,203 pregnant adolescents who did not receive the additional milk and eggs in their diets (Dubois et al., 1997). The adolescents in the intervention group increased their protein intake from 73 g/d to approximately 125 g/d in addition to significantly increasing their energy intake. Participation in the intervention resulted in significantly increased mean birth weights and reduced the rate of low birth weights by 39 percent ($p < 0.001$) in adolescent girls, which again is attributed to the increased consumption of foods rich in protein and energy.

Protein EAR Summary, Pregnancy

Based upon the nitrogen balance study of King and coworkers (1973) and the estimated average protein deposition during pregnancy based on

potassium retention in six studies (Table 10-15), the average requirement for additional protein needed for adult pregnant women at the end of the trimester during pregnancy in adult women is calculated and given in Table 10-16. It is composed of two components: the amount needed to maintain the new pregnant tissue and the amount needed for initial deposition. The amount of protein deposition is corrected for the efficiency of protein deposition (using the estimate from the slope of 0.43 from the King and coworkers study [1973], recalculated as described above). Since little weight gain occurs during the first trimester, it is assumed that roughly one-third of the total increase in protein deposition during the 40 weeks of pregnancy (~ 925 g) occurs during the second trimester, with two-thirds occurring during the third trimester.

As described above, by the end of the third trimester, ~17 g/d is needed to allow for adequate protein deposition; it can be assumed that roughly half that amount is needed for growth during the second trimester, or 8 g/d (Table 10-16). Given the small amount of protein accretion expected to occur during the first trimester (as demonstrated by Thompson and Halliday [1992] in protein turnover studies during each trimester), the need for additional protein is rather low at this stage. Thus no additional increase in protein requirements is estimated for the first trimester. Averaging the overall protein needs over the last two trimesters of pregnancy, the EAR is set at 21 g/d above protein needs at the prepregnancy weight. Since this figure includes the protein needs for the additional tissue deposited, when calculating the amount needed per kilogram of body weight to use with pregnant women, only the amount needed for protein deposition is considered. Thus the increased amount on a body-weight basis is +12.6 g of protein/d ÷ 57 kg (reference woman) = +0.22 g of protein/kg/d. This is added to the factor for nonpregnant women of 0.66 g of protein/kg/d, and results in an EAR of 0.88 g of protein/kg/d.

Pregnant individuals who were studied ranged from 15 to 19 years of age (King et al., 1973); however, they were considered mature and physiologically similar to adults, as all but one of the ten young women was 4 to 7 years post-menarche. For adolescents, the additional need for protein during the second and third trimesters is assumed to be the same as for adult women.

EAR for Pregnancy

All age groups	**0.88 g/kg/d of protein or +21 g/d of additional protein**

Protein RDA Summary, Pregnancy

The protein RDA for pregnancy is in addition to the RDA for the nonpregnant woman, which is based on an estimated CV of about 12 percent (see "Protein RDA Summary, Adults 19 Years and Older"). Data for the variability of protein deposition in the fetus and mother was not available. The RDA is thus equal to the EAR + 24 percent. Thus the 1.24 multiplied by the EAR of +21 g protein/d = 26 g; rounded to the nearest 5 g/d, the RDA = +25 g/d.

Again, in considering the amount needed per kilogram of body weight, only that due to protein deposition is considered. The increase in the RDA is thus +12.6 g/d × 1.24 ÷ 57 kg (reference woman) = +0.27 g protein/kg/d. This is added to the factor for the RDA for non-pregnant women of 0.8 g protein/kg/d = 1.1 g protein/kg/d.

RDA for Pregnancy	
All age groups	**1.1 g/kg/d of protein or +25 g/d of additional protein**

Special Considerations

It is well recognized that multiparous pregnancies are associated with a marked increase in low birth weight and perinatal mortality (Hays and Smeltzer, 1986). Thus, it is logical to assume that a woman supporting the growth of twins has higher protein needs than a woman having a singleton birth. In a study in which the mothers of twins received nutritional intervention (target supplementation was an additional 50 g of protein/d and 1,000 kcal/d) from the 20th week, pregnancy outcome was improved, with a decrease in the low birth weight rate by 25 percent and the very low birth weight rate by 50 percent (Dubois et al., 1991). Although this study did not measure the dietary protein or energy intake of the women bearing twins, they gained 2 kg more than the controls. No study could be found that investigated dietary protein intervention in twin pregnancy. On the basis of these data, it seems prudent to provide women carrying twins with protein intakes of an additional 50 g/d beginning in the second trimester, along with sufficient energy to utilize the protein as efficiently as possible.

Lactation

Evidence Considered in Estimating the Average Requirement

The literature on the relationship between nutritional status and lactation performance is not extensive and suggests that most lactating women, even those who are undernourished with chronically low body mass index,

establish adequate lactation (Prentice et al., 1994). While it appears that the concentration of protein in human milk is not influenced by diet or body composition even in undernourished mothers (Lönnerdal 1986), protein intakes of 1 g/kg of body weight/d promoted the conservation of skeletal muscle in order to maintain good milk production in lactating mothers (Motil et al., 1996). Lactating women with these protein intakes appear to adapt by down-regulating protein metabolism (Motil et al., 1996).

The factorial approach is utilized for determining the protein requirement during lactation. In this approach, it is assumed that the process of lactation does not alter the maintenance protein requirement of the nonlactating woman and that the protein and amino acid requirements are increased in proportion to milk production. It is important to emphasize that human milk is characterized by a relatively high concentration of nonprotein nitrogenous substances, which contribute approximately 20 to 27 percent of total milk nitrogen (Butte et al., 1984a, 1984b; Dewey et al., 1996). The quantitatively important component of this fraction of milk is urea. Whether this merely reflects a diversion of urea loss from urine (plus some colonic fermentation) to milk is not known, but in the calculations it is assumed that part of the increased nitrogen needs of the lactating woman will of necessity be derived from her dietary protein. The factor of 6.25, the figure that is utilized to convert nitrogen to protein, was used to convert nonprotein nitrogenous substances to protein.

The additional protein requirement for lactation therefore is defined as the output of total protein and nonprotein nitrogen in milk. Data on the output of protein in human milk are summarized in Table 10-17. This table shows the factorial estimate of the increase in protein requirement associated with lactation and assumes that the incremental efficiency of nitrogen utilization of 0.47 in adults (Table 10-12) and in adolescents (data on the efficiency of nitrogen utilization are not available in this age group) is the same as that noted for the restoration of nitrogen equilibrium in nonlactating women and adolescents. It is assumed that the cost of making protein for maintenance requirements is the same as that for growth and lactation. Whether this assumption is valid is not known.

Protein EAR Summary, Lactation

To estimate the increase in the EAR for lactation, the average protein equivalent of human milk nitrogen output during the first six months of lactation was divided by the average incremental efficiency of dietary protein utilization (0.47 for lactating mothers 19 years of age and older [Table 10-12] and 0.47 for mothers 14 through 18 years of age because data were not available in this age group). The values shown in Table 10-17

TABLE 10-17 Factorial Estimate of the Increment in Protein Requirement Associated with Lactation

Stage (mo)	Protein Content of Human Milk (g protein/d)	Nonprotein Nitrogen Content of Human Milk[a] (g protein/d)	Total Human Milk Nitrogen Output (g protein/d)	Increase in Protein Need[b] (g/d)	
				14–18 y	> 18 y
1	8.93 ± 1.97[a]	2.05 ± 0.4	11.0 ± 2.4	23.4	23.4
2	8.26 ± 1.08[c]	2.02 ± 1.6	10.3 ± 2.7	21.9	21.9
3	8.24 ± 1.54[d]	1.71 ± 1.1	10.0 ± 2.6	21.3	21.3
4–6	7.29 ± 1.27[c]	1.28 ± 0.5	8.6 ± 1.8	18.3	18.3
Mean	8.18	1.76		21.2	21.2

[a] Butte et al. (1984b); Lemons et al. (1982).
[b] The increase in the Estimated Average Requirement (EAR) for protein was calculated by dividing the average protein equivalent of milk nitrogen output by the average incremental efficiency of dietary protein utilization (0.47 for lactating mothers 19 years of age and older [Table 10-12] as well as for lactating mothers 14–18 years of age because data are not available for this age group).
[c] Butte et al. (1984b).
[d] Butte et al. (1984b); Dewey and Lönnerdal (1983); Heinig et al. (1993); Motil et al. (1998); Nommsen et al. (1991).

for the various months of lactation were then averaged to set the amount by which the EAR for nonlactating girls or women should be increased. The result was +21.2 g/d. When the absolute increase was converted to weight-specific intakes by using the reference weights of adolescent girls 14 to 18 years (54 kg) and adult women 19 to 50 years (57 kg) from Chapter 1 (Table 1-1), the numbers were quite close, so the highest value (that for the 14- to 18-year-old category) is provided as the overall recommendation. Adding the average requirement for additional protein needed is calculated as +21.2 ÷ 54 kg (reference weight) = +0.39 g of protein/kg/d. This is added to the recommendation for nonpregnant women of 0.66 g of protein/kg/d to obtain 1.05 g of protein/kg/d.

EAR for Lactation

All age groups	**1.05 g/kg/d of protein or +21 g/d of additional protein**

Protein RDA Summary, Lactation

The RDA for protein for lactation is set by assuming a CV of 12 percent used for total protein in nonlactating women (see "Protein RDA Summary, Ages 19 Years through 50 Years"). Again, given the closeness of the values, one value is recommended for all age groups. The recommendations are rounded to the nearest +5 g/d and +0.05 g/kg/d of additional protein.

The RDA is thus equal to the EAR plus 24 percent. So, 1.24 multiplied by the EAR of + 21 g of protein/d = +26 g; rounded to the nearest 5 g/d, the RDA = +25 g/d.

Again, in considering the amount needed per kg of body weight, the increase in the RDA is calculated as the EAR of +21 g/d × 1.24 ÷ 54 kg (reference weight) = +0.48 g of protein/kg/d. This is added to the factor for the RDA for nonpregnant women of 0.8 g of protein/kg/d = 1.3 g of protein/kg/d (rounded to nearest 0.1g).

RDA for Lactation

All age groups	**1.3 g/kg/d of protein or +25 g/d of additional protein**[4]

[4]Due to a calculation error in the prepublication copy, the value is changed from 1.1 g/kg/d to 1.3 g/kg/d.

Special Considerations

Physical Activity

Although there have been few studies of the requirement for protein by individuals undertaking high levels of physical exercise, it is commonly believed by athletes that a higher than normal protein intake is required to maintain optimum physical performance (Lemon, 1996). Whether or not this is true has significance not only for athletes, but also for those with muscle wasting who wish to preserve muscle mass by training, such as elderly or immobile adults, or those suffering from muscle-wasting diseases. The available literature includes studies of both resistance (body-building) and endurance training.

Endurance Training. Endurance training does not result in muscle building, which would increase muscle protein deposition, but it is well recognized that endurance exercise is accompanied by an increase in the oxidation of branched chain amino acids (Lemon et al., 1982, 1985; Rennie et al., 1981; Wagenmakers, 1998; White and Brooks, 1981), which has been suggested to imply an increased need for dietary protein (Lemon, 1996). However, these were acute studies performed around the time of the exercise itself, and did not take into account the remaining part of the day. An examination of leucine oxidation over a 24-hour period, including exercise during each of the fed and fasting periods, showed that the increase in oxidation, although statistically significant, was small in relation to the total daily amount of oxidation (4 to 7 percent) (El-Khoury et al., 1997). Moreover, the increase in leucine oxidation was proportionally similar with diets containing 1 or 2.5 g/kg/d fed over 7 days prior to the measurement of oxidation during exercise on day 7 (Forslund et al., 1998). Neither leucine nor nitrogen balance was significantly negative, suggesting that the exercise did not compromise body protein homeostasis at either level of protein intake. Although no control group without exercise was studied, the results were similar to those reported previously from individuals at an intake of 1 g/kg/d of protein undergoing the same experimental procedures without exercise (El-Khoury et al., 1994b). Similarly, a study designed to determine the protein requirement of endurance-trained men led to an average requirement estimate in young and older men of 0.94 g/kg/d (Meredith et al., 1989). This value is higher than that derived from the meta-analysis of data from nonexercising individuals (see "Protein EAR Summary, Ages 19 Through 50 Years"). However, as no controls without exercise were included in the study, it is not possible to conclude that the exercise led to a higher protein requirement.

Resistance Training. The effects of resistance training on nitrogen balance have been investigated in older adults (8 men and 4 women, aged 56 to 80 years) at one of two levels of protein intake, 0.8 or 1.6 g/kg/d (Campbell et al., 1995). Before training began, the mean corrected nitrogen balance was not significantly different from zero in the three men and three women receiving the lower protein intake, and was positive in the five men and one woman receiving the higher intake, suggesting a requirement about 0.8 g/kg/d. However, after 12 weeks of resistance training, nitrogen balance became more positive by a similar amount at the two intakes, which the authors suggested was the result of an increased efficiency of protein retention that was more pronounced in those on the lower protein diet as a percent of protein intake. In particular, the improvement in nitrogen balance was independent of the protein intake. However, various aspects of body composition, as well as mid-thigh composition and areas of Type I and II muscle fibers, did not change with resistance training, making the increase in nitrogen retention difficult to interpret.

A similar study was performed by Lemon and coworkers (1992), which compared protein intakes of 1.35 and 2.62 g/kg/d during the first 12 weeks of resistance training in young male strength athletes. Linear interpolation of the nitrogen balances (–3.4 and +8.9 g/d) suggested a protein requirement of 1.4 to 1.5 g/kg/d. However, this estimate of requirement cannot be taken as realistic, because the positive nitrogen balance of 8.9 g/d would correspond to an increase of lean tissue of about 300 g/d. Measurements of body composition showed no changes in lean body mass, creatinine excretion, or biceps muscle nitrogen content in either dietary group. In addition, although there were increases in some measurements of strength, there was no effect attributable to diet. Therefore, the available data do not support the conclusion that the protein requirement for resistance training individuals is greater than that of nonexercising subjects.

Summary. In view of the lack of compelling evidence to the contrary, no additional dietary protein is suggested for healthy adults undertaking resistance or endurance exercise.

Vegetarians

In North America, plant proteins (e.g., those found in cereals, pulses, nuts, starchy roots, vegetables, fruits) account for only about 65 percent of the available food protein per capita (FAO/Agrostat, 1991). Individuals who restrict their diet to plant foods may be at risk of not getting adequate amounts of certain indispensable amino acids because the concentration of lysine, sulfur amino acids, and threonine are sometimes lower in plant food proteins than in animal food proteins (FAO/WHO/UNU, 1985).

However, vegetarian diets that include complementary mixtures of plant proteins can provide the same quality of protein (see "Protein Quality") as that from animal proteins (Young and Pellett, 1994). Plant proteins are generally less digestible than animal proteins; however, digestibility can be altered through processing and preparation. Therefore, consuming a varied diet ensures an adequate intake of protein for vegetarians.

Adult vegetarians consume less protein in their diet than non-vegetarians (Alexander et al., 1994; Ball and Bartlett, 1999; Barr and Broughton, 2000; Haddad et al., 1999; Janelle and Barr, 1995). However, only one of these studies indicated that total protein intakes of 10 of the 25 vegan women were potentially inadequate (Haddad et al., 1999). As was shown in Table 10-13, the nitrogen requirement for adults based on high-quality plant food proteins as determined by regression analysis was not significantly different than the requirement based on animal protein or protein from a mixed diet. In conclusion, available evidence does not support recommending a separate protein requirement for vegetarians who consume complementary mixtures of plant proteins.

FINDINGS BY LIFE STAGE AND GENDER GROUP FOR INDISPENSABLE AMINO ACIDS

The original technique used to determine amino acid requirements in individuals studied with graded levels of intake of the test amino acid was nitrogen balance (see "Nitrogen Balance Method"). Several new methods have been developed and applied in the last few decades. However, nitrogen balance could not be applied to histidine since individuals take 56 days or more to go into negative nitrogen balance on a low histidine or histidine-free diet (Cho et al., 1984), and there haven't been any useful studies on isoleucine, using either nitrogen balance or any of the newer methods.

The amino acid requirements thus developed are used as the basis for recommended protein scoring patterns discussed in a subsequent section.

Infants Ages 0 Through 6 Months

Method Used to Estimate the Adequate Intake

Human milk is recognized as the optimal source of nutrients for infants throughout at least the first year of life and is recommended as the sole nutritional source for infants during the first 4 to 6 months of life (IOM, 1991). Further, there are no reports of healthy full-term infants exclusively and freely fed human milk who manifest any sign of amino acid or protein deficiency (Heinig et al., 1993). Therefore, determination of

the adequate intake (AI) for amino acids for infants is based on data from infants fed human milk as the principal source of nutrients during the periods 0 through 6 months of age. The AI is set for ages 0 through 6 months at the mean value of each indispensable amino acid calculated from studies in which the intake of human milk was measured by test weighing volume, and the average concentration of the amino acid in human milk was determined using average values from several reported studies.

Four recent studies on the indispensable amino acid composition of human milk and their mean are shown in Table 10-18. The indispensable amino acid intake on a mg/L basis was calculated from the mean of the amino acid composition of mixed human milk proteins expressed as mg amino acid/g protein (Table 10-18) times the average protein content of human milk of 11.9 g/L from mothers whose infants were 0 through 6 months as assessed by Butte and coworkers (1984a), Dewey and Lönnerdal (1983), Dewey and coworkers (1984), and Nommsen and coworkers (1991) and is in the range of protein content reported in other studies in Table 10-7.

Indispensable Amino Acids AI Summary, Ages 0 Through 6 Months

The AI for infants 0 through 6 months of age is based on the average volume of milk intake of 0.78 L/d (Allen et al., 1991; Heinig et al., 1993), and the mean indispensable amino acid content of human milk (Table 10-18). Multiplying the mean concentration of histidine (274 mg/L), for example, by the average intake of human milk at 0 through 6 months, the AI would be 274 g/L × 0.78 L/d = 214 mg/d. This process was repeated for all the indispensable amino acids. As with the AI for protein, the AIs (which remain essentially the same from 2 weeks to 6 months of age) were converted to weight specific intakes by using the reference weight of 6 kg from Table 1-1.

AI for Infants	
0–6 months	**214 mg/d or 36 mg/kg/d of histidine**
	529 mg/d or 88 mg/kg/d of isoleucine
	938 mg/d or 156 mg/kg/d of leucine
	640 mg/d or 107 mg/kg/d of lysine
	353 mg/d or 59 mg/kg/d of methionine + cysteine
	807 mg/d or 135 mg/kg/d of phenylalanine + tyrosine
	436 mg/d or 73 mg/kg/d of threonine
	167 mg/d or 28 mg/kg/d of tryptophan
	519 mg/d or 87 mg/kg/d of valine

TABLE 10-18 Amino Acid Content of Human Milk

Amino Acid	Heine et al. (1991) (mg/g protein)	Davis et al. (1994)[a] (mg/g protein)	Villalpando et al. (1998)[a] (mg/g protein)
n	Not given	6	70
Stage of lactation	Not given	> 10 d pp[d]	4 or 6 mo pp
Histidine	23	23 ± 2	21± 2
Isoleucine	58	53 ± 3	64 ± 11
Leucine	101	104 ± 1	105 ± 11
Lysine	62	71 ± 6	79 ± 9
Methionine	18	16 ± 1	14 ± 3
Cysteine	17	20 ± 3	26 ± 3
Phenylalanine	44	37 ± 1	43 ± 15
Tyrosine	47	46 ± 2	58 ± 9
Threonine	46	44 ± 1	47 ± 5
Tryptophan	18	ND[e]	17 ± 2
Valine	60	51 ± 2	63 ± 8

[a] Mean ± Standard Deviation.
[b] Mean ± Standard Error.

Children Ages 7 Months Through 18 Years

Evidence Considered in Estimated the Average Requirement

Nitrogen Balance. The only data derived directly from experiments to determine the indispensable amino acids requirements of children have been obtained by studying nitrogen balance. Pineda and coworkers (1981) conducted nitrogen balance studies in 42 Guatemalan children ranging in age from 21 to 27 months. The children were considered to be in nitrogen balance if all children retained nitrogen in the amount of at least 16 mg/kg/d, the nitrogen requirement for growth in children in this age range derived by FAO/WHO (1973) when given a diet lacking one indispensable amino acid with all other indispensable amino acids at levels considered to be adequate. Their mean amino acid estimates were reported to be: lysine, 66 mg/kg/d; threonine, 37 to 53 mg/kg/d; tryptophan, 13 mg/kg/d; methionine + cysteine, 28 mg/kg/d; isoleucine, 32 mg/kg/d; and valine, 39 mg/kg/d. Unfortunately, with the exception of lysine, no estimates of variance were published.

Darragh and Moughan (1998)[b] (mg/g protein)	Mean (mg/g protein)	Mean[c] (mg/L)
20		
10–14 wk pp		
24 ± 2	23	274
52 ± 4	57	678
94 ± 5	101	1,202
64 ± 4	69	821
14 ± 1	16	190
27 ± 3	22	262
38 ± 9	40	476
38 ± 2	47	559
50 ± 9	47	559
ND[e]	18	214
51 ± 5	56	666

[c] Mean (mg/g total protein) × 11.9 g protein/L of human milk.
[d] pp = Postpartum.
[e] ND = Not determined.

For older children, the only data are those published by Nakagawa and coworkers in the 1960s (1961a, 1961b, 1962, 1963, 1964) on Japanese boys 10 to 12 years of age. Although these data seem to be accurate as there was uniformly negative nitrogen balance when the test amino acid was at zero, the maximum rate of nitrogen retention found when the amino acids were given in adequate quantities was 33 ± 14 mg/kg/d. This is approximately 5-fold higher than that predicted for 11-year-old boys, 7.7 mg/kg/d, as calculated from estimates of the protein deposition for boys this age (48 mg of protein/kg/d ÷ 6.25 mg of protein/mg of nitrogen, from Table 10-9). Thus, it is likely that the values generated in this series of studies are overestimates of the actual requirement. Similar problems of interpreting nitrogen balance studies are apparent in the data for infants aged 0 to 6 months from a number of detailed studies in which infants were given multiple levels of amino acids (Pratt et al., 1955; Snyderman et al., 1955, 1959a, 1959b, 1961a, 1961b, 1963, 1964a, 1964b;). With these studies also, the measured nitrogen balance was higher than what would be expected from the growth rates observed or estimated.

An attempt was made to reanalyze the data from these studies in order to obtain estimates of the mean requirement and its interindividual vari-

ance. Nonlinear regression analysis was used to fit the data for nitrogen balance versus amino acid intake to various curves, such as exponential, sigmoid, and bilinear crossover, in order to detect an approach to an asymptote or a breakpoint that could be equated with a requirement. However, these attempts did not lead to interpretable results, which proved to be too sensitive to the specific criteria employed to define the point on the curve that would identify a requirement.

In view of the reservations expressed above, the data from nitrogen balance studies in children were not utilized. Instead, the factorial approach was employed for children from 7 months through 18 years of age.

Factorial Estimate. In view of the doubts about the accuracy of the values generated by the empirical data, the factorial approach using data for growth (and its amino acid composition) and maintenance was utilized to determine requirements. In this model, the growth component was estimated from estimates of the rate of protein deposition at different ages (Table 10-9), the amino acid composition of whole body protein (Table 10-19), and incremental efficiency of protein utilization as derived from the studies in Table 10-8.

The obligatory need for protein deposition (growth) was calculated as the product of the rate of protein deposition (Table 10-9) and the amino acid composition of whole body protein (Table 10-19). This was then converted to a dietary requirement for protein deposition by dividing the need by the incremental efficiency of dietary protein utilization, which is estimated by the average slope of the regression analyses evaluating the protein requirement from studies done in children 7 months through

TABLE 10-19 Indispensable Amino Acid Composition of Whole Body Protein

Amino Acid	mg/g Protein ± 1 Standard Deviation (from interspecies comparison)
Histidine	27 ± 2
Isoleucine	35 ± 3
Leucine	75 ± 2
Lysine	73 ± 3
Methionine + cysteine	35 ± 1
Phenylalanine + tyrosine	73 ± 4
Threonine	42 ± 3
Tryptophan	12 (no extensive data)
Valine	49 ± 4

SOURCE: Davis et al. (1994).

13 years (0.58) from Table 10-8 and in children 14 through 18 years (0.47) from Table 10-12.

It is also necessary to determine a maintenance amino acid requirement since by 7 months of age, the dietary requirement necessary to maintain the body in nitrogen equilibrium accounts for more than 50 percent of the total indispensable amino acid requirement. This was determined in three ways.

First, estimates of the amino acid requirements needed for maintenance were calculated based on estimates of the obligatory nitrogen loss, which is the total rate of loss of nitrogen by all routes (urine, feces, and miscellaneous) in children receiving a protein-free or very low protein intake. Assuming that each individual amino acid contributed to this loss in proportion to its content in body protein, and that this represents the minimal rate of loss for this amino acid, the amount of this amino acid that must be given to replace the loss and achieve nitrogen balance is taken as the maintenance requirement when corrected for the efficiency of nitrogen utilization. Thus, the lysine requirement for maintenance for children 7 months through 13 years of age is calculated by multiplying the obligatory nitrogen loss of 57.4 mg/kg/d (mean intercept from Table 10-8), which is equivalent to 359 mg of protein/kg/d (57.4 × 6.25), by the estimate of the proportion of lysine in body protein of 0.073 (Table 10-19), to yield a value for lysine of 26.2 mg/kg/d (i.e., 359 mg/kg/d × 0.073). Then this is divided by the slope of the regression line of protein intake versus nitrogen balance, which represents the efficiency protein utilization of 0.58 (Table 10-8) for children to yield a value of 45 mg/kg/d (i.e., 26.2 mg/kg/d divided by 0.58) for the lysine maintenance requirement. The calculated values for each indispensable amino acid are shown in Table 10-20.

A second method for estimating maintenance requirements is to assume that at nitrogen equilibrium, the relative requirement of each indispensable amino acid is in proportion to its contribution to body protein. Thus, the maintenance protein requirement of 688 mg/kg/d (110 mg of N/kg/d for children through age 13 in Table 10-8 × 6.25) can be converted into requirements for individual amino acids by multiplying the maintenance protein requirement by the proportional contribution of the amino acid to body protein (Table 10-19). This method is mathematically equivalent to the method described above, but because the values for obligatory loss and maintenance protein requirement were taken from the regression of protein intake against nitrogen balance, for statistical reasons they give slightly different results, and both are given in the Table 10-20.

Since it was noted that the maintenance nitrogen requirement of 110 mg/kg/d (Table 10-8) does not vary with age in children, and the value in children is very similar to that found for adults of 105 mg/kg/d

TABLE 10-20 Factorial Estimates of Maintenance Amino Acid Requirements for Children in Comparison to Adults

	Children		Adults		
Amino Acid	Based on Obligatory Nitrogen Loss (mg/kg/d)[a]	Based on Maintenance Protein Requirement (mg/kg/d)[b]	Based on Maintenance Protein Requirement (mg/kg/d)[c]	Direct Measurement of EAR (mg/kg/d)[d]	Ratio of Maintenance Amino Acid Requirements to EAR
Histidine	17	19	18	ND[e]	—
Isoleucine	22	24	23	ND[e]	—
Leucine	46	52	49	34	1.4
Lysine	45	50	48	31	1.5
Methionine + cysteine	22	24	23	15	1.5
Phenylalanine + tyrosine	45	50	48	27	1.7
Threonine	26	29	28	16	1.7
Tryptophan	7	8	8	4	2.0
Valine	30	34	32	19	1.7

[a] Determined by multiplying the estimated obligatory nitrogen (N) loss in children, 57.4 mg N kg/d × 6.25 (Table 10-8) by the estimates for the amino acid content of whole body protein (Table 10-19) and then dividing by the efficiency of protein utilization, 0.58 for children (slope in Table 10-8) and 0.47 for adults (slope in Table 10-12).
[b] Determined by multiplying the total protein maintenance needs in children aged 7 months through 13 years, 110 mg N/kg/d × 6.25 (Table 10-8) by the amino acid content of whole body protein (Table 10-19).
[c] Determined by multiplying the total protein maintenance needs in adults, 105 mg N/kg/d × 6.25 (Table 10-12) by the amino acid content of whole body protein (Table 10-19).
[d] EAR = Estimated Average Requirement.
[e] ND = Not determined. There have been no direct measurements of isoleucine or histidine requirements in adults.

(Table 10-12), the values for maintenance amino acid requirements were taken to be independent of age in subsequent calculations. However, for adults, who are by definition at maintenance, direct measurements of the estimated average requirement (EAR) for each amino acid have been determined (see "Adults Ages 19 Years and Older"), and are shown in Table 10-20 for comparison with the factorially derived estimates. For all amino acids for adults, the EAR as derived from direct measurements is lower than the factorial approach by a factor of 1.3 to 2.0, depending on the amino acid. This difference is predictable because of the imperfections in the factorial approach. It is likely that the obligatory loss of one amino acid is higher than that for other amino acids in relation to their content in body protein. If this loss cannot be reduced further under basal conditions, then this amino acid will determine the obligatory loss for all other amino acids, which can no longer be used for anabolic processes. In theory, this "limiting" amino acid should be identified as having the lowest ratio between the requirement estimates from maintenance and by direct measurement, which is isoleucine in this report (Table 10-20). However, this is the amino acid with no direct measurements of requirement, as the adult EAR was estimated from its content in egg protein in relation to the other branched chain amino acids.

The important conclusion from the above discussion is that the calculation of the maintenance requirement in adults from the obligatory nitrogen loss gives values in adults that are in general higher than the measured values, and therefore appear to overestimate true maintenance. Moreover, as the maintenance protein requirement is estimated to be the same per kilogram of body weight in adults and children, it is reasonable to conclude that the amino acid values for maintenance needs derived from the obligatory nitrogen loss are likely to be overestimates in children as well as in adults. Therefore, in the factorial calculations to estimate total requirements for indispensable amino acid needs in children, the maintenance requirements for the individual amino acids are those derived on a weight basis from direct measurements or the EAR in adults (Table 10-20).

Indispensable Amino Acid EAR and RDA Summary, Ages 7 Months Through 18 Years

To calculate a factorial estimate of the EAR for individual indispensable amino acids, the amino acid needs for growth or protein deposition are first calculated as the product of the average rate of protein deposition (Table 10-9) and the average amino acid composition of body protein (Table 10-19). Thus, for a 9- through 12-month-old infant depositing on average 242 mg of protein/kg/d (Table 10-9, average of 232 mg/kg/d for girls and 252 mg/kg/d for boys), the obligatory need for lysine (amino

acid deposition) is 242 × 0.073 (Table 10-19) = 17.7 mg/kg/d. This is then divided by the partial efficiency of protein deposition (0.58 as shown in Table 10-8 for children aged 7 months through 13 years and 0.47 for children aged 14 through 18 years [see "Adolescents, Ages 14 Through 18 Years"]) to yield a value of 30 mg/kg/d for protein deposition. (The same result would be achieved by multiplying the amino acid deposition figure by 1.72 [reciprocal of 0.58] or 2.13 [reciprocal of 0.47] as indicated in Table 10-21.) This value is then added to the estimated maintenance requirement, which is the same as the EAR in adults on a body weight basis (31 mg/kg/d in Tables 10-20 and 10-21). This gives an EAR for the 9- through 12-month-old infant of 62 mg of lysine/kg/d. In the same way, the EARs for each of the indispensable amino acids at different age groups were calculated and the results are shown in Table 10-21.

The RDA for the indispensable amino acids for children is set by determining the coefficients of variation for maintenance and for protein deposition. Since the maintenance requirement in adults was utilized, the estimate of the coefficient of variation in adults (12 percent) (see "Protein RDA Summary, Ages 19 Through 50 Years") was also utilized to determine the RDA for maintenance requirements for children. A coefficient of variation of 43 percent for protein deposition was determined in the study of Butte and coworkers (2000), and this varied little with age and gender. Therefore, this value was used for variation in growth for all ages. Since the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group, the protein RDA is equal to the EAR + 2 × square root $[(0.12 \times \text{Maintenance})^2 + (0.43 \times 1.72$ for children 7 mo–13 y or 2.13 for children 14–18 y $\times$ Protein Deposition$)^2]$. The RDAs for each indispensable amino acid for each age group are shown in Table 10-21.

Adults Ages 19 Years and Older

Evidence Considered in Estimating the Average Requirement

Several different indicators have been used to determine indispensable amino acid requirements, which include nitrogen balance (N-balance), plasma amino acid concentrations, direct amino acid oxidation (DAAO), 24-hour amino acid balance (AAB), and indicator amino acid oxidation (IAAO). An explanation of each of these indicators is found in the section, "Selection of Indicators for Estimating the Requirement for Individual Amino Acids." In general, the latter three methods, which depend on amino acid kinetic measurements, give higher values for amino acid requirements than do the (classical) nitrogen balance studies.

Resolution of a Controversy. All of the above five methods are based on measuring a change in the particular endpoint in response to graded levels of the test amino acid. A key observation regarding nitrogen balance as an endpoint is that there is a curvilinear relationship between nitrogen balance and test amino acid intake, so that nitrogen retention (nitrogen balance) becomes less efficient as zero balance is approached (Figure 10-7) (Rand and Young, 1999). Furthermore, the earlier work did not include miscellaneous losses in their nitrogen balances. Finally, most studies did not attempt to consider the effect of between-individual variance.

Only two studies were found in which several individuals were studied at four or more different levels of intake of the test amino acid (Jones et al., 1956; Reynolds et al., 1958). Rand and Young (1999) reanalyzed the lysine data of Jones et al. (1956) using regression techniques and found that curvilinear models best fit the data (Figure 10-7). They also examined the effect of adding either 5 or 8 mg/kg/d of miscellaneous nitrogen losses. Whereas Jones and coworkers (1956) had concluded, based on their data, that the lysine requirement was 8 mg/kg/d, the reanalysis by Rand and Young (1999) came to the conclusion that the lysine requirement was in the range of 17 to 36 mg/kg/d, and that the data strongly support a requirement of about 30 mg/kg/d. As shown in Table 10-22, this requirement approximates values derived from DAAO (Meredith et al., 1986), is similar to values derived from 24-hour amino acid balances (Kurpad et al., 2001a, 2002b), and is comparable to values derived from two IAAO studies (Kriengsinyos et al., 2002; Zello et al., 1993).

It is important to note that in growing animals, nitrogen balance and IAAO give comparable values (Zello et al., 1995) as do DAAO and IAAO. All three approaches are based on different assumptions. The reanalysis of the Jones et al. (1956) data by Rand and Young (1999) using nonlinear regression and including miscellaneous losses, has closed the apparent gap between nitrogen balance and the amino acid oxidation techniques.

Twenty-four Hour Amino Acid Balance. As shown in Table 10-22, 24-hour amino acid balance studies have been completed for four amino acids: leucine (El-Khoury et al., 1994a; Kurpad et al., 2001b), lysine (Kurpad et al., 2001a, 2002a), phenylalanine + tyrosine (Basile-Filho et al., 1998), and most recently threonine (Borgonha et al., 2002; Kurpad et al., 2002b). Of the studies, lysine (Kurpad et al., 2001a, 2002a) and threonine (Borgonha et al., 2002; Kurpad et al., 2002b) employed the 24-hour indicator balance method. Furthermore, the initial 24-hour balance study for leucine (El-Khoury et al., 1994b) also included measurement of urea production as further support for the leucine requirement estimate obtained from DAAO (Meguid et al., 1986a). Similarly, the 24-hour lysine balance data lend

TABLE 10-21 Calculations of Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) for Amino Acids for Children Ages 7 Months Through 18 Years

Age and Gender/Amino Acid	Maintenance[a] (mg/kg/d)	Amino Acid Deposition[b] (mg/kg/d)	Total = EAR[c] (mg/kg/d)	RDA[d] (mg/kg/d)
7–12 mo, Boys, Girls				
Histidine	11	7	22	32
Isoleucine	15	9	30	43
Leucine	34	18	65	93
Lysine	31	18	62	89
Methionine + cysteine	15	9	30	43
Phenylalanine + tyrosine	27	18	58	84
Threonine	16	10	34	49
Tryptophan	4	3	9	13
Valine	19	12	39	58
1–3 y, Boys, Girls				
Histidine	11	3	16	21
Isoleucine	15	4	22	28
Leucine	34	8	48	63
Lysine	31	8	45	58
Methionine + cysteine	15	4	22	28
Phenylalanine + tyrosine	27	8	41	54
Threonine	16	5	24	32
Tryptophan	4	1	6	8
Valine	19	5	28	37

4–8 y, Boys, Girls				
Histidine	11	1	13	16
Isoleucine	15	2	18	22
Leucine	34	4	40	49
Lysine	31	3	37	46
Methionine + cysteine	15	2	18	22
Phenylalanine + tyrosine	27	3	33	41
Threonine	16	2	19	24
Tryptophan	4	1	5	6
Valine	19	2	23	28
9–13 y, Boys				
Histidine	11	1	13	17
Isoleucine	15	2	18	22
Leucine	34	4	40	49
Lysine	31	4	37	46
Methionine + cysteine	15	2	18	22
Phenylalanine + tyrosine	27	4	33	41
Threonine	16	2	19	24
Tryptophan	4	1	5	6
Valine	19	42	23	28

continued

TABLE 10-21 Continued

Age and Gender/Amino Acid	Maintenance[a] (mg/kg/d)	Amino Acid Deposition[b] (mg/kg/d)	Total = EAR[c] (mg/kg/d)	RDA[d] (mg/kg/d)
9–13 y, Girls				
Histidine	11	1	12	15
Isoleucine	15	1	17	21
Leucine	34	2	38	47
Lysine	31	2	35	43
Methionine + cysteine	15	1	17	21
Phenylalanine + tyrosine	27	2	31	38
Threonine	16	1	18	22
Tryptophan	4	< 0.5	5	6
Valine	19	2	22	27
14–18 y, Boys				
Histidine	11	1	12	15
Isoleucine	15	1	17	21
Leucine	34	2	38	47
Lysine	31	2	35	43
Methionine + cysteine	15	1	17	21
Phenylalanine + tyrosine	27	2	31	38
Threonine	16	1	18	22
Tryptophan	4	< 0.5	5	6
Valine	19	1	22	27

14–18 y, Girls				
Histidine	11	< 0.5	12	14
Isoleucine	15	< 0.5	16	19
Leucine	34	1	35	44
Lysine	31	1	32	40
Methionine + cysteine	15	< 0.5	16	19
Phenylalanine + tyrosine	27	1	28	35
Threonine	16	< 0.5	17	21
Tryptophan	4	< 0.5	4	5
Valine	19	1	20	24

[a] Derived from the adult EAR for specified amino acids (from Table 10-20).
[b] Derived using the following equation: Amino acid deposition = mean protein deposition (from Table 10-9) × amino acid composition of whole body protein (from Table 10-19).
[c] EAR for ages 7 mo–13 y = maintenance + amino acid deposition × 1.72. EAR for ages 14–18 y = maintenance + amino acid deposition x 2.13.
[d] RDA for ages 7 mo–13 y = EAR + $2 \times \sqrt{[(0.12 \times \text{maintenance})^2 + (0.43 \times 1.72 \times \text{mean protein deposition})^2]}$. RDA for ages 14–18y = EAR + $2 \times \sqrt{[(0.12 \times \text{maintenance})^2 + (0.43 \times 2.13 \times \text{mean protein deposition})^2]}$.

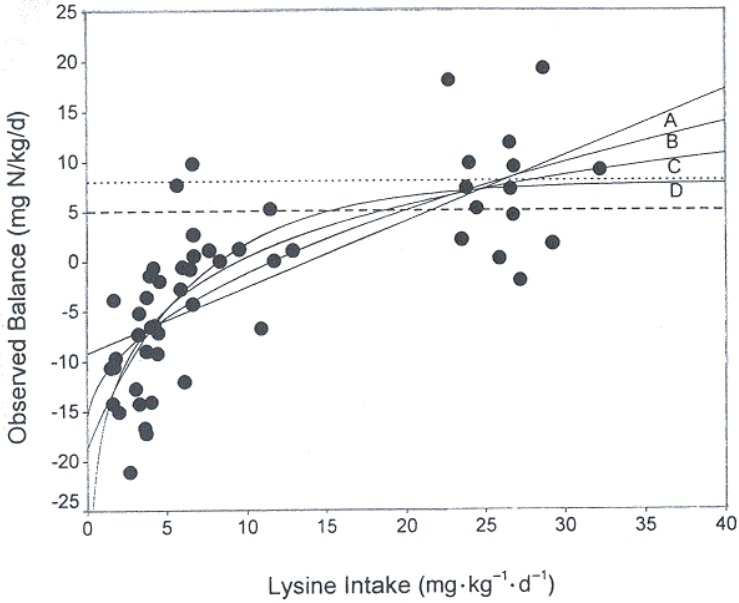

FIGURE 10-7 Relationship between nitrogen balance and test amino acid intake using four different one-fit regression equations: linear (A), square root (B), log (C), and exponential asymptotic (D), superimposed on the original data. Reprinted, with permission, from Rand and Young (1999). Copyright 1999 by the American Society for Nutritional Sciences.

support to the lysine DAAO estimate (Kurpad et al., 2001a; Meredith et al., 1986).

The 24-hour balance model is regarded as being the best from a theoretical point of view, especially when performed with the indicator approach. However, from a practical point of view, the 24-hour amino acid balance studies are very labor intensive with the result that only three or four levels of intake of the test amino acid have been studied for each of leucine, lysine, phenylalanine + tyrosine, and threonine.

Direct Amino Acid Oxidation. The DAAO method has been utilized to investigate six or seven amino acid levels, so it was possible to reanalyze these data using two-phase linear crossover regression analysis and define a breakpoint (which is regarded as the EAR). DAAO can only be used if the carboxyl group of the test amino acid is released to the body bicarbonate pool when the amino acid is committed to degradation. As shown in

TABLE 10-22 Indispensable Amino Acid Studies in Adults

Reference	Amino Acid	Method Used[a] (Number of Levels/ Number of Data Points)	Estimated Average Requirement (mg/kg/d)
Meguid et al., 1986a	Leucine	DAAO reanalyzed (8/52)	24.5
El-Khoury et al., 1994a	Leucine	24-h AAB (3/10)	38.3
Kurpad et al., 2001b	Leucine	24-h AAB (4/40)	40
Meredith et al., 1986	Lysine	DAAO reanalyzed (8/28)	26.6
Zello et al., 1993	Lysine	IAAO (7/42)	36.9
Rand and Young, 1999	Lysine	N-Balance reanalyzed (8/53)	30
Kurpad et al., 2001a	Lysine	24-h IAAB (4/32)	29
Kriengsinyos et al., 2002	Lysine	IAAO (5/60)	35
Kurpad et al., 2002a	Lysine	24-h IAAB (4/36)	29
Reynolds et al., 1958	Methionine + cysteine	N-balance reanalyzed (6/42)	20
Young et al., 1991	Methionine + cysteine	Methionine balance (1/5)	13
Di Buono et al., 2001	Methionine + cysteine	IAAO (6/36)	12.6
Zello et al., 1990	Phenylalanine	DAAO (7/41)	9.1
Roberts et al., 2001	Tyrosine	IAAO (7/42)	6.0
	Phenylalanine + tyrosine		15.1
Basile-Filho et al., 1998	Phenylalanine + tyrosine	24-h AAB	39.0
Zhao et al., 1986	Threonine	DAAO reanalyzed (7/33)	13.5
Wilson et al., 2000	Threonine	IAAO (7/36)	19.0
Borgonha et al., 2002	Threonine	24-h IAAB (3/15)	15.0
Kurpad et al., 2002b	Threonine	24-h IAAB (6/48)	15.0
Lazaris-Brunner et al., 1998	Tryptophan	IAAO (8/36)	4.0
Meguid et al., 1986b	Valine	DAAO reanalyzed (7/37)	19.2

[a] AAB = amino acid balance, DAAO = direct amino acid oxidation, IAAB = indicator amino acid balance and oxidation, IAAO = indicator amino acid oxidation.

Table 10-22, DAAO studies of indispensable amino acid requirements are limited to leucine (Meguid et al., 1986a), lysine (Meredith et al., 1986), phenylalanine (Zello et al., 1990), and valine (Meguid et al., 1986b). DAAO was also utilized to determine the threonine requirement (Zhao et al., 1986). However there are theoretical concerns for this amino acid,

since there are two pathways of degradation for threonine; the second pathway, threonine dehydrogenase (TDG), ends in the label being retained in glycine. In practical terms this may not be a serious error since others have shown that the TDG pathway is a minor pathway in adults (Darling et al., 2000).

Indicator Amino Acid Oxidation. IAAO has the advantage that the requirement of any amino acid can be determined, since either phenylalanine (in the presence of an excess of tyrosine to ensure that there is no label retention in the body tyrosine pools) or lysine can and have been used as indicator amino acids in humans and in animals (Bross et al., 2000; Brunton et al., 1998; Zello et al., 1995). A further strength of the IAAO studies is that each adult was fed at six or seven levels of the test amino acid, which has made it possible to define requirements for individuals by two-phase, linear cross-over regression analysis (Brunton et al., 1998; Zello et al., 1995). As shown in Table 10-22, IAAO estimates have been reported for lysine (Kriengsinyos et al., 2002; Zello et al., 1993), methionine + cysteine (Di Buono et al., 2001), tyrosine (Roberts et al., 2001), threonine (Wilson et al., 2000), and tryptophan (Lazaris-Brunner et al., 1998).

As shown in Table 10-22, currently there are amino acid oxidation estimates in which two-phase linear crossover regression analysis has been performed for leucine (DAAO), lysine (both DAAO and IAAO), methionine + cysteine (IAAO), phenylalanine (DAAO), tyrosine (IAAO), threonine (both DAAO and IAAO), tryptophan (IAAO), and valine (DAAO).

Other Indicators. Nonlinear regression was used on two sets of nitrogen balance data as shown by Rand and Young (1999). The first was for lysine in which the original data were in women, each of whom were studied at two to five levels (Jones et al., 1956). This data set was reanalyzed using nonlinear regression, including the addition of 5 or 8 mg of nitrogen/kg/d as miscellaneous losses (Rand and Young, 1999), and these reanalyzed data are included in Table 10-22. Using a similar approach, the data of Reynolds and coworkers (1958) for methionine + cysteine were reanalyzed, and these data are included in Table 10-22. The result is consistent with the data of Zezulka and Calloway (1976a, 1976b), who studied the effect on nitrogen balance of three levels of methionine added to soy protein at a constant and adequate level of total nitrogen. Since there are no direct estimates of the isoleucine requirement, it is estimated from the leucine and valine estimates. The isoleucine requirement was therefore calculated by multiplying the isoleucine requirement calculated from the protein requirement (Table 10-20) by 1.55, the average of the ratios for leucine and valine. Similarly, the requirement for histidine, for which there have also been no direct determinations, is calculated from the protein require-

ment (Table 10-20) multiplied by 1.7, the average ratio for all amino acids in Table 10-19.

Indispensable Amino Acid EAR Summary, Ages 19 Years and Older

An EAR was derived for each of the indispensable amino acids from the data in Table 10-22. Where more than one EAR was given for an amino acid in Table 10-22, the values were averaged and rounded to the nearest whole number. This approach is weakest with the phenylalanine + tyrosine requirements where there is a large range—from 15.1 to 39 mg/kg/d giving an average value of 27 mg/kg/d. Lysine is the indispensable amino acid with the most estimates (six in all), with the EAR varying from 26.6 to 36.9 mg/kg/d for an average value of 31 mg/kg/d. Given the very few studies available, separate requirements could not be determined for women versus men, or for young and older adults.

EAR for Adults	
19 years and older	**11 mg/kg/d of histidine**
	15 mg/kg/d of isoleucine
	34 mg/kg/d of leucine
	31 mg/kg/d of lysine
	15 mg/kg/d of methionine + cysteine
	27 mg/kg/d of phenylalanine + tyrosine
	16 mg/kg/d of threonine
	4 mg/kg/d of tryptophan
	19 mg/kg/d of valine

Indispensable Amino Acid RDA Summary, Ages 19 Years and Older

With protein (see "Protein RDA Summary, Ages 19 Through 50 Years"), because the distribution of individual requirements for protein is not a normal distribution and is skewed, its calculated standard deviation and coefficient of variation do not have the usual intuitive meaning (the mean plus two standard deviations exceeding all but about 2.5 percent of the population's requirement). However, an approximate standard deviation was calculated as half of the distance from the 16th to the 84th percentile of the protein requirement distribution as estimated from the log normal distribution of requirements. This gives, for comparative purposes, an approximate standard deviation of 12.5 mg N/kg/d (a CV = 12 percent). Given the paucity of data, it is assumed that for amino acids a similar deviation should be used; thus the RDA = EAR + 2 CV for amino acids as well as for protein, or RDA = 1.24 × EAR. The calculated RDA is rounded to the nearest whole number.

RDA for Adults	
19 years and older	**14 mg/kg/d of histidine**
	19 mg/kg/d of isoleucine
	42 mg/kg/d of leucine
	38 mg/kg/d of lysine
	19 mg/kg/d of methionine + cysteine
	33 mg/kg/d of phenylalanine + tyrosine
	20 mg/kg/d of threonine
	5 mg/kg/d of tryptophan
	4 mg/kg/d of valine

Pregnancy

Method Used to Estimate the Average Requirement

There are essentially no data with regard to amino acid requirements during pregnancy, so it is generally assumed that indispensable amino acid needs increase in proportion to the increased protein needs during pregnancy. Since the pregnancy EAR for total protein is 0.88 g/kg/d for women, the amino acid EARs for nonpregnant women were multiplied by 1.33 and rounded to the nearest whole number.

Amino Acid EAR and RDA Summary, Pregnancy

EAR for Pregnancy	
For all ages	**15 mg/kg/d of histidine**
	20 mg/kg/d of isoleucine
	45 mg/kg/d of leucine
	41 mg/kg/d of lysine
	20 mg/kg/d of methionine + cysteine
	36 mg/kg/d of phenylalanine + tyrosine
	21 mg/kg/d of threonine
	5 mg/kg/d of tryptophan
	25 mg/kg/d of valine

The RDA for amino acids for pregnancy is set by increasing the EAR by the variation in protein derived for adults ages 19 years and older (1.24 × EAR) and rounded to nearest whole number.

RDA for Pregnancy

For all ages	**18 mg/kg/d of histidine**
	25 mg/kg/d of isoleucine
	56 mg/kg/d of leucine
	51 mg/kg/d of lysine
	25 mg/kg/d of methionine + cysteine
	44 mg/kg/d of phenylalanine + tyrosine
	26 mg/kg/d of threonine
	7 mg/kg/d of tryptophan
	31 mg/kg/d of valine

Lactation

Method Used to Estimate the Average Requirement

There are essentially no data with regard to amino acid requirements during lactation, so it is generally assumed that indispensable amino acid needs will increase over the nonlactating needs by the amount of amino acids found in human milk (Table 10-18).

To estimate the EAR for amino acids for lactation, the average amounts of amino acids in human milk during the first 6 months of lactation expressed as mg/kg/d based on the reference weight of the adult woman in Table 1-1 (see "AI for Infants 0–6 Months"), are added to the EAR for amino acids for the nonlactating woman, expressed as mg/kg/d (see sections "Amino Acids EAR and RDA Summary, Ages 7 Months Through 18 Years" and "Amino Acids EAR and RDA Summary, Ages 19 Years and Older"). The calculated EARs in mg/kg body weight/d are rounded to the nearest whole number.

Amino Acid EAR and RDA Summary, Lactation

EAR for Lactation

For all ages	**15 mg/kg/d of histidine**
	24 mg/kg/d of isoleucine
	50 mg/kg/d of leucine
	42 mg/kg/d of lysine
	21 mg/kg/d of methionine + cysteine
	41 mg/kg/d of phenylalanine + tyrosine
	24 mg/kg/d of threonine
	7 mg/kg/d of tryptophan
	28 mg/kg/d of valine

The RDA for amino acids for lactation is set by assuming the same (CV) as that for total protein for lactation, 12 percent. The RDA is defined as the EAR plus twice the assumed CV to cover the needs of 97 to 98 percent of the individuals in the group. Therefore, for amino acids the RDA is 124 percent of the EAR for adolescents and adults. The calculated RDA in mg/kg of body weight/d is rounded.

RDA for Lactation	
For all ages	**19 mg/kg/d of histidine**
	30 mg/kg/d of isoleucine
	62 mg/kg/d of leucine
	52 mg/kg/d of lysine
	26 mg/kg/d of methionine + cysteine
	51 mg/kg/d of phenylalanine + tyrosine
	30 mg/kg/d of threonine
	9 mg/kg/d of tryptophan
	35 mg/kg/d of valine

INTAKE OF TOTAL PROTEIN AND AMINO ACIDS

Protein Quality

Different sources of protein vary widely in their chemical composition as well as in their nutritional value. The quality of a source of protein (or more specifically the source of nitrogen, since dietary protein is generally measured analytically in terms of nitrogen) is an expression of its ability to provide the nitrogen and amino acid requirements for growth, maintenance, and repair. In practice, protein quality is principally determined by two factors: digestibility and the amino acid composition of the protein in question. In food as opposed to relatively pure protein, the contribution of all of the indispensable amino acids to the total nitrogen content of the food has to be considered in assessing the overall protein quality of the diet.

Digestibility

Nitrogen is excreted in the feces in amounts that usually vary between 10 and 25 percent of the nitrogen intake. As mentioned earlier, only a part of this is derived directly from dietary nitrogen that was not absorbed; the other parts result from protein and other secretions into the gastrointestinal tract during the process of digestion and from nitrogen con-

tained in fecal bacteria. The unabsorbed part represents mainly proteins that, by reason of their physical characteristics or chemical composition, are resistant to breakdown by the proteolytic digestive enzymes. There is probably a variable contribution of nitrogen contained in other nonabsorbable components, such as amino sugars and other nitrogen-containing materials found in cell walls.

On the other hand, the secretions consist of specific proteins, such as mucins, which represent a loss that is of nutritional importance. These secretions appear to be rich in threonine and cysteine (Roberton et al., 1991), and thus contribute to the requirement for both amino acids. However, both the nonabsorbed and secreted components that make up nitrogen loss are difficult to quantify with any confidence, except in terms of total nitrogen, because of the overwhelming modifying effect of the intestinal microflora. Thus, digestibility (as estimated by nitrogen excretion) is usually determined by measuring the fecal nitrogen (N_{FP}) in individuals consuming the specific nitrogen source and subtracting the fecal nitrogen values obtained when a protein-free diet is given (N_{F0}). This value is then subtracted from the total nitrogen intake (N_I) and expressed as a proportion of the nitrogen intake.

$$\text{True Digestibility} = D_F = (N_I - N_{F\Delta}) / N_I,$$

where $N_{FD} = N_{FP} - N_{F0}$.

Fecal nitrogen from a protein-free diet is a measure of the amount of nitrogen from intestinal secretions, on the assumption (probably incorrect) that this component does not vary with different diets (de Lange et al., 1989). The values thus calculated are called "true" digestibility and represent the proportion of the dietary nitrogen that is absorbed. This portion can generally be assumed to be available to the host for meeting the needs for maintenance and growth.

It must be noted that a number of recent studies with isotopically labeled proteins suggest that true digestibility exceeds 90 percent for many common foods such as milk, cereals, and soy and other legumes (Darragh and Hodgkinson, 2000, de Vrese et al., 2000; Mariotti et al., 1999, Gausserès et al., 1997; Gaudichon et al., 1999). It should also be noted that, at present, calculation of the availability (or digestibility) of amino acids from food protein sources is based on the digestibility of total nitrogen as contrasted to that for the individual amino acid. However, there can be quite large differences between the digestibility coefficients for total nitrogen and the individual amino acid. These and other related aspects of protein quality have been reviewed elsewhere (Darragh and Hodgkinson, 2000; Schaafsma, 2000).

The digestive and intestinal phase of dietary protein utilization is currently an active area of research, but it is still, from a practical standpoint, not possible to make major improvements over the estimates of true protein digestibility made some years ago by the Food and Agriculture Organization and the World Health Organization (FAO/WHO, 1991). Therefore, the determination of true digestibility of proteins, diets, and amino acids in this report are based on the approaches and values proposed by FAO/WHO in 1991.

Nitrogen Versus Amino Acids

Absorbed nitrogen is mainly in the form of amino acids, but a proportion is in other compounds such as nucleic acids, creatine, amino sugars, ammonia, and urea. The quantitative extent to which these contribute to nitrogen retention and homeostasis is not known. Creatine can probably be utilized (Metges et al., 1999b), but in general it is unknown to what extent these different compounds can have a sparing effect on the utilization of the amino acids for which they are precursors. However, the major requirement for total nitrogen or protein is for the specific indispensable amino acids (and/or conditionally indispensable amino acids) and an additional source of α-amino nitrogen. At appropriate intakes these maintain protein homeostasis and adequate synthesis of those physiologically important compounds for which amino acids are the obligatory precursors (Table 10-5).

It is conventional to use a value of 6.25 to express the weight ratio of protein to the nitrogen content in foods, which assumes that nitrogen is, on average, 16 percent by weight of mixed protein. However, this factor is in fact quite variable among different proteins. For example, when protein intake is calculated by summing the weight of amino acids as analyzed in a food (less the water of hydrolysis), the protein/nitrogen ratio is 5.38 for egg, 5.62 for whole milk, 4.86 for cooked ham, 5.70 for whole-meal wheat bread, and 6.07 for soymilk. Thus when converting the amount of nitrogen present in a specific foodstuff to total protein, this factor becomes important to use.

These differences in the protein-to-nitrogen ratio of food proteins are not of specific importance in reference to the development of the recommendations for protein requirements given herein. This is because these recommendations have been based initially on nitrogen balance determinations, which in turn were based on analytical measurements of nitrogen intake (from different test proteins or mixtures of proteins). The nitrogen intake values were then converted to protein intakes using the conventional 6.25 factor, irrespective of the protein source used in the various experiments.

However, the protein-to-nitrogen conversion factor does matter in considering the quality of food protein sources when the protein-specific nitrogen conversion factor has been used to convert the chemically determined nitrogen content of the protein to a protein value. In this case, protein intakes and the relation between the amino acid concentrations in the protein should all be referred back to a nitrogen base. For this reason, amino acid requirement patterns delineated below are given in reference to both conventional protein (nitrogen × 6.25) and to a nitrogen basis.

Amino Acids Content of Proteins

The second and generally more important factor that influences the nutritional value of a protein source is the relative content and metabolic availability of the individual indispensable amino acids. If the content of a single indispensable amino acid in the diet is less than the individual's requirement, then it will limit the utilization of other amino acids and thus prevent normal rates of protein synthesis even when the total nitrogen intake level is adequate. Thus, the "limiting amino acid" will determine the nutritional value of the total nitrogen or protein in the diet. This has been illustrated in experiments comparing the relative ability of different protein sources to maintain nitrogen balance. For example, studies have shown, depending on its source and preparation, that more soy protein might be needed to maintain nitrogen balance when compared to egg-white protein, and that the difference may be eliminated by the addition of methionine to the soy diet. This indicates that sulfur amino acids can be limiting in soy (Zezulka and Calloway, 1976a, 1976b). Similarly, the limiting amino acid in wheat protein is lysine (Young et al., 1975a).

The concept of the limiting amino acid has led to the practice of amino acid (or chemical) scoring, whereby the indispensable amino acid composition of the specific protein source is compared with that of a reference amino acid composition profile. Earlier the amino acid composition of a good quality protein such as egg, which is regarded as being well balanced in amino acid content in relation to human needs (FAO/WHO, 1973), was used as a reference or benchmark. Table 10-23 shows the composition of various food protein sources expressed as mg of amino acid per g of protein (nitrogen × 6.25). The composition of amino acids of egg and milk proteins is similar with the exception of the sulfur amino acids methionine and cysteine. However, wheat and beans have lower proportions of indispensable amino acids, especially of lysine and sulfur amino acids, respectively.

The nutritional implications of these differences in the amino acid content of different proteins or mixtures of proteins can be evaluated by

TABLE 10-23 Amino Acid Composition of Major Food Protein Sources (mg/g protein)[a]

Amino Acid	Whole Wheat Flour	Navy Beans	Milk	Eggs
Histidine	22	28	28	24
Isoleucine	40	42	60	63
Leucine	63	76	98	88
Lysine	26	72	79	70
Methionine + cysteine	35	19	34	56
Phenylalanine + tyrosine	81	77	96	98
Threonine	27	39	45	49
Tryptophan	11	10	14	16
Valine	43	46	67	72

[a] Values for protein composition (N × 6.25) are from Young and Pellett (1990).

comparing the amino acid composition of the protein source with a suitable reference amino acid pattern.

Amino Acid Scoring and Protein Quality

In recent years, the amino acid requirement values for humans have been used to develop reference amino acid patterns for purposes of evaluating the quality of food proteins or their capacity to efficiently meet both the nitrogen and indispensable amino acid requirements of the individual. Based on the estimated average requirements for the individual indispensable amino acids presented earlier (Tables 10-20 and 10-21) and for total protein (nitrogen × 6.25) (Tables 10-9 and 10-13), it is possible to establish an amino acid requirement (or scoring) pattern for preschool children and for adults. These are given in Table 10-24 together with the amino acid requirement pattern used for breast-fed infants. It should be noted that this latter pattern is that for human milk and so it is derived quite differently compared to that for the other age groups.

There are three important points that need to be highlighted about the proposed amino acid scoring patterns. First, there are relatively small differences between the amino acid requirement and thus scoring patterns for children and adults, therefore use amino acid requirement pattern for 1 to 3 years of age is recommended as the reference pattern for purposes of assessment and planning of the protein component of diets.

Second, the requirement pattern proposed here for adults is fundamentally different from a number of previously recommended requirement patterns (Table 10-25). The pattern for adults (FAO/WHO/UNU,

TABLE 10-24 Proposed Amino Acid Scoring Patterns for Infants, Preschool Children, and Adults Based on Estimated Requirements for Protein and Indispensable Amino Acids

	Infants[a]	Preschool Children (1–3 y)		Adults (18+ y)	
Amino Acid	(mg/g protein)	(mg/g protein)[b]	(mg/g N)[c]	(mg/g protein)[b]	(mg/g N)[c]
Histidine	23	18	114	17	104
Isoleucine	57	25	156	23	142
Leucine	101	55	341	52	322
Lysine	69	51	320	47	294
Methionine + cysteine	38	25	156	23	142
Phenylalanine + tyrosine	87	47	291	41	256
Threonine	47	27	170	24	152
Tryptophan	18	7	43	6	38
Valine	56	32	199	29	180

[a] Pattern based on amino acid composition of human milk (from Table 10-18).
[b] Pattern derived from (EAR for amino acid ÷ EAR for protein); for 1–3 y group, where EAR for protein = 0.88 g/kg/d; for adults, EAR for protein = 0.66 g/kg/d. EAR is Estimated Average Requirement.
[c] Calculated as (mg/g protein) × 6.25.

TABLE 10-25 FNB/IOM Scoring Pattern Compared to Other Proposed Patterns (mg/g protein)

Amino Acid	MIT Pattern[a]	Millward Pattern[b]	FAO/WHO/ UNU Pattern[c]	Recommended FNB/IOM Pattern[d]
Histidine	—	—	—	18
Isoleucine	35	30	13	25
Leucine	65	44	19	55
Lysine	50	31	16	51
Methionine + cysteine	25	27	17	25
Phenylalanine + tyrosine	65	33	19	47
Threonine	25	26	9	27
Tryptophan	10	6	5	7
Valine	35	23	13	32

[a] Young and Pellett (1990).
[b] Millward et al. (1990).
[c] FAO/WHO/UNU (1985).
[d] Based on 1- to 3-year-old Estimated Average Requirements for protein and indispensable amino acids.

1985) has uniformly lower proportions of all the indispensable amino acids, as these requirement values were determined from studies of nitrogen balance, which are now considered to be not as reliable as values derived from metabolic amino acid data (see previous discussion). The other requirement patterns shown in Table 10-25 for adults were published in two recent reviews (Millward, 1999; Young and Borgonha, 2000). The pattern suggested by Millward (1999) is based on a reanalysis of nitrogen balance data that yields values that are generally lower than either the FNB/IOM reference pattern, based on the EARs estimated above, or the MIT pattern (Young and Borgonha, 2000). The MIT pattern includes much of the oxidation and carbon balance data contained in the EAR estimates given in this report, but the reference pattern recommended here is derived from a larger body of data than that used by Young and Borgonha. Thus, the reference amino acid scoring patterns shown in Table 10-24 are designed for use in the evaluation of dietary protein quality.

Third, in generating these amino acid scoring patterns, the EARs for the amino acids and for total protein were used. However, two important statistical considerations need to be raised here: first, the extent to which there is a correlation between nitrogen (protein) and the requirement for a specific indispensable amino acid; second, the impact of the variance for both protein and amino acid requirements on the derived amino acid reference pattern. The extent to which the requirements for specific indispensable amino acids and total protein are correlated is not known. In this report it is assumed that the variance in requirement for each indispensable amino acid is the same as that for the adult protein requirement.

This analysis illustrates one of the uncertainties faced in establishing a reference or scoring pattern and judging the nutritional value of a protein source for an individual. However, on the basis of different experimental studies in groups of subjects, experience shows that a reasonable approximation of the mean value for the relative quality of a protein source or mixture of proteins can be obtained by use of the amino acid scoring pattern proposed in Table 10-26 and a standard amino acid scoring approach, examples of which are given in the following section.

Calculation of Amino Acid Scores for Different Food Proteins

The method for evaluating the relative nutritional quality of different protein sources that is used in this report is based on calculating the protein digestibility corrected amino acid score (PDCAAS) as proposed by FAO/WHO (1991). It is calculated as follows:

TABLE 10-26 Summary FNB/IOM 2002 Amino Acid Scoring Pattern for Use in Children ≥ 1 Year of Age and in All Other Older Age Groups

Amino Acid	mg/g protein[a]	mg/g N
Histidine	18	114
Isoleucine	25	156
Leucine	55	341
Lysine	51	320
Methionine + cysteine	25	156
Phenylalanine + tyrosine	47	291
Threonine	27	170
Tryptophan	7	43
Valine	32	199

[a] Protein = nitrogen × 6.25.

$$\text{PDCAAS (\%)} = \frac{\text{[mg of limiting amino acid in 1-g test protein]}}{\text{mg of same amino acid in 1-g reference protein}} \times \text{[true digestibility } (D_F)\text{(\%)]}$$

As mentioned earlier, in comparing the amino acid reference (or scoring) patterns (Table 10-24) for 1- through 3-year-old children and the adult age groups, it would be hard to justify proposing separate amino acid scoring patterns for these populations for practical purposes. Therefore, for calculation of the amino acid score, corrected for digestibility (PDCAAS, %), it is recommended that one scoring pattern be used to cover all ages from 1 year and above, as shown in Table 10-26.

A number of examples of the PDCAAS for different food proteins or diets based on three major protein sources are given in Table 10-27. As shown, wheat (lysine limiting) and chickpea proteins (sulfur amino acid limiting) have a PDCAAS of 44 and 87 percent, respectively. For a diet based on a mixture of wheat, chickpea, and skim milk proteins the PDCAAS is 110 percent, which is truncated to a value of 100, since the relative efficiency of utilization of the limiting amino acid cannot be greater than that of the amino acid scoring pattern at nitrogen intakes sufficient to meet nitrogen needs. Finally, it should be noted that PDCAAS scores have only been calculated here based on four indispensable amino acids (lysine, sulfur amino acids, threonine, and tryptophan). These are

TABLE 10-27 Calculation of PDCAAS[a] for Selected Individual Food Proteins and for a Mixture of These Proteins, Based on the FNB/IOM 2002 Amino Acid Scoring Pattern

Protein	Amino Acid Content (mg/g protein)[b]				Protein Digestibility	PDCAAS (%)
	Lys	SAA	Thr	Trp		
Wheat	25	35	30	11	0.85	42 (Lysine)[c]
Chickpea	70	25	42	13	0.80	80 (SAA)
Milk powder	80	30	37	12	0.95	100 (114—SAA)[d]
Mixture (% of protein)						
Wheat (19)						
Chickpea (32)						
Milk powder (49)						
For combination[e]	64	29	37	12	0.88	100 (102—SAA)

[a] Data for proteins taken from Table 10 of FAO/WHO (1991) using the procedure described therein to determine PDCAAS (Protein Digestibility Corrected Amino Acid Score).
[b] Lys = lysine; SAA = sulfur amino acids; Thr = threonine; Trp = Tryptophan.
[c] Lysine or sulfur amino acid = limiting amino acid.
[d] Where relevant, the nontruncated value for the PDCAAS is given prior to truncation to a value of 100.
[e] Weighted values based on the proportion of the total protein in the mixture that is contributed by each protein source.

the most likely limiting amino acids in common food protein sources and so have been considered here for illustrative purposes.

There have been discussions on ways to improve the PDCAAS procedure and further developments in this context are needed. Until better methods are developed, the foregoing procedure is recommended, using the digestibility values proposed by FAO/WHO (1991).

Comments on Protein Quality for Adults

While the importance of considering protein quality in relation to the protein nutrition of the young has been firmly established and accepted over the years, the significance of protein quality (other than digestibility) of protein sources in adults has been controversial or less clear. The amino acid scoring pattern given in Table 10-24 for adults is not markedly different from that for the preschool age group, implying that protein quality should also be an important consideration in adult protein nutrition.

In the published meta-analysis of nitrogen balance studies by Rand and coworkers (2003), there were no significant differences in the intakes of dietary nitrogen required to meet nitrogen equilibrium between those studies that supplied dietary protein predominantly from animal, vegetable, or mixed protein sources. It is important to realize however, that this aggregate analysis does not suggest that dietary protein quality is of no importance in adult protein nutrition. The examined and aggregated studies included an analysis of those that were designed to compare good quality soy protein (Istfan et al., 1983; Young et al., 1984) as well as one that involved comparison of whole-wheat proteins (Young et al., 1975a) with animal proteins sources using parallel experimental diet groups. The results of these studies showed clearly that the quality of well-processed soy proteins was equivalent to animal protein in the adults evaluated (which would be predicted from the amino acid reference pattern in Table 10-26), while wheat proteins were used with significantly lower efficiency than the animal protein (beef) (again this would be predicted from the procedure above). Similar studies compared rice and egg proteins (Inoue et al., 1973), wheat gluten and egg proteins (Yanez et al., 1982), and lupin and egg proteins (Egana et al., 1992), all demonstrating the higher quality of the animal protein reference sources.

Thus, the aggregate analyses of all available studies analyzed by Rand and coworkers (2003) obscured these results and illustrate the conservative nature of their meta-analysis of the primary nitrogen balance. Moreover, this discussion and presentation of data in Table 10-27 underscores the fact that while lysine is likely to be the most limiting of the indispensable amino acids in diets based predominantly on cereal proteins, the risk of a lysine inadequacy is essentially removed by inclusion of relatively modest amounts of animal or other vegetable proteins, such as those from legumes and oilseeds, or through lysine fortification of cereal flour.

Food Sources

Protein from animal sources such as meat, poultry, fish, eggs, milk, cheese, and yogurt provide all nine indispensable amino acids, and for this reason are referred to as "complete proteins." Proteins from plants, legumes, grains, nuts, seeds, and vegetables tend to be deficient in one or more of the indispensable amino acids and are called "incomplete proteins." Three ounces of lean meat or poultry contain about 25 g of protein, and 3 ounces of fish or 1 cup of soybeans supplies about 20 g of protein. The protein content of 1 cup of yogurt is approximately 8 g, 1 cup of milk is 8 g, and 1 egg or 1 ounce of cheese contains about 6 g. One cup of legumes has approximately 15 g of protein. Cereals, grains, nuts, and vegetables contain about 2 g of protein per serving.

Dietary Intake

Data from nationally representative U.S. and Canadian surveys are available to estimate protein intakes (Appendix Tables E-16 and F-5). In the United States, the median dietary intake of protein by adult men during 1994–1996 and 1998 ranged from 71 to 101 g/d for various age groups (Appendix Table E-16). For women, the median intake ranged from 55 to 62 g/d. For both men and women, protein provided approximately 15 percent of total calories (Appendix Table E-17). Similarly, in Canada, protein provided approximately 15 percent of total calories for adults (Appendix Table F-5).

The amino acids intakes for the U.S. population are found in Appendix Tables D-2 through D-19. The median dietary intake of lysine by adult men during 1988–1994 ranged from 4.65 to 7.50 g/d for various ages (Appendix Table D-11), and by adult women from 3.59 to 4.56 g/d. The median dietary intake of threonine by adult men during 1988–1994 ranged from 2.74 to 4.21 g/d for various ages (Appendix Table D-16) and by adult women from 2.10 to 2.59 g/d. The median dietary intake of tryptophan by adult men and women during 1988–1994 ranged from 0.84 to 1.26 g/d and from 0.65 to 0.78 g/d, respectively (Appendix Table D-17).

TOLERABLE UPPER INTAKE LEVELS FOR PROTEIN

Humans consume a wide range of intakes of protein. As intake is increased, the concentrations of free amino acids and urea in the blood increase postprandially. The nitrogenous substances in the urine also increase, especially urea. These changes are part of the normal regulation of the amino acids and nitrogen and represent no hazards per se, at least within the range of intakes normally consumed by apparently healthy individuals. Nonetheless, a number of adverse effects have been reported, especially at the very high intakes that might be achieved with supplement use, but also at more modest levels.

In addition, some naturally occurring proteins are allergenic to certain sensitive individuals; for example, the glycoprotein fractions of foods have been implicated in allergic responses. However, relatively few protein foods cause most allergic reactions: milk, eggs, peanuts, and soy in children; and fish, shellfish, peanuts, and tree nuts in adults.

Hazard Identification

Adverse Effects

There is little scientific literature on the effects of consuming very high protein diets, but it has been suggested from evidence of the dietary

practices of hunter-gatherer populations, both present day and historical, that humans avoid diets that contain too much protein (Cordain et al., 2000; Speth, 1989). Even when meat is the dominant food, diets of a wide range of populations do not usually contain more than about 40 percent of energy as protein (Speth, 1989). Indeed, Eskimos, when eating only meat, maintain a protein intake below 50 percent of energy by eating fat; protein intake estimated from data collected in 1855 was estimated to be about 44 percent (Krogh and Krogh, 1913).

There have been case reports of high levels of intake. Two arctic explorers, Stefansson and Andersen, ate only meat for a whole year while living in New York City (Lieb, 1929; McClellan and Du Bois, 1930; McClellan et al., 1930, 1931). For most of the period, the diet contained 15 to 25 percent of energy as protein, with fat (75 to 85 percent) and carbohydrate (1 to 2 percent) providing the rest, and no ill effects were observed (McClellan and Du Bois, 1930). However, consumption of greater portions of lean meat (45 percent of calories from protein) by one of the two explorers led rapidly to the development of weakness, nausea, and diarrhea, which was resolved when the dietary protein content was reduced to 20 to 25 percent of calories (McClellan and Du Bois, 1930).

If continued, a diet too high in protein results in death after several weeks, a condition known as "rabbit starvation" by early American explorers, as rabbit meat contains very little fat (Speth and Spielmann, 1983; Stefansson, 1944a). Similar symptoms of eating only lean meat were described by Lewis and Clark (McGilvery, 1983). Conversely, an all-meat diet with a protein content between 20 and 35 percent has been reported in explorers, trappers, and hunters during the winters in northern America surviving exclusively on pemmican for extended periods with no adverse effects (McGilvery, 1983; Speth, 1989; Stefansson, 1944b). Pemmican is a concentrated food made by taking lean dried meat that has been pounded finely and then blending it with melted fat. It contains about 20 to 35 percent protein; the remainder is fat (Stefansson, 1944b).

Nitrogen Balance Studies. Nitrogen balance studies at protein intakes of 212 to 300 g/d consistently have shown positive nitrogen balance (Fisher et al. 1967; Oddoye and Margen, 1979; Tarnopolsky et al., 1988), although this is usually attributed to the cumulative errors of the nitrogen balance procedure (Garlick et al., 1999; Hegsted, 1978; Oddoye and Margen, 1979). In particular, no negative nitrogen balances were reported, suggesting that the high protein intake had no detrimental effect on protein homeostasis.

Maximum Urea Synthesis. Rudman and coworkers (1973) studied the effect of meals containing graded levels of protein on the rate of urea production by human liver in vivo. With increasing protein content of the

meals, a maximum rate of urea synthesis of 65 mg of urea nitrogen/hour/kg body weight$^{0.75}$ was observed. At higher intakes, the rate was not increased further, but the maximum rate continued longer. In a 70-kg sedentary person, this maximum rate corresponds to about 250 g/d of protein, or about 40 percent of energy. The correspondence of this maximum to the apparent upper level of protein intake (45 percent of energy) described in the earlier section related to the experiences reported by explorers has therefore been suggested as cause and effect (Cordain et al., 2000). However, this interpretation should be made with caution, as there was no period of adaptation to the meal in the study of Rudman's group (1973). It is probable that when high protein diets are given, the capacities to oxidize amino acids and synthesize urea are increased, as has been demonstrated in animals (Das and Waterlow, 1974). However, this does not appear to have been investigated in humans.

Chronic Disease. High protein intakes have also been implicated in chronic diseases such as osteoporosis, renal stones, renal insufficiency, cancer, coronary artery disease, and obesity (see "High Protein Diets" in Chapter 11). However, the current state of the literature does not permit any recommendation of the upper level for protein to be made on the basis of chronic disease risk.

Dose–Response Assessment

The data on the potential for high protein diets to produce gastrointestinal effects, changes in nitrogen balance, maximum urea synthesis, or chronic disease are often conflicting and do not provide dose–response information or clear indications of a lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL) for these endpoints. Thus, there are insufficient data to establish a Tolerable Upper Intake Level (UL) for total protein. Because of the current widespread use of protein supplements, more research is needed to assess the safety of high protein intakes from supplements; until such information is available, caution is warranted.

The potential implications of high dietary protein for bone and kidney stone metabolism are not sufficiently clear at present to make recommendations for the general population to restrict their protein intake. However, in those who have idiopathic hypercalciuria, the occurrence of kidney stones is much increased, and although there is no evidence to indicate reducing protein intake will decrease the risk of developing kidney stones, these individuals should not be encouraged to consume more protein than the Recommended Dietary Allowance (RDA).

Intake Assessment

Based on distribution data from the 1994–1996, 1998 Continuing Survey of Food Intakes by Individuals (CSFII), the highest mean intake of protein from diet for any gender and life stage group was estimated to be 104 g/d (Appendix Table E-16) for men aged 19 through 30 years of age. For the 70-kg reference man (Table 1-1), this would equate to 1.5 g/kg/d. This life stage group also had the highest reported protein intake at the 99th percentile of intake at 190 g/d, or 2.7 g/kg/d, for the reference 70 kg-man.

Risk Characterization

The risk of adverse effects resulting from excess intakes of protein from foods appears to be very low at the highest intake noted above. Based on distribution data from the 1994–1996, 1998 CSFII (Appendix Table E-17), these 19-30-year-old men would be consuming a mean of 15.2 percent of their energy from protein, and at the 99th percentile, 21.5 percent. Women over the age of 50 had the highest reported percentage of total energy from protein at the 99th percentile of 23.7 percent. Although a UL for protein could not be established, this does not mean that there is not a potential for adverse effects resulting from high protein intakes from food or supplements. Because the data on adverse effects resulting from high protein intakes are limited, caution may be warranted.

TOLERABLE UPPER INTAKE LEVELS FOR INDIVIDUAL AMINO ACIDS

In establishing tolerable upper intake levels (ULs) for amino acids several general points, common to all the amino acids, were noted.

- There is no evidence that amino acids derived from usual or even high intakes of protein from foodstuffs present any risk. Therefore, attention was focused on intakes of amino acids from dietary supplements and when utilized as food ingredients, such as monosodium glutamate in food or aspartic acid and phenylalanine in aspartame.
- This review was confined to those amino acids that are found in dietary protein and only the L-forms of amino acids were considered.
- Recognizing that the ULs are for chronic intake and in keeping with the UL model, only limited emphasis was placed on the results of acute and short-term toxicity studies, while longer-term studies were considered most appropriate for establishing ULs.

- More emphasis was placed on observations of adverse effects in humans than on effects observed in animals. Pharmacokinetic studies were sought to bridge potential differences between animals and humans.
- It was noted that blood concentrations could be considerably higher when amino acids were consumed as supplements as opposed to a component of protein in food, and this was considered in establishing ULs.
- Many animal studies of amino acid toxicity were conducted with diets deficient in protein. Less emphasis was placed on these studies than those with adequate protein diets because of concern over the creation of amino acid imbalances.
- For some well-studied amino acids, there were no adverse effects reported at the highest dose tested in long-term studies. In such cases it was not possible to establish a Lowest-Observed-Adverse-Effect Level (LOAEL) or a No-Observed-Adverse-Effect Level (NOAEL) that was supported by toxicity data. Under these circumstances, it was not possible to establish a UL in keeping with the criteria and procedures required by the UL model.

Alanine

L-Alanine is a dispensable amino acid with glycogenic properties. Studies of food intake, growth, and hematological changes resulting from the oral ingestion of L-alanine in animals and humans reveal little data to suggest a LOAEL or a NOAEL (LSRO, 1992). Based on intake distribution data from the 1988–1994 (NHANES III) mean daily intake for all life stage and gender groups of alanine from food and supplements is approximately 3.6 g/d (Appendix Table D-2). Men 51 through 70 years of age had the highest reported intake at the 99th percentile of 8.5 g/d.

Hazard Identification

Adverse Effects in Animals. In animals, L-alanine exhibits neural inhibitory actions as well as hypothermogenicity (Glyn and Lipton, 1981). There are no adequate data to characterize dose–response relationships for L-alanine in animals.

Adverse Effects in Humans. Oral administration of a single L-alanine dose, up to 50 g/d, increased plasma insulin levels (Genuth, 1973; Genuth and Castro, 1974; Rose et al., 1977). However, there are no chronic studies that can be utilized to establish a UL for supplemental L-alanine in humans.

Dose–Response Assessment

The very limited data on adverse effects of L-alanine intake from dietary supplements (Genuth, 1973; Genuth and Castro, 1974) were considered insufficient for a dose–response assessment and derivation of a UL for L-alanine.

Arginine

L-Arginine is incorporated into tissue proteins, and is required for the synthesis of other amino acids, polyamines, and creatine, as well as for the detoxification of ammonia via the urea cycle (Rodwell, 1990). It is a dispensable glycogenic amino acid, synthesized in adequate amounts from the urea cycle intermediate ornithine. Ornithine, in turn, can be synthesized from proline and possibly from glutamate (Brunton et al., 1999). However, in children with congenital defects of argininosuccinic acid synthetase or argininosuccinase, both urea cycle enzymes, arginine is an indispensable amino acid with daily supplementation required (Brusilow and Horwich, 1989). Based on intake distribution data from the 1988–1994 NHANES III, mean daily intakes for all life stage and gender groups of arginine from food and supplements is approximately 4.2 g/d (Appendix Table D-3). Men 51 through 70 years of age had the highest reported intake at the 99th percentile of 10.1 g/d.

Hazard Identification

Adverse Effects in Animals. Feeding low-protein diets supplemented with 4, 5, or 7.5 percent arginine resulted in depressed body weight gains in rats (Harper et al., 1966; Sauberlich, 1961). However, the growth suppression by excess arginine was lessened when the protein content of the diet was increased and when the quality of protein was improved (Harper et al., 1970).

Oral doses of L-arginine of 0.1, 0.5, and 1.0 g/kg of body weight were given to rats 1 hour before behavioral trials for a period of 5 or 7 days. Avoidance behavior was increased in CDR rats (a strain with poor learning capacity) at the highest dose only. Conditioned avoidance was not affected in Wistar rats, but increased locomotion was reported (Drago et al., 1984).

Studies on the effects of orally administered arginine on the immune system have provided conflicting results. Barbul and coworkers (1980) reported significant increases in thymus weights, thymic lymphocyte content, and in vitro activity of thymic lymphocytes after supplementing the diet of male mice with 0.5, 1, 2, and 3 percent arginine hydrochloride (one-half in the diet and one-half in drinking water) for 6 days. No dose–

response was found, with the maximum stimulation noted at 0.5 percent supplementation of the normal chow diet containing 1.8 percent arginine. Reynolds and coworkers (1990) reported significantly increased thymus weight, spleen cell mitogenesis, and inducible natural killer cell activity in mice after oral arginine (drinking water) doses of 60, 120, or 240 mg/kg of body weight/d. No dose–response was reported with maximum stimulation noted at 60 mg/kg of body weight/d. In young or aged rats, ingestion of diets supplemented with 3 percent L-arginine for 15 days did not result in increased thymus weights and little effect was reported on lymphocyte proliferation or interleukin-2 production as compared to controls (Ronnenberg et al., 1991).

Adverse Effects in Humans. Feeding 30 g of L-arginine hydrochloride/d for 7 days to 21 healthy human volunteers resulted in no changes in liver function, blood urea nitrogen (BUN), creatinine, or blood glucose (Barbul et al., 1981). The nausea and diarrhea reported by two and three adults, respectively, were ameliorated by altering the amount given at any time without decreasing the total daily intake. However, administration of 5 or 10 g of arginine as arginine aspartate for 80 days produced such dose-related reversible effects as increased weight, gastrointestinal disturbances, and somnolence (De Aloysio et al., 1982).

Thirty-six healthy volunteers were divided into 3 equal groups of 12 and orally administered 30 g of arginine hydrochloride (24.8 g of free arginine), 30 g of arginine aspartate (17 g free arginine), or a placebo daily for 14 days (Barbul et al., 1990). Dietary consumption of arginine was not controlled. Supplementation with arginine hydrochloride resulted in the development of mild hyperchloremic acidosis. Side effects of bloating, mild anorexia, and diarrhea were reported by one in the group receiving placebo, three in the group receiving arginine aspartate, and six in the group receiving arginine hydrochloride (Barbul et al., 1990). In another study of 30 elderly adults receiving 17 g of free arginine/d as arginine aspartate for 14 days, no adverse effects were observed (Hurson et al., 1995).

Park and coworkers (1992) administered orally 30 g of arginine free base/d to 10 patients with breast cancer during the three days immediately prior to surgery. A second group of ten cancer patients did not receive arginine supplementation prior to surgery and served as controls. The daily median rate of tumor protein synthesis in arginine-supplemented patients was slightly more than double that found in controls (25.6 percent/d, range 9 to 37 percent/d; 10 percent/d, range 5.5 to 15.8 percent/d, respectively). In addition, in patients receiving arginine supplementation there was a marked stimulation in the expression of the activation antigen Ki67 as measured histologically (~40 percent tumor cells staining with Ki67

compared to ~9 percent in controls). These data indicate that large oral doses of arginine may stimulate tumor growth in humans.

Studies in experimental animals have indicated a suppression of tumor growth after oral administration of arginine (Barbul, 1986; Reynolds et al., 1988; Tachibana, et al., 1985). Paradoxically, there are also published studies showing that arginine can stimulate tumor growth in animal models. Yeatman and coworkers (1991) showed that an arginine-enriched diet stimulated the growth of a murine colon tumor, whereas an arginine-depleted diet inhibited the tumor growth. Arginine was also shown to stimulate tumors in total parenteral nutrition-fed rats, while substitution of ornithine for arginine abolished the effect (Grossie et al., 1992). Moreover, Levy and coworkers (1954) showed that subcutaneous injections of arginine either inhibited or stimulated the tumor, depending on its size at the start of treatment. The mechanism of these effects is unknown, but might in part involve the immune system. Reynolds and coworkers (1988) observed an inhibition of tumor growth with tumors of high immunogenicity, but stimulation when a tumor of low immunogenicity was used, suggesting that inhibition might only occur when tumors can be recognized and killed by the immune system.

Batshaw and coworkers (1984) treated 17 hyperammonemic infants with 175 to 350 mg L-arginine/kg of body weight/d for 6 to 8 weeks. No adverse effects were reported. Plasma arginine concentrations were approximately twice those in the controls but less than one-third of the minimal concentration postulated to result in neurological effects in hyperargininemia. A follow-up at 18 months of age showed similar IQ scores in all groups. It should be mentioned that Brusilow and coworkers (1984) have used arginine supplements of 210 to 840 mg/kg of body weight/d for 5 years in the treatment of children with inborn errors of urea synthesis. No evidence of intellectual deterioration or visual effects was reported in these patients. In addition, there are several reports regarding patients treated intravenously with arginine hydrochloride for metabolic alkalosis or as a provocative test for growth hormone, where life-threatening hyperkalemia (Bushinsky and Gennari, 1978; Massara et al., 1981) or fatal hyponatremia (Gerard and Luisiri, 1997) were observed. These are acute toxicity reports and thus are not useful to evaluate chronic intakes.

Dose–Response Assessment

Studies of oral administration of supplemental arginine in humans (in excess of normal dietary intakes of approximately 5.4 g/100 g of mixed dietary proteins) were not designed to systematically study the toxicity of chronic oral exposure to this amino acid. They are generally of short dura-

tion, do not present dose–response data, and involve small numbers of individuals. Although data from these studies do not support the development of an LOAEL and thus a UL, they do give some indication of the effects from oral arginine intakes of up to 30 g/d. Oral intakes of arginine aspartate providing 5 and 10 g/d of free arginine for 80 days resulted in dose-related weight increases, digestive disturbances, and sleepiness (De Aloysio et al., 1982). Daily intakes of 20 to 30 g of arginine hydrochloride for 7 to 14 days resulted in gastrointestinal disturbances (Barbul et al., 1981, 1990). Such effects were considered mild and responded to lowering the oral dose at various times during the day without affecting the total daily intake.

Although the data appear to indicate minimal effects from arginine supplementation at intakes up to 24.8 g/d of free arginine base, the unconfirmed finding that 30 g/d of arginine for 3 days resulted in a stimulation of tumor growth in breast cancer patients (Park et al., 1992) indicates that dietary supplementation with arginine is not advisable other than in at-risk children with congenital defects of argininosuccinic acid synthetase or argininosuccinase. Therefore, since neither a NOAEL nor LOAEL can be identified for intake of L-arginine from dietary supplements in healthy individuals, a UL could not be determined.

Asparagine

L-Asparagine is a dispensable amino acid, the amide of the dicarboxylic amino acid aspartic acid that is either deaminated during food processing or converted into aspartate by the mucosal cells. Daily human intakes of L-asparagine from dietary protein are about 7.4 g/100 g of dietary protein (LSRO, 1992).

Hazard Identification

There are no data available regarding the toxicity of L-asparagine as a single amino acid supplement, which are relevant for setting an UL.

Dose–Response Assessment

There are no data to characterize a dose–response assessment for supplemental asparagine. However, asparagine is rapidly converted to aspartic acid in the gastrointestinal tract, and the potential adverse health effects from asparagine intake should be considered when developing the UL for aspartic acid.

Aspartic Acid

L-Aspartic acid is a dispensable dicarboxylic amino acid that can be produced by the transamination of oxaloacetic acid arising from glucose breakdown. In the presence of α-ketoglutarate, aspartate is converted to oxaloacetate and glutamate. Based on distribution data from the 1988–1994 NHANES III, mean daily intakes for all life stage and gender groups of aspartic acid from food and supplements are 6.5 g/d (Appendix Table D-4). Men 31 through 50 years of age had the highest intake at the 99th percentile of 15.4 g/d.

Hazard Identification

Adverse Effects in Animals. Neonatal mice (24-hours postpartum) received four subcutaneous injections of L-aspartic acid at 2 g/kg of body weight and were followed for 7 months (Schainker and Olney, 1974). When compared to controls, there was an increase in hypothalmic lesions, obesity, skeletal stunting, and reduced reproductive organ size. Neither blood nor brain concentrations of aspartic acid were measured. Using a similar protocol, Pizzi and coworkers (1978) replicated these findings in mice given gradually increasing doses of monosodium L-aspartic acid (2.2 to 4.4 g/kg of body weight) by subcutaneous injection on days 2 to 11 of life. Animals were followed for 150 days for growth and reproductive behavior and sacrificed between 200 and 300 days of age. Females had reduced litter sizes and fewer pregnancies, and males had reduced fertility. At 190 and 195 days of age, behavioral tests were carried out on the male mice and significant reductions in activity and exploratory behavior were observed in treated animals.

Finkelstein and coworkers (1988) have proposed that some of the adverse effects reported may be the result of insufficient carbohydrate in the diet of mice receiving large acute doses of aspartic acid. When neonatal mice were orally administered 750 mg aspartate/kg of body weight, the characteristic hypothalmic lesions were observed. However, when mice were treated simultaneously by gavage with aspartate and 1 g of Polycose®/kg of body weight, no lesions were found. At a dose of 1 g of aspartate/kg of body weight administered with carbohydrate, there was a reduction of more than 60 percent in the lesions observed compared to the animals treated with aspartate only. Prior injection of insulin (at pharmacological doses) 4 hours before aspartate treatment (750 mg/kg of body weight) reduced, but did not eliminate, the numbers of animals with lesions from 12/12 to 6/10 and decreased the maximum number of necrotic neurons per brain section. This paper reported a threshold dose for a single oral

administration of aspartate producing neurotoxicity in infant mice at 650 mg/kg of body weight (Finkelstein et al., 1988).

Finkelstein and coworkers (1983) also conducted an oral exposure study with L-aspartic acid in slightly older infant mice (8 days old). Aspartic acid was administered by oral gavage at a single dose of 0, 250, 500, 650, 750, or 1,000 mg/kg of body weight. Brain regions were assessed at 5 hours after exposure. No hypothalamic neuronal necrosis was observed in animals treated with a single dose of aspartic acid up to and including 500 mg/kg of body weight. Increasing numbers of animals with hypothalamic lesions and severity of lesions (as assessed by numbers of necrotic neurons per brain section) were observed with increasing doses. In contrast, Reynolds and coworkers (1980) gave infant monkeys a single dose of 2 g/kg of body weight of aspartame by gastric tube and found no hypothalamic damage.

None of the above studies on the effects of aspartic acid on hypothalamic structure and function include data on food consumption of the treated animals and the observations of adverse effects have been made in rodents only. The only study in nonhuman primates found no change in the hypothalamus of infant monkeys given an acute dose of aspartame (Reynolds et al., 1980).

Adverse Effects in Humans. Carlson and coworkers (1989) measured the effects of a 10-g bolus dose of L-aspartic acid on pituitary hormone secretion in healthy male and female adults. Aspartic acid had no consistent effect on any hormone measured.

The potassium magnesium salt of aspartic acid (KMA) has been used as a supplement in exercise regimens (Ahlborg et al., 1968; de Haan et al., 1985; Maughan and Sadler, 1983; Sen Gupta and Srivastava, 1973). Acute oral doses in these studies ranged from approximately 75 to 130 mg of KMA/kg of body weight. While no adverse effects were reported, it was not clear from the reports what adverse effects were examined, and plasma aspartic acid concentrations were not reported.

Since the artificial sweetener aspartame contains about 40 percent aspartic acid, studies on the effects of oral administration of this dipeptide provide useful information on the safety of aspartic acid. Twelve normal adults were orally given 34 mg/kg of body weight of aspartame and the equimolar amount of aspartic acid (13 mg/kg of body weight) in a crossover design (Stegink et al., 1977). No increase in plasma or erythrocyte aspartate was found during the 24 hours after dosing. Plasma phenylalanine levels doubled over fasting concentrations 45 to 60 minutes after dosing with aspartame but returned to baseline after 4 hours. Plasma concentrations of other amino acids remained unchanged.

Frey (1976) studied the effects of the oral administration of aspartame to 126 children and adolescents (30 to 77 mg of aspartame/kg body weight/d,

equal to 12 to 30 mg of aspartate/kg body weight/d) for 13 weeks in a double-blind study. Each child received a physical examination and special eye examinations before and after the study. In addition, tests for liver and renal function, hematological status, and plasma levels of phenylalanine and tyrosine were conducted. The results of all tests were within normal limits. Using a similar study design and a dose of 36 mg aspartame/kg body weight/d (14 mg aspartate/kg/d) given orally to young adults (mean age 19.3 years), Knopp and coworkers (1976) reported no meaningful effects on plasma triglycerides and cholesterol nor on tests measuring hematological parameters, and liver and renal function.

Dose–Response Assessment

All human studies on the effects of aspartic acid involve acute exposures (Ahlborg et al., 1968; Carlson et al., 1989; de Haan et al., 1985; Maughan and Sadler, 1983; Sen Gupta and Srivastava, 1973). There are some subchronic studies on the oral administration of aspartame to humans (Frey, 1976; Stegink et al., 1977); however, in both studies no dose–response data are available. Although some studies in experimental animals were designed to obtain dose–response data, the effects measured were usually found in all doses studied. Therefore, even if the protocol had used dosing regimens appropriate for the development of a UL, no NOAEL was identified.

The most serious endpoint identified in animal studies was the development of neuronal necrosis in the hypothalamus of newborn rodents after dosing with aspartic acid a few days postpartum. This is a property of dicarboxylic amino acids, since glutamic acid dosing in this animal model results in similar necrotic effects (Stegink, 1976; Stegink et al., 1974). There is still some uncertainty over the relevance to humans of the newborn rodent model for assessing the neuronal necrosis potential of aspartic acid. Neuronal necrosis in the hypothalamus was not found in newborn nonhuman primates with levels of plasma dicarboxylic amino acids 10 times those found in newborn mice with neuronal necrosis (Stegink, 1976; Stegink et al., 1974). In addition, human studies where high doses of aspartic acid or aspartame were given failed to find a significant increase in the plasma level of aspartic acid.

In view of the ongoing scientific debate regarding the sensitivity of newborn animals to the consumption of supplemental dicarboxylic amino acids, it is concluded that aspartic acid dietary supplements are not advisable for infants and pregnant women. Although the scientific data are not sufficient to develop a UL for aspartic acid, it should be noted that dietary supplement doses of up to 8 g/d (approximately 120 mg/kg body weight/d) have not resulted in any documented adverse effects.

Branched-Chain Amino Acids (Leucine, Isoleucine, Valine)

The branched-chain amino acids (BCAA)—leucine, isoleucine, and valine—differ from most other indispensable amino acids in that the enzymes initially responsible for their catabolism are found primarily in extrahepatic tissues. Each undergoes reversible transamination, catalyzed by a branched-chain aminotransferase (BCAT), and yields α-ketoisocaproate (KIC, from leucine), α-keto-β-methylvalerate (KMV, from isoleucine), and α-ketoisovalerate (KIV, from valine). Each of these ketoacids then undergoes an irreversible, oxidative decarboxylation, catalyzed by a branched-chain ketoacid dehydrogenase (BCKAD). The latter is a multienzyme system located in mitochondrial membranes (Danner et al., 1979). The products of these oxidation reactions undergo further transformations to yield acetyl CoA, propionyl CoA, acetoacetate, and succinyl CoA; the BCAA are thus keto- and glucogenic.

Based on distribution data from the 1988–1994 NHANES III, mean daily intakes for all life stage and gender groups of leucine (Appendix Table D-10), isoleucine (Appendix Table D-9) and valine (Appendix Table D-19) from food and supplements are 6.1, 3.6, and 4.0 g/d, respectively. Men 51 through 70 years of age had the highest intakes at the 99th percentile for leucine at 14.1 g/d, isoleucine at 8.2 g/d, and valine at 9.1 g/d.

Hazard Identification

Blood and tissue concentrations of BCAA are altered by several disease and abnormal physiological states, including diabetes mellitus, liver dysfunction, starvation, protein–calorie malnutrition, alcoholism, and obesity. These and other conditions sometimes produce drastic alterations in plasma pools of BCAA (Amen and Yoshimura, 1981). Markedly elevated concentrations of BCAA and branched-chain α-keto acids are associated with maple-syrup urine disease; the latter is caused by an inborn error of metabolism in which BCKAD is low or absent (Hutson and Harper, 1981). BCAA imbalances appear not to cause these various diseases and physiological abnormalities, but rather result from them. Numerous investigations of interrelationships of BCAA in patients having one or more of these conditions have been undertaken; their usefulness for assessing risks to healthy populations is in most cases questionable (LSRO, 1992).

One other set of interactions, in this case concerning BCAA and other amino acids, may be of significance in assessing human risks associated with supplementation. Thus, it has been well established that the BCAA compete with other large neutral amino acids (LNAA, particularly tryptophan and tyrosine) for membrane transport (Anderson and Johnston, 1983). Although the BCAA do not act as direct precursors for neurotransmitters,

they can affect transport of certain LNAA across the blood–brain barrier, and thereby influence central nervous system concentrations of certain neurotransmitters. Fernstrom and coworkers (1973) demonstrated, for example, that brain tryptophan levels in rats decrease as the ratio of plasma tryptophan to other LNAA, including the BCAA, declines.

Influences on and Consequences of Metabolism. BCAA-transaminase (BCAAT) exists in at least three different subtypes, and its tissue and cellular distribution varies across species. Differences between rats and humans in this regard raise the possibility that, to the extent that adverse biological effects of the BCAA are dependent upon metabolism, rodent data may not be completely predictive of human responses (Harper et al., 1984). BCKA-dehydrogenase (BCKAD) appears to display similar interspecies variability. It should be noted, however, that in most of the animal studies reported below, it is not entirely clear that these various enzyme activities are critical determinants of the effects seen. Thus, while the animal data must be interpreted with caution, there is no well-established basis for disregarding them entirely.

Among the BCAA, leucine appears to exhibit the highest degree of metabolic activity, although this conclusion may arise at least partially because it has been the subject of more study than isoleucine and valine. Leucine may affect muscle protein turnover (Elia and Livesey, 1983) and stimulate insulin release and tissue sensitivity (Frexes-Steed et al., 1990) as well as somatostatin, glycogen, and zinc release (Danner and Elsas, 1989). It is unclear whether any of these effects have adverse health consequences.

Adverse Effects in Humans. BCAA-enriched protein or amino acid mixtures and, in some cases, BCAA alone, have been used in the treatment of a variety of metabolic disorders. These amino acids have received considerable attention in efforts to reduce brain uptake of aromatic amino acids and to raise low circulating levels of BCAA in patients with chronic liver disease and encephalopathy (LSRO, 1992; Marchesini et al., 1990; Skeie et al., 1990). They have also been used in parenteral nutrition of patients with sepsis and other abnormalities. Although no adverse effects have been reported in these studies, it is not clear that such effects have been carefully monitored (Skeie et al., 1990). Additionally, the data from these studies, because they involved patients with significant and sometimes unusual disease states, are not directly relevant to the problem of assessing risks to normal, healthy humans.

Most studies of the effects of BCAA supplementation involving healthy individuals have been directed at their potential for improving physical or mental performance. It has been hypothesized that BCAA supplementation may reduce muscle catabolism associated with exercise, fasting, or

metabolic stress (Hood and Terjung, 1990), and may reduce fatigue associated with increased central nervous system concentrations of serotonin (Newsholme et al., 1991). The first hypothesis is based on the fact that, in humans, the highest concentrations of BCAAT, the catalyst for BCAA oxidation, are found in muscle; the second hypotheses relates to the fact that high circulatory levels of BCAA interfere with the transport of tryptophan, a serotonin precursor, across the blood–brain barrier. Of the individual BCAA, leucine has received the most study, because of its relatively greater rate of oxidation and because it is associated with the rapid release of glucogenic precursors from muscle.

There have been several reports of clinical trials in which groups of healthy humans, in most cases trained athletes, were given high doses of leucine by intravenous infusion (Abumrad et al., 1982; Elia and Livesey, 1983; Eriksson et al., 1983; Hagenfeldt et al., 1980; Tarnopolsky et al., 1991). Most of the studies involved a single dose of the amino acid. These trials measured physical and mental performance, the impact on blood levels of other amino acids, and in one case, of insulin and glucose output. Although some evidence of reduced muscle catabolism and clear evidence of an impact on blood concentrations of other amino acids (most especially, declines in the other BCAA and several other neutral amino acids) can be found in these reports, none of these provides evidence of an adverse effect of leucine. In fact, in one study glutamine output from forearm muscle was significantly increased (Abumrad et al., 1982). It should be noted, however, that possible side effects in all studies were those that might have been recognized subjectively. No potential functional changes were investigated in any of these studies. Thus, although this collection of studies provides no evidence of adverse effects of high doses of leucine, they are of highly limited value in assessing health risks.

Maple Syrup Urine Disease (MSUD). The most common disorder associated with genetic anomalies in BCAA metabolism is Maple Syrup Urine Disease (MSUD), a condition brought about by lack of adequate function in BCKAD. The disorder, which can be diagnosed in the neonatal period, is characterized by very high plasma levels of BCAA, especially leucine. There are six other forms of the condition that have onsets later in life; these different forms are associated with different abnormal subtypes of BCKAD. MSUD is associated with mental retardation and even early death and is treated by dietary control of BCAA. Other less common metabolic disorders are associated with genetic anomalies in specific enzymes involved in BCAA metabolism (LSRO, 1992; Sweetman, 1989). Information on these disorders provides no data helpful to assessing risks in normal populations; the affected populations require medical management involving severe restriction of BCAA consumption.

Adverse Effects in Animals. There have been a relatively large number of studies in rats of high levels of BCAA administration and, in some cases, of individual BCAA (particularly leucine). The largest share of these investigations followed the observation that the BCAA compete with other LNAA (tryptophan, tyrosine) for the blood–brain carrier system (Ashley and Anderson, 1975; Fernstrom et al., 1973). Of particular interest has been the effect of BCAA-induced changes in LNAA/BCAA ratios, and the effects of LNAA and neurotransmitter brain concentrations on food intake and body weight.

Peters and Harper (1987) demonstrated that protein intake was, however, not affected by BCAA-induced changes in neurotransmitter concentrations. In another study, BCAA dosing lowered plasma and brain concentrations of all indispensable amino acids, but there appeared to be no consistent association of these alterations with protein selection (Anderson et al., 1990). Indeed, given a choice, rats adjusted their dietary intakes in response to supplementation with BCAA.

It appears, however, that the creation of imbalances among the BCAA (e.g., by dosing with high levels of any one of them) may sometimes induce reductions in appetite and growth (Block, 1989; Harper et al., 1984). However, these imbalances, which lead to catabolism of muscle, occur only in rats on marginally adequate protein diets (Block, 1989). Thus, for example, Harper et al. (1984) demonstrated that high dietary levels of leucine suppressed the growth of rats fed a low protein diet, and that the growth suppression could be prevented by supplementation with isoleucine and valine. There have been a number of attempts to study BCAA antagonisms in various tissues, and it appears that muscle is the major contributor to the depletion of isoleucine and valine pools in animals consuming high leucine diets. It is not at all clear that induced BCAA imbalances (except possibly in the case of animals on marginally adequate protein diets) have any adverse effects on growth.

The consequences of reduced brain concentrations of neurotransmitters observed in these animal studies that may be associated with high level BCAA supplementation are not entirely clear, nor is their relevance to humans certain, given the known interspecies differences in the activities and tissue distribution of BCAAT and BCKAD.

Kawabe and coworkers (1996) reported on a subchronic feeding study in which L-isoleucine was administered to groups of 10 rats at dietary concentrations of 0, 1.25, 2.5, 5.0, or 8.0 percent for 13 weeks. The amino acid caused no changes in body weights, food consumption, or hematological parameters. At the highest dietary level, increased urine volumes and relative kidney weights and urine pH, together with some alterations in serum electrolytes, were clearly related to treatment. Minimal changes were observed at the 5.0 percent dietary level, although no histopathological

alterations were observed in any organs of either gender. No alterations of any type were observed at the 2.5 percent dietary level (corresponding to about 1,800 mg/kg/d).

There is evidence that isoleucine acts as a promoter of urinary bladder carcinogenesis in rats (Kakizoe et al., 1983; Nishio et al., 1986). Thus, Kakizoe and coworkers (1983) exposed 6-week-old rats to low doses of N-butyl-N (4-hydroxybutyl) nitrosamine (BHBN), a known initiator of cancer of the urinary bladder, and supplemented their diets with isoleucine or leucine. After 40 weeks, the incidence of papillomas was significantly elevated in rats receiving isoleucine plus BHBN over that observed in the group receiving BHBN alone. In a follow-up study of similar design, Nishio and coworkers (1986) extended the experimental period to 60 weeks and included diets supplemented with 2 or 4 percent isoleucine or leucine. In this case, both dose levels of both amino acids significantly increased bladder carcinoma incidence over groups receiving BHBN alone or groups receiving amino acids alone (see Table 10-28). It thus appears that both leucine and isoleucine are potent promoters of bladder neoplasms in rats at dietary levels of 2 percent and above; a no-effect level was not identified in either of the above studies. There is no evidence that either amino acid is carcinogenic in the absence of an initiating agent.

Developmental Studies. Persaud (1969) reported that leucine is a teratogen when it is administered by intraperitoneal injection in pregnant female rats at doses as low as 15 mg/kg of body weight. The author suggested that the effects, which were multiple and serious, may have resulted from amino acid imbalances that adversely affected protein synthesis dur-

TABLE 10-28 Incidences of Bladder Carcinomas in Rats After 60 Weeks

	Dietary Levels[a]		
Added Substance	0%	2%	4%
Isoleucine or leucine	0	0	0
BHBN	0		
BHBN and isoleucine		46	77
BHBN and leucine		52	74

[a] Dietary level refers to level of amino acid addition. N-butyl-N (4-hydroxybutyl) nitrosamine (BHNB) was administered at a dose below that known to induce bladder tumors. No papillomas or preneoplastic lesions were observed in the control groups or in the amino acid groups.

ing embryonic development. No attempt has been made to determine whether orally administered BCAA have any such effect.

Matsueda and Niiyama (1982) reported on the effects of dietary supplementation with the individual BCAA on maintenance and outcome of pregnancy in rats. Pregnant rats were fed a low protein (6 percent casein) diet supplemented with 5 percent leucine, isoleucine, or valine. Four control groups were administered the 6 percent casein diet; it was stated (without documentation) that the four control groups were given the 6 percent diets in amounts matching those of pair-fed BCAA groups.

Only 11 out of 20 possible pregnancies were maintained in rats administered leucine and isoleucine (2/10 for the leucine groups and 9/10 for the isoleucine groups). No consistent effects on food intake and maternal body weight gain were observed, except for an increase in both in valine-supplemented dams. All fetal weights in the BCAA groups were less than those in ad libitum controls, and fetal weights in the isoleucine and valine groups (but not the leucine groups) were less than those in pair-fed controls; this same pattern was observed when fetal brain weights were analyzed. In all three BCAA-fed groups, brain concentrations of BCAA, histidine, and arginine were greatly increased relative to ad libitum controls, but no such effects were seen for glutamate or phenylalanine.

This study suggests that BCAA when administered to pregnant rats at high doses (dietary levels of 5 percent, corresponding roughly to a daily dose of 2,000 mg/kg) may reduce fetal body weight and relative brain weights and cause sharp increases in brain concentrations of certain amino acids.

Thoemke and Huether (1984) bred rats for three generations on diets enriched with BCAA at 10 g/kg for each amino acid. They also concurrently studied the effects of tryptophan, tyrosine, and phenylalanine supplementation. Feeding of the supplemented diets commenced in both genders two weeks before mating, and continued through three generations (F1, F2, F3). BCAA caused, as expected, decreases in serum levels of tryptophan and tyrosine in F3 dams, and increases in serum glycine. There were, however, no such differences observed in dams of the F1 and F2 generations and no changes in BCAA levels were observed in any generation. In the F1 generation, diets supplemented with BCAA caused significant decreases in brain weights at days 5 and 10 postpartum, but weights were, in all cases, normal by day 20. In the F2 and F3 generations, however, pup brain weights were reduced at day 5 and did not recover by day 20. The concentrations of neurotransmitters were decreased in the brain in all three generations, with the most significant decrease seen for aspartate; no functional measurements were made to assess the possible effects of these declines in neurotransmitter concentrations.

It is thus clear that alterations in brain chemistry, most especially declines in neurotransmitter concentrations and reductions in brain weight, can be seen in offspring of rats fed supplemental BCAA at 30 g/kg diet (10 g/kg for each amino acid). Assuming that female rats weigh an average of 200 g during gestation and consume about 15 g food/d, then the 30 g/kg level of BCAA corresponds to about 450 mg/d, or a daily dose of 2,250 mg/kg (about 750 mg/kg for each amino acid). This study involved only a single level of supplementation, so a "no-effect" level was not identified.

Summary. There are no reports of adverse health effects associated with normal diets containing BCAA, nor have such effects been reported in healthy persons receiving single, infused supplemental BCAA doses as high as 9.75 g. The several studies in which such large supplemental doses were given are highly limited as a basis for reaching conclusions about safety because most involved only a single dose, and none involved an attempt to assess any functional changes. In some human studies, especially those involving high doses of leucine, metabolic alterations were observed, typically expressed as declines in blood levels of LNAA, including neurotransmitter precursors. In one study, insulin sensitivity was increased by BCAA supplementation.

The effects of BCAA on plasma and whole blood concentrations of amino acids have been convincingly and repeatedly observed under a variety of conditions in experimental animal studies. BCAA compete among themselves and with other LNAA, and these competitive interactions may affect growth and appetite (although significant only in animals on diets marginally adequate in protein). Changes in brain concentrations of neurotransmitters precursors (tryptophan and tyrosine) have also been demonstrated at various levels of supplementation.

Developmental studies in rats also reveal the effect of BCAA supplementation on fetal brain concentrations of neurotransmitters in successive generations of animals. Fetal brain weights are also reduced across generations. Decreases in viable pregnancies have been seen in rats administered supplemental leucine and isoleucine.

Leucine and isoleucine have both been shown to promote bladder carcinogenesis in a two-stage rat model. Neither has been demonstrated to be carcinogenically active in the absence of an initiating agent. A recent 13-week study in rats involving isoleucine provided no evidence that this amino acid could induce pre-neoplastic lesions in the urinary bladder, but did reveal that isoleucine could increase urine volume and pH and relative kidney weights at very high dietary levels. Such effects are generally species specific.

Dose–Response Assessment

There are no adequate dose–response data from human or animal studies upon which to base a UL for BCAA. Tumor promotion data from rat studies cannot be used reliably to assess human risk. It is not at all clear that such two-stage models, involving an initiating agent, are relevant to expected conditions of human exposure (Williams and Whysner, 1996).

Cysteine

L-Cysteine, a dispensable amino acid, is formed metabolically from L-methionine and L-serine. It is interconvertible to cystine, and for purposes of this report, L-cysteine and L-cystine are considered together. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of cysteine from food and supplements is 1.0 g/d (Appendix Table D-5). Men 51 through 70 years of age had the highest intakes at the 99th percentile of 2.2 g/d.

Hazard Identification

Acute Adverse Effects in Animals. L-Cysteine is mutagenic in bacteria (Glatt, 1989), but not in mammalian cells (Glatt, 1990). L-Cysteine has been identified as a neuro excitotoxin due to its interaction with N-methyl-D-aspartate (NDMA) receptors (Olney, 1994). Administration to perinatal mice or rats that have an immature blood–brain barrier produces neurotoxicity. Swiss Webster albino mice, 10 to 12 days old, were given a single oral dose of 3 g/kg of body weight of L-cysteine (Olney and Ho, 1970). At 5 hours after treatment, necrosis of hypothalamic neurons was found, as well as retinal lesions.

In male Wistar rats injected intraperitoneally with 1.0 mmol/kg of body weight of cysteine, blood levels of cysteine peaked at about 2 mM at 30 minutes (Calabrese et al., 1997). At 1 hour, exposure produced elevated brain levels of malondialdehyde in the substantia nigra. Subcutaneous injection of 4-day-old Sprague-Dawley rats with L-cysteine 0.5 g/kg of body weight produced no subsequent effect on neurotransmitter or neuropeptide systems in the striatum at 35 days of age (Sivam and Chermak, 1992).

In addition to the report of Olney and Ho (1970) on retinal lesions in mice, subcutaneous injection of 9- to 10-day-old Wistar rats with L-cysteine at 1.2 mg/g body weight produced permanent dystrophy of the inner layers of the retina (Karlsen and Pedersen, 1982).

Acute administration of L-cysteine to rats at a dose of 1.9 g/kg was reported to produce ultrastructural alterations of testicular Sertoli cells and spermatids (Bernacchi et al., 1993).

Acute Adverse Effects in Humans. Single oral doses of 5 and 10 g of L-cysteine have produced nausea and light-headedness in normal humans (Carlson et al., 1989). Reports of chronic administration of L-cysteine to humans were not found.

Dose–Response Assessment

The data on adverse effects of L-cysteine and L-cystine intake from supplements were not considered sufficient for a dose–response assessment and derivation of a UL.

Glutamic Acid, Including Its Sodium Salt

Dietary glutamate is almost totally extracted by the gut and is metabolized rapidly by transamination to α-ketoglutarate, and hence to other intermediary metabolites, notably alanine. The glutamate that escapes capture by the gut is largely taken up by the liver. Glutamate is also synthesized endogenously as a product of transamination of other amino acids during the catabolism of arginine, proline, and histidine, and by the action of glutaminase on glutamine. Its importance in metabolism is that it is a dispensable amino acid that plays a role in the shuttle of nitrogen from amino acid catabolism to urea synthesis through its transamination reamination reactions, and behaves as a neurotransmitter in the brain.

Based on distribution data from the 1988–1994 NHANES III, mean daily intakes for all life stage and gender groups of glutamic acid from food and supplements are approximately 15 g/d (Appendix Table D-6). Men 31 through 50 years of age had the highest intakes at the 99th percentile of 33.7 g/d.

Hazard Identification

Most of the body's free glutamate pool is concentrated in the tissues, especially brain (homogenate, 10 mmol/L; synaptic vesicles, 100 mmol/L) (Meldrum, 2000). By contrast, the concentration of glutamate in the blood is low, typically about 50 μmol/L in the fasting state (Stegink et al., 1982a, 1983a, 1983b). During absorption of a high-protein meal (1g protein/kg/d), there is about a twofold rise in the concentration of glutamic acid in the systemic plasma (Stegink et al., 1982a), returning to baseline 8 hours after the meal. Addition of monosodium glutamate (34 mg/kg) to the meal,

which increased the total glutamate intake by 16 percent, did not result in any further increase in glutamate concentration. However, a larger dose of glutamate, 150 mg/kg/d, which increased the total intake by 69 percent, resulted in a larger increase in glutamate level than the meal alone (by about 50 percent) (Stegink et al., 1983b). Both the peak level achieved and the time course of rise in glutamate level have been shown to be highly dependent on the way in which the glutamate is ingested. A single drink of glutamate (150 mg/kg) in water resulted in a large and rapid rise in the plasma level, peaking at about 12 times the basal level at 45 minutes, and falling quickly thereafter (Stegink et al., 1983a). By contrast, a meal consisting of a liquid formula substantially inhibited the rise in glutamate level (Stegink et al., 1983a).

Adverse Effects in Animals. The adverse effects of glutamic acid and its salts have been reviewed in great detail by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JECFA, 1988) and the American Institute of Nutrition of the Federation of American Societies for Experimental Biology (FASEB) (Raiten et al., 1995). The acute toxicity has been evaluated in several animal species, with LD_{50} values for the oral route of administration ranging from 16,200 to 19,200 mg/kg of body weight in mice, 10,000 to 19,900 mg/kg of body weight in rats, and greater than 2,300 mg/kg of body weight in rabbits (JECFA, 1988), indicating a low level of acute toxicity. Subchronic studies in mice showed an increase in body fat and female sterility in animals that had been subcutaneously injected with glutamate (2.2 to 4.2 g/kg/d) from day 1 to day 10 of life (Olney, 1969). Mice given subcutaneous injections of glutamate (3 g/kg) at 2 days of age were also found to have higher body weights (Olney, 1969). In similar studies on rats given up to 2.0 g/kg/d of glutamate, no effects on body weight, growth, and the volume and weights of several organs were detected (Hara et al., 1962). Other studies showed no effects of glutamate on learning or recovery from electroconvulsive shock (Porter and Griffin, 1950; Stellar and McElroy, 1948).

Longer-term investigations of the effects of glutamate in animals have revealed few adverse effects. In two studies on mice given glutamate (1 or 4 percent of the diet) for 2 years, no increase in the incidence of malignant tumors was shown, and in other respects the animals were normal (Ebert, 1979b; JECFA, 1988). Similar negative results were reported from chronic studies (2 year) in rats given diets containing 0, 0.1, and 0.4 percent glutamate (JECFA, 1988) and in rats given diets containing 0, 1, 2, and 4 percent glutamate (Owen et al., 1978a). In addition, rats given diets with 0.1 or 0.4 percent glutamate showed no adverse effects on fertility and survival of the young (Ebert, 1979a). Moreover, no adverse effects on body weight gain, food consumption, behavior, electrocardiogram, ophthal-

mology, hematology, blood chemistry, organ weights, kidney function, or mortality were observed in dogs given diets with 0, 2.5, 5, or 10 percent glutamate (Owen et al., 1978b).

Adverse Effects in Humans. In humans there is a direct relationship between serum glutamate level and nausea and vomiting with concentrations above 1 mmol/L resulting in vomiting in 50 percent of the individuals (Levey et al., 1949). Glutamate has been used for treatment of a variety of medical conditions. For example, arginine glutamate has been given to treat ammonia intoxication, at a dose of 50 g every 8 hours, but no more than 25 g over 1 to 2 hours in order to avoid vomiting (Martindale, 1967). Chronic glutamate treatment of children with approximately 0.3 g/d of glutamic acid for 6 months (Zimmerman and Burgemeister, 1959) and adults with 45 g/d for 10 weeks (Himwich et al., 1954) showed no adverse effects.

Despite the generally low level of toxicity of glutamic acid demonstrated in the studies on animals and humans, there has remained concern over its continued use as a flavor-enhancing agent. This has been fueled by the discovery that high doses of glutamate can under certain circumstances be neurotoxic (Olney, 1969), and by the reported occurrence of distressing symptoms after the consumption of Asian foods, generally known as Chinese restaurant syndrome. As glutamate is an excitatory neurotransmitter, its potential for neurotoxicity has been studied extensively. In 1957 it was shown that injection of glutamate into suckling mice resulted in degeneration of the inner neural layers of the retina (Lucas and Newhouse, 1957). Later work showed that neuronal destruction also occurred in several regions of the brain in mice after glutamate was parenterally administered (Olney, 1969). Neurons are destroyed by excessive activation by glutamate of excitatory receptors located on the dendrosomal surfaces of neurons (Olney, 1989). The most sensitive areas of the brain are those that are relatively unprotected by the blood–brain barrier, notably the arcuate nucleus of the hypothalamus.

In a detailed analysis of the literature on the neurotoxic effects of glutamate in several species, JECFA (1988) concluded that parenteral administration of glutamate results in reproducible lesions in the central nervous system. However, lesions have never been observed in animals taking glutamate with food, although lesions were noted when the glutamate was given as a large dose by gavage. The neonatal mouse is the most sensitive, the sensitivity declining in weanlings through adults. Moreover, the sensitivity is lower in rats, hamsters, guinea pigs, and rabbits, and effects have rarely been detected in nonhuman primates. In addition, there have been a number of reports of behavioral abnormalities in mice and rats given large doses of glutamate in the early neonatal period (Berry et

al., 1974; Iwata et al., 1979; Nikoletseas, 1977; Olivo et al., 1986; Pinto-Scognamiglio et al., 1972; Poon and Cameron, 1978; Pradhan and Lynch, 1972). There are also reports of reproductive abnormalities in animals given glutamate as neonates (Lamperti and Blaha, 1976, 1980; Matsuzawa et al., 1979; Pizzi et al., 1977). However, a number of other studies have shown no effect on reproduction (Anantharaman, 1979; Prosky and O'Dell, 1972; Yonetani et al., 1979), and one study reported an enhancement of fertility (Semprini et al., 1971).

No signs of neurological damage have been reported in humans. For example, in adult males given a chemically defined diet in which glutamate was the only source of dispensable nitrogen for periods of 14 to 42 days, no changes in neurologic or hepatic function were detected (Bazzano et al., 1970). However, concern was raised by a report that a large dose of glutamate taken orally stimulated the secretion of prolactin and cortisol (Carlson et al., 1989). Earlier findings that rats injected with 1 g/kg of glutamate showed stimulation in the secretion of luteinizing hormone and testosterone (Olney et al., 1976) were interpreted as indicating that the high concentration of glutamate had penetrated the neuroendocrine parts of the hypothalamus. Similarly, it was shown that the same dose of glutamate stimulated release of prolactin and inhibited the release of growth hormone (Terry et al., 1981). The data of Carlson and coworkers (1989) might therefore be interpreted to imply that the elevated concentration of glutamate was penetrating the hypothalamus in humans, and that neuroendocrine disturbances might be a potential consequence. However, a more recent and more strictly controlled study, employing 12.7 g of monosodium glutamate (160 mg/kg of body weight), failed to show significant changes in prolactin and cortisol or of luteinizing hormone, follicle stimulating hormone, growth hormone, or thyroid stimulating hormone (Fernstrom et al., 1996).

Chinese Restaurant Syndrome. Despite the failure to show any neurological damage in humans resulting from glutamate ingestion, there are many reports of symptoms associated with Chinese Restaurant Syndrome, also called MSG (monosodium glutamate) Symptom Complex (Raiten et al., 1995) and Idiosyncratic Intolerance. These symptoms, which have frequently been reported anecdotally after eating Asian food, have been described as a burning sensation at the back of the neck, forearms, and chest; facial pressure or tightness; chest pain; headache; nausea; upper body tingling and weakness; palpitation; numbness in the back of the neck, arms, and back; and drowsiness. After initial reports of this complaint, the symptoms were attributed to the high concentration of MSG in Asian food (Ambos et al., 1968; Schaumburg and Byck, 1968).

Studies indicated that some of those who reported being susceptible were sensitive to less than 3 g, and that all but one of those studied suffered some symptom at sufficiently high doses (Schaumburg et al., 1969). Later work suggested that as many as 25 to 30 percent of the population might be susceptible (Kenney and Tidball, 1972; Reif-Lehrer, 1976). However, a more recent assessment, using a randomized double-blind crossover design in which the characteristic taste of MSG had been carefully disguised, failed to detect any greater incidence of adverse symptoms after consuming glutamate at a meal (1.5 or 3 g) compared with the placebo (Tarasoff and Kelly, 1993). In fact, a significant negative correlation was found between MSG dose and adverse symptoms. In another study, six adults who believed themselves to be sensitive to MSG were challenged with MSG (6 g) or placebo in a strongly flavored drink to mask the MSG in a double-blind study (Kenney, 1986). Four of the six did not react to either MSG or the placebo, whereas the other two reacted to both. Similarly, 24 individuals, 18 of whom believed themselves to be subject to flushing symptoms after eating Chinese food, were challenged with MSG (3 to 18.5 g), but no cases of flushing occurred (Wilkin, 1986).

Thus in 1988, JECFA concluded that properly conducted and controlled clinical trials had failed to establish a relationship between Chinese Restaurant Syndrome and the ingestion of MSG. Subsequently, the FASEB report (Raiten et al., 1995) concluded that there was no scientifically verifiable evidence of adverse effects in most individuals exposed to high levels of MSG.

FASEB (Raiten et al., 1995) also acknowledged that there was sufficient evidence for the existence of a small subgroup of healthy people that were sensitive to MSG, and that they showed symptoms when exposed to an oral dose of 3 g in the absence of food. A recent double-blind, placebo-controlled study on a self-selected group of individuals who believed themselves to be sensitive to MSG has shown that many have the specific symptoms under experimental conditions that they had previously identified as representing their sensitivity to MSG (Yang et al., 1997). They also identified a dose of 2.5 g as the threshold for the induction of symptoms. A more recent study of similar design confirmed these findings, and also reported that responses did not occur when MSG was given with food (Geha et al., 2000). It was also noted that neither persistent nor serious effects from MSG were observed.

Asthma. Triggering of asthma was another, and potentially more serious, symptom of the MSG Symptom Complex listed by FASEB (Raiten et al., 1995). A recent review by Stevenson (2000) analyzed six studies on asthmatic patients, and has pointed out a number of deficiencies. Two studies indicated that single-blind administration of MSG (1.5 to 2.5 g) was

associated with bronchospasm in 14 of 32 (Allen et al., 1987) and 2 of 30 asthmatics (Moneret-Vautrin, 1987). However, the subsequent four studies, employing double-blind approaches, showed no incidence of bronchospasm after MSG ingestion in a total of 45 asthmatic patients (Germano et al., 1991; Schwartzstein et al., 1987; Woessner et al., 1999; Woods et al., 1998). Clearly there is a need for further study in this area to clarify the inconsistencies, but overall they show no convincing evidence that MSG precipitates asthma attacks.

It has also been suggested that MSG exacerbates urticaria. In a single systematic study of patients with chronic idiopathic urticaria, involving single- and double-blind, placebo-controlled challenges, two patients had positive single-blind, but neither had positive double-blind challenges, suggesting that only a very small proportion of the patients, if any, were sensitive to MSG (Simon, 2000).

Dose–Response Assessment

Despite the large number of studies of glutamate toxicity in animals and humans, there appear to be very few adverse effects of L-glutamate consumption that have significance for humans. The possible involvement of glutamate in the MSG Symptom Complex is not yet established and is of little concern, as there is no evidence that it has any impact on overall health. Although there is no convincing evidence that MSG precipitates asthma attacks, this is an area that needs further study. There is continuing controversy about the potential neurotoxicity of glutamate, but data in this area are conflicting and not sufficient for a dose–response assessment. Thus, a UL for L-glutamate from supplements cannot be established at the present time.

Glutamine

L-Glutamine, a dispensable amino acid, taken orally, is metabolized primarily in the splanchnic tissues. After absorption it is extensively metabolized to citrulline, arginine, glutamate, and proline (Reeds and Burrin, 2001). Extensive metabolism also occurs in lymphocytes, kidney, and liver. However, glutamine is simultaneously being synthesized in many tissues, especially muscle, intestine, brain, and liver (LSRO, 1992). The endogenous rate of production by the adult whole body has been estimated to be 60 to 100 g/d (van Acker et al., 1999). The two enzymes primarily responsible for glutamine metabolism are glutaminase, which converts glutamine to glutamate and ammonia, and glutamine synthetase, which synthesizes glutamine from glutamate and ammonia. Because high concentrations of either glutamic acid or ammonia are known to be

neurotoxic, hyperammonemia and hyperglutamic-acidemia are important potential hazards of glutamine consumption.

Hazard Identification

Ziegler and coworkers (1990) performed several individual studies to examine glutamine safety under different circumstances. In the first study, six volunteers were given a single oral dose of glutamine at three different doses (0, 0.1, and 0.3 g/kg of body weight) and monitored for 4 hours. A second study in nine volunteers was performed to investigate the effects of intravenous infusion of glutamine at three doses (0, 0.0125, and 0.025 g/kg body weight/hour) for 4 hours. A third study in seven volunteers was designed to investigate the effects of glutamine-supplemented total parenteral nutrition (TPN) (0, 0.285, and 0.570 g/kg body weight/d) over 5 days. A pharmacokinetic study over 4 hours was also performed in three volunteers. After single oral doses, plasma glutamine concentrations rose in proportion to the dose given, by approximately twofold after 1 hour for the higher dose, and returned to basal within 4 hours. During infusions of glutamine in volunteers, with or without TPN, the plasma glutamine concentration remained elevated by about 30 percent, and no significant changes in plasma glutamate or ammonia were seen. In the two studies of glutamine-supplemented TPN, when serial assessments of mental status were made, there was no evidence of neurotoxicity. Overall, there were no indications of adverse effects at any dose when glutamine was given by either the oral or intravenous route.

Hornsby-Lewis and coworkers (1994) examined the effects of glutamine supplementation in seven patients for up to 4 weeks while receiving TPN plus glutamine at a single dose of 0.285 g/kg body weight/d. There was no significant increase in plasma glutamine concentration, and no other adverse effects were observed, but the authors noted their concern regarding elevations in liver enzymes.

In a randomized, double-blind, controlled study, normal TPN in 60 patients was compared with isonitrogenous TPN including alanyl-glutamine (0.5 g/kg body weight/d, equivalent to 0.34 g/kg/d of glutamine) in 60 patients for 6 days (Jiang et al., 1999). After 6 days the plasma glutamine was increased by 8 percent in the treated group compared with a decrease of 15 percent in the controls. No indications of adverse effects were apparent. Morlion and coworkers (1998) described the results of 28 elective surgery patients given TPN containing alanyl-glutamine (0.3 g/kg/d) or an isonitrogenous control. Plasma glutamine was modestly increased and nitrogen balances were improved compared with the control group. In addition, no adverse effects were observed.

Lacey and coworkers (1996) carried out a randomized, double-blind study of glutamine-supplemented parenteral nutrition (20 percent of amino acids) in 44 preterm neonates for 15 days. On the basis of plasma ammonia and glutamate levels and the absence of clinical signs of neurotoxicity, it was concluded that glutamine at this dose is safe in preterm infants. Also, Roig and coworkers (1996) reported no increases in the concentrations of glutamine, glutamate, and ammonia in very low birthweight infants given enteral supplements of glutamine (0.3 g/kg/d).

It is notable that despite the substantial number of published investigations in which glutamine has been administered to humans, very few, if any adverse effects have been reported. However, the published studies of toxicity have not fully taken account of a number of important factors, including the chronic consumption of glutamine. Glutamine is an important fuel utilized by most rapidly growing tumors (Kovacevic and Morris, 1972), which may deplete the body's ability to provide glutamine (Chen et al., 1991, 1993; Klimberg and McClellan, 1996). Moreover, tumor cells are dependent on a supply of glutamine for growth (Colquhoun and Newsholme, 1997), and the growth rates correlate with the activity of glutaminase (Knox et al., 1969; Linder-Horowitz et al., 1969). Therefore, although providing supplemental glutamine might restore the body glutamine pool, it is also important to examine the possibility that glutamine supplements may promote cancer. However, the evidence points to the contrary, and in vivo studies have not confirmed this suspicion (Klimberg and McClellan, 1996; Souba, 1993). Oral administration of glutamine did not enhance tumor growth in rats in vivo (Klimberg et al., 1990), and may even depress tumor growth (Fahr et al., 1994; Klimberg and McClellan, 1996).

Dose–Response Assessment

The only reported adverse effect of glutamine was an increase in liver enzymes in patients on TPN supplemented with glutamine (0.285 g/kg body weight/d, corresponding to about 20 g/d), which resolved after cessation of treatment (Hornsby-Lewis et al., 1994). However, in other studies, doses up to 0.57 g/kg/d have been given without any adverse effect being reported. Thus, the data on L-glutamine from supplements are conflicting and are not sufficient for a dose–response assessment and derivation of a UL.

Glycine

Glycine is a dispensable amino acid with glycogenic properties. It is the only amino acid that does not have an asymmetric carbon atom, and its metabolism is linked to that of L-serine. Based on distribution data

from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of glycine from food and supplements is 3.2 g/d (Appendix Table D-7). Men 19 through 30 years of age had the highest intakes at the 99th percentile of 7.8 g/d.

Hazard Identification

Adverse Effects in Animals. Growth depression in rats and chicks has been reported after feeding diets containing as much as l0 percent glycine (Harper et al., 1970). Nitrosated glycine can be genotoxic in vitro (Gaspar et al., 1996). It is not, however, mutagenic using a modified Ames test (Hoorn, 1989).

Adverse Effects in Humans. Surgical irrigation solutions of glycine containing 1.5 or 2.2 percent glycine reportedly cause some transient adverse effects (e.g., nausea, diarrhea, and visual disturbances) in patients after transurethral resection of the prostate (Creel et al., 1987; Hahn, 1988; Mizutani et al., 1990; Wang et al., 1989). In patients with schizophrenia, oral doses of approximately 60 g/d of glycine for several weeks failed to reveal adverse effects (Leiderman et al., 1996). There have been no chronic dose–response studies with L-glycine in healthy humans.

Dose–Response Assessment

The data on adverse effects of glycine intake from supplements were considered not sufficient for a dose–response assessment and derivation of a UL.

Histidine

Although histidine is generally regarded as an indispensable amino acid (FAO/WHO/UNU, 1985), removal of histidine from the diet, unlike the eight classical indispensable amino acids, does not induce negative nitrogen balance in the first 10 days (Rose et al., 1951). Further, men fed amino acid-based diets containing 10 g of nitrogen/d devoid of histidine remained in nitrogen balance for up to 2.4 months (Rose, 1957). There were similar reports in women (Reynolds et al., 1958) and children (Nakagawa et al., 1963). Conversely, it has been observed that nitrogen balance becomes gradually negative over a longer period of time and nitrogen balance rapidly became positive upon the reintroduction of histidine (Kopple and Swendseid, 1975).

Histidine is an important component of hemoglobin (8 percent), with the bulk being in the globin portion. The rate of erythropoiesis decreases

and hemoglobin falls in adults on a histidine-free diet that is reversed when histidine is restored (Kopple and Swendseid, 1975). In addition, the dipeptide carnosine, found in skeletal muscle, is a large store of histidine and serve as a source of histidine (Christman, 1971). Because of these large body pools of histidine it takes a prolonged period (more than 60 days) to deplete an adult of histidine. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of histidine from food and supplements is 2.2 g/d (Appendix Table D-8). Men 51 through 70 years of age had the highest intakes at the 99th percentile of 5.2 g/d.

Hazard Identification

Adverse Effects in Animals. Histidine given acutely by intraperitoneal injection or intravenously has been shown to result in changes in the concentration of brain amino acids (Oishi et al., 1989) and histamine (Schwartz et al., 1972). Young rats (4 to 5 weeks old) treated with an inhibitor of histidinase exhibited reduced locomotor activity after an intraperitoneal injection of histidine (250 mg/kg of body weight) (Dutra-Filho et al., 1989). Pilc and coworkers (1982) reported "bizarre behavior" in rats dosed intraperitoneally with histidine (400 to 800 mg/kg of body weight). These effects have not been examined in rats fed L-histidine and are of minimal use in deriving a UL for the chronic exposure of humans to oral L-histidine.

Feeding low-protein diets supplemented with L-histidine for 3 to 4 weeks resulted in significant body weight losses after only several days in rats. However, the effects became less as increasing levels of high-quality protein were added to the diet (Benevenga and Steele, 1984).

Short-term feeding studies (7 to 46 days) in rats have shown growth retardation, hepatomegaly, and hypercholesterolemia at L-histidine levels of approximately 2 to 4 g/kg body weight/d (Harvey et al., 1981; Hitomi-Ohmura et al., 1992; Ohmura et al., 1986; Solomon and Geison, 1978). Harvey and coworkers (1981) reported significantly reduced concentrations of copper and zinc in the plasma and reduced liver concentrations of copper after feeding diets containing 8 percent L-histidine (~4 g/kg body weight/d) for 46 days. Hypercholesterolemia was eliminated by the simultaneous feeding of an L-histidine- and copper-supplemented diet, supporting the hypothesis that the histidine-induced hypercholesterolemia was a result of changes in copper status. Feeding mice 1.3 g L-histidine/kg body weight/d for 21 days resulted in an increase in the absorption and utiliza-

tion of zinc with higher concentrations of zinc in liver, muscle, spleen, and pancreas (van Wouwe et al., 1989).

The long-term toxicity and carcinogenicity of L-histidine monohydrochloride (HMHC) was studied in 50 male and 50 female rats (Ikezaki et al., 1996). Male rats were fed diets containing 0.47 and 0.96 g/kg body weight/d of HMHC for 104 weeks; female rats were fed 0.56 and 1.1 g/kg body weight/d for the same period. No significant treatment-related increases in any tumors were reported when compared to matched controls. No neoplastic changes were reported in controls or treatment groups. In male rats fed 0.96 g of HMHC/kg body weight/d, increases in red blood cell counts, hemoglobin concentrations, and hematocrit were reported. No evidence of sperm granulomas were observed in male rats fed either 1.6 g of HMHC/kg body weight/d for 13 weeks or 0.97 g/kg body weight/d for 104 weeks (Ikezaki et al., 1994, 1996).

Adverse Effects in Humans. Pinals and coworkers (1977) treated 30 rheumatoid arthritis patients and 30 controls daily with capsules containing 4.5 g of L-histidine for 30 weeks in a double-blind trial followed by 19 patients receiving this dosage for 10 additional months in a period of open treatment. It is not clear which adverse effects were examined; however, the authors concluded that no adverse effects of the histidine therapy were noted. In a similar double-blind treatment design, Blumenkrantz and coworkers (1975) treated 42 patients (16 chronic uremic and 26 undergoing maintenance dialysis) with oral doses of 4 g/d of L-histidine for 17.5 weeks. No adverse effects were reported; however, it was not evident from the report which adverse effects were examined.

Studies on the effects of L-histidine on taste and smell acuity in humans have produced conflicting results. Henkin and coworkers (1975) reported decreased taste and smell acuity in six patients given 8 to 65 g of histidine/d for up to 24 days. In view of the increased urinary excretion of zinc and a decreased concentration of serum zinc, the authors postulated that the effects of histidine administration were due to a zinc-deficient state. In a study of eight healthy men given 4 g/d of histidine for 2 weeks, no effects on smell or taste acuity were reported (Schechter and Prakash, 1979). Similarly, Geliebter and coworkers (1981) failed to find any effect of L-histidine on taste and smell after oral dosing of L-histidine between 24 and 64 g/d for 4 weeks. Even at the lower dose (4 g/d), adverse effects such as headaches, weakness, drowsiness, and nausea were reported, while at the highest doses (24 and 64 g/d) anorexia, painful sensations in the eyes, and changes in visual acuity were reported in two females.

Zlotkin (1989) reported an approximate 70 percent increase in urinary zinc excretion in infants on TPN when the fluid contained 165 mg of

histidine/kg body weight/d compared to 95 mg/kg body weight/d in controls. Although the study examined parental administration, it provides further evidence that excess histidine intake in humans can lead to histidine/zinc interactions that might lead to a zinc-deficient state.

Dose–Response Assessment

In experimental animals, the only dose–response study on the chronic oral administration of L-histidine was that of Ikezaki and coworkers (1996). However, this study utilized only two doses, neither of which demonstrated any adverse effects. In addition, no data were reported on the possible effect of the doses on zinc or copper metabolism, an effect reported in both humans and experimental animals.

None of the studies in humans on the effects of L-histidine were designed for developing a UL—they were designed to study the efficacy of utilizing L-histidine as a therapeutic agent in certain disease states. They provide only minimal support for the evaluation of a UL for histidine for apparently healthy individuals. The chronic study on the effects of orally administered histidine in rodents was not considered appropriate for the development of a UL.

There is evidence in humans that doses of L-histidine between 4 and 4.5 g/d over the amounts found in the diet do not result in adverse effects. However, this evidence should be considered tentative given the few individuals studied and lack of dose–response information. There is evidence from studies in experimental animals and humans that intakes of high levels of histidine can alter copper and zinc metabolism. However, the lack of dose–response data precludes identifying the intake concentrations in humans required to elicit such responses.

In conclusion, the available scientific data are not adequate to derive a UL for the chronic oral intake of L-histidine from supplements.

Lysine

L-Lysine, a dibasic amino acid, is indispensable in humans. Lysine, as well as threonine, does not participate in transamination reactions. Carnitine is required for the transport of long-chain fatty acids and is synthesized from lysine and methionine in the liver and kidney (Mayes, 1990). Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of lysine from food and supplements is 5.3 g/d (Appendix Table D-11). Men 51 through 70 years of age had the highest intakes at the 99th percentile of 12.6 g/d.

Hazard Identification

Acute intake of high levels of lysine interferes with dietary protein metabolism and competes with the transport of arginine, suggesting that adverse effects from high levels of lysine are more likely to occur if protein intake or dietary arginine intake is low. Intravenous L-lysine (16.5 to 41.3 g/d in young men) has been shown to inhibit renal tubular protein reabsorption (Mogensen and Solling, 1977). L-Lysine shares an intestinal transport system with L-arginine (McCarthy et al., 1964; Rosenberg et al., 1966), and competes with L-arginine for reabsorption from renal tubules (Kamin and Handler, 1951; Webber et al., 1961). In addition, increased liver total lipids, triacylglycerol, and cholesterol concentrations were seen in rats fed 5 percent L-lysine and 15 percent casein for 2 weeks (Hevia et al., 1980a), an effect that can be reversed by feeding arginine (Hevia et al., 1980b).

Acute Adverse Effects in Animals. Administration of lysine to pregnant rats does not appear to result in gross morphological changes, but higher fetal mortality and decreases in maternal and fetal body and brain weights have been found (Cohlan and Stone, 1961; Funk et al., 1991, Matsueda and Niiyama, 1982).

Adverse Effects in Humans. Studies of lysine tolerance of human infants have not found adverse effects. In one study, six infants (4 to 11 months of age) were given 60 to 1,080 mg of lysine monohydrochloride per 8 ounces of milk in a series of seven incremental doses for 3 to 4 days at each dose. No behavioral effects were observed, nor was there anorexia, diarrhea, or other signs of gastrointestinal upset, and no evidence of cystinuria (Dubow et al., 1958). Similarly, no adverse effects were reported when 1- to 5-month-old infants were given up to 220 mg/kg body weight of lysine for 15 days (Snyderman et al., 1959b).

Higher plasma and urinary concentrations of carnitine were found in six healthy adult males given a single 5-g oral dose of lysine (Vijayasarathy et al., 1987). In another study of eight healthy males (15 to 20 years of age) given a single oral dose of 1.2 g of L-lysine hydrochloride, growth hormone release was not significantly stimulated and no side effects were reported (Isidori et al., 1981).

Several clinical trials of lysine intakes from 0.6 to 3.0 g/d for 3 to 6 months in people with herpes infections have, in general, not found or reported any adverse effects (DiGiovanna and Blank, 1984, 1985; Griffith et al., 1978, 1987; McCune et al., 1984; Milman et al., 1980; Simon et al., 1985; Thein and Hurt, 1984). The one adverse effect was an upset stomach in 3 of 27 patients given 3 g/d of L-lysine hydrochloride for 6 months and in 1 of the 25 controls (Griffith et al., 1987).

A limitation of these clinical studies is that they were done in humans with a disease. Also, the longest study was only 6 months. Finally, only a limited number of endpoints were investigated. McCune and coworkers (1984) reported no effects on plasma sodium, potassium, and chloride in 41 patients treated for 24 weeks with 1,248 mg/d of L-lysine monohydrochloride.

Dose–Response Assessment

As mentioned above, very few adverse effects of L-lysine have been observed in humans or animals after high, mostly acute, doses. Thus, the data on the adverse effects of L-lysine from supplements were considered not sufficient for a dose–response assessment and derivation of a UL for apparently healthy humans.

Methionine

L-Methionine is an indispensable amino acid with glycogenic properties. In animal studies, it has been described as one of the more toxic amino acids (Health and Welfare Canada, 1990). Humans, as well as other mammals, cannot fix inorganic sulfur into organic molecules and must rely on ingested sulfur amino acids, such as methionine, for the synthesis of protein and biologically active sulfur. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of methionine from food and supplements is 1.8 g/d (Appendix Table D-12). Men 51 through 70 years of age had the highest intakes at the 99th percentile of 4.1 g/d.

Hazard Identification

Adverse Effects in Animals. Dietary excesses of L-methionine (2.7 percent of the diet) for 6, 13, or 20 days have been associated with erythrocyte engorgement and accumulation of hemosiderine in rats (Benevenga et al., 1976), and there was a depression of growth and splenic damage. A single dietary dose (2.7 percent of the diet) of L-methionine decreased body growth and also reduced food intake in rats (Steele et al., 1979).

Dietary intakes of 2 to 4 percent of L-methionine caused slight changes in liver cells in rats (Stekol and Szaran, 1962) and slight decreases in liver iron content (Klavins et al., 1963). Darkened spleens caused by increases in iron deposition have been observed in weanling rats fed 1.8 percent methionine diets for 28 days (Celander and George, 1963).

Viau and Leathem (1973) fed pregnant rats 4 percent of their diet as methionine and reported subnormal fetal and placental weights. However, supplemental methionine prevented neural tube defects in rat embryos treated with teratogenic antivisceral yolk sac serum (Fawcett et al., 2000). In the mouse, the administration of methionine reduced experimentally induced spina bifida (Ehlers et al., 1994). Other studies in rodent and primate models support the beneficial effect of methionine supplementation in improving pregnancy outcomes (Chambers et al., 1995; Chatot et al., 1984; Coelho and Klein, 1990; Ferrari et al., 1994; Moephuli et al., 1997).

Adverse Effects in Humans. Single oral doses of about 0.6 g (adults) and 0.08 g (infants) led to increased plasma levels of L-methionine and L-alanine, and decreased plasma concentrations of leucine, isoleucine, valine, tyrosine, tryptophan, and phenylalanine (Stegink et al., 1980, 1982b). Neither report included mention of any adverse effects. Methionine supplements (5 g/d) for periods of weeks were reportedly innocuous in humans (Health and Welfare Canada, 1990). A single oral dose of 7 g has been associated with increased plasma concentrations of methionine and the presence of mixed sulfides (Brattstrom et al., 1984). Single oral doses of 7 g produced lethargy in six individuals and oral administration of 10.5 g of L-methionine to one produced nausea and vomiting (Perry et al., 1965). After an oral administration of 8 g/d of methionine (isomer not specified) for 4 days, serum folate concentrations were decreased in five otherwise healthy adults (Connor et al., 1978).

High doses of methionine (~100 mg/kg of body weight) led to elevated plasma methionine and homocysteine concentrations (Brattstrom et al., 1984, 1990; Clarke et al., 1991; Wilcken et al., 1983). Thus, it was concluded that elevated plasma homocysteine concentrations may be a risk factor for coronary disease (Clarke et al., 1991).

Infants more rapidly metabolized methionine than adults (Stegink et al., 1982b). In women whose average daily intake of methionine was above the lowest quartile of intake (greater than 1.34 g/d), a 30 to 40 percent reduction in neural tube defect-affected pregnancies was observed (Shaw et al., 1997). These reductions were observed for both anencephaly and spina bifida.

Dose–Response Assessment

There are no adequate data to characterize a dose–response relationship for L-methionine. Thus the data on the adverse effects of L-methionine from supplements were considered not sufficient for a dose–response assessment and derivation of a UL for apparently healthy humans.

Phenylalanine

L-Phenylalanine is an indispensable amino acid that has both glycogenic and ketogenic properties. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of phenylalanine from food and supplements is 3.4 g/d (Appendix Table D-13). Men 31 through 50 years of age had the highest intakes at the 99th percentile of 7.7 g/d. About 16 percent of the ingested L-phenylalanine is converted to tyrosine in humans (Clarke and Bier, 1982). Unlike most other amino acids, excessive ingestion of L-phenylalanine can be complicated by the coexistence of genetic disorders.

Hazard Identification

Adverse Effects in Animals. Because of major species differences in phenylalanine metabolism between humans and rodents (Clarke and Bier, 1982; Moldawer et al., 1983), studies in which high doses of L-phenylalanine were fed to rodents could not be utilized in developing a UL for L-phenylalanine. There is one study indicating that high concentrations of L-phenylalanine (3 g/kg body weight/d) fed to monkeys from a few days after birth until 2 or 3 years of age can produce irreversible brain damage (Waisman and Harlow, 1965). However, this study does not provide any dose–response data to utilize in determining a UL.

Adverse Effects in Humans. Data are not available on the effects of chronic ingestion of supplemental phenylalanine by apparently healthy adults. Adverse effects were not evident following acute single oral doses of L-phenylalanine as high as l0 g in 13 adult men (Ryan-Harshman et al., 1987).

Most of the literature on the consumption of large doses of L–phenylalanine consists of studies on the effects of large doses of the artificial sweetener aspartame, which is 50 percent by weight phenylalanine. In adults given oral doses of aspartame ranging from 4 to 200 mg/kg of body weight (2 to 100 mg/kg of body weight L-phenylalanine), dose-related increases in plasma phenylalanine were observed (Filer and Stegink, 1988). Ingestion of single doses up to 60 mg/kg of body weight aspartame (30 mg/kg of body weight L-phenylalanine) by normal weight adults had no effect on behavior or cognitive performance (Lieberman et al., 1988; Stokes et al., 1991).

Dose–Response Assessment

The data on the adverse effects of L-phenylalanine intake from supplements were not available for a dose–response assessment and derivation of a UL in apparently healthy humans.

Special Considerations

Phenylketonuria (PKU) is a genetic disorder that impairs phenylalanine hydroxylase (PAH) activity. Impaired PAH activity allows phenylalanine or its catabolic byproducts to accumulate above normal levels in the plasma during critical periods of brain development. Persistently elevated levels of L-phenylalanine in the plasma before and during infancy and childhood can result in irreversible brain damage, growth retardation, and dermatologic abnormalities if dietary phenylalanine is not restricted within 1 month of birth and continued at least through childhood and adolescence (Scriver et al., 1989). Restriction of phenylalanine intake throughout life in PKU patients is necessary to keep plasma phenylalanine levels low and to promote normal growth and brain development (Scriver et al., 1989). If PKU is detected early and treated effectively through strict metabolic control, infants can live a normal life-span (Hellekson, 2001). In the United States, approximately 1 of every 15,000 infants is born with PKU (Hellekson, 2001).

Maternal hyperphenylalaninemia due to deficient phenylalanine hydroxylation is a recognized human teratogen (Lenke and Levy, 1980). Because phenylalanine is actively transported across the placenta (Kudo and Boyd, 1990), a pregnant woman with PKU exposes her developing fetus to potentially harmful levels of phenylalanine. High maternal plasma phenylalanine levels are associated with high incidence of mental retardation, microcephaly, intrauterine growth delay, and congenital heart malformations in the fetus (Scriver et al., 1989). The fetal demand for phenylalanine for protein synthesis is exceeded by the placental supply of L-phenylalanine by only a small amount, suggesting that the safety margin of placental transfer may be small (Chien et al., 1993). Careful maintenance of plasma phenylalanine levels in the mother through dietary control, before conception and throughout her pregnancy, may prevent the teratogenic effects of phenylalanine.

Proline

L-Proline is a dispensable amino acid that can be formed from and converted to glutamic acid. It is incorporated into tissue proteins and can then be hydroxylated to form hydroxproline. Both proline and hydroxy-

proline are found in large quantities in collagen. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of proline from food and supplements is 5.2 g/d (Appendix Table D-14). Boys 14 through 18 years of age had the highest intakes at the 99th percentile of 12.0 g/d.

Hazard Identification

Adverse Effects in Animals. There are minimal data on the adverse effects of L-proline in either experimental animals or humans. Female Sprague Dawley rats given L-proline in drinking water for 1 month (mean dose 50 mg/kg body weight/d) did not exhibit any adverse effects (Kampel et al., 1990).

Genetically hyperprolinemic mice have 6 to 7 times the concentration of proline in the brain as control animals and 10 times the concentration of proline in plasma (Baxter et al., 1985). Hyperprolinemic hybrid mice took longer than control mice to make an initial avoidance response to foot shock in a T-maze and required more trials before learning of the avoidance response (Baxter et al., 1985). No other studies in experimental animals relevant to the evaluation of the toxicity of orally administered L-proline or hydroxyproline could be found.

Adverse Effects in Humans. The only study in humans on the effects of long-term oral administration of proline was a clinical study on the efficacy of proline (isomer not specified) to alter the progression of gyrate atrophy of the choriod and retina (Hayasaka et al., 1985). Four patients (aged 4 to 32 years) were treated with doses of proline between 2 and 10 g/d (mode = 3 g/d) for up to 5 years. No overt adverse effects were reported; however, it was uncertain from the paper which effects were studied.

Dose–Response Assessment

The data on adverse effects of L-proline intake from supplements were not available for a dose–response assessment and derivation of a UL in apparently healthy individuals.

Serine

Serine is a dispensable amino acid that is synthesized endogenously from D-3 phosphoglycerate or glycine. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of serine from food and supplements is 3.5 g/d (Appendix

Table D-15). Men 31 through 50 years of age had the highest intakes at the 99th percentile of 7.9 g/d.

Hazard Identification

Adverse Effects in Animals. There are limited data pertaining to the toxicity of supplemental serine. In rats given 100 mg/d of L-serine via stomach tube for 14 days, there was a decrease in food consumption but no other effects were noted (Artom et al., 1945). Other authors (Morehead et al., 1945; Wachstein, 1947) have reported that supplemental L-serine at levels as low as 10 mg/d resulted in decreased appetite, increased mortality, and renal necrosis in rats.

Adverse Effects in Humans. In four healthy adults given a single oral dose of 15 g of serine, no adverse effects were reported (Pepplinkhuizen et al., 1980). There are no studies in humans that would permit an evaluation of the possible adverse effects of repeated administration, thus the safety of repeated dose oral administration of supplemental serine cannot be assessed.

Dose–Response Assessment

The data on the adverse effects of L-serine intake from supplements were not available for a dose–response assessment and derivation of a UL in apparently healthy humans.

Threonine

L-Threonine is a large neutral amino acid that is indispensable. Similar to L-lysine, L-threonine does not take part in transamination reactions. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of threonine from food and supplements is 3.0 g/d (Appendix Table D-16). Men 51 through 70 years of age had the highest intakes at the 99th percentile of 7.1 g/d.

Hazard Identification

Adverse Effects in Animals. In rats fed 5 percent threonine added to a 10 percent casein diet, weight gain was reduced compared to controls fed casein alone but there were no changes in liver weight or hepatic DNA, RNA, or protein content (Muramatsu et al., 1971). The evidence indicates

that excess threonine is converted to carbohydrate, liver lipids, and carbon dioxide (Yamashita and Ashida, 1971). In weanling pigs, adding 0.5, 1, 2, or 4 percent L-threonine to a 20 percent crude protein diet did not change weight gain, food intake, and gain:feed ratios in comparison to the controls (Edmonds and Baker, 1987; Edmonds et al., 1987).

Adverse Effects in Humans. No data were found on apparently healthy humans given oral L-threonoine supplements. However, L-threonine has been used clinically with the aim of increasing glycine concentrations in the cerebral spinal fluid of patients with spasticity. When given in amounts of 4.5 to 6.0 g/d for 14 days, no adverse clinical effects were noted in such patients (Growdon et al., 1991). Threonine also has been studied in low birth weight infants. In a study of 163 low birth weight infants, threonine serum concentrations were directly related to the threonine concentrations of the formula (Rigo and Senterre, 1980). The authors suggested that threonine intakes should not exceed about 140 mg/kg body weight/d for premature infants.

Dose–Response Assessment

The data on the adverse effects of L-threonine intake from supplements were not available for a dose–response assessment and derivation of a UL in apparently healthy humans.

Tryptophan

L-Tryptophan, an indispensable amino acid, serves as a precursor for several small molecules of functional significance including the vitamin niacin, the neurotransmitter serotonin, the metabolite tryptamine, and the pineal hormone melatonin. Increases in tryptophan have been shown to increase synthesis of the neurotransmitters in brain, blood, and other body organs (Fregly et al., 1989; Leathwood and Fernstrom, 1990; Young, 1986). Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of tryptophan from food and supplements is 0.9 g/d (Appendix Table D-17). Men 51 through 70 years of age had the highest intakes at the 99th percentile of 2.1 g/d.

Hazard Identification

Adverse Effects in Animals. Several rodent studies have demonstrated that supplementation of low-protein diets with L-tryptophan (5 percent) reduces food intake and weight gain over a 4-day to 4-week period

(reviewed by Benevenga and Steele, 1984; Harper et al., 1970). Funk and coworkers (1991) found that rats given a 20 percent casein diet supplemented with 14.3 percent tryptophan for 4 weeks developed scaly tails and thinning hair. However, no adverse effects were seen when the diets contained 1.4 or 2.9 percent L-tryptophan. No cancers were observed over an 80-week period when rats were fed diets containing 2 percent added L-tryptophan (Birt et al., 1987). Addition of 2.5 or 5 percent L-tryptophan to diets of rats and mice for 2 years resulted in decreased body weights of male and female mice and male (but not female) rats (DHEW, 1978). In pigs, supplementation with 0.1 or 1 percent L-tryptophan for up to 40 days did not affect weight gain, but 2 or 4 percent decreased weight gain and 4 percent also decreased food intake (Chung et al., 1991).

Several developmental studies have shown that maternal weight gain is impaired and fetal weight is reduced when maternal rat diets are supplemented with 1.4 to 6 percent L-tryptophan (Funk et al., 1991; Matsueda and Niiyama, 1982). Decreased brain weights were observed when 1 percent L-tryptophan was added to diets of male and female rats beginning 2 weeks before mating (Thoemke and Huether, 1984). Over three successive generations, brain weights decreased with each generation.

Adverse Effects in Humans. Serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in human blood and brain cerebrospinal fluid (CSF) increase after tryptophan loading, which is similar to the effects of L-tryptophan in animals. For example, Young and Gauthier (1981) found elevations in blood and 5-HIAA and CSF serotonin after single doses of 3 or 6 g of L-tryptophan. However, Benedict and coworkers (1983) conducted a double-blind, placebo-controlled trial in six normal men fed 3 g/d of L-tryptophan in divided doses with meals for 3 days, and found a 113 percent elevation in plasma tryptophan, but no changes in platelet or plasma serotonin or in plasma catecholamines. They also found no changes in urinary catecholamines. Additionally, they found no changes in blood pressure, heart rate, plasma sodium levels or 24-hour sodium excretion in urine.

L-Tryptophan administration (2 g) as a single dose before a meal has been found to decrease subjective hunger ratings, food intake, and alertness in men (Hrboticky et al., 1985), but not women (Leiter et al., 1987). Hrboticky and coworkers (1985) also tested 15 humans only once with 0, 1, 2, and 3 g of L-tryptophan. Individuals receiving 2 and 3 g of L-tryptophan had decreased hunger and alertness and increased faintness and dizziness. Administration of 1 g of L-tryptophan with 10 g of carbohydrates before each meal (3 g L-tryptophan/d) for 3 months did not affect body weight of obese humans (Strain et al., 1985). Wurtman and coworkers (1981) found that daily doses of 2.4 g of L-tryptophan for 2 weeks did not produce a significant reduction in the consumption of carbohydrate snacks in the

majority of the 24 individuals. Ten healthy adults given 5 g of L-tryptophan in a double-blind, placebo-controlled study reported severe nausea and headache and increased drowsiness soon after ingestion (Greenwood et al., 1975).

Smith and Prockop (1962) reported sustained nystagmus and drowsiness in seven adults given 70 and 90 mg/kg of body weight of L-tryptophan orally in single doses, but found that these effects were absent at 30 or 50 mg/kg. However, Lieberman and coworkers (1985) reported decreased self-ratings of vigor and alertness and increased subjective fatigue in 20 men treated with a single oral dose of 50 mg/kg of tryptophan. Yuwiler and coworkers (1981) also reported that five individuals given 50 or 100 mg/kg/d of L-tryptophan as a single dose or 50 mg/kg/d for 14 days experienced prolonged lethargy and drowsiness within 30 minutes of ingestion under all loading conditions.

Newborns (2 to 3 days of age) given infant formula supplemented with L-tryptophan (about 20 mg) were found to enter active and then quiet sleep sooner than those newborns given unsupplemented formula (Yogman and Zeisel, 1983). In a later study, these same investigators found that low doses of L-tryptophan have sleep-inducing properties in full-term infants (Yogman and Zeisel, 1985).

Finally, retrospective studies covering the time prior to the 1989 eosinophilia-myalgia syndrome (EMS) outbreak—thought to be caused by L-tryptophan contaminated with 1,1-ethylidene-bis[tryptophan] (EBT)—indicate that use of L-tryptophan alone may increase risk of eosinophilic fasciitis. Blauvelt and Falanga (1991) examined the history of L-tryptophan use in 49 patients with cutaneous fibrosis. Eleven of 17 patients reported using L-tryptophan prior to onset of eosinophilic fasciitis, as did two of ten patients with localized scleroderma, but use of L-tryptophan was not reported in any of 22 patients with systemic sclerosis. Intakes of L-tryptophan were from 0.5 to 5 g/d for 1 month to 10 years before the onset of symptoms of eosinophilic fasciitis were noted. L-tryptophan use in individuals with localized scleroderma occurred for 3 or 10 months before onset of symptoms, and intake was 1.5 to 2 g/d. Hibbs and coworkers (1992) found that 9 of 45 patients with eosinophilic fasciitis used 0.5 to 2.5 g/d of L-tryptophan for 1 month to 10 years before symptom onset. It is unknown whether or not these results occurred because of impurities in the L-tryptophan supplements.

Dose–Response Assessment

Taken together, the above studies in humans indicate that relatively short-term (acute and subacute) use of L-tryptophan is associated with appetite suppression, nausea, and drowsiness. However, in the absence of

data on the relationship between chronic consumption of L-tryptophan and the potential for adverse effects, and because of continuing uncertainty of the possible role of L-tryptophan in the development of eosinophilic fasciitis, a UL was not established for L-tryptophan.

Tyrosine

L-Tyrosine is considered a conditionally indispensable amino acid because it can be synthesized from L-phenylalanine in the liver. L-Tyrosine is a precursor of several biologically active substances, including catecholamine neurotransmitters, hormones, and melanin skin pigments. Based on distribution data from the 1988–1994 NHANES III, the mean daily intake for all life stage and gender groups of tyrosine from food and supplements is 2.8 g/d (Appendix Table D-18). Men 31 through 50 years of age had the highest intakes at the 99th percentile of 6.4 g/d.

Hazard Identification

Adverse Effects in Animals. In the mouse with elevated tissue concentrations of tyrosine, decarboxylation to tyramine becomes increasingly important, reducing lethality (David et al., 1974). Evidence has been provided that hepatic biotransformation of tyrosine yields a toxic metabolite, possibly an epoxide (David, 1976).

In rodents, feeding studies document the toxicity of large supplements of L-tyrosine (Benevenga and Steele, 1984; Harper et al., 1970). Effects of tyrosine on weight-gain suppression are a function of the protein content of the diet. For example, feeding rats a low-protein diet, 6 or 9 percent casein, retarded weight gain over a 3-week period. This effect of an inadequate protein intake was exacerbated by the addition of 3 to 8 percent L-tyrosine in the diet (Ip and Harper, 1973). With higher protein intakes of 15 or 24 percent, the toxicity of L-tyrosine was reduced, although 8 percent L-tyrosine still resulted in mortality.

Gipson and coworkers (1975) reported corneal lesions in rats fed L-tyrosine. Subsequently, Rich and coworkers (1973) reported that young adult Simonson albino or Long-Evans pigmented rats fed diets containing 5 or 10 percent L-tyrosine for 15 days developed elevated serum tyrosine levels and experienced reduced weight gain. At 10 percent L-tyrosine in the diet, deaths occurred within 10 days. Corneal disease was the first sign of toxicity; keratopathy was evident by 1 day and progressed in severity. The change began as haziness of the cornea, followed by opacities, and vascularization. The corneal changes were accompanied by elevations of tyrosine concentration in the aqueous humor.

Thoemke and Huether (1984) fed 8-week-old rats a diet containing 2.64 percent L-tyrosine. Rats were fed the diet for 2 weeks prior to mating and continually for three generations. No details were reported on overall pregnancy outcomes or behavioral endpoints. Brain weight was measured in all three generations and no differences were seen except at days 15 and 20 postpartum in the F2 generation (92 and 95 percent of controls). Serum concentration of tyrosine of F3 generation rats was increased at postnatal day 5.

Adverse Effects in Humans. No adverse effects have been reported for L-tyrosine from food. Large single doses of L-tyrosine (500 mg/kg/d) or smaller daily doses (100 mg/kg/d) have not been associated with any adverse affects (Al-Damluji et al., 1988; Glaeser et al., 1979; Sole et al., 1985). Nevertheless, the occurrence of corneal and skin lesions in humans with the autosomal recessive genetic disease, tyrosinemia II, in which tyrosine blood levels can be elevated tenfold, suggests that high chronic intakes leading to high-sustained concentrations of tyrosine in plasma and tissues may have adverse effects.

Single oral doses of 100 or 150 mg/kg of L-tyrosine administered to humans lead to a two- to threefold increase in plasma tyrosine concentrations (Cuche et al., 1985; Glaeser et al., 1979) and in urinary excretion of catecholamines and their metabolites (Alonso et al., 1982). Similar amounts given over the day in three equal doses result in similar increments in plasma tyrosine (Benedict et al., 1983; Melamed et al., 1980) and an increase in urinary catecholamines (Agharanya et al., 1981) and their metabolites (Alonso et al., 1982). Tyrosine given at 7.5 g/d decreased both free and conjugated plasma norepinephrine concentrations (Benedict et al., 1983). An increase in the dopamine metabolite, homovanillic acid, has been found in cerebral spinal fluid after L-tyrosine loads (Growdon et al., 1982).

Loads of L-tyrosine of 100 to 150 mg/kg/d have not been found to have any adverse effects on physiological systems (Benedict et al., 1983; Glaeser et al., 1979; Neri et al., 1995). In 13 patients with mild hypertension and given 2.5 g of L-tyrosine for 2 weeks, blood tyrosine was doubled 2 hours after the supplement, but no differences were found in systolic, diastolic, or mean blood pressure, heart rate, or plasma nonepinephrine (Sole et al., 1985). No data on blood concentrations in humans predictive of corneal lesions are available.

Dose–Response Assessment

In the absence of dose response data to describe more fully the relationship of L-tyrosine loads to alteration in catecholamine synthesis, physiological function, and corneal lesions in humans, a UL for L-tyrosine cannot be set for apparently healthy humans.

Intake Assessment

Although no ULs could be set for any of the amino acids, highest median and 99th percentile intakes for the amino acids are found in Table 10-29. All amino acids had their highest median intake for any life stage and gender group in men aged 19 through 30 years. The highest intakes at the 99th percentile were also found in men, with those 51

TABLE 10-29 Highest Median and 99th Percentile of Usual Daily Intake of Amino Acids, United States, Third National Health and Nutrition Examination Survey, 1998–1994

Amino Acid	Highest Median Intake[a] (g/d)	Highest 99th Percentile of Intake (g/d)
Alanine	5.2	8.5[b]
Arginine	5.9	10.1[b]
Aspartic acid	9.2	15.4[c]
Cysteine	1.4	2.2[b]
Glutamic acid	21.1	33.7[c]
Glycine	4.6	7.8[a]
Histidine	3.1	5.2[b]
Isoleucine	4.9	8.2[b]
Leucine	8.5	14.1[b]
Lysine	7.5	12.6[b]
Methionine	2.5	4.1[b]
Phenylalanine	4.8	7.7[c]
Proline	7.2	12.0[d]
Serine	4.8	7.9[c]
Threonine	4.2	7.1[b]
Tryptophan	1.3	2.1[b]
Tyrosine	3.9	6.4[c]
Valine	5.5	9.1[b]

[a] Males, 19–30 y.
[b] Males, 51–70 y.
[c] Males, 31–50 y.
[d] Males, 14–18 y.
NOTE: Data are from Appendix Tables D-2 through D-19.

through 70 years of age consuming the highest intakes for the majority of the amino acids surveyed.

Risk Characterization

Since there is no evidence that amino acids derived from usual or even high intakes of protein from food present any risk, attention was focused on intakes of the L-form of the amino acid found in dietary protein and amino acid supplements. Even from well-studied amino acids, adequate dose–response data from human or animal studies on which to base a UL were not available, but this does not mean that there is no potential for adverse effects resulting from high intakes of amino acids from dietary supplements. Since data on the adverse effects of high levels of amino acids intakes from dietary supplements are limited, caution may be warranted.

RESEARCH RECOMMENDATIONS

- Research is needed on high-protein intakes (>145 mg N/kg/d) in relationship to positive nitrogen balance and requirement estimates, metabolic and possible toxic effects in children and adults, and pathways affected by these high intakes.
- More data are needed on indispensable amino acid requirements for infants, children, and adolescents, as they are very sparse.
- Few studies on additional needs for protein during pregnancy, including estimates of changes in efficiency of conversion of dietary protein for maintenance and tissue accretion, are available. Thus more studies conducted during the length of pregnancy are needed.
- New methods, other than nitrogen balance, need to be validated to determine protein requirements, particularly in regard to long-term health.
- The role of the gastrointestinal system in the metabolism of amino acids, the nature of the amino acid losses, and the extent of synthesis of indispensable amino acids need to be investigated.
- Research on adaptation mechanisms at various intakes of protein is needed.
- Currently protein data for the elderly are sparse and more data are needed. Available data for the very elderly, namely those from 80 to 100 years of age, consists of only two or three adults in their early 80s, and thus studies conducted with this age group need to be done.
- Since ULs could not be established for any of the amino acids (some of which are known to result in toxic effects at high doses) due to insuffi-

cient data on dose–response relationships, more data are needed on adverse effects of high intakes of amino acids.

REFERENCES

Abumrad NN, Robinson RP, Gooch BR, Lacy WW. 1982. The effect of leucine infusion on substrate flux across the human forearm. *J Surg Res* 32:453–463.

Agharanya JC, Alonso R, Wurtman RJ. 1981. Changes in catecholamine excretion after short-term tyrosine ingestion in normally fed human subjects. *Am J Clin Nutr* 34:82–87.

Ahlborg B, Ekelund LG, Nilsson CG. 1968. Effect of potassium-magnesium-aspartate on the capacity for prolonged exercise in man. *Acta Physiol Scand* 74:238–245.

Al-Damluji S, Ross G, Touzel R, Perrett D, White A, Besser GM. 1988. Modulation of the actions of tyrosine by α-2-adrenoceptor blockade. *Br J Pharmacol* 95:405–412.

Alexander D, Ball MJ, Mann J. 1994. Nutrient intake and haematological status of vegetarians and age-sex matched omnivores. *Eur J Clin Nutr* 48:538–546.

Allen DH, Delohery J, Baker G. 1987. Monosodium L-glutamate-induced asthma. *J Allergy Clin Immunol* 80:530–537.

Allen JC, Keller RP, Archer P, Neville MC. 1991. Studies in human lactation: Milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutr* 54:69–80.

Allison SP. 1992. The uses and limitations of nutritional support. *Clin Nutr* 11:319–330.

Allison SP. 1995. Cost-effectiveness of nutritional support in the elderly. *Proc Nutr Soc* 54:693–699.

Alonso R, Gibson CJ, Wurtman RJ, Agharanya JC, Prieto L. 1982. Elevation of urinary catecholamines and their metabolites following tyrosine administration in humans. *Biol Psychiatry* 17:781–790.

Ambos M, Leavitt NR, Marmorek L, Wolschina SB. 1968. Sin Cib-Syn: Accent on glutamate. *N Engl J Med* 279:105.

Amen RJ, Yoshimura NN. 1981. The pharmacology of branched-chain amino acids. *Nutr Pharmacol* 4:73–116.

Anantharaman K. 1979. In utero and dietary administration of monosodium L-glutamate to mice: Reproductive performance and development in a multigeneration study. In: Filer LJ, ed. *Glutamic Acid: Advances in Biochemistry and Physiology.* Pp. 231–253.

Anderson DM, Williams FH, Merkatz RB, Schulman PK, Kerr DS, Pittard WB. 1983. Length of gestation and nutritional composition of human milk. *Am J Clin Nutr* 37:810–814.

Anderson GH, Johnston JL. 1983. Nutrient control of brain neurotransmitter synthesis and function. *Can J Physiol Pharmacol* 61:271–281.

Anderson GH, Atkinson SA, Bryan MH. 1981. Energy and macronutrient content of human milk during early lactation from mothers giving birth prematurely and at term. *Am J Clin Nutr* 34:258–265.

Anderson SA, Tews JK, Harper AE. 1990. Dietary branched-chain amino acids and protein selection by rats. *J Nutr* 120:52–63.

ARS (Agricultural Research Service). 2001. *USDA Nutrient Database for Standard Reference, Release 14*. Online. U.S. Department of Agriculture. Available at http://www.nal.usda.gov/fnic/foodcomp/Data/SR14/sr14.html. Accessed July 3, 2002.

Artom C, Fishman WH, Morehead RP. 1945. The relative toxicity of l- and dl-serine in rats. *Proc Soc Exp Biol Med* 60:284–287.

Ashley DV, Anderson GH. 1975. Correlation between the plasma tryptophan to neutral amino acid ratio and protein intake in the self-selecting weanling rat. *J Nutr* 105:1412–1421.

Atkinson SA, Anderson GH, Bryan MH. 1980. Human milk: comparison of the nitrogen composition in milk from mothers of premature and full-term infants. *Am J Clin Nutr 33:811-814*.

Ball MJ, Bartlett MA. 1999. Dietary intake and iron status of Australian vegetarian women. *Am J Clin Nutr* 70:353–358.

Barbul A. 1986. Arginine: Biochemistry, physiology, and therapeutic implications. *J Parenter Enteral Nutr* 10:227–238.

Barbul A, Wasserkrug HL, Sisto DA, Seifter E, Rettura G, Levenson SM, Efron G. 1980. Thymic stimulatory actions of arginine. *J Parenter Enteral Nutr* 4:446–449.

Barbul A, Sisto DA, Wasserkrug HL, Efron G. 1981. Arginine stimulates lymphocyte immune response in healthy human beings. *Surgery* 90:244–251.

Barbul A, Lazarou SA, Efron DT, Wasserkrug HL, Efron G. 1990. Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery* 108:331–337.

Barr SI, Broughton TM. 2000. Relative weight, weight loss efforts and nutrient intakes among health-conscious vegetarian, past vegetarian and nonvegetarian women ages 18 to 50. *J Am Coll Nutr* 19:781–788.

Basile-Filho A, Beaumier L, El-Khoury AE, Yu Y, Kenneway M, Gleason RE, Young VR. 1998. Twenty-four-hour L-[1-^{13}C]tyrosine and L-[3,3-$^{2}H_2$]phenylalanine oral tracer studies at generous, intermediate, and low phenylalanine intakes to estimate aromatic amino acid requirements in adults. *Am J Clin Nutr* 67:640–659.

Batshaw ML, Wachtel RC, Thomas GH, Starrett A, Brusilow SW. 1984. Arginine-responsive asymptomatic hyperammonemia in the premature infant. *J Pediatr* 105:86–91.

Baxter CF, Baldwin RA, Davis JL, Flood JF. 1985. High proline levels in the brains of mice as related to specific learning deficits. *Pharmacol Biochem Behav* 22:1053–1059.

Bazzano G, D'Elia JA, Olson RE. 1970. Monosodium glutamate: Feeding of large amounts in man and gerbils. *Science* 169:1208–1209.

Benabe JE, Martinez-Maldonado M. 1998. The impact of malnutrition on kidney function. *Mineral Electrolyte Metab* 24:20–26.

Benedict CR, Anderson GH, Sole MJ. 1983. The influence of oral tyrosine and tryptophan feeding on plasma catecholamines in man. *Am J Clin Nutr* 38:429–435.

Benevenga NJ, Steele RD. 1984. Adverse effects of excessive consumption of amino acids. *Annu Rev Nutr* 4:157–181.

Benevenga NJ, Yeh M-H, Lalich JJ. 1976. Growth depression and tissue reaction to the consumption of excess dietary methionine and S-methyl-L-cysteine. *J Nutr* 106:1714–1720.

Bergner H, Schwandt H, Kruger U. 1990. Determination of a prececal N-absorption from natural feed by ^{15}N-labeled laboratory rats using the isotope diluation method. *Arch Tierernahr* 40:569–582.

Bernacchi AS, DeFerreyra EC, DeCastro CR, Castro JA. 1993. Ultrastructural alterations in testes from rats treated with cysteine. *Biomed Environ Sci* 6:172–178.

Berry HK, Butcher RE, Elliot LA, Brunner RL. 1974. The effect of monosodium glutamate on the early biochemical and behavioral development of the rat. *Dev Psychobiol* 7:165–173.

Birt DF, Julius AD, Hasegawa R, St. John M, Cohen S. 1987. Effect of L-tryptophan excess and vitamin B_6 deficiency on rat urinary bladder cancer promotion. *Cancer Res* 47:1244–1250.

Bistrian BR. 1990. Recent advances in parenteral and enteral nutrition: A personal perspective. *J Parenteral Enteral Nutr* 14:329–334.

Blauvelt A, Falanga V. 1991. Idiopathic and L-tryptophan-associated eosinophilic fasciitis before and after L-tryptophan contamination. *Arch Dermatol* 127:1159–1166.

Block KP. 1989. Interactions among leucine, isoleucine, and valine with special reference to the branched-chain amino acid antagonism. In: Friedman M, ed. *Absorption and Utilization of Amino Acids,* Vol. 1. Boca Raton, FL: CRC Press. Pp. 229–244.

Blumenkrantz MJ, Shapiro DJ, Swendseid ME, Kopple JD. 1975. Histidine supplementation for treatment of anaemia of uraemia. *Br Med J* 2:530–533.

Borgonha S, Regan MM, Oh SH, Condon M, Young VR. 2002. Threonine requirement of healthy adults, derived with a 24-h indicator amino acid balance technique. *Am J Clin Nutr* 75:698–704.

Brattstrom LE, Hardebo JE, Hultberg BL. 1984. Moderate homocysteinemia—A possible risk factor for arteriosclerotic cerebrovascular disease. *Stroke* 15:1012–1016.

Brattstrom L, Israelsson B, Norrving B, Bergqvist D, Thorne J, Hultberg B, Hamfelt A. 1990. Impaired homocysteine metabolism in early-onset cerebral and peripheral occlusive arterial disease. *Atherosclerosis* 81:51–60.

Bross R, Ball RO, Pencharz PB. 1998. Development of a minimally invasive protocol for the determination of phenylalanine and lysine kinetics in humans during the fed state. *J Nutr* 128:1913–1919.

Bross R, Ball RO, Clarke JTR, Pencharz PB. 2000. Tyrosine requirements in children with classical PKU determined by indicator amino acid oxidation. *Am J Physiol* 278:E195–E201.

Brunton JA, Ball RO, Pencharz PB. 1998. Determination of amino acid requirements by indicator amino acid oxidation: Applications in health and disease. *Curr Opin Clin Nutr Metab Care* 1:449–453.

Brunton JA, Bertolo RF, Pencharz PB, Ball RO. 1999. Proline ameliorates arginine deficiency during enteral but not parenteral feeding in neonatal piglets. *Am J Physiol* 277:E223–E231.

Brusilow SW, Horwich AL. 1989. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease, 6th ed.* New York: McGraw-Hill. Pp. 629–663.

Brusilow SW, Danney M, Waber LJ, Batshaw M, Burton B, Levitsky L, Roth K, McKeethren C, Ward J. 1984. Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. *N Engl J Med* 310:1630–1634.

Burke BS, Harding VV, Stuart HC. 1943. Nutrition studies during pregnancy. IV. Relation of protein content of mother's diet during pregnancy to birth length, birth weight, and condition of infant at birth. *J Pediatr* 23:506–515.

Bushinsky DA, Gennari FJ. 1978. Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 89:632–634.

Butte NF, Garza C, Johnson CA, O'Brian Smith E, Nichols BL. 1984a. Longitudinal changes in milk composition of mothers delivering preterm and term infants. *Early Hum Dev* 9:153–162.

Butte NF, Garza C, O'Brian Smith E, Nichols BL. 1984b. Human milk intake and growth in exclusively breast-fed infants. *J Pediatr* 104:187–195.

Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ. 2000. Body composition during the first 2 years of life: An updated reference. *Pediatr Res* 47:578–585.

Calabrese V, Rausa N, Antico A, Mangiameli S, Rizza V. 1997. Cysteine-induced enhancement of lipid peroxidation in substantia nigra: Comparative effect with exogenous administration of reduced glutathione. *Drugs Exp Clin Res* 23:25–31.

Calloway DH. 1974. Nitrogen balance during pregnancy. In: Winnick M, ed. *Nutrition and Fetal Development*, Vol. 2. New York: John Wiley and Sons. Pp. 79–94.

Calloway DH, Margen S. 1971. Variation in endogenous nitrogen excretion and dietary nitrogen utilization as determinants of human protein requirement. *J Nutr* 101:205–216.

Calloway DH, Odell AC, Margen S. 1971. Sweat and miscellaneous nitrogen losses in human balance studies. *J Nutr* 101:775–786.

Campbell WW, Evans WJ. 1996. Protein requirements of elderly people. *Eur J Clin Nutr* 50:S180–S185.

Campbell WW, Crim MC, Dallal GE, Young VR, Evans WJ. 1994. Increased protein requirements in elderly people: New data and retrospective reassessments. *Am J Clin Nutr* 60:501–509.

Campbell WW, Crim MC, Young VR, Joseph LJ, Evans WJ. 1995. Effects of resistance training and dietary protein intake on protein metabolism in older adults. *Am J Physiol* 268:E1143–E1153.

Campbell WW, Trappe TA, Wolfe RR, Evans WJ. 2001. The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. *J Gerontol A Biol Sci Med Sci* 56:M373–M380.

Carlson HE, Miglietta JT, Roginsky MS, Stegink LD. 1989. Stimulation of pituitary hormone secretion by neurotransmitter amino acids in humans. *Metabolism* 38:1179–1182.

Carmichael S, Abrams B, Selvin S. 1997. The pattern of maternal weight gain in women with good pregnancy outcomes. *Am J Public Health* 87:1984–1988.

Castaneda C, Charnley JM, Evans WJ, Crim MC. 1995a. Elderly women accommodate to a low-protein diet with losses of body cell mass, muscle function, and immune response. *Am J Clin Nutr* 62:30–39.

Castaneda C, Dolnikowski GG, Dallal GE, Evans WJ, Crim MC. 1995b. Protein turnover and energy metabolism of elderly women fed a low-protein diet. *Am J Clin Nutr* 62:40–48.

Celander DR, George MJ. 1963. Dietary interrelationships of ethionine and methionine in the weanling rat. *Biochem J* 87:143–146.

Chambers BJ, Klein NW, Nosel PG, Khairallah LH, Romanow JS. 1995. Methionine overcomes neural tube defects in rat embryos cultured on sera from laminin-immunized monkeys. *J Nutr* 125:1587–1599.

Chatot CL, Klein NW, Clapper ML, Resor SR, Singer WD, Russman BS, Holmes GL, Mattson RH, Cramer JA. 1984. Human serum teratogenicity studied by rat embryo culture: Epilepsy, anticonvulsant drugs, and nutrition. *Epilepsia* 25:205–216.

Chen MK, Salloum RM, Austgen TR, Bland JB, Bland KI, Copeland EM, Souba WW. 1991. Tumor regulation of hepatic glutamine metabolism. *J Parenter Enteral Nutr* 15:159–164.

Chen MK, Espat NJ, Bland KI, Copeland EM, Souba WW. 1993. Influence of progressive tumor growth on glutamine metabolism in skeletal muscle and kidney. *Ann Surg* 217:655–667.

Cheng AH, Gomez A, Bergan JG, Lee TC, Monckeberg F, Chichester CO. 1978. Comparative nitrogen balance study between young and aged adults using three levels of protein intake from a combination wheat-soy-milk mixture. *Am J Clin Nutr* 31:12–22.

Chien PFW, Smith K, Watt PW, Scrimgeour CM, Taylor DJ, Rennie MJ. 1993. Protein turnover in the human fetus studied at term using stable isotope tracer amino acids. *Am J Physiol* 265:E31–E35.

Chipponi JX, Bleier JC, Santi MT, Rudman D. 1982. Deficiencies of essential and conditionally essential nutrients. *Am J Clin Nutr* 35:1112–1116.

Cho ES, Anderson HL, Wixom RL, Hanson KC, Krause GF. 1984. Long-term effects of low histidine intake on men. *J Nutr* 114:369–384.

Christman AA. 1971. Determination of anserine, carnosine, and other histidine compounds in muscle extractives. *Anal Biochem* 39:181–187.

Chung TK, Gelberg HB, Dorner JL, Baker DH. 1991. Safety of L-tryptophan for pigs. *J Anim Sci* 69:2955–2960.

Ciechanover A, DiGiuseppe JA, Bercovich B, Orian A, Richter JD, Schwartz AL, Brodeur GM. 1991. Degradation of nuclear oncoproteins by the ubiquitin system in vitro. *Proc Natl Acad Sci USA* 88:139–143.

Clarke JTR, Bier DM. 1982. The conversion of phenylalanine to tyrosine in man. Direct measurement by continuous intravenous tracer infusions of L-[ring-$^{2}H_{5}$] phenylalanine and L-[1-^{13}C] tyrosine in the postabsorptive state. *Metabolism* 31:999–1005.

Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, Graham I. 1991. Hyperhomocysteinemia: An independent risk factor for vascular disease. *N Engl J Med* 324:1149–1155.

Coelho CN, Klein NW. 1990. Methionine and neural tube closure in cultured rat embryos: Morphological and biochemical analyses. *Teratology* 42:437–451.

Cohlan SQ, Stone SM. 1961. Effects of dietary and intraperitoneal excess of L-lysine and L-leucine on rat pregnancy and offspring. *J Nutr* 74:93–95.

Colquhoun A, Newsholme EA. 1997. Aspects of glutamine metabolism in human tumour cells. *Biochem Mol Biol Int* 41:583–596.

Connor H, Newton DJ, Preston FE, Woods HF. 1978. Oral methionine loading as a cause of acute serum folate deficiency: Its relevance to parental nutrition. *Postgrad Med J* 54:318–320.

Cordain L, Miller JB, Eaton SB, Mann N, Holt SH, Speth JD. 2000. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. *Am J Clin Nutr* 71:682–692.

Corish CA, Kennedy NP. 2000. Protein-energy undernutrition in hospital in-patients. *Br J Nutr* 83:575–591.

Creel DJ, Wang JM, Wong KC. 1987. Transient blindness associated with transurethral resection of the prostate. *Arch Ophthalmol* 105:1537–1539.

Cuche JL, Prinseau J, Selz F, Ruget G, Tual JL, Reingeissen L, Devoisin M, Baglin A, Guedon J, Fritel D. 1985. Oral load of tyrosine or L-dopa and plasma levels of free and sulfoconjugated catecholamines in healthy men. *Hypertension* 7:81–89.

Cuervo AM, Dice JF. 1998. Lysosomes, a meeting point of proteins, chaperones, and proteases. *J Mol Med* 76:6–12.

Danner DJ, Elsas LF. 1989. Disorders of branched chain amino acid and keto acid metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease, 6th ed.*, Vol. I. New York: McGraw-Hill. Pp. 671–692.

Danner DJ, Lemmon SK, Besharse JC, Elsas LJ. 1979. Purification and characterization of branched chain alpha-ketoacid dehydrogenase from bovine liver mitochondria. *J Biol Chem* 254:5522–5526.

Darling PB, Grunow J, Rafii M, Brookes S, Ball RO Pencharz PB. 2000. Threonine dehydrogenase is a minor degradative pathway of threonine catabolism in human adults. *Am J Physiol* 278:E877–E884.

Darragh AJ, Hodgkinson SM. 2000. Quantifying the digestibility of dietary protein. *J Nutr* 130:1850S–1856S.

Darragh AJ, Moughan PJ. 1998. The amino acid composition of human milk corrected for amino acid digestibility. *Br J Nutr* 80:25–34.

Das TK, Waterlow JC. 1974. The rate of adaptation of urea cycle enzymes, aminotransferases and glutamic dehydrogenase to changes in dietary protein intake. *Br J Nutr* 32:353–373.

David JC. 1976. Evidence for the possible formation of a toxic tyrosine metabolite by the liver microsomal drug metabolizing system. *Naunyn Schmiedebergs Arch Pharmacol* 292:79–86.

David JC, Dairman W, Udenfriend S. 1974. Decarboxylation to tyramine: A major route of tyrosine metabolism in mammals. *Proc Natl Acad Sci USA* 71:1771–1775.

Davis TA, Nguyen HV, Garcia-Bravo R, Fiorotto ML, Jackson EM, Lewis DS, Lee DR, Reeds PJ. 1994. Amino acid composition of human milk is not unique. *J Nutr* 124:1126–1132.

De Aloysio D, Mantuano R, Mauloni M, Nicoletti G. 1982. The clinical use of arginine aspartate in male infertility. *Acta Eur Fertil* 13:133–167.

de Blaauw I, Deutz NEP, Von Meyenfeldt MF. 1996. In vivo amino acid metabolism of gut and liver during short and prolonged starvation. *Am J Physiol* 270:G298–G306.

de Haan A, van Doorn JE, Westra HG. 1985. Effects of potassium + magnesium aspartate on muscle metabolism and force development during short intensive static exercise. *Int J Sports Med* 6:44–49.

Dekker J, Aelmans PH, Strous GJ. 1991. The oligomeric structure of rat and human gastric mucins. *Biochem J* 277:423–427.

de Lange CFM, Sauer WC, Mosenthin R, Souffrant WB. 1989. The effect of feeding different protein-free diets on the recovery and amino acid composition of endogenous protein collected from the distal ileum and feces in pigs. *J Anim Sci* 67:746–754.

de Vrese M, Frik R, Roos N, Hagemeister H. 2000. Protein-bound D-amino acids, and to a lesser extent lysinoalanine, decrease true ileal protein digestibility in minipigs as determined with ^{15}N-labeling. *J Nutr* 130:2026–2031.

Dewey KG, Lönnerdal B. 1983. Milk and nutrient intake of breast-fed infants from 1 to 6 months: Relation to growth and fatness. *J Pediatr Gastroenterol Nutr* 2:497–506.

Dewey KG, Finley DA, Lönnerdal B. 1984. Breast milk volume and composition during late lactation (7–20 months). *J Pediatr Gastroenterol Nutr* 3:713–720.

Dewey KG, Beaton G, Fjeld C, Lönnerdal B, Reeds P. 1996. Protein requirements of infants and children. *Eur J Clin Nutr* 50:S119–S150.

DHEW (U.S. Department of Health, Education and Welfare). 1978. *Bioassay of L-Tryptophan for Possible Carcinogenicity.* National Cancer Institute Technical Report Series No. 71. Washington, DC: U.S. Government Printing Office.

Di Buono M, Wykes LJ, Ball RO, Pencharz PB. 2001. Total sulfur amino acid requirement in young men determined by indicator amino acid oxidation with L-[1-^{13}C] phenylalanine. *Am J Clin Nutr* 74:756–760.

Diem K. 1962. *Documenta Geigy Scientific Tables, 6th ed.* Ardsley, NY: Geigy Pharmaceuticals. Pp.528.

DiGiovanna JJ, Blank H. 1984. Failure of lysine in frequently recurrent herpes simplex infection. Treatment and prophylaxis. *Arch Dermatol* 120:48–51.

DiGiovanna JJ, Blank H. 1985. Failure of lysine? *Arch Dermatol* 121:21.

Drago F, Continella G, Alloro MC, Auditore S, Pennisi G. 1984. Behavioral effects of arginine in male rats. *Pharmacol Res Commun* 16:899–907.

Dubois S, Dougherty C, Duquette M-P, Hanley JA, Moutquin J-M. 1991. Twin pregnancy: The impact of the Higgins Nutrition Intervention Program on maternal and neonatal outcomes. *Am J Clin Nutr* 53:1397–1403.

Dubois S, Coulombe C, Pencharz P, Pinsonneault O, Duquette M-P. 1997. Ability of the Higgins Nutrition Intervention Program to improve adolescent pregnancy outcome. *J Am Diet Assoc* 97:871–878.

Dubow E, Maher A, Gish D, Erk V. 1958. Lysine tolerance in infants. *J Pediatr* 52:30–37.

Duffy B, Gunn T, Collinge J, Pencharz PB. 1981. The effect of varying protein quality and energy intake on the nitrogen metabolism of parenterally fed very low birthweight (<1600 g) infants. *Pediatr Res* 15:1040–1044.

Dutra-Filho CS, Wannmacher CM, Pires RF, Gus G, Kalil AM, Wajner M. 1989. Reduced locomotor activity of rats made histidinemic by injection of histidine. *J Nutr* 119:1223–1227.

Ebert AG. 1979a. The dietary administration of L-monosodium glutamate, DL-monosodium glutamate, and L-glutamic acid to rats. *Toxicol Lett* 3:71–78.

Ebert AG. 1979b. The dietary administration of monosodium glutamate or glutamic acid to C-57 black mice for 2 years. *Toxicol Lett* 3:65–70.

Edmonds MS, Baker DH. 1987. Amino acid excesses for young pigs: Effects of excess methionine, tryptophan, threonine or leucine. *J Anim Sci* 64:1664–1671.

Edmonds MS, Gonyou HW, Baker DH. 1987. Effect of excess levels of methionine, tryptophan, arginine, lysine or threonine on growth and dietary choice in the pig. *J Anim Sci* 65:179–185.

Egana JI, Fuentes A, Uauy R. 1984. Protein needs of Chilean pre-school children fed milk and soy protein isolate diets. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo, Japan: United Nations University Press. Pp. 249–257.

Egana JI, Uauy R, Cassorla X, Barrera G, Yanez E. 1992. Sweet lupin protein quality in young men. *J Nutr* 122:2341–2347.

Ehlers K, Drews E, Nau H. 1994. The amino acid methionine reduces the valproic acid-induced spina bifida rate in the mouse. *Teratology* 50:28A.

Elia M, Livesey G. 1983. Effects of ingested steak and infused leucine on forelimb metabolism in man and the fate of the carbon skeletons and amino groups of branched-chain amino acids. *Clin Sci* 64:517–526.

El-Khoury AE, Fukagawa NK, Sanchez M, Tsay RH, Gleason RE, Chapman TE, Young VR. 1994a. The 24-h pattern and rate of leucine oxidation, with particular reference to tracer estimates of leucine requirements in healthy adults. *Am J Clin Nutr* 59:1012–1020.

El-Khoury AE, Fukagawa NK, Sanchez M, Tsay RH, Gleason RE, Chapman TE, Young VR. 1994b. Validation of the tracer-balance concept with reference to leucine: 24-h intravenous tracer studies with L-[1-^{13}C]leucine and [^{15}N-^{15}N]urea. *Am J Clin Nutr* 59:1000–1011.

El-Khoury AE, Forslund A, Olsson R, Branth S, Sjodin A, Andersson A, Atkinson A, Selvaraj A, Hambraeus L, Young VR. 1997. Moderate exercise at energy balance does not affect 24-h leucine oxidation or nitrogen retention in healthy men. *Am J Physiol* 273:E394–E407.

El-Khoury AE, Pereira PC, Borgonha S, Basile-Filho A, Beaumier L, Wang SY, Metges CC, Ajami AM, Young VR. 2000. Twenty-four-hour oral tracer studies with L-[1-^{13}C]lysine at a low (15 $mg \cdot kg^{-1} \cdot d^{-1}$) and intermediate (29 $mg \cdot kg^{-1} \cdot d^{-1}$) lysine intake in healthy adults. *Am J Clin Nutr* 72:122–130.

Ellis KJ, Shypailo RJ, Abrams SA, Wong WW. 2000. The reference child and adolescent models of body composition. A contemporary comparison. *Ann NY Acad Sci* 904:374–382.

Emerson K, Poindexter EL, Kothari M. 1975. Changes in total body composition during normal and diabetic pregnancy: Relation to oxygen consumption. *Obstet Gynecol* 45:505–511.

Eriksson LS, Hagenfeldt L, Felig P, Wahren J. 1983. Leucine uptake by splanchnic and leg tissues in man: Relative independence of insulin levels. *Clin Sci* 65:491–498.

Fahr MJ, Kornbluth J, Blossom S, Schaeffer R, Klimberg VS. 1994. Harry M. Vars Research Award. Glutamine enhances immunoregulation of tumor growth. *J Parenter Enteral Nutr* 18:471–476.

FAO (Food and Agriculture Organization). 2000. *The State of Food and Agriculture 2000.* Rome: FAO.

FAO/Agrostat. 1991. *Computerized information series No. 1. Food balance sheets.* Rome: FAO.

FAO/WHO (World Health Organization). 1965. *Protein Requirements.* Report of a Joint FAO/WHO Expert Group. Technical Report Series No. 37. Rome: FAO.

FAO/WHO. 1973. *Energy and Protein Requirements.* Report of a Joint FAO/WHO Ad Hoc Expert Committee. Technical Report Series No. 522. Geneva, Switzerland: WHO.

FAO/WHO. 1991. *Protein Quality Evaluation.* FAO Food and Nutrition Paper 51. Rome: FAO.

FAO/WHO/UNU (United Nations University). 1985. *Energy and Protein Requirements.* Report of a Joint FAO/WHO/UNU Expert Consultation. Technical Report Series No. 724. Geneva, Switzerland: WHO.

Fawcett LB, Pugarelli JE, Brent RL. 2000. Effects of supplemental methionine on antiserum-induced dysmorphology in rat embryos cultured in vitro. *Teratology* 61:332–341.

Fee BA, Weil WB. 1963. Body composition of infants of diabetic mothers by direct analysis. *Ann NY Acad Sci* 110:869.

Fernstrom JD, Larin F, Wurtman RJ. 1973. Correlations between brain tryptophan and plasma neutral amino acid levels following food consumption in rats. *Life Sci* 13:517–524.

Fernstrom JD, Cameron JL, Fernstrom MH, McConaha C, Weltzin TE, Kaye WH. 1996. Short-term neuroendocrine effects of a large oral dose of monosodium glutamate in fasting male subjects. *J Clin Endocrinol Metab* 81:184–191.

Ferrari DA, Gilles PA, Klein NW, Nadler D, Weeks BS, Lammi-Keefe CJ, Hillman RE, Carey SW, Ying Y-K, Maier D, Olsen P, Wemple DW, Greenstein R, Muechler EK, Miller RK, Mariona FG. 1994. Rat embryo development on human sera is related to numbers of previous spontaneous abortions and nutritional factors. *Am J Obstet Gynecol* 170:228–236.

Filer LJ, Stegink LD. 1988. Effect of aspartame on plasma phenylalanine concentration in humans. In: Wurtman RJ, Ritter-Walker E, eds. *Dietary Phenylalanine and Brain Function.* Boston: Birkhauser. Pp. 18–40.

Finkelstein MW, Daabees TT, Stegink LD, Applebaum AE. 1983. Correlation of aspartate dose, plasma dicarboxylic amino acid concentration, and neuronal necrosis in infant mice. *Toxicology* 29:109–119.

Finkelstein MW, Daabees TT, Stegink LD, Applebaum AE. 1988. Aspartate-induced neuronal necrosis in infant mice: Protective effect of carbohydrate and insulin. *J Toxicol Environ Health* 23:395–406.

Fisher H, Brush MK, Griminger P, Sostman ER. 1967. Nitrogen retention in adult man: A possible factor in protein requirements. *Am J Clin Nutr* 20:927–934.

Fomon S. 1991. Requirements and recommended dietary intakes of protein during infancy. *Pediatr Res* 30:391–395.

Forbes GB. 1987. *Human Body Composition: Growth, Aging, Nutrition, and Activity.* New York: Springer-Verlag.

Forslund AH, Hambraeus L, Olsson RM, El-Khoury AE, Yu Y-M, Young VR. 1998. The 24-h whole body leucine and urea kinetics at normal and high protein intakes with exercise in healthy adults. *Am J Physiol* 275:E310–E320.

Forsum E, Sadurskis A, Wager J. 1988. Resting metabolic rate and body composition of healthy Swedish women during pregnancy. *Am J Clin Nutr* 47:942–947.

Fregly MJ, Rowland NE, Sumners C. 1989. Effect of chronic dietary treatment with L-tryptophan on spontaneous salt appetite of rats. *Pharmacol Biochem Behav* 33:401–406.

Frexes-Steed M, Warner ML, Bulus N, Flakoll P, Abumrad NN. 1990. Role of insulin and branched-chain amino acids in regulating protein metabolism during fasting. *Am J Physiol* 258:E907–E917.

Frey GH. 1976. Use of aspartame by apparently healthy children and adolescents. *J Toxicol Environ Health* 2:401–415.

Frisancho AR, Matos J, Flegel P. 1983. Maternal nutritional status and adolescent pregnancy outcome. *Am J Clin Nutr* 38:739–746.

Fuller MF, Garlick PJ. 1994. Human amino acid requirements: Can the controversy be resolved? *Annu Rev Nutr* 14:217–241.

Fuller MF, Reeds PJ. 1998. Nitrogen cycling in the gut. *Annu Rev Nutr* 18:385–411.

Funk DN, Worthington-Roberts B, Fantel A. 1991. Impact of supplemental lysine or tryptophan on pregnancy course and outcome in rats. *Nutr Res* 11:501–512.

Furst P. 1989. Amino acid metabolism in uremia. *J Am Coll Nutr* 8:310–323.

Garlick PJ, Reeds PJ. 1993. Proteins. In: Garrow JS, James WPT, Ralph A, eds. *Human Nutrition and Dietetics.* Edinburgh: Churchill Livingstone. Pp. 56–76.

Garlick PJ, McNurlan MA, Patlak CS. 1999. Adaptation of protein metabolism in relation to limits to high dietary protein intake. *Eur J Clin Nutr* 53:S34–S43.

Garza C, Scrimshaw NS, Young VR. 1976. Human protein requirements: The effect of variations in energy intake within the maintenance range. *Am J Clin Nutr* 29:280–287.

Garza C, Scrimshaw NS, Young VR. 1977a. Human protein requirements: A long-term metabolic nitrogen balance study in young men to evaluate the 1973 FAO/WHO safe level of egg protein intake. *J Nutr* 107:335–352.

Garza C, Scrimshaw NS, Young VR. 1977b. Human protein requirements: Evaluation of the 1973 FAO/WHO safe level of protein intake for young men at high energy intakes. *Br J Nutr* 37:403–420.

Garza C, Scrimshaw NS, Young VR. 1978. Human protein requirements: Interrelationships between energy intake and nitrogen balance in young men consuming the 1973 FAO/WHO safe level of egg protein, with added nonessential amino acids. *J Nutr* 108:90–96.

Gaspar J, Laires A, Va S, Pereira S, Mariano A, Quina M, Rueff J. 1996. Mutagenic activity of glycine upon nitrosation in the presence of chloride and human gastric juice: A possible role in gastric carcinogenesis. *Teratog Carcinog Mutagen* 16:275–286.

Gattas V, Barrera GA, Riumallo JS, Uauy R. 1990. Protein-energy requirements of prepubertal school-age boys determined by using the nitrogen-balance response to a mixed-protein diet. *Am J Clin Nutr* 52:1037–1042.

Gattas V, Barrera GA, Riumallo JS, Uauy R. 1992. Protein-energy requirements of boys 12-14 y old determined by using the nitrogen-balance response to a mixed-protein diet. *Am J Clin Nutr* 56:499–503.

Gaudichon C, Mahe S, Benamouzig R, Luengo C, Fouillet H, Dare S, Van Oycke M, Ferriere F, Rautureau J, Tome D. 1999. Net postprandial utilization of [15N]-labeled milk protein nitrogen is influenced by diet composition in humans. *J Nutr* 129:890–895.

Gausserès N, Mahé S, Benamouzig R, Luengo C, Ferriere F, Rautureau J, Tomé D. 1997. [^{15}N]-Labeled pea flour protein nitrogen exhibits good ileal digestibility and postprandial retention in humans. *J Nutr* 127:1160–1165.

Geha RS, Beiser A, Ren C, Patterson R, Greenberger P, Grammer LC, Ditto AM, Harris KE, Shaughnessy MA, Yarnold PR, Corren J, Saxon A. 2000. Multicenter, double blind, placebo-controlled, multiple-challenge evaluation of reported reactions to monosodium glutamate. *J Allergy Clin Immunol* 106:973–980.

Geliebter AA, Hashim SA, Van Itallie TB. 1981. Oral L-histidine fails to reduce taste and smell acuity but induces anorexia and urinary zinc excretion. *Am J Clin Nutr* 34:119–120.

Genuth SM. 1973. Effects of oral alanine administration in fasting obese subjects. *Metabolism* 22:927–937.

Genuth SM, Castro J. 1974. Effect of oral alanine on blood beta-hydroxybutyrate and plasma glucose, insulin, free fatty acids, and growth hormone in normal and diabetic subjects. *Metabolism* 23:375–386.

Gerard JM, Luisiri A. 1997. A fatal overdose of arginine hydrochloride. *Clin Toxicol* 35:621–625.

Germano P, Cohen SG, Hahn B, Metcalfe DD. 1991. An evaluation of clinical reactions to monosodium glutamate (MSG) in asthmatics, using a blinded placebo-controlled challenge. *J Allergy Clin Immunol* 87:177.

Gersovitz M, Motil K, Munro HN, Scrimshaw NS, Young VR. 1982. Human protein requirements: Assessment of the adequacy of the current Recommended Dietary Allowance for dietary protein in elderly men and women. *Am J Clin Nutr* 35:6–14.

Gipson IK, Burns RP, Wolfe-Lande JD. 1975. Crystals in corneal epithelial lesions of tyrosine-fed rats. *Invest Ophthalmol* 14:937–941.

Glaeser BS, Melamed E, Growdon JH, Wurtman RJ. 1979. Evaluation of plasma tyrosine after a single oral dose of L-tyrosine. *Life Sci* 25:265–271.

Glatt H. 1989. Mutagenicity spectra in *Salmonella typhimurium* strains of glutathione, L-cysteine and active oxygen species. *Mutagenesis* 4:221–227.

Glatt H. 1990. Endogenous mutagens derived from amino acids. *Mutat Res* 238:235–243.

Glyn JR, Lipton JM. 1981. Effects of central administration of alanine on body temperature of the rabbit: Comparisons with the effects of serine, glycine and taurine. *Brain Res Bull* 6:467–472.

Goldberg AL, Rock KL. 1992. Proteolysis, proteasomes and antigen presentation. *Nature* 357:375–379.

Greenwood MH, Lader MH, Kantameneni BD, Curzon G. 1975. The acute effects of oral (–)-tryptophan in human subjects. *Br J Clin Pharmacol* 2:165–172.

Griffith RS, Norins AL, Kagan C. 1978. A multicentered study of lysine therapy in herpes simplex infection. *Dermatologica* 156:257–267.

Griffith RS, Walsh DE, Myrmel KH, Thompson RW, Behforooz A. 1987. Success of L-lysine therapy in frequently recurrent herpes simplex infection. Treatment and prophylaxis. *Dermatologica* 175:183–190.

Grossie VB, Nishioka K, Ajani JA, Ota DM. 1992. Substituting ornithine for arginine in total parenteral nutrition eliminates enhanced tumor growth. *J Surg Oncol* 50:161–167.

Growdon JH, Melamed E, Logue M, Hefti F, Wurtman RJ. 1982. Effects of oral L-tyrosine administration on CSF tyrosine and homovanillic acid levels in patients with Parkinson's disease. *Life Sci* 30:827–832.

Growdon JH, Nader TM, Schoenfeld J, Wurtman RJ. 1991. L-threonine in the treatment of spasticity. *Clin Neuropharmacol* 14:403–412.

Haddad EH, Berk LS, Kettering JD, Hubbard RW, Peters WR. 1999. Dietary intake and biochemical, hematologic, and immune status of vegans compared with nonvegetarians. *Am J Clin Nutr* 70:586S–593S.

Hagenfeldt L, Eriksson S, Wahren J. 1980. Influence of leucine on arterial concentrations and regional exchange of amino acids in healthy subjects. *Clin Sci* 59:173–181.

Hahn RG. 1988. Serum amino acid patterns and toxicity symptoms following the absorption of irrigant containing glycine in transurethral prostatic surgery. *Acta Anaesthesiol Scand* 32:493–501.

Hamilton B, Moriarty M. 1929. Comparison of growth in infancy. *Am J Dis Child* 37:1169.

Hansen RD, Raja C, Allen BJ. 2000. Total body protein in chronic diseases and in aging. *Ann NY Acad Sci* 904:345–352.

Hara S, Shibuya T, Nakakawaji K, Kyu M, Nakamura Y, Hoshikawa H, Takeuchi T, Iwao T, Ino H. 1962. Observations of pharmacological actions and toxicity of sodium glutamate, with comparisons between natural and synthetic products. *J Tokyo Med Coll* 20:69–100.

Harper AE. 1983. Dispensable and indispensable amino acid interrelationships. In: Blackburn GL, Grant JP, Young VR, eds. *Amino Acids. Metabolism and Medical Applications*. Boston: John Wright-PSG. Pp. 105–121.

Harper AE, Becker RV, Stucki WP. 1966. Some effects of excessive intakes of indispensable amino acids. *Proc Soc Exp Biol Med* 121:695–699.

Harper AE, Benevenga NJ, Wohlhueter RM. 1970. Effects of ingestion of disproportionate amounts of amino acids. *Physiol Rev* 50:428–558.

Harper AE, Miller RH, Block KP. 1984. Branched-chain amino acid metabolism. *Annu Rev Nutr* 4:409–454.

Harvey PW, Hunsaker HA, Allen KG. 1981. Dietary L-histidine-induced hypercholesterolemia and hypocupremia in the rat. *J Nutr* 111:639–647.

Hayasaka S, Saito T, Nakajima H, Takahashi O, Mizuno K, Tada K. 1985. Clinical trials of vitamin B_6 and proline supplementation for gyrate atrophy of the choroid and retina. *Br J Ophthalmol* 69:283–290.

Hays PM, Smeltzer JS. 1986. Multiple gestation. *Clin Obstet Gynecol* 29:264–285.

Health and Welfare Canada. 1990. *Report of the Expert Advisory Committee on Amino Acids.* Minister of Supply and Services Canada: Ottawa, Canada.

Hediger ML, Scholl TO, Ances IG, Belsky DH, Salmon RW. 1990. Rate and amount of weight gain during adolescent pregnancy: Associations with maternal weight-for-height and birth weight. *Am J Clin Nutr* 52:793–799.

Hegsted DM. 1963. Variation in requirements of nutrients: amino acids. *Fed Proc* 22:1420-1430.

Hegsted DM. 1976. Balance studies. *J Nutr* 106:307–311.

Hegsted DM. 1978. Assessment of nitrogen requirements. *Am J Clin Nutr* 31:1669–1677.

Heine WE, Klein PD, Reeds PJ. 1991. The importance of α-lactalbumin in infant nutrition. *J Nutr* 121:277–283.

Heinig MJ, Nommsen LA, Peerson JM, Lönnerdal B, Dewey KG. 1993. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: The DARLING Study. *Am J Clin Nutr* 58:152–161.

Heird WC, Driscoll JM, Schullinger JN, Grebin B, Winters RW. 1972. Intravenous alimentation in pediatric patients. *J Pediatr* 80:351–372.

Hellekson KL. 2001. NIH consensus statement on phenylketonuria. *Am Fam Physician* 63:1430–1432.

Henkin RI, Patten BM, Re PK, Bronzert DA. 1975. A syndrome of acute zinc loss. Cerebellar dysfunction, mental changes, anorexia, and taste and smell dysfunction. *Arch Neurol* 32:745–751.

Hershko A, Ciechanover A. 1998. The ubiquiten system. *Ann Rev Biochem* 67:425–479.

Hevia P, Kari FW, Ulman EA, Visek WJ. 1980a. Serum and liver lipids in growing rats fed casein with L-lysine. *J Nutr* 110:1224–1230.

Hevia P, Ulman EA, Kari FW, Visek WJ. 1980b. Serum lipids of rats fed excess L-lysine and different carbohydrates. *J Nutr* 110:1231–1239.

Hibbs JR, Mittleman B, Hill P, Medsger TA. 1992. L-Tryptophan-associated eosinophilic fasciitis prior to the 1989 eosinophilia-myalgia syndrome outbreak. *Arthritis Rheum* 35:299–303.

Higgins AC. 1976. Nutritional status and the outcome of pregnancy. *J Can Diet Assoc* 37:17–35.

Hill GL. 1992. Body composition research: Implications for the practice of clinical nutrition. *J Parenteral Enteral Nutr* 16:197–218.

Himwich WA, Petersen IM, Graves JP. 1954. Ingested sodium glutamate and plasma levels of glutamic acid. *J Appl Physiol* 1:196–199.

Hitomi-Ohmura E, Amano N, Aoyama Y, Yoshida A. 1992. The effect of a histidine-excess diet on cholesterol synthesis and degradation in rats. *Lipids* 27:755–760.

Hood DA, Terjung RL. 1990. Amino acid metabolism during exercise and following endurance training. *Sports Med* 9:23–35.

Hoorn AJ. 1989. Dimethylglycine and chemically related amines tested for mutagenicity under potential nitrosation conditions. *Mutat Res* 222:343–350.

Hornsby-Lewis L, Shike M, Brown P, Klang M, Pearlstone D, Brennan MF. 1994. L-Glutamine supplementation in home total parenteral nutrition patients: Stability, safety, and effects on intestinal absorption. *J Parenteral Enteral Nutr* 18:268–273.

Howat PM, Korslund MK, Abernathy RP, Ritchy SJ. 1975. Sweat losses by and nitrogen balance of preadolescent girls consuming three levels of dietary protein. *Am J Clin Nutr* 28:879–882.

Hrboticky N, Leiter LA, Anderson GH. 1985. Effects of L-tryptophan on short term food intake in lean men. *Nutr Res* 5:595–607.

Huang P-C, Lin CP, Hsu JY. 1980. Protein requirements of normal infants at the age of 1 year: Maintenance nitrogen requirement and obligatory nitrogen losses. *J Nutr* 110:1727–1735.

Hurson M, Regan MC, Kirk SJ, Wasserkrug HL, Barbul A. 1995. Metabolic effects of arginine in a healthy elderly population. *J Parenteral Enteral Nutr* 19:227–230.

Hutson SM, Harper AE. 1981. Blood and tissue branched-chain amino and α-keto acid concentrations: Effect of diet, starvation, and disease. *Am J Clin Nutr* 34:173–183.

Hytten FE, Leitch I. 1971. *The Physiology of Human Pregnancy, 2nd ed.* Oxford: Blackwell.

Ikezaki S, Nishikawa A, Furukawa F, Imazawa T, Enami T, Mitsui M, Takahashi M. 1994. 13-Week subchronic toxicity study of L-histidine monohydrochloride in F344 rats. *Eisei Shikenjo Hokoku* 112:57–63.

Ikezaki S, Nishikawa A, Furukawa F, Enami T, Mitsui M, Tanakamaru Z, Kim HC, Lee IS, Imazawa T, Takahashi M. 1996. Long-term toxicity/carcinogenicity study of L-histidine monohydrochloride in F344 rats. *Food Chem Toxicol* 34:687–691.

Inoue G, Fujita Y, Niiyama Y. 1973. Studies on protein requirements of young men fed egg protein and rice protein with excess and maintenance energy intakes. *J Nutr* 103:1673–1687.

Intengan CL. 1984. Protein requirements of Filipino children 22–29 months old consuming local diets. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo, Japan: United Nations University Press.

Intengan CL, Roxas BV, Loyola A, Carlos E. 1981. Protein requirements of Filipino children 20 to 29 months old consuming local diets. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo, Japan: United Nations University Press. Pp. 172–181.

Inubushi T, Shikiji M, Endo K, Kakegawa H, Kishino Y, Katunuma N. 1996. Hormonal and dietary regulation of lysosomal cysteine proteinases in liver under gluconeogenesis conditions. *Biol Chem* 377:539–542.

Iob V, Swanson WW. 1934. Mineral growth of the human fetus. *Am J Dis Child* 47:302.

IOM (Institute of Medicine). 1990. *Nutrition During Pregnancy.* Washington, DC: National Academy Press.

IOM. 1991. *Nutrition During Lactation.* Washington, DC: National Academy Press.

Ip CC, Harper AE. 1973. Effects of dietary protein content and glucagon administration on tyrosine metabolism and tyrosine toxicity in the rat. *J Nutr* 103:1594–1607.

Isidori A, Lo Monaco A, Cappa M. 1981. A study of growth hormone release in man after oral administration of amino acids. *Curr Med Res Opin* 7:475–481.

Istfan N, Murray E, Janghorbani M, Young VR. 1983. An evaluation of the nutritional value of a soy protein concentrate in young adult men using the short-term N-balance method. *J Nutr* 113:2516–2523.

Iwata S, Ichimura M, Matsuzawa Y, Takasaki Y, Sasaoka M. 1979. Behavioural studies in rats treated with monosodium L-glutamate during the early stages of life. *Toxicol Lett* 4:345–357.

Jackson AA. 1989. Optimizing amino acid and protein supply and utilization in the newborn. *Proc Nutr Soc* 48:293–301.

Jackson AA. 1991. The glycine story. *Eur J Clin Nutr* 45:59–65.

Janas LM, Picciano MF, Hatch TF. 1985. Indices of protein metabolism in term infants fed human milk, whey-predominant formula, or cow's milk formula. *Pediatrics* 75:775–784.

Janas LM, Picciano MF, Hatch TF. 1987. Indices of protein metabolism in term infants fed either human milk or formulas with reduced protein concentration and various whey/casein ratios. *J Pediatrics* 10:838–848

Janelle KC, Barr SI. 1995. Nutrient intakes and eating behavior scores of vegetarian and nonvegetarian women. *J Am Diet Assoc* 95:180–186, 189.

Järvenpää AL, Räihä NCR, Rassin DK, Gaull GE. 1982a Milk protein quantity and quality in the term infant. I. Metabolic responses and effect on growth. *Pediatrics* 70:214–220.

Järvenpää AL, Räihä NCR, Rassin DK, Gaull GE. 1982b. Milk protein quantity and quality in the term infant. II. Effects on acidic and neutral amino acids. *Pediatrics* 70:221–230.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). 1988. *Toxicological Evaluation of Certain Food Additives.* WHO Food Additive Series No. 22. Geneva: WHO/FAO.

Jefferson LS, Kimball S. 2001. Amino acid regulation of gene expression. *J Nutr* 131:2460S–2466S.

Jelliffe DB. 1966. The assessment of the nutritional status of the community. WHO Monograph Series No. 53. Geneva: WHO.

Jiang ZM, Cao JD, Zhu XG, Zhao WX, Yu JC, Ma EL, Wang XR, Zhu MW, Shu H, Liu YW. 1999. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: A randomized, double-blind, controlled study in 120 patients. *J Parenter Enteral Nutr* 23:S62–S66.

Jones EM, Baumann CA, Reynolds MS. 1956. Nitrogen balances of women maintained on various levels of lysine. *J Nutr* 60:549–562.

Jungas RL, Halperin ML, Brosnan JT. 1992. Quantitative analysis of amino acid oxidation and related gluconeogenesis in humans. *Physiol Rev* 72:419–448.

Kakizoe T, Nishio Y, Honma Y, Niijima T, Sugimura T. 1983. L-Isoleucine and L-leucine are promoters of bladder cancer in rats. *Princess Takamatsu Symp* 14:373–380.

Kalhan SC. 2000. Protein metabolism in pregnancy. *Am J Clin Nutr* 71:1249S–1255S.

Kalhan SC, Devapatla S. 1999. Pregnancy, insulin resistance and nitrogen accretion. *Curr Opin Clin Nutr Metab Care* 2:359–363.

Kalhan SC, Rossi KQ, Gruca LL, Super DM, Savin SM. 1998. Relation between transamination of branched-chain amino acid and urea synthesis: Evidence from human pregnancy. *Am J Physiol* 275:E423–E431.

Kamin H, Handler P. 1951. Effect of infusion of single amino acids upon excretion of other amino acids. *Am J Physiol* 164:654–661.

Kampel D, Kupferschmidt R, Lubec G. 1990. Toxicity of D-proline. In: Lubec G, Rosenthal GA, eds. *Amino Acids: Chemistry, Biology, and Medicine.* ESCOM: Leiden, The Netherlands. Pp. 1164–1171.

Karlsen RL, Pedersen OO. 1982. A morphological study of the acute toxicity of L-cysteine on the retina of young rats. *Exp Eye Res* 34:65–69.

Katagiri M, Nakamura K. 2002. Animals are dependent on preformed α-amino nitrogen as an essential nutrient. *Life* 53:125–129.

Kawabe M, Takesada Y, Tamano S, Hagiwara A, Ito N, Shirai T. 1996. Subchronic toxicity study of L-isoleucine in F344 rats. *J Toxicol Environ Health* 47:499–508.

Kenney RA. 1986. The Chinese Restaurant Syndrome: An anecdote revisited. *Food Chem Toxicol* 24:351–354.

Kenney RA, Tidball CS. 1972. Human susceptibility to oral monosodium L-glutamate. *Am J Clin Nutr* 25:140–146.

Khatri IA, Forstner GG, Forstner F. 1998. Susceptibility of the cysteine-rich N-terminal and C-terminal ends of rat intestinal mucin Muc 2 to proteolytic cleavage. *Biochem J* 331:323–330.

Kim KI, McMillan I, Bayley HS. 1983. Determination of amino acid requirements of young pigs using an indicator amino acid. *Br J Nutr* 50:369–382.

King JC. 1975. Protein metabolism during pregnancy. *Clin Perinatol* 2:243–254.

King JC, Calloway DH, Margen S. 1973. Nitrogen retention, total body ^{40}K and weight gain in teenage pregnant girls. *J Nutr* 103:772–785.

Kirschner M. 1999. Intracellular proteolysis. *Trends Cell Biol* 9:M42–M45.

Klavins JV, Kinney TD, Kaufman N. 1963. Body iron levels and hematologic findings during excess methionine feeding. *J Nutr* 79:101–104.

Klein DG. 1990. Physiologic response to traumatic shock. *AACN Clin Issues Crit Care Nurs* 1:505–521.

Klimberg VS, McClellan J. 1996. Glutamine, cancer, and its therapy. *Am J Surg* 172:418–424.

Klimberg VS, Souba WW, Salloum RM, Plumley DA, Cohen FS, Dolson DJ, Bland KI, Copeland EM. 1990. Glutamine-enriched diets support muscle glutamine metabolism without stimulating tumor growth. *J Surg Res* 48:319–323.

Knopp RH, Brandt K, Arky RA. 1976. Effects of aspartame in young persons during weight reduction. *J Toxicol Environ Health* 2:417–428.

Knox WE, Horowitz ML, Friedell GH. 1969. The proportionality of glutaminase content to growth rate and morphology of rat neoplasms. *Cancer Res* 29:669–680.

Kopple JD. 1987. Uses and limitations of the balance technique. *J Parenter Enteral Nutr* 11:79S–85S.

Kopple JD, Swendseid ME. 1975. Evidence that histidine is an essential amino acid in normal and chronically uremic men. *J Clin Invest* 55:881–891.

Korslund MK, Leung EY, Meiners CR, Crews MG, Taper J, Abernathy RP, Ritchey SJ. 1976. The effects of sweat nitrogen losses in evaluating protein utilization by preadolescent children. *Am J Clin Nutr* 29:600–603.

Kovacevic Z, Morris HP. 1972. The role of glutamine in the oxidative metabolism of malignant cells. *Cancer Res* 32:326–333.

Kriengsinyos W, Wykes LJ, Ball RO, Pencharz PB. 2002. Oral and intravenous tracer protocols of the indicator amino acid oxidation method provide the same estimate of the lysine requirement in healthy men. *J Nutr* 132:2251–2257.

Krogh A, Krogh M. 1913. *A Study of the Diet and Metabolism of Eskimos.* Bianco Luno, Copenhagen.

Kudo Y, Boyd CA. 1990. Transport of amino acids by the human placenta: Predicted effects thereon of maternal hyperphenylalaninaemia. *J Inherit Metab Dis* 13:617–626.

Kurpad AV, Raj T, El-Khoury A, Beaumier L, Kuriyan R, Srivatsa A, Borgonha S, Selvaraj A, Regan MM, Young VR. 2001a. Lysine requirements of healthy adult Indian subjects, measured by an indicator amino acid balance technique. *Am J Clin Nutr* 73:900–907.

Kurpad AV, Raj T, El-Khoury A, Kuriyan R, Maruthy K, Borgonha S, Chandakudlu D, Regan MM, Young VR. 2001b. Daily requirement for and splanchnic uptake of leucine in healthy adult Indians. *Am J Clin Nutr* 74:747–755.

Kurpad AV, Regan MM, Raj T, El-Khoury A, Kuriyan R, Vaz M, Chandakudlu D, Venkataswamy VG, Borgonha S, Young VR. 2002a. Lysine requirements of healthy adult Indian subjects receiving long-term feeding, measured with a 24-h indicator amino acid oxidation and balance technique. *Am J Clin Nutr* 76:404–412.

Kurpad AV, Raj T, Regan MM, Vasudevan J, Caszo B, Nazareth D, Gnanou J, Young VR. 2002b. Threonine requirements of healthy Indian adults, measured by a 24-h indicator amino acid oxidation and balance technique. *Am J Clin Nutr* 76:789–797.

Labow BI, Souba WW. 2000. Glutamine. *World J Surg* 24:1503–1513.

Lacey JM, Crouch JB, Benfell K, Ringer SA, Wilmore CK, Maguire D, Wilmore DW. 1996. The effects of glutamine-supplemented parenteral nutrition in premature infants. *J Parenter Enteral Nutr* 20:74–80.

Laidlaw SA, Kopple JD. 1987. Newer concepts of the indispensable amino acids. *Am J Clin Nutr* 46:593–605.

Lammi-Keefe CJ, Ferris AM, Jensen RG. 1990. Changes in human milk at 0600, 1000, 1400, 1800, and 2200 h. *J Pediatr Gastroenterol Nutr* 11:83–88.

Lamperti A, Blaha G. 1976. The effects of neonatally-administered monosodium glutamate on the reproductive system of adult hamsters. *Biol Reprod* 14:362–369.

Lamperti A, Blaha G. 1980. Further observations on the effects of neonatally administered monosodium glutamate on the reproductive axis of hamsters. *Biol Reprod* 22:687–693.

Lazaris-Brunner G, Rafii M, Ball RO, Pencharz P. 1998. Tryptophan requirement in young adult women as determined by indicator amino acid oxidation with L-[^{13}C]-phenylalanine. *Am J Clin Nutr* 68:303–310.

Leathwood PD, Fernstrom JD. 1990. Effect of an oral tryptophan/carbohydrate load on tryptophan, large neutral amino acid, and serotonin and 5-hydroxyindoleacetic acid levels in monkey brain. *J Neural Transm Gen Sect* 79:25–34.

Leiderman E, Zylberman I, Zukin SR, Cooper TB, Javitt DC. 1996. Preliminary investigation of high-dose oral glycine on serum levels and negative symptoms in schizophrenia: An open-label trial. *Biol Psychiatry* 39:213–215.

Leiter LA, Hrboticky N, Anderson GH. 1987. Effects of L-tryptophan on food intake and selection in lean men and women. *Ann NY Acad Sci* 499:327–328.

Lemon PWR. 1996. Is increased dietary protein necessary or beneficial for individuals with a physically active lifestyle? *Nutr Rev* 54:S169–S175.

Lemon PW, Nagle FJ, Mullin JP, Benevenga NJ. 1982. In vivo leucine oxidation at rest and during two intensities of exercise. *J Appl Physiol* 53:947–954.

Lemon PW, Benevenga NJ, Mullin JP, Nagle FJ. 1985. Effect of daily exercise and food intake on leucine oxidation. *Biochem Med* 33:67–76.

Lemon PW, Tarnopolsky MA, MacDougall JD, Atkinson SA. 1992. Protein requirements and muscle mass/strength changes during intensive training in novice bodybuilders. *J Appl Physiol* 73(2):767-775.

Lemons JA, Moye L, Hall D, Simmons M. 1982. Differences in the composition of preterm and term human milk during early lactation. *Pediatr Res* 16:113–117.

Lenke RR, Levy HL. 1980. Maternal phenylketonuria and hyperphenylalaninemia. An international survey of the outcome of untreated and treated pregnancies. *N Engl J Med* 303:1202–1208.

Lentner C. 1981. *Geigy Scientific Tables, 8th ed.*, Vol. 1. *Units of Measurement, Body Fluids, Composition of the Body, Nutrition.* West Caldwell, NJ: Ciba-Geigy Corporation.

Leverton RM, Gram MR, Brodovsky E, Chaloupka M, Mitchell A, Johnson N. 1956a. The quantitative amino acid requirements of young women. II. Valine. *J Nutr* 58:83–93.

Leverton RM, Gram MR, Chaloupka M, Brodovsky E, Mitchell A. 1956b. The quantitative amino acid requirements of young women. I. Threonine. *J Nutr* 58:59–81.

Leverton RM, Johnson N, Ellison J, Geschwender D, Schmidt F. 1956c. The quantitative amino acid requirements of young women. IV. Phenylalanine, with and without tyrosine. *J Nutr* 58:341–353.

Leverton RM, Johnson N, Pazur J, Ellison J. 1956d. The quantitative amino acid requirements of young women. III. Tryptophan. *J Nutr* 58:219–229.

Levey S, Harroun JE, Smyth CJ. 1949. Serum glutamic acid levels and the occurrence of nausea and vomiting after the intravenous administration of amino acid mixtures. *J Lab Clin Med* 34:1238–1248.

Levy HM, Montanez G, Feaver ER, Murphy EA, Dunn MS. 1954. Effect of arginine on tumor growth in rats. *Cancer Res* 14:198–200.

Lieb CW. 1929. The effects on human beings of a twelve months' exclusive meat diet. *J Am Med Assoc* 93:20–22.

Lieberman HR, Corkin S, Spring BJ, Wurtman RJ, Growdon JH. 1985. The effects of dietary neurotransmitter precursors on human behavior. *Am J Clin Nutr* 42:366–370.

Lieberman HR, Caballero B, Emde GG, Bernstein JG. 1988. The effects of aspartame on human mood, performance, and plasma amino acid levels. In: Wurtman RJ, Ritter-Walker E, eds. *Dietary Phenylalanine and Brain Function.* Boston. Birkhauser. Pp. 198–200.

Linder-Horowitz M, Knox WE, Morris HP. 1969. Glutaminase activities and growth rates of rat hepatomas. *Cancer Res* 29:1195–1199.

Longenecker JB, Hause NL. 1959. Relationship between plasma amino acids and composition of ingested protein. *Arch Bioch Biophys* 84:46.

Longenecker JB, Hause NL. 1961. Relationship between plasma amino acids and composition of ingested protein. II. A shortened procedure to determine plasma amino acid (PAA) ratios. *Am J Clin Nutr* 9:356–362.

Lönnerdal B. 1986. Effects of maternal nutrition in human lactation. In: Hamosh M, Goldman AS, eds. *Human Lactation 2: Maternal and Environmental Factors.* New York: Plenum Press. Pp. 301–323.

Lönnerdal B, Chen CL. 1990. Effects of formula protein level and ration on infant growth, plasma amino acids and serum trace elements I: Cow's milk formula. *Acta Paediatr Scand* 79:257–265.

Lönnerdal B, Woodhouse LR, Glazier C. 1987. Compartmentalization and quantitation of protein in human milk. *J Nutr* 117:1385–1395.

LSRO (Life Sciences Research Office). 1992. *Safety of Amino Acids Used as Dietary Supplements.* Bethesda, MD: LSRO.

Lucas DR, Newhouse JP. 1957. The toxic effect of sodium L-glutamate on the inner layers of the retina. *AMA Arch Ophthalmol* 58:193–201.

Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. 1992. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* 339:261–264.

MacGillivray I, Buchanan TJ. 1958. Total exchangeable sodium and potassium in non-pregnant women and in normal and pre-eclamptic pregnancy. *Lancet* 2:1090–1093.

Manatt MW, Garcia PA. 1992. Nitrogen balance: Concepts and techniques. In: Nissen S, ed. *Modern Methods in Protein Nutrition and Metabolism.* San Diego: Academic Press. Pp. 9–63.

Marchesini G, Dioguardi FS, Bianchi GP, Zoli M, Bellati G, Roffi L, Martines D, Abbiati R. 1990. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy. A randomized double-blind casein-controlled trial. The Italian Multicenter Study Group. *J Hepatol* 11:92–101.

Mariotti F, Mahe S, Benamouzig R, Luengo C, Dare S, Gaudichon C, Tome D. 1999. Nutritional value of [^{15}N]-soy protein isolate assessed from ileal digestibility and postprandial protein utilization in humans. *J Nutr* 129:1992–1997.

Martindale LW. 1967. *Extra Pharmacopoeia, 25th ed.*. London: Pharmaceutical Press.

Massara F, Cagliero E, Bisbocci D, Passarino G, Carta Q, Molinatti GM. 1981. The risk of pronounced hyperkalaemia after arginine infusion in the diabetic subject. *Diabete Metab* 7:149–153.

Matsueda S, Niiyama Y. 1982. The effects of excess amino acids on maintenance of pregnancy and fetal growth in rats. *J Nutr Sci Vitaminol* 28:557–573.

Matsuzawa Y, Yonetani S, Takasaki Y, Iwata S, Sekine S. 1979. Studies on reproductive endocrine function in rats treated with monosodium L-glutamate early in life. *Toxicol Lett* 4:359–371.

Matthews DE. 1999. Proteins and amino acids. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease, 9th ed.* Baltimore: Williams and Wilkins. Pp. 11–48.

Maughan RJ, Sadler DJ. 1983. The effects of oral administration of salts of aspartic acid on the metabolic response to prolonged exhausting exercise in man. *Int J Sports Med* 4:119–123.

Mayes PA. 1990. Oxidation of fatty acids: Ketogenesis. In: Murray RK, Granner DK, Mayes PA, Rodwell VW, eds. *Harper's Biochemistry, 22nd ed.* Norwalk, CT: Appleton and Lange. Pp. 206–217.

McCarthy CF, Borland JL, Lynch HJ, Owen EE, Tyor MP. 1964. Defective uptake of basic amino acids and L-cystine by intestinal mucosa of patients with cystinuria. *J Clin Invest* 43:1518–1524.

McClellan WS, Du Bois EF. 1930. Clinical calorimetry XLV. Prolonged meat diets with a study of kidney function and ketosis. *J Biol Chem* 87:651–668.

McClellan WS, Rupp VR, Toscani V. 1930. Clinical calorimetry XLVI. Prolonged meat diets with a study of the metabolism of nitrogen, calcium and phosphorus. *J Biol Chem* 87:669–680.

McClellan WS, Spencer HJ, Falk EA 1931. Clinical calorimetry XLVII. Prolonged meat diets with a study of the respiratory metabolism. *J Biol Chem* 93:419–434.

McCune MA, Perry HO, Muller SA, O'Fallon WM. 1984. Treatment of recurrent herpes simplex infections with L-lysine monohydrochloride. *Cutis* 34:366–373.

McGilvery RW. 1983. *Biochemistry—A Functional Approach.* Philadelphia: WB Saunders. Pp. 791–793.

McNurlan MA, Garlick PJ. 1980. Contribution of rat liver and gastrointestinal tract to whole-body protein synthesis in the rat. *Biochem J* 186:381–383.

Meakins TS, Jackson AA. 1996. Salvage of exogenous urea nitrogen enhances nitrogen balance in normal men consuming marginally inadequate protein diets. *Clin Sci* 90:215–225.

Meguid MM, Matthews DE, Bier DM, Meredith CN, Soeldner JS, Young VR. 1986a. Leucine kinetics at graded leucine intakes in young men. *Am J Clin Nutr* 43:770–780.

Meguid MM, Matthews DE, Bier DM, Meredith CN, Young VR. 1986b. Valine kinetics at graded valine intakes in young men. *Am J Clin Nutr* 43:781–786.

Melamed E, Glaeser B, Growdon JH, Wurtman RJ. 1980. Plasma tyrosine in normal humans: Effects of oral tyrosine and protein-containing meals. *J Neural Trans* 47:299–306.

Meldrum BS. 2000. Glutamate as a neurotransmitter in the brain: Review of physiology and pathology. *J Nutr* 130:1007S–1015S.

Meredith CN, Wen ZM, Bier DM, Matthews DE, Young VR. 1986. Lysine kinetics at graded lysine intakes in young men. *Am J Clin Nutr* 43:787–794.

Meredith CN, Zackin MJ, Frontera WR, Evans WJ. 1989. Dietary protein requirements and body protein metabolism in endurance-trained men. *J Appl Physiol* 66:2850–2856.

Metges CC, El-Khoury AE, Henneman L, Petzke KJ, Grant I, Bedri S, Pereira PP, Ajami AM, Fuller MF, Young VR. 1999a. Availability of intestinal microbial lysine for whole body lysine homeostasis in human subjects. *Am J Physiol* 277:E597–E607.

Metges CC, Petzke KJ, El-Khoury AE, Henneman L, Grant I, Bedri S, Regan MM, Fuller MF, Young VR. 1999b. Incorporation of urea and ammonia nitrogen into ileal and fecal microbial proteins and plasma free amino acids in normal men and ileostomates. *Am J Clin Nutr* 70:1046–1058.

Millward DJ. 1998. Metabolic demands for amino acids and the human dietary requirement: Millward and Rivers (1988) revisited. *J Nutr* 128:2563S–2576S.

Millward DJ. 1999. The nutritional value of plant-based diets in relation to human amino acid and protein requirements. *Proc Nutr Soc* 58:249–260.

Millward DJ, Roberts SB. 1996. Protein requirements of older individuals. *Nutr Res Rev* 9:67–87.

Millward DJ, Price GM, Pacy PJ, Halliday D. 1990. Maintenance protein requirements: The need for conceptual re-evaluation. *Proc Nutr Soc* 49:473–487.

Millward DJ, Fereday A, Gibson N, Pacy PJ. 1997. Aging, protein requirements, and protein turnover. *Am J Clin Nutr* 66:774–786.

Milman N, Scheibel J, Jessen O. 1980. Lysine prophylaxis in recurrent herpes simplex labialis: A double-blind, controlled crossover study. *Acta Derm Venereol* 60:85–87.

Mizutani AR, Parker J, Katz J, Schmidt J. 1990. Visual disturbances, serum glycine levels and transurethral resection of the prostate. *J Urol* 144:697–699.

Moephuli SR, Klein NW, Baldwin MT, Krider HM. 1997. Effects of methionine on the cytoplasmic distribution of actin and tubulin during neural tube closure in rat embryos. *Proc Natl Acad Sci USA* 94:543–548.

Mogensen CE, Solling K. 1977. Studies on renal tubular protein reabsorption: Partial and near complete inhibition by certain amino acids. *Scand J Clin Lab Invest* 37:477–486.

Moldawer LL, Kawamura I, Bistrian BR, Blackburn GL. 1983. The contribution of phenylalanine to tyrosine in vivo: Studies in the post-absorptive and phenylalanine-loaded rat. *Biochem J* 210:811–817.

Moneret-Vautrin DA. 1987. Monosodium glutamate induced asthma: A study of the potential risk in 30 asthmatics and review of the literature. *Allerg Immunol (Paris)* 19:29–35.

Morehead RP, Fishman WH, Artom C. 1945. Renal injury in the rat following the administration of serine by stomach tube. *Am J Pathol* 21:803–815.

Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Koller M, Konig W, Furst P, Puchstein C. 1998. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: A randomised, double-blind, controlled study. *Ann Surg* 227:302–308.

Motil KJ, Opekun AR, Montandon CM, Berthold HK, Davis TA, Klein PD, Reeds PJ. 1994. Leucine oxidation changes rapidly after dietary protein intake is altered in adult women but lysine flux is unchanged as is lysine incorporation into VLDL-apolipoprotein B-100. *J Nutr* 124:41–51.

Motil KJ, Davis TA, Montandon CM, Wong WW, Klein PD, Reeds PJ. 1996. Whole-body protein turnover in the fed state is reduced in response to dietary protein restriction in lactating women. *Am J Clin Nutr* 64:32–39.

Motil KJ, Sheng H-P, Kertz BL, Montandon CM, Ellis KJ. 1998. Lean body mass of well-nourished women is preserved during lactation. *Am J Clin Nutr* 67:292–300.

Munro, HN. 1970. Free amino acid pools and their role in regulation. In: Munro HN, ed. *Mammalian Protein Metabolism*, Vol. IV. New York: Academic Press. Chap 34.

Muramatsu K, Odagiri H, Morishita S, Takeuchi H. 1971. Effect of excess levels of individual amino acids on growth of rats fed casein diets. *J Nutr* 101:1117–1125.

Nakagawa I, Takahashi T, Suzuki T. 1961a. Amino acid requirements of children: Isoleucine and leucine. *J Nutr* 73:186–190.

Nakagawa I, Takahashi T, Suzuki T. 1961b. Amino acid requirements of children: Minimal needs of lysine and methionine based on nitrogen balance method. *J Nutr* 74:401–407.

Nakagawa I, Takahashi T, Suzuki T, Kobayashi K. 1962. Amino acid requirements of children: Minimal needs of threonine, valine and phenylalanine based on nitrogen balance method. *J Nutr* 77:61–68.

Nakagawa I, Takahashi T, Suzuki T, Kobayashi K. 1963. Amino acid requirements of children: Minimal needs of tryptophan, arginine and histidine based on nitrogen balance method. *J Nutr* 80:305–310.

Nakagawa I, Takahashi T, Suzuki T, Kobayashi K. 1964. Amino acid requirements of children: Nitrogen balance at the minimal level of essential amino acids. *J Nutr* 83:115–118.

Neale RJ, Waterlow JC. 1974. The metabolism of ^{14}C-labelled essential amino acids given by intragastric or intravenous infusion to rats on normal and protein-free diets. *Br J Nutr* 32:11–25.

Neri DF, Wiegmann D, Stanny RR, Shappell SA, McCardie A, McKay DL. 1995. The effects of tyrosine on cognitive performance during extended wakefulness. *Aviat Space Environ Med* 66:313–319.

Neville MC, Keller RP, Seacat J, Casey CE, Allen JC, Archer P. 1984. Studies on human lactation. I. Within-feed and between-breast variation in selected components of human milk. *Am J Clin Nutr* 40:635–646.

Newsholme EA, Blomstrand E, Hassmen P, Ekblom B. 1991. Physical and mental fatigue: Do changes in plasma amino acids play a role? *Biochem Soc Trans* 19:358–362.

Nikoletseas MM. 1977. Obesity in exercising, hypophagic rats treated with monosodium glutamate. *Physiol Behav* 19:767–773.

Nishio Y, Kakizoe T, Ohtani M, Sato S, Sugimura T, Fukushima S. 1986. L-isoleucine and L-leucine: Tumor promoters of bladder cancer in rats. *Science* 231:843–845.

Nommsen LA, Lovelady CA, Heinig MJ, Lönnerdal B, Dewey KG. 1991. Determinants of energy, protein, lipid, and lactose concentrations in human milk during the first 12 mo of lactation: The DARLING Study. *Am J Clin Nutr* 53:457–465.

Oddoye EA, Margen S. 1979. Nitrogen balance studies in humans: Long-term effect of high nitrogen intake on nitrogen accretion. *J Nutr* 109:363–377.

Ohmura E, Aoyama Y, Yoshida A. 1986. Changes in lipids in liver and serum of rats fed a histidine-excess diet or cholesterol-supplemented diets. *Lipids* 21:748–753.

Oishi R, Furuno K, Gomita Y, Araki Y, Saeki K. 1989. Effect of acute treatment of mice with L-histidine on the brain levels of amino acids. *Jpn J Pharmacol* 49:143–146.

Olivo M, Kitahama K, Valatx JL, Jouvet M. 1986. Neonatal monosodium glutamate dosing alters the sleep-wake cycle of the mature rat. *Neurosci Lett* 67:186–190.

Olney JW. 1969. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* 164:719–721.

Olney JW. 1989. Glutamate, a neurotoxic transmitter. *J Child Neurol* 4:218–226.

Olney JW. 1994. Excitotoxins in foods. *Neuro Toxicol* 15:535–544.

Olney JW, Ho OL. 1970. Brain damage in infant mice following oral intake of glutamate, aspartate or cysteine. *Nature* 227:609–611.

Olney JW, Cicero TJ, Meyer ER, de Gubareff T. 1976. Acute glutamate-induced elevations in serum testosterone and luteinizing hormone. *Brain Res* 112:420–424.

Owen G, Cherry CP, Prentice DE, Worden AN. 1978a. The feeding of diets containing up to 4% monosodium glutamate to rats for 2 years. *Toxicol Lett* 1:221–226.

Owen G, Cherry CP, Prentice DE, Worden AN. 1978b. The feeding of diets containing up to 10% monosodium glutamate to beagle dogs for 2 years. *Toxicol Lett* 1:217–219.

Park KG, Heys SD, Blessing K, Kelly P, McNurlan MA, Eremin O, Garlick PJ. 1992. Stimulation of human breast cancers by dietary L-arginine. *Clin Sci* 82:413–417.

Patrick J, Pencharz PB, Belmonte M, Ste-Marie M, Boland MP, Issenman RM, Van Aerde JEE, Rousseau-Harsany E. 1994. Undernutrition in children with neurodevelopmental disability. *Can Med Assoc J* 151:753–759.

Pellett PL, Young VR. 1992. The effects of different levels of energy intake on protein metabolism and of different levels of protein intake on energy metabolism: A statistical evaluation from the published literature. In: Scrimshaw NS, Schürch B, eds. *Protein-Energy Interaction.* Lausanne, Switzerland: IDECG, Nestlé Foundation. Pp. 81–121.

Pencharz PB. 1985. Body composition and growth. In: Walker A, ed. *Nutrition in Pediatrics. Basic Science and Clinical Application.* Boston. Little, Brown. Pp. 77–85.

Pencharz PB, Azcue M. 1996. Use of bioelectrical impedance analysis (BIA) measurements in the clinical management of malnutrition. *Am J Clin Nutr* 64:S485–S488.

Pencharz BP, House JD, Wykes LJ, Ball RO. 1996. What are the essential amino acids for the preterm and term infant? In: Bindels JG, Goedhart A, Visser HKA, eds. *Recent Developments in Infant Nutrition. Nutricia Symposia Vol. 9.* Dordrecht, The Netherlands: Kluwer Academic Publishers. Pp. 278–296.

Pepplinkhuizen L, Bruinvels J, Blom W, Moleman P. 1980. Schizophrenia-like psychosis caused by a metabolic disorder. *Lancet* 1:454–456.

Perry TL, Hardwick DF, Dixon GH, Dolman CL, Hansen S. 1965. Hypermethioninemia: A metabolic disorder associated with cirrhosis, islet cell hyperplasia, and renal tubular degeneration. *Pediatrics* 36:236–250.

Persaud TV. 1969. The foetal toxicity of leucine in the rat. *West Indian Med J* 18:34–39.

Peters JC, Harper AE. 1987. Acute effects of dietary protein on food intake, tissue amino acids, and brain serotonin. *Am J Physiol* 252:R902–R914.

Picou D, Halliday D, Garrow JS. 1966. Total body protein, collagen and non-collagen protein in infantile protein malnutrition. *Clin Sci* 30:345–351.

Pilc A, Rogoz Z, Skuza G. 1982. Histidine-induced bizarre behaviour in rats: The possible involvement of central cholinergic system. *Neuropharmacology* 21:781–785.

Pinals RS, Harris ED, Burnett JB, Gerber DA. 1977. Treatment of rheumatoid arthritis with L-histidine: A randomized, placebo-controlled, double-blind trial. *J Rheumatol* 4:414–419.

Pineda O, Torun B, Viteri FE, Arroyave G. 1981. Protein quality in relation to estimates of essential amino acids requirements. In: Bodwell CE, Adkins JS, Hopkins DT, eds. *Protein Quality in Humans: Assessment and In Vitro Estimation.* Westport, CT: AVI Publishing. Pp. 29–42.

Pinto-Scognamiglio W, Amorico L, Gatti GL. 1972. Toxicity and tolerance to monosodium glutamate studied by a conditioned avoidance test. *Farmaco* 27:19–27.

Pipe NGJ, Smith T, Halliday D, Edmonds CJ, Williams C, Coltart TM. 1979. Changes in fat, fat-free mass and body water in human normal pregnancy. *Br J Obstet Gynaecol* 86:929–940.

Pizzi WJ, Barnhart JE, Fanslow DJ. 1977. Monosodium glutamate administration to the newborn reduces reproductive ability in female and male mice. *Science* 196:452–454.

Pizzi WJ, Tabor JM, Barnhart JE. 1978. Somatic, behavioral, and reproductive disturbances in mice following neonatal administration of sodium L-aspartate. *Pharmacol Biochem Behav* 9:481–485.

Pollitt E. 2000. Developmental sequel from early nutritional deficiencies: Conclusive and probability judgements. *J Nutr* 130:350S–353S.

Poon TK, Cameron DP. 1978. Measurement of oxygen consumption and locomotor activity in monosodium glutamate-induced obesity. *Am J Physiol* 234:E532–E534.

Porter PB, Griffin AC. 1950. Effects of glutamic acid on maze learning and recovery from electroconvulsive shocks in albino rats. *J Comp Physiol Psychol* 43:1–15.

Pradhan SN, Lynch JF. 1972. Behavioral changes in adult rats treated with monosodium glutamate in the neonatal stage. *Arch Int Pharmacodyn Ther* 197:301–304.

Pratt EL, Snyderman SE, Cheung MW, Norton P, Holt LE. 1955. The threonine requirement of the normal infant. *J Nutr* 56:231–251.

Prentice AM, Goldberg GR, Prentice A. 1994. Body mass index and lactation performance. *Eur J Clin Nutr* 48:S78–S86.

Prosky L, O'Dell RG. 1972. Biochemical changes of brain and liver in neonatal offspring of rats fed monosodium-L-glutamate. *Experientia* 28:260–263.

Raguso CA, Pereira P, Young VR. 1999. A tracer investigation of obligatory oxidative amino acids losses in healthy, young adults. *Am J Clin Nutr* 70:474–483.

Räihä N, Minoli I, Moro G. 1986a. Milk protein intake in the term infant I: Metabolic responses and effects on growth. *Acta Paediatr Scand* 75:881–886.

Räihä N, Minoli I, Moro G. 1986b. Milk protein intake in the term infant II: Effects on plasma amino acid concentrations. *Acta Paediatr Scand* 75:887–892.

Raiten DJ, Talbot JM, Fisher KD. 1995. *Analysis of Adverse Reactions to Monosodium Glutamate (MSG).* Bethesda, MD: Federation of American Societies for Experimental Biology.

Ramsey BW, Farrell P, Pencharz PB. 1992. Nutritional assessment and management in cystic fibrosis: a consensus report. *Am J Clin Nutr* 55:108–116.

Rand WM, Young VR. 1999. Statistical analysis of nitrogen balance data with reference to the lysine requirement in adults. *J Nutr* 129:1920–1926.

Rand WM, Young VR, Scrimshaw NS. 1976. Change of urinary nitrogen excretion in response to low-protein diets in adults. *Am J Clin Nutr* 29:639–644.

Rand WM, Scrimshaw NS, Young VR. 1981. Conventional ("long-term") nitrogen balance studies for protein quality evaluation in adults: Rationale and limitations. In: Bodwell CE, Adkins JS, Hopkins DT, eds. *Protein Quality in Humans: Assessment and In Vitro Estimation*. Westport, CT: AVI Publishing. Pp. 61–94.

Rand RM, Pellett PL, Young VR. 2003. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. *Am J Clin Nutr* 77:109–127.

Reeds PJ, Burrin DG. 2001. Glutamine and the bowel. *J Nutr* 131:2505S–2508S.

Reeds PJ, Garlick PJ. 1984. Nutrition and protein turnover in man. *Adv Nutr Res* 6:93–138.

Reeds PJ, Field CR, Jahoor F. 1994. Do the differences between the amino acid compositions of acute-phase and muscle proteins have a bearing on nitrogen loss in traumatic states? *J Nutr* 124:906–910.

Reif-Lehrer L. 1976. Possible significance of adverse reactions to glutamate in humans. *Fed Proc* 35:2205–2211.

Rennie MJ, Edwards RH, Krywawych S, Davies CT, Halliday D, Waterlow JC, Millward DJ. 1981. Effect of exercise on protein turnover in man. *Clin Sci (Lond)* 61:627–639.

Reynolds JV, Thom AK, Zhang SM, Ziegler MM, Naji A, Daly JM. 1988. Arginine, protein malnutrition, and cancer. *J Surg Res* 45:513–522.

Reynolds JV, Daly JM, Shou J, Sigal R, Ziegler MM, Naji A. 1990. Immunologic effects of arginine supplementation in tumor-bearing and non-tumor-bearing hosts. *Ann Surg* 211:202–210.

Reynolds JV, O'Farrelly C, Feighery C, Murchan P, Leonard N, Fulton G, O'Morain C, Keane FB, Tanner WA. 1996. Impaired gut barrier function in malnourished patients. *Br J Surg* 83:1288–1291.

Reynolds MS, Steel DL, Jones EM, Baumann CA. 1958. Nitrogen balances of women maintained on various levels of methionine and cystine. *J Nutr* 64:99–111.

Reynolds WA, Stegink LD, Filer LJ Jr, Renn E. 1980. Aspartame administration to the infant monkey: Hypothalamic morphology and plasma amino acid levels. *Anat Rec* 198:73–85.

Rich LF, Beard ME, Burns RP. 1973. Excess dietary tyrosine and corneal lesions. *Exp Eye Res* 17:87–97.

Rigo J, Senterre H. 1980. Optimal threonine intake for preterm infants fed on oral or parenteral nutrition. *J Parenteral Enteral Nutr* 4:15–17.

Roberton AM, Rabel B, Harding CA, Tasman-Jones C, Harris PJ, Lee SP. 1991. Use of the ileal conduit as a model for studying human small intestinal mucus glycoprotein secretion. *Am J Physiol* 261:G728–G734.

Roberts S. 1996. Energy requirements of older individuals. *Eur J Clin Nutr* 50:S112–S118.

Roberts S, Thorpe JM, Ball RO, Pencharz PB. 2001. Tyrosine requirement of healthy men receiving a fixed phenylalanine intake determined by using indicator amino acid oxidation. *Am J Clin Nutr* 73:276–282.

Rodwell VW. 1990. Conversion of amino acids to specialized products. In: Murray RK, Mayes PA, Granner DK, Rodwell VW, eds. *Harper's Biochemistry*, 22nd ed. Norwalk, CT: Appleton & Lange. Pp. 307–313.

Rogan WJ, Gladen BC. 1993. Breast-feeding and cognitive development. *Early Human Dev* 31:181–193.

Roig JC, Meetze WH, Auestad N, Jasionowski T, Veerman M, McMurray CA, Neu J. 1996. Enteral glutamine supplementation for the very low birthweight infant: Plasma amino acid concentrations. *J Nutr* 126:1115S–1120S.

Ronnenberg AG, Gross KL, Hartman WJ, Meydani SN, Prior RL. 1991. Dietary arginine supplementation does not enhance lymphocyte proliferation or interleukin-2 production in young and aged rats. *J Nutr* 121:1270–1278.

Rose DP, Leklem JE, Fardal L, Baron RB, Shrago E. 1977. Effect of oral alanine loads on the serum triglycerides of oral contraceptive users and normal subjects. *Am J Clin Nutr* 30:691–694.

Rose WC. 1957. The amino acid requirements of adult man. *Nutr Abs Rev* 27:631–647.

Rose WC, Haines WJ, Warner DT, Johnson JE. 1951. The amino acid requirements of man. II. The role of threonine and histidine. *J Biol Chem* 188:49–58.

Rose WC, Borman A, Coon MJ, Lambert GF. 1955a. The amino acid requirements of man. X. The lysine requirement. *J Biol Chem* 214:579–587.

Rose WC, Coon MJ, Lambert GF. 1955b. The amino acid requirements of man. VIII. The metabolic availability of the optical isomers of acetyltryptophan. *J Biol Chem* 212:201–205.

Rose WC, Coon MJ, Lockhart HB, Lambert GF. 1955c. The amino acid requirements of man. XI. The threonine and methionine requirements. *J Biol Chem* 215:101–110.

Rose WC, Eades CH, Coon MJ. 1955d. The amino acid requirements of man. XII. The leucine and isoleucine requirements. *J Biol Chem* 216:225–234.

Rose WC, Leach BE, Coon MJ, Lambert GF. 1955e. The amino acid requirements of man. IX. The phenylalanine requirement. *J Biol Chem* 213:913–922.

Rose WC, Wixom RL, Lockhart HB, Lambert GF. 1955f. The amino acid requirements of man. XV. The valine requirement; Summary and final observations. *J Biol Chem* 217:987–995.

Rosenberg LE, Downing S, Durant JL, Segal S. 1966. Cystinuria: Biochemical evidence for three genetically distinct diseases. *J Clin Invest* 45:365–371.

Rudman D, DiFulco TJ, Galambos JT, Smith RB, Salam AA, Warren WD. 1973. Maximal rates of excretion and synthesis of urea in normal and cirrhotic subjects. *J Clin Invest* 52:2241–2249.

Ryan-Harshman M, Leiter LA, Anderson GH. 1987. Phenylalanine and aspartame fail to alter feeding behavior, mood and arousal in men. *Physiol Behav* 39:247–253.

Said AK, Hegsted DM. 1970. Response of adult rats to low dietary levels of essential amino acids. *J Nutr* 100:1362–1375.

Sauberlich HE. 1961. Studies on the toxicity and antagonism of amino acids for weanling rats. *J Nutr* 75:61–72.

Schaafsma G. 2000. The protein digestibility-corrected amino acid score. *J Nutr* 130:1865S–1867S.

Schainker B, Olney JW. 1974. Glutamate-type hypothalamic-pituitary syndrome in mice treated with aspartate or cysteate in infancy. *J Neural Trans* 35:207–215.

Schaumburg HH, Byck R. 1968. Sin cib-syn: Accent on glutamate. *N Engl J Med* 279:105.

Schaumburg HH, Byck R, Gerstl R, Mashman JH. 1969. Monosodium L-glutamate: Its pharmacology and role in the Chinese restaurant syndrome. *Science* 163:826–828.

Schechter PJ, Prakash NJ. 1979. Failure of oral L-histidine to influence appetite or affect zinc metabolism in man: A double-blind study. *Am J Clin Nutr* 32:1011–1014.

Scholl TO, Hediger ML, Ances IG. 1990. Maternal growth during pregnancy and decreased infant birth weight. *Am J Clin Nutr* 51:790–793.

Scholl TO, Hediger ML, Schall JI, Khoo C-S, Fischer RL. 1994. Maternal growth during pregnancy and the competition for nutrients. *Am J Clin Nutr* 60:183–188.

Schwartz JC, Lampart C, Rose C. 1972. Histamine formation in rat brain in vivo: Effects of histidine loads. *J Neurochem* 19:801–810.

Schwartzstein RM, Kelleher M, Weinberger SE, Weiss JW, Drazen JM. 1987. Airways effects of monosodium glutamate in subjects with chronic stable asthma. *J Asthma* 24:167–172.

Scrimshaw NS, Hussein MA, Murray E, Rand WM, Young VR. 1972. Protein requirements of man: Variations in obligatory urinary and fecal nitrogen losses in young men. *J Nutr* 102:1595–1604.

Scriver CR, Kaufman S, Woo SL. 1989. The hyperphenylalaninemias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease*, 6th ed. New York: McGraw-Hill. Pp. 495–546.

Semprini ME, Frasca MA, Mariani A. 1971. Effects of monosodium glutamate (MSG) administration on rats during the intrauterine life and the neonatal period. *Quaderni delle Nutrizione* 31:85–100.

Sen Gupta J, Srivastava KK. 1973. Effect of potassium-magnesium aspartate on endurance work in man. *Ind J Exp Biol* 11:392–394.

Shaw GM, Velie EM, Schaffer DM. 1997. Is dietary intake of methionine associated with a reduction in risk for neural tube defect-affected pregnancies? *Teratology* 56:295–299.

Simon CA, Van Melle GD, Ramelet AA. 1985. Failure of lysine in frequently recurrent herpes simplex infection. *Arch Dermatol* 121:167–168.

Simon RA. 2000. Additive-induced urticaria: Experience with monosodium glutamate (MSG). *J Nutr* 130:1063S–1066S.

Sivam SP, Chermak T. 1992. Neonatal administration of L-cysteine does not produce long-term effects on neurotransmitter or neuropeptide systems in the rat striatum. *Res Comm Chem Pathol Pharm* 77:219–225.

Skeie B, Kvetan V, Gil KM, Rothkopf MM, Newsholme EA, Askanazi J. 1990. Branch-chain amino acids: Their metabolism and clinical utility. *Crit Care Med* 18:549–571.

Smith B, Prockop DJ. 1962. Central-nervous-system effects of ingestion of L-tryptophan by normal subjects. *N Engl J Med* 267:1338–1341.

Snyderman SE, Pratt EL, Cheung MW, Norton P, Holt LE, Hansen AE, Panos TC. 1955. The phenylalanine requirement of the normal infant. *J Nutr* 56: 253–263.

Snyderman SE, Holt LE, Smellie F, Boyer A, Westall RG. 1959a. The essential amino acid requirements of infants: Valine. *Am J Dis Child* 97:186–191.

Snyderman SE, Norton PM, Fowler DI, Holt LE. 1959b. The essential amino acid requirements of infants: Lysine. *Am J Dis Child* 97:175–185.

Snyderman SE, Boyer A, Phansalkar SV, Holt LE. 1961a. Essential amino acid requirements of infants. Tryptophan. *Am J Dis Child* 102:41–45.

Snyderman SE, Roitman EL, Boyer A, Holt LE. 1961b. Essential amino acid requirements of infants. Leucine. *Am J Dis Child* 102:35–40.

Snyderman SE, Boyer A, Roitman E, Holt LE, Prose PH. 1963. The histidine requirement of the infant. *Pediatrics* 31:786–801.

Snyderman SE, Boyer A, Norton PM, Roitman E, Holt LE. 1964a. The essential amino acid requirements of infants. IX. Isoleucine. *Am J Clin Nutr* 15:313–321.

Snyderman SE, Boyer A, Norton PM, Roitman E, Holt LE. 1964b. The essential amino acid requirements of infants. X. Methionine. *Am J Clin Nutr* 15:322–330.
Sole MJ, Benedict CR, Myers MG, Leenen FH, Anderson GH. 1985. Chronic dietary tyrosine supplements do not affect mild essential hypertension. *Hypertension* 7:593–596.
Solomon JK, Geison RL. 1978. Effect of excess dietary L-histidine on plasma cholesterol levels in weanling rats. *J Nutr* 108:936–943.
Souba WW. 1993. Glutamine and cancer. *Ann Surg* 218:715–728.
Speth JD. 1989. Early hominid hunting and scavenging: The role of meat as an energy source. *J Hum Evol* 18:329–343.
Speth JD, Spielmann KA. 1983. Energy source, protein metabolism, and hunter-gatherer subsistence strategies. *J Anthropol Archaeol* 2:1–31.
Stechmiller JK, Treloar D, Allen N. 1997. Gut dysfunction in critically ill patients: A review of the literature. *Am J Crit Care* 6:204–209.
Steele RD, Barber TA, Lalich J, Benevenga NJ. 1979. Effects of dietary 3-methylthiopropionate on metabolism, growth and hematopoiesis in the rat. *J Nutr* 109:1739–1751.
Stefansson V. 1944a. *Arctic Manual.* New York: Macmillan.
Stefansson V. 1944b. Pemmican. *Military Surg* 95:89–98.
Stegink LD. 1976. Absorption, utilization, and safety of aspartic acid. *J Toxicol Environ Health* 2:215–242.
Stegink LD, Shepherd JA, Brummel MC, Murray LM. 1974. Toxicity of protein hydrolysate solutions: Correlation of glutamate dose and neuronal necrosis to plasma amino acid levels in young mice. *Toxicology* 2:285–299.
Stegink LD, Filer LJ, Baker GL. 1977. Effect of aspartame and aspartate loading upon plasma and erythrocyte free amino acid levels in normal adult volunteers. *J Nutr* 107:1837–1845.
Stegink LD, Filer LJ, Baker GL. 1980. Plasma methionine levels in normal adult subjects after oral loading with L-methionine and N-acetyl-L-methionine. *J Nutr* 110:42–49.
Stegink LD, Filer LJ, Baker GL. 1982a. Plasma and erythrocyte amino acid levels in normal adult subjects fed a high protein meal with and without added monosodium glutamate. *J Nutr* 112:1953–1960.
Stegink LD, Filer LJ, Baker GL. 1982b. Plasma and urinary methionine levels in one-year-old infants after oral loading with L-methionine and N-acetyl-L-methionine. *J Nutr* 112:597–603.
Stegink LD, Filer LJ Jr, Baker GL. 1983a. Effect of carbohydrate on plasma and erythrocyte glutamate levels in humans ingesting large doses of monosodium L-glutamate in water. *Am J Clin Nutr* 37:961–968.
Stegink LD, Filer LJ Jr, Baker GL. 1983b. Plasma amino acid concentrations in normal adults fed meals with added monosodium L-glutamate and aspartame. *J Nutr* 113:1851–1860.
Stekol JA, Szaran J. 1962. Pathological effects of excessive methionine in the diet of growing rats. *J Nutr* 77:81–90.
Stellar E, McElroy WD. 1948. Does glutamic acid have any effect on learning? *Science* 108:281–283.
Stephenson LS, Lathan MC, Ottesen EA. 2000. Global malnutrition. *Parasitology* 121:S5–S22.
Stevenson DD. 2000. Monosodium glutamate and asthma. *J Nutr* 130:1067S–1073S.

Stokes AF, Belger A, Banich MT, Taylor H. 1991. Effects of acute aspartame and acute alcohol ingestion upon the cognitive performance of pilots. *Aviat Space Environ Med* 62:648–653.

Stoll B, Henry J, Reeds PJ, Yu H, Jahoor F, Burrin DG. 1998. Catabolism dominates the first-pass intestinal metabolism of dietary essential amino acids in milk protein-fed piglets. *J Nutr* 128:606–614.

Strain GW, Strain JJ, Zumoff B. 1985. L-Tryptophan does not increase weight loss in carbohydrate-craving obese subjects. *Int J Obes* 9:375–380.

Sweetman L. 1989. Branched chain organic acidurias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease*, 6th ed. New York: McGraw-Hill. Pp. 791–819.

Swick RW, Benevenga NJ. 1977. Labile protein reserves and protein turnover. *J Dairy Sci* 60:505–515.

Tachibana K Mukai K, Hiraoka I, Moriguchi S, Takama S, Kishino Y. 1985. Evaluation of the effect of arginine-enriched amino acid solution on tumor growth. *J Parenter Enteral Nutr* 9:428–434.

Tarasoff L, Kelly MF. 1993. Monosodium L-glutamate: A double-blind study and review. *Food Chem Toxicol* 31:1019–1035.

Tarnopolsky MA, MacDougall JD, Atkinson SA. 1988. Influence of protein intake and training status on nitrogen balance and lean body mass. *J Appl Physiol* 64:187–193.

Tarnopolsky MA, Atkinson SA, MacDougall JD, Senor BB, Lemon PW, Schwarcz H. 1991. Whole body leucine metabolism during and after resistance exercise in fed humans. *Med Sci Sports Exer*c 23:326–333.

Taverner MR, Hume ID, Farrell DJ. 1981. Availability to pigs of amino acids in cereal grains. 1. Endogenous levels of amino acids in ileal digesta and faeces of pigs given cereal diets. *Br J Nutr* 46:149–158.

Terry LC, Epelbaum J, Martin JB. 1981. Monosodium glutamate: Acute and chronic effects on rhythmic growth hormone and prolactin secretion, and somatostatin in the undisturbed male rat. *Brain Res* 217:129–142.

Thein DJ, Hurt WC. 1984. Lysine as a prophylactic agent in the treatment of recurrent herpes simplex labialis. *Oral Surg* 58:659–666.

Thoemke F, Huether G. 1984. Breeding rats on amino acid imbalanced diets for three consecutive generations affects the concentrations of putative amino acid transmitters in the developing brain. *Int J Dev Neurosci* 2:567–574.

Thompson GN, Halliday D. 1992. Protein turnover in pregnancy. *Eur J Clin Nutr* 46:411–417.

Torun B, Viteri FE. 1981. Obligatory nitrogen losses and factorial calculations of protein requirements of pre-school children. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data*. Tokyo, Japan: United Nations University Press. Pp. 159–163.

Torun B, Cabrera Santiago M, Viteri FE. 1981. Protein requirements of pre-school children: Milk and soybean protein isolate. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data*. Tokyo, Japan: United Nations University Press. Pp. 182–190.

Uauy R, Scrimshaw NS, Young VR. 1978. Human protein requirements: Nitrogen balance response to graded levels of egg protein in elderly men and women. *Am J Clin Nutr* 31:779–785.

Uauy R, Yanez E, Ballester D, Barrera G, Guzman E, Saitua MT, Zacaris I. 1981. Obligatory urinary and faecal nitrogen losses in young Chilean men fed two levels of dietary energy intake. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo, Japan: United Nations University Press.

van Acker BA, von Meyenfeldt MF, van der Hulst RR, Hulsewe KW, Wagenmakers AJ, Deutz NE, de Blaauw I, Dejong CH, van Kreel BK, Soeters PB. 1999. Glutamine: The pivot of our nitrogen economy? *J Parenter Enteral Nutr* 23:S45–S48.

van der Schoor SRD, van Goudoever JB, Stoll B, Henry JF, Rosenberger JR, Burrin DG, Reeds PJ. 2001. The pattern of intestinal substrate oxidation is altered by protein restriction in pigs. *Gastroenterology* 121:1167–1175.

van Raaij JMA, Pee MEM, Vermaat-Miedema SH, Schonk CM, Hautvast JGAJ 1988. New equations for estimating body fat mass in pregnancy from body density or total body water. *Am J Clin Nutr* 48:24–29.

van Wouwe JP, Hoogenkamp S, Van den Hamer CJ. 1989. Histidine supplement and Zn status in Swiss random mice. *Biol Trace Elem Res* 22:35–43.

Viau AT, Leathem JH. 1973. Excess dietary methionine and pregnancy in the rat. *J Reprod Fertil* 33:109–111.

Vijayasarathy C, Khan-Siddiqui L, Murthy SN, Bamji MS. 1987. Rise in plasma trimethyllysine levels in humans after oral lysine load. *Am J Clin Nutr* 46:772–777.

Villalpando S, Butte NF, Flores-Huerta S, Thotathuchery M. 1998. Qualitative analysis of human milk produced by women consuming a maize-predominant diet typical of rural Mexico. *Ann Nutr Metab* 42:23–32.

Viteri FE, Martinez C. 1981. Integumental nitrogen losses of pre-school children with different levels and sources of dietary protein intake. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo, Japan: United Nations University Press.

Wachstein M. 1947. Nephrotoxic action of dl-serine in the rat. II. The protective action of various amino acids and some other compounds. *Arch Pathol* 43:515–526.

Wagenmakers AJ. 1998. Muscle amino acid metabolism at rest and during exercise: Role in human physiology and metabolism. *Exerc Sport Sci Rev* 26:287–314.

Waisman HA, Harlow HF. 1965. Experimental phenylketonuria in infant monkeys: A high phenylalanine diet produces abnormalities simulating those of the hereditary disease. *Science* 147:685–695.

Wang JML, Creel DJ, Wong KC. 1989. Transurethral resection of the prostate, serum glycine levels, and ocular evoked potentials. *Anesthesiology* 70:36–41.

Waterlow JC. 1969. The assessment of protein nutrition and metabolism in the whole animal, with special reference to man. In: Munro HN ed. *Mammalian Protein Metabolism*, Vol III. New York: Academic Press. Pp. 347–348.

Waterlow JC. 1984. Protein turnover with special reference to man. *Quart J Exp Physiol* 69:409–438.

Waterlow JC, Garlick PJ, Millward DJ. 1978. *Protein Turnover in Mammalian Tissues and in the Whole Body.* Amsterdam: North-Holland Publishing.

Webber WA, Brown JL, Pitts RF. 1961. Interactions of amino acids in renal tubular transport. *Am J Physiol* 200:380–386.

White TP, Brooks GA. 1981. [U-^{14}C]glucose, -alanine, and -leucine oxidation in rates at rest and two intensities of running. *Am J Physiol* 240:E155–E165.

Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. *Mineral Metabolism: An Advanced Treatise*, Vol 2. New York: Academic Press.

Wilcken DE, Reddy SG, Gupta VJ. 1983. Homocysteinemia, ischemic heart disease, and the carrier state for homocystinuria. *Metabolism* 32:363–370.

Wilkin JK. 1986. Does monosodium glutamate cause flushing (or merely "glutamania")? *J Am Acad Dermatol* 15:225–230.

Willard MD, Gilsdorf RB, Price RA. 1980. Protein-calorie malnutrition in a community hospital. *J Am Med Assoc* 243:1720–1722.

Williams GM, Whysner J. 1996. Epigenetic carcinogens: Evaluation and risk assessment. *Exp Toxicol Pathol* 48:189–195.

Wilson DC, Pencharz PB. 1997. Nutritional care of the chronically ill. In: Tsang RC, Zlotkin SH, Nichols BL, Hansen JW, eds. *Nutrition During Infancy: Birth to 2 Years.* Cincinnati: Digital Educational Publishing, Inc. Pp. 37–56.

Wilson D, Rafii M, Ball RO, Pencharz PB. 2000. Threonine requirement in young men determined by indicator amino acid oxidation with use of L-[1-^{13}C]-phenylalanine. *Am J Clin Nutr* 71:757–764.

Woessner KM, Simon RA, Stevenson DD. 1999. Monosodium glutamate sensitivity in asthma. *J Allergy Clin Immunol* 104:305–310.

Woods RK, Weiner JM, Thien F, Abramson M, Walters EH. 1998. The effects of monosodium glutamate in adults with asthma who perceive themselves to be monosodium glutamate-intolerant. *J Allergy Clin Immunol* 101:762–771.

Wurtman JJ, Wurtman RJ, Growdon JH, Henry P, Lipscomb A, Zeisel SH. 1981. Carbohydrate craving in obese people: Suppression by treatments affecting serotoninergic transmission. *Int J Eating Disord* 1:2–15.

Wynn M, Wynn A. 1979. *Prevention of Handicap and the Health of Women.* London: Routledge and Kegan Paul. Pp. 43–81.

Yamashita K, Ashida K. 1971. Effect of excessive levels of lysine and threonine on the metabolism of these amino acids in rats. *J Nutr* 101:1607–1614.

Yanez E, Uauy R, Ballester D, Barrera G, Chavez N, Guzman E, Saitua MT, Zacarias I. 1982. Capacity of the Chilean mixed diet to meet the protein and energy requirements of young adult males. *Br J Nutr* 47:1–10.

Yang WH, Drouin MA, Herbert M, Mao Y, Karsh J. 1997. The monosodium glutamate symptom complex: Assessment in a double-blind, placebo-controlled, randomized study. *J Allergy Clin Immunol* 99:757–762.

Yeatman TJ, Risley GL, Brunson ME. 1991. Depletion of dietary arginine inhibits growth of metastatic tumor. *Arch Surg* 126:1376–1382.

Yogman MW, Zeisel SH. 1983. Diet and sleep patterns in newborn infants. *N Engl J Med* 309:1147–1149.

Yogman MW, Zeisel SH. 1985. Nutrients, neurotransmitters and infant behavior. *Am J Clin Nutr* 42:352–360.

Yonetani S, Ishii H, Kirimura J. 1979. Effect of dietary administration of monosodium L-glutamate on growth and reproductive functions in mice. *Oyo Yakuri (Pharmacometrics)* 17:143–152.

Young SN. 1986. The clinical psychopharmacology of tryptophan. In: Wurtman RJ, Wurtman JJ, eds. *Nutrition and the Brain,* Vol. 7. New York: Raven Press. Pp. 49–88.

Young SN, Gauthier S. 1981. Effect of tryptophan administration on tryptophan, 5-hydroxyindoleacetic acid and indoleacetic acid in human lumbar and cisternal cerebrospinal fluid. *J Neurol Neurosurg Psychiatry* 44:323–327.

Young VR. 1987. 1987 McCollum Award Lecture. Kinetics of human amino acid metabolism: Nutritional implications and some lessons. *Am J Clin Nutr* 46:709–725.

Young VR, Borgonha S. 2000. Nitrogen and amino acid requirements: The Massachusetts Institute of Technology Amino Acid Requirement Pattern. *J Nutr* 130:1841S–1849S.

Young VR, Pellett PL. 1990. Current concepts concerning indispensable amino acid needs in adults and their implications for international nutrition planning. *Food Nutr Bull* 12:289–300.

Young VR, Pellett PL. 1994. Plant proteins in relation to human protein and amino acid nutrition. *Am J Clin Nutr* 59:1203S–1212S.

Young VR, Hussein MA, Scrimshaw JS. 1968. Estimate of loss of labile body nitrogen during acute protein deprivation in young adults. *Nature.* 218:568–569.

Young VR, Tontisirin K, Ozalp I, Lakshmanan F, Scrimshaw NS. 1972. Plasma amino acid response curve and amino acid requirements in young men: Valine and lysine. *J Nutr* 102:1159–1169.

Young VR, Taylor YS, Rand WM, Scrimshaw NS. 1973. Protein requirements of man: Efficiency of egg protein utilization at maintenance and sub-maintenance levels in young men. *J Nutr* 103:1164–1174.

Young VR, Fajardo L, Murray E, Rand WM, Scrimshaw NS. 1975a. Protein requirements of man: Comparative nitrogen balance response within the submaintenance-to-maintenance range of intakes of wheat and beef proteins. *J Nutr* 105:534–542.

Young VR, Steffee WP, Pencharz PB, Winterer JC, Scrimshaw NS. 1975b. Total human body protein synthesis in relation to protein requirements at various ages. *Nature* 253:192–194.

Young VR, Puig M, Queiroz E, Scrimshaw NS, Rand WM. 1984. Evaluation of the protein quality of an isolated soy protein in young men: Relative nitrogen requirements and effect of methionine supplementation. *Am J Clin Nutr* 39:16–24.

Young VR, Gucalp C, Rand WM, Matthews DE, Bier DM. 1987. Leucine kinetics during three weeks at submaintenance-to-maintenance intakes of leucine in men: Adaptation and accommodation. *Hum Nutr Clin Nutr* 41:1–18.

Young VR, Bier DM, Pellett PL. 1989. A theoretical basis for increasing current estimates of the amino acid requirements in adult man, with experimental support. *Am J Clin Nutr* 50:80–92.

Young VR, Marchini JS, Cortiella J. 1990. Assessment of protein nutritional status. *J Nutr* 120:1496–1502.

Young VR, Wagner DA, Burini R, Storch KJ. 1991. Methionine kinetics and balance at the 1985 FAO/WHO/UNU intake requirement in adult men studied with L-[$^{2}H_{3}$-methyl-1-^{13}C]methionine as a tracer. *Am J Clin Nutr* 54:377–385.

Young VR, El-Khoury AE, Raguso CA, Forslund AH, Hambraeus L. 2000. Rates of urea production and hydrolysis and leucine oxidation change linearly over widely varying protein intakes in healthy adults. *J Nutr* 130:761–766.

Yuwiler A, Brammer GL, Morley JE, Raleigh MJ, Flannery JW, Geller E. 1981. Short-term and repetitive administration of oral tryptophan in normal men. Effects on blood tryptophan, serotonin, and kynurenine concentrations. *Arch Gen Psychiatry* 38:619–626.

Zanni E, Calloway DH, Zezulka AY. 1979. Protein requirements of elderly men. *J Nutr* 109:513–524.

Zello GA, Pencharz PB, Ball RO. 1990. Phenylalanine flux, oxidation and conversion to tyrosine in humans studied with L-[1-^{13}C]phenylalanine. *Am J Physiol* 259:E835–E843.

Zello GA, Pencharz PB, Ball RO. 1993. Dietary lysine requirement of young adult males determined by oxidation of L-[1-^{13}C]phenylalanine. *Am J Physiol* 264:E677–E685.

Zello GA, Wykes LJ, Ball RO, Pencharz PB. 1995. Recent advances in methods of assessing dietary amino acid requirements for adult humans. *J Nutr* 125:2907–2915.

Zezulka AY, Calloway DH. 1976a. Nitrogen retention in men fed isolated soybean protein supplemented with L-methionine, D-methionine, N-acetyl-L-methionine, or inorganic sulfate. *J Nutr* 106:1286–1291.

Zezulka AY, Calloway DH. 1976b. Nitrogen retention in men fed varying levels of amino acids from soy protein with or without added L-methionine. *J Nutr* 106:212–221.

Zhao X-H, Wen ZM, Meredith CN, Matthews DE, Bier DM, Young VR. 1986. Threonine kinetics at graded threonine intakes in young men. *Am J Clin Nutr* 43:795–802.

Ziegler TR, Benfell K, Smith RJ, Young LS, Brown E, Ferrari-Baliviera E, Lowe DK, Wilmore DW. 1990. Safety and metabolic effects of L-glutamine administration in humans. *J Parenter Enteral Nutr* 14:137S–146S.

Zimmerman FT, Burgemeister BB. 1959. A controlled experiment of glutamic acid therapy. *AMA Arch Neurol Psych* 81:639–648.

Zlotkin SH. 1989. Nutrient interactions with total parenteral nutrition: Effect of histidine and cysteine intake on urinary zinc excretion. *J Pediatr* 114:859–864.

11

Macronutrients and Healthful Diets

SUMMARY

Acceptable Macronutrient Distribution Ranges (AMDRs) for individuals have been set for carbohydrate, fat, *n*-6 and *n*-3 polyunsaturated fatty acids, and protein based on evidence from interventional trials, with support of epidemiological evidence that suggests a role in the prevention or increased risk of chronic diseases, and based on ensuring sufficient intakes of essential nutrients.

The AMDR for fat and carbohydrate is estimated to be 20 to 35 and 45 to 65 percent of energy for adults, respectively. These AMDRs are estimated based on evidence indicating a risk for coronary heart disease (CHD) at low intakes of fat and high intakes of carbohydrate and on evidence for increased risk for obesity and its complications (including CHD) at high intakes of fat. Because the evidence is less clear on whether low or high fat intakes during childhood can lead to increased risk of chronic diseases later in life, the estimated AMDRs for fat for children are primarily based on a transition from the high fat intakes that occur during infancy to the lower adult AMDR. The AMDR for fat is 30 to 40 percent of energy for children 1 to 3 years of age and 25 to 35 percent of energy for children 4 to 18 years of age. The AMDR for carbohydrate for children is the same as that for adults—45 to 65 percent of energy. The AMDR for protein is 10 to 35 percent of energy for adults and 5 to 20 percent and 10 to 30 percent for children 1 to 3 years of age and 4 to 18 years of age, respectively.

Based on usual median intakes of energy, it is estimated that a lower boundary level of 5 percent of energy will meet the Adequate Intake (AI) for linoleic acid (Chapter 8). An upper boundary for linoleic acid is set at 10 percent of energy for three reasons: (1) individual dietary intakes in the North American population rarely exceed 10 percent of energy, (2) epidemiological evidence for the safety of intakes greater than 10 percent of energy are generally lacking, and (3) high intakes of linoleic acid create a pro-oxidant state that may predispose to several chronic diseases, such as CHD and cancer. Therefore, an AMDR of 5 to 10 percent of energy is estimated for *n*-6 polyunsaturated fatty acids (linoleic acid).

An AMDR for α-linolenic acid is estimated to be 0.6 to 1.2 percent of energy. The lower boundary of the range meets the AI for α-linolenic acid (Chapter 8). The upper boundary corresponds to the highest α-linolenic acid intakes from foods consumed by individuals in the United States and Canada. A growing body of literature suggests that higher intakes of α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) may afford some degree of protection against CHD. Because the physiological potency of EPA and DHA is much greater than that for α-linolenic acid, it is not possible to estimate one AMDR for all *n*-3 fatty acids. Approximately 10 percent of the AMDR can be consumed as EPA and/or DHA.

No more than 25 percent of energy should be consumed as added sugars. This maximal intake level is based on ensuring sufficient intakes of certain essential micronutrients that are not present in foods and beverages that contain added sugars. A daily intake of added sugars that individuals should aim for to achieve a healthy diet was not set.

A Tolerable Upper Intake Level (UL) was not set for saturated fatty acids, *trans* fatty acids, or cholesterol (see Chapters 8 and 9). This chapter provides some guidance in ways of minimizing the intakes of these three nutrients while consuming a nutritionally adequate diet.

INTRODUCTION

Unlike micronutrients, macronutrients (fat, carbohydrate, and protein) are sources of body fuel that can be used somewhat interchangeably. Thus, for a certain level of energy intake, increasing the proportion of one macronutrient necessitates decreasing the proportion of one or both of the other macronutrients. The majority of energy is consumed as carbo-

hydrate (approximately 35 to 70 percent, primarily as starch and sugars), and fat (approximately 20 to 45 percent), while the contribution of protein to energy intake is smaller and less varied (10 to 23 percent) (Appendix Tables E-3, E-6, and E-17). Therefore, a high fat diet (high percent of energy from fat) is usually low in carbohydrate and vice versa. In addition to these macronutrients, alcohol can provide on average up to 3 percent of energy of the adult diet (Appendix Table E-18).

A small amount of carbohydrate and as *n*-6 (linoleic acid) and *n*-3 (α-linolenic acid) polyunsaturated fatty acids and a number of amino acids that are essential for metabolic and physiological processes, are needed by the brain. The amounts needed, however, each constitute only a small percentage of total energy requirements. Food sources vary in their content of particular macro- and micronutrients. While some nutrients are present in both animal- and plant-derived foods, others are only present or are more abundant in either animal or plant foods. For example, animal-derived foods contain significant amounts of protein, saturated fatty acids, long-chain *n*-3 polyunsaturated fatty acids, and the micronutrients iron, zinc, and vitamin B_{12}, while plant-derived foods provide greater amounts of carbohydrate, *Dietary Fiber*, linoleic and α-linolenic acids, and micronutrients such as vitamin C and the B vitamins. It may be difficult to achieve sufficient intakes of certain micronutrients when consuming foods that contain very low amounts of a particular macronutrient. Alternatively, if intake of certain macronutrients from nutrient-poor sources is too high, it may also be difficult to consume sufficient micronutrients and still remain in energy balance. Therefore, a diet containing a variety of foods is considered the best approach to ensure sufficient intakes of all nutrients. This concept is not new and has been part of nutrition education programs since the early 1900s. For example, the first U.S. food guide was developed by the U.S. Department of Agriculture in 1916 and suggested consumption of a combination of five different food groups (Guthrie and Derby, 1998). This food guide has evolved to become known as the Food Guide Pyramid (USDA, 1996). Similarly, Canada has developed Canada's Food Guide to Healthy Eating (Health Canada, 1997).

A growing body of evidence indicates that an imbalance in macronutrients (e.g., low or high percent of energy), particularly with certain fatty acids and relative amounts of fat and carbohydrate, can increase risk of several chronic diseases. Much of this evidence is based on epidemiological studies of clinical endpoints such as coronary heart disease (CHD), diabetes, cancer, and obesity. However, these studies demonstrate associations; they do not necessarily infer causality, such as would be derived from controlled clinical trials. Robust clinical trials with specified clinical endpoints are generally lacking for macronutrients. Of importance, factors other than diet contribute to chronic disease, and multifactorial cau-

sality of chronic disease can confound the long-term adverse effects of a given macronutrient distribution. It is not possible to determine a defined level of intake at which chronic disease may be prevented or may develop. For example, high fat diets may predispose to obesity, but at what percent of energy intake does this occur? The answer depends on whether energy intake exceeds energy expenditure or is balanced with physical activity.

This chapter reviews the scientific evidence on the role of macronutrients in the development of chronic disease. In addition, the nutrient limitations that can occur with the consumption of too little or too much of a particular macronutrient are discussed. In consideration of the interrelatedness of macronutrients, their role in chronic disease, and their association with other essential nutrients in the diet, Acceptable Macronutrient Distribution Ranges (AMDRs) are estimated and represented as percent of energy intake. These ranges represent (1) intakes that are associated with reduced risk of chronic disease, (2) intakes at which essential dietary nutrients can be consumed at sufficient levels, and (3) intakes based on adequate energy intake and physical activity to maintain energy balance. When intakes of macronutrients fall above or below the AMDR, the risk for development of chronic disease (e.g., diabetes, CHD, cancer) appears to increase.

DIETARY FAT AND CARBOHYDRATE

There are a number of adverse health effects that may result from consuming a diet that is too low or high in fat or carbohydrate (starch and sugars). Furthermore, chronic consumption of a low fat, high carbohydrate or high fat, low carbohydrate diet may result in the inadequate intake of certain essential nutrients.

Low Fat, High Carbohydrate Diets of Adults

The chronic diseases of greatest concern with respect to relative intakes of macronutrients are CHD, diabetes, and cancer. In this section, the relationship between total fat and total carbohydrate intakes are considered. Comparisons are made in terms of *percentage* of total energy intake. For example, a low fat diet signifies a lower percentage of fat relative to total energy. It does not imply that total energy intake is reduced because of consumption of a low amount of fat. The distinction between *hypocaloric* diets and *isocaloric* diets is important, particularly with respect to impact on body weight. Low and high fat diets can still be isocaloric. The failure to identify this distinction has led to considerable confusion in terms of the role of dietary fat in chronic disease.

In the past few decades, the prevalence of overweight and obesity has increased at an alarming rate in many populations, particularly in the United States. Overweight and obesity contribute significantly to various chronic diseases. Consequently, there are two issues to consider for the distribution of fat and carbohydrate intakes in high-risk populations: the distributions that predispose to the development of overweight and obesity, and the distributions that worsen the metabolic consequences in populations that are already overweight or obese. These issues will be considered in the following sections.

Maintenance of Body Weight

A first issue is whether a certain macronutrient distribution interferes with sufficient intake of total energy, that is, sufficient energy to maintain a healthy weight. Sonko and coworkers (1994) concluded that an intake of 15 percent fat was too low to maintain body weight in women, whereas an intake of 18 percent fat was shown to be adequate even with a high level of physical activity (Jéquier, 1999). Moreover, some populations, such as those in Asia, have habitual very low fat intakes (about 10 percent of total energy) and apparently maintain adequate health (Weisburger, 1988). Whether these low fat intakes and consequent low energy consumptions have contributed to a historically small stature in these populations is uncertain.

An issue of more importance for well-nourished but sedentary populations, such as that of the United States, is whether the distribution between intakes of total fat and total carbohydrate influences the risk for weight gain (i.e., for development of overweight or obesity). It has been shown that when men and women were fed isocaloric diets containing 20, 40, or 60 percent fat, there was no difference in total daily energy expenditure (Hill et al., 1991). Similar observations were reported for individuals who consumed diets containing 10, 40, or 70 percent fat, where no change in body weight was observed (Leibel et al., 1992), and for men fed diets containing 9 to 79 percent fat (Shetty et al., 1994). Horvath and colleagues (2000) reported no change in body weight after runners consumed a diet containing 16 percent fat for 4 weeks. These studies contain two important findings: fat and carbohydrate provide similar amounts of metabolic energy predicted from their true energy content, and isocaloric diets provide similar metabolic energy expenditure, regardless of their fat–carbohydrate distribution. In other words, at isocaloric intakes, low fat diets do not produce weight loss.

A number of short- and long-term intervention studies have been conducted on normal-weight or moderately obese individuals to ascertain the effects of altering the fat and energy density content of the diet on body weight (Table 11-1). In general, significant reductions in the percent of

TABLE 11-1 Decreased Fat Intake and Body Weight Change in Normal-Weight or Moderately Obese Individuals

Reference	Study Design	Dietary Fat (% of energy)	Weight Change (kg)	Comments
Short-term studies (< 1 year)				
Boyar et al., 1988	19 women 6-mo intervention Ad libitum diet	34 → 21%	–5.1	Decreased fat intake associated with decreased energy intake
Buzzard et al., 1990	29 postmenopausal women 3-mo parallel Ad libitum diet	38 → 23% 39 → 35%	–2.8 –1.3	Decreased fat intake associated with decreased energy intake
Bloemberg et al., 1991	80 men 26-wk parallel Ad libitum diet	39 → 34% 38 → 37%	–0.94 +0.06	
Kendall et al., 1991	13 women 11-wk crossover Controlled diet	20–25% 35–40%	–2.54 –1.26	Decreased fat intake associated with decreased energy intake Low fat diet, hypocaloric
Leibel et al., 1992	13 men and women 15- to 56-d intervention Controlled diet	0, 40, or 70%	No significant changes in body weight	Isocaloric diets
Westerterp et al., 1996	217 men and women 6-mo parallel Ad libitum diet	35 → 33% 36 → 41%	+0.3 +1.1	

Raben et al., 1997	11 women 14-d crossover Ad libitum	46 → 28%	–0.7		Decreased fat intake associated with decreased energy intake
Gerhard et al., 2000	22 women 4-wk crossover Controlled diet	20% 40%	–1.1 –0.3		Low fat diet, hypocaloric
Saris et al., 2000	398 men and women 6-mo parallel Ad libitum diet	36 → 26% 36 → 28% 36 → 37%	–0.9 –1.8 +0.8		Decreased fat intake associated with decreased energy intake
Long-term studies (≥ 1 year)					
Lee-Han et al., 1988	57 women 1-y parallel Ad libitum diet		6 mo	12 mo	Decreased fat intake associated with decreased energy intake
		36 → 23 → 26%	–1.16	–0.93	
		36 → 34 → 36%	+0.07	+0.62	
Boyd et al., 1990	206 women 1-y parallel Ad libitum diet	37 → 21% 37 → 35%	–1.0 0		
Sheppard et al., 1991	276 women 1- and 2-y parallel Ad libitum diet	0 to 1 y			Decreased fat intake associated with decreased energy intake
		39 → 22%	–3.0		
		39 → 37%	–0.4		
		1 y to 2 y			
		22 → 23%	+1.1		

continued

TABLE 11-1 Continued

Reference	Study Design	Dietary Fat (% of energy)	Weight Change (kg)	Comments
Baer, 1993	70 men 1-y parallel Ad libitum diet	38 → 31% 37 → 36%	–5.0 +1.0	Decreased fat intake associated with decreased energy intake
Kasim et al., 1993	72 women 1-y parallel Ad libitum diet	36 → 18% 36 → 34 %	–3.4 –0.8	Decreased fat intake associated with decreased energy intake
Black et al., 1994	76 men and women 2-y parallel Ad libitum diet	40 → 21% 39 → 39%	–2.0 –1.0	
Knopp et al., 1997	137 men 1-y parallel Ad libitum diet	36 → 27% 35 → 22%	–2.9 –2.9	
Stefanick et al., 1998	177 postmenopausal women and 190 men 1-y parallel Ad libitum diet	Women / Men 23% / 22% 28% / 30%	Women / Men –2.7 / –2.8 +0.8 / +0.5	Decreased fat intake associated with decreased energy intake
Kasim-Karakas et al., 2000	54 postmenopausal women 1-y intervention Controlled diet 4 mo Ad libitum diet 8 mo	34 → 14 → 12%	4 mo / 12 mo –1.3 / –5.9	

energy consumed as fat (greater than 4 percent) resulted in small losses in body weight. The only study that provided isocaloric diets showed no differences in weight gain or loss, despite a wide range in the percent of energy from fat (Leibel et al., 1992). Four meta-analyses of long-term intervention studies associating a low fat diet with body weight concluded that lower fat diets lead to modest weight loss or prevention of weight gain (Astrup et al., 2000; Bray and Popkin, 1998; Hill et al., 2000; Yu-Poth et al., 1999). These studies thus suggest that low fat diets (low percentage of fat) tend to be slightly hypocaloric compared to higher fat diets when compared in outpatient intervention trials.

The finding that higher fat diets are moderately hypercaloric when compared with reduced fat intakes under ad libitum conditions provides a rationale for setting an upper boundary for percentage of fat intake in a population that already has a high prevalence of overweight and obesity. However, a second issue must also be addressed: whether the distribution of fat and carbohydrate modifies the metabolic consequences of overweight and obesity. Two of the more important consequences of obesity are dyslipidemic changes in serum lipoproteins (which predispose to CHD) and changes in glucose and insulin metabolism that accentuate an underlying insulin resistance (which may predispose to both CHD and diabetes). These consequences are discussed in the following sections.

Risk of CHD

Low fat, high carbohydrate diets, compared to higher fat intakes, can induce a lipoprotein pattern called the atherogenic lipoprotein phenotype (Krauss, 2001) or atherogenic dyslipidemia (National Cholesterol Education Program, 2001). In populations where people are routinely physically active and lean, the atherogenic lipoprotein phenotype is minimally expressed. In sedentary populations that tend to be overweight or obese, very low fat, high carbohydrate diets clearly promote the development of this phenotype. Whether this phenotype promotes development of coronary atherosclerosis when it is specifically induced by low fat diets is uncertain, but it is a pattern that is associated with increased risk for CHD when expressed in the general American population. The atherogenic lipoprotein phenotype is characterized by higher triacylglycerol and decreased high density lipoprotein (HDL) cholesterol concentrations and small low density lipoprotein (LDL) particles. A predominance of small LDL particles is associated with a greater risk of CHD (Austin et al., 1990), but it is not known if this association is independent of increased triacylglycerol and decreased HDL cholesterol concentrations.

Table 11-2 and Figures 11-1 and 11-2 show that with decreasing fat and increasing carbohydrate intake, plasma triacylglycerol concentrations

TABLE 11-2 Fat and Carbohydrate Intake and Blood Lipid Concentrations in Healthy Individuals

Reference	Study Design[a]	Total Fat/ Carbohydrate Intake (% of energy)
Coulston et al., 1983	11 men and women 10-d crossover P/S = 1.2–1.3	 21 41
Bowman et al., 1988	19 men 10-wk parallel P/S = 0.4	29/60 33/58 45/42 46/42
Borkman et al., 1991	8 men and women 3-wk crossover	20/55 P/S = 0.46 50/31 P/S = 0.22
Kasim et al., 1993	72 women 1-y parallel P/S = 0.68–0.75	18 34
Leclerc et al., 1993	7 men and women 7-d crossover	11/64 30/45 40/45
Krauss and Dreon, 1995	105 men 6-wk crossover P/S = 0.69–0.74	24/60 46/39
O'Hanesian et al., 1996	10 men and women 10-d crossover	17/63 P/S = 0.25 28/57 P/S = 2.2 42/39 P/S = 1.7
Jeppesen et al., 1997	10 postmenopausal women 3-wk crossover P/S = 1.0	25/60 45/40
Kasim-Karakas et al., 1997	14 postmenopausal women 4-mo intervention	14 P/S = 1.2 23 P/S = 1.0 31 P/S = 0.9
Yost et al., 1998	25 men and women 15-d crossover P/S = 0.3	25/55 50/30
Straznicky et al., 1999	14 men 2-wk crossover	25/54 P/S = 1.3 47/36 P/S = 0.1
Kasim-Karakas et al., 2000	54 postmenopausal women 4- to 12-mo crossover P/S = 0.64	12/71 14/69 34/50

Postintervention Blood Lipid Concentration (mmol/L)[b]		
Triacylglycerol	HDL-C	LDL-C
1.51[c]	0.98[c]	
1.02[d]	1.16[d]	
0.91[c]	1.42[c]	2.35[c]
1.11[c]	1.22[c]	2.17[c]
0.84[c]	1.53[c]	2.59[c]
1.01[c]	1.50[c]	2.40[c]
0.82[c] (+49%)	0.84[c] (–24%)	2.88[c] (–20%)
0.55[c]	1.10[d]	3.60[d]
1.35[c]	1.44[c] (–8%)	2.79[c] (–10%)
1.25[d]	1.56[d]	3.09[d]
1.11[c]	1.03[c]	2.29[c]
1.29[c]	1.15[d]	2.47[c]
0.87[d]	1.32[e]	3.05[d]
1.59[c]	1.09[c]	3.26[c]
1.13[d]	1.27[d]	3.69[d]
0.8	1.1	2.4
0.8	1.2	2.5
0.8	1.3	3.0
1.97[c]	1.38[c]	2.74[c]
1.29[d]	1.49[d]	2.81[c]
2.47[c]	1.24[c]	2.61[c]
2.10[d]	1.32[d]	2.93[d]
1.85[e]	1.34[d]	2.89[d]
1.14[c]	1.22[c]	
0.88[d]	1.30[d]	
0.8[c]	1.05[c]	2.6[c]
0.8[c]	1.28[d]	3.5[d]
1.49[c]	1.40[c]	3.49[c]
2.00[c]	1.29[c]	3.18[c]
1.57[c]	1.53[d]	3.57[c]

continued

TABLE 11-2 Continued

Reference	Study Design[a]	Total Fat/ Carbohydrate Intake (% of energy)
Marckmann et al., 2000	20 women 2-wk crossover	28/59 P/S = 0.7 46/41 P/S = 0.4
Obarzanek et al., 2001b	459 men and women, 8-wk parallel	27/58 P/S = 1.1 37/52 P/S = 0.5

[a] P/S = polyunsaturated/saturated fatty acid ratio.
[b] HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol.

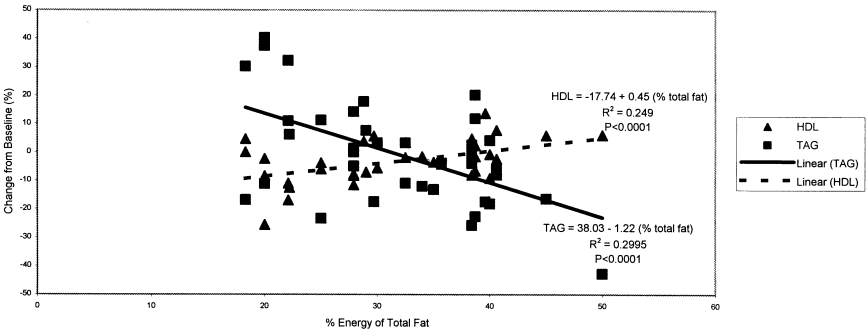

FIGURE 11-1 Relationship between percent of total fat intake and change in triacylglycerol (TAG) (—) and high density lipoprotein (HDL) cholesterol (---) concentrations. Regression equations for percent change in serum TAG and HDL cholesterol predicted by percent total fat in the experimental diets of controlled-feeding studies comparing low fat, high carbohydrate diets to high fat diets. Weighted least-squares regression analyses were performed using the mixed procedure to test for differences in lipid concentrations (SAS Statistical package, version 8.00, SAS Institute, Inc., 1999). Percent of energy from total fat varied from 18.3% to 50%. All diets were low in saturated fat (less than 10% energy). Using these equations, for every 5% decrease in total fat, HDL cholesterol would decrease by 2.2% and triacylglycerol would increase by 6%.
DATA SOURCES: Berry et al. (1992); Curb et al. (2000); Garg et al. (1988, 1992a, 1994); Ginsberg et al. (1990); Grundy (1986); Grundy et al. (1988); Jansen et al. (1998); Kris-Etherton et al. (1999); Lefevre et al., unpublished; Lopez-Segura et al. (1996); Mensink and Katan (1987); Nelson et al. (1995); Parillo et al. (1992); Pelkman et al. (2001); Perez-Jimenez et al. (1995, 1999, 2001).

Postintervention Blood Lipid Concentration (mmol/L)[b]		
Triacylglycerol	HDL-C	LDL-C
0.81[c]	1.34[c]	2.43[c]
0.70[d]	1.56[d]	2.71[d]
+0.4	–0.09	–0.29
–0.09	–0.005	–0.05

[c,d,e] Within each study, LDL-C, HDL-C, or Lp(a) concentrations that are significantly different between treatment groups have a different superscript.

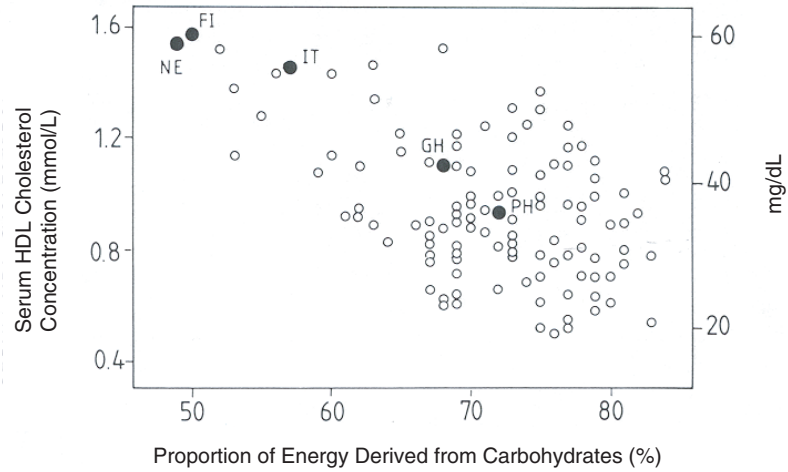

FIGURE 11-2 Relationship between proportion of energy from carbohydrates and serum high density lipoprotein (HDL) cholesterol concentration. • = Mean values for approximately 120 boys from five countries, o = individuals values for boys from the Philippines, FI= Finland, NE = Netherlands, GH = Ghana, IT = Italy, PH = Philippines.
SOURCE: Knuiman et al. (1987).

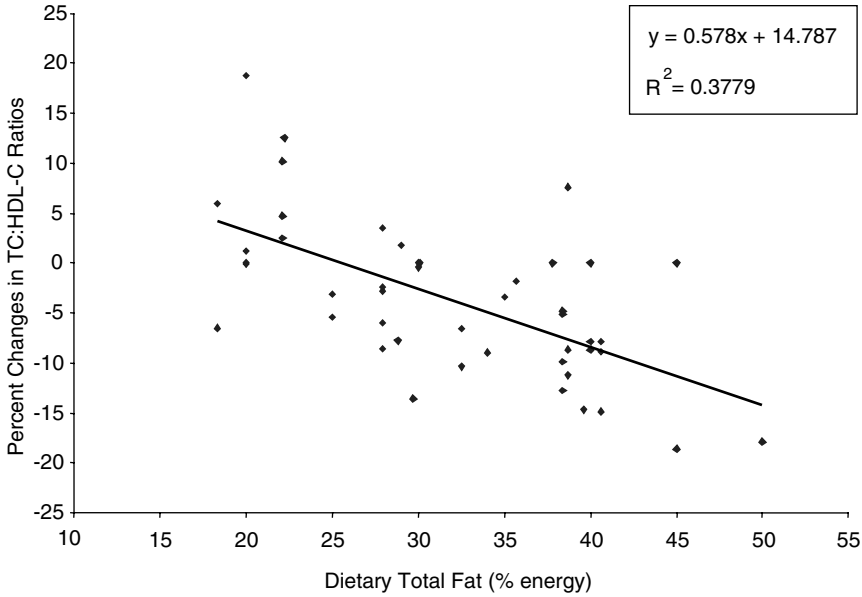

FIGURE 11-3 Relationship between total fat intake and change in total cholesterol (TC):high density lipoprotein (HDL) cholesterol ratio. Weighted least-squares regression analyses were performed using the mixed procedure to test for differences in lipid concentrations (SAS Statistical package, version 8.00, SAS Institute, Inc., 1999).
DATA SOURCES: Berry et al. (1992); Curb et al. (2000); Garg et al. (1988, 1992a, 1994); Ginsberg et al. (1990); Grundy (1986); Grundy et al. (1988); Jansen et al. (1998); Kris-Etherton et al. (1999); Lefevre et al., unpublished; Lopez-Segura et al. (1996); Mensink and Katan (1987); Nelson et al. (1995); Parillo et al. (1992); Pelkman et al. (2001); Perez-Jimenez et al. (1995, 1999, 2001).

increase and plasma HDL cholesterol concentrations decrease. The reduction in HDL cholesterol concentration with low fat intake results in a rise in the total:HDL cholesterol concentration ratio (Figure 11-3). The total:HDL cholesterol ratio has been shown to be an important risk factor for CHD (Castelli et al., 1992; Kannel, 2000). Whether diet-induced changes in the total:HDL cholesterol ratio predispose to CHD remains unclear (Brussard et al., 1982; Jeppesen et al., 1997; Krauss and Dreon, 1995; West et al., 1990; Yost et al., 1998).

In support of the interventional studies, carbohydrate intake is negatively associated with HDL cholesterol concentrations (Table 11-3). Nonetheless, the association between atherogenic lipoprotein phenotype (higher

TABLE 11-3 Epidemiological Studies on Carbohydrate Intake and Blood Lipid Concentrations

Reference	Study Design	Low Density Lipoprotein (LDL) Cholesterol Concentration	High Density Lipoprotein (HDL) Cholesterol Concentration	Triacylglycerol Concentration
Ernst et al., 1980	4,855 men and women Cross-sectional		Inversely related to carbohydrate intake	
Knuiman et al., 1987	Multicountry regression analysis		Inversely related to carbohydrate intake	
Fehily et al., 1988	653 men Cross-sectional regression analysis	No association	Negative association between carbohydrate intake and HDL concentration	No association
West et al., 1990	719 boys Multicountry regression analysis	Decreased with increased carbohydrate intake	Decreased with increased carbohydrate intake	Increased with increased carbohydrate intake
Tillotson et al., 1997	Prospective cohort, 6-y follow-up			
	< 29% carbohydrate	4.18	1.13	2.11
	29–36% carbohydrate	4.13	1.11	2.26
	36–41% carbohydrate	4.13	1.09	2.23
	41–48% carbohydrate	4.11	1.07	2.25
	> 48% carbohydrate	4.14	1.05	2.13

total:HDL cholesterol ratios) and CHD risk provides one rationale for establishing a lower boundary for the Acceptable Macronutrient Distribution Range (AMDR) for high-risk populations.

Risk of Hyperinsulinemia, Glucose Intolerance, and Type 2 Diabetes

Other potential abnormalities accompanying changes in distribution of fat and carbohydrate intakes include increased postprandial responses in plasma glucose and insulin concentrations. These abnormalities are more likely to occur with low fat, high carbohydrate diets. They potentially could be related to the development of both type 2 diabetes and CHD. In particular, repeated daily elevations in postprandial glucose and insulin concentrations could "exhaust" pancreatic β-cells of insulin supply, which could hasten the onset of type 2 diabetes. Some investigators have further suggested these repeated elevations could worsen baseline insulin sensitivity, which could cause susceptible persons to be at increased risk for type 2 diabetes. This form of diabetes, defined by an elevation of fasting serum glucose concentration, is characterized by two defects in glucose metabolism: insulin resistance, a defect in insulin-mediated uptake of glucose by cells, particularly skeletal muscle cells, and a decline in insulin secretory capacity by pancreatic β-cells (Turner and Clapham, 1998). Insulin resistance typically precedes the development of type 2 diabetes by many years. It is known to be the result of obesity, physical inactivity, and genetic factors (Turner and Clapham, 1998). Before the onset of diabetic hyperglycemia, the pancreatic β-cells are able to respond to insulin resistance with an increased insulin secretion, enough to maintain normoglycemia. However, in some persons who are insulin resistant, insulin secretory capacity declines and hyperglycemia ensues (Reaven, 1988, 1995).

The mechanisms for the decline in insulin secretion are not well understood, but one theory is that continuous overstimulation of insulin secretion by the presence of insulin resistance leads to "insulin exhaustion" and hence to decreased insulin secretory capacity (Turner and Clapham, 1998). Whether insulin exhaustion is secondary to a metabolic dysfunction of cellular production of insulin or to a loss of β-cells is uncertain. The accumulation of pancreatic islet-cell amyloidosis may be one mechanism for loss of insulin-secretory capacity (Höppener et al., 2000).

High carbohydrate diets frequently causes greater insulin and plasma glucose responses than do low carbohydrate diets (Chen et al., 1988; Coulston et al., 1987). These excessive responses theoretically could predispose individuals to the development of type 2 diabetes because of prolonged overstimulation of insulin secretion (Grill and Björklund, 2001). The reasoning is similar to that for insulin resistance, namely, excessive stimulation of insulin secretion over a period of many years could result in

insulin exhaustion, and hence to hyperglycemia (Turner and Clapham, 1998). This mechanism, although plausible, remains hypothetical. Nonetheless, in the mind of some investigators, it deserves serious consideration.

Other consequences of hyperglycemic responses to high carbohydrate diets might be considered. For example, higher postprandial glucose responses might lead to other changes such as "desensitization" of β-cells for insulin secretion and production of glycated products or advanced glycation end-products, which could either promote atherogenesis or the "aging" process (Lopes-Virella and Virella, 1996). Again, these are hypothetical consequences that need further examination.

Epidemiological Evidence. A number of noninterventional, epidemiological studies have shown no relationship between carbohydrate intake and risk of diabetes (Colditz et al., 1992; Lundgren et al., 1989; Marshall et al., 1991; Meyer et al., 2000; Salmerón et al., 1997), whereas other studies have shown a positive association (Bennett et al., 1984; Feskens et al., 1991a).

Interventional Evidence. Interventional studies in healthy individuals on the influence of high carbohydrate diets on biomarker precursors for type 2 diabetes are lacking and the available data are mixed (Table 11-4) (Beck-Nielsen et al., 1980; Chen et al., 1988; Dunnigan et al., 1970; Fukagawa et al., 1990; Rath et al., 1974; Reiser et al., 1979). Factors such as carbohydrate quality, body weight, exercise, and genetics make the interpretation of such findings difficult. Nonetheless, in overweight and sedentary groups (which carry a heavy burden of insulin resistance and are common in North America), the accentuation of postprandial glucose and insulin concentrations that accompany high carbohydrate diets are factors to consider when setting an upper boundary for AMDRs for dietary carbohydrate (and a lower boundary for dietary fat).

Risk of Nutrient Inadequacy or Excess

Diets Low in Fats. For usual diets that are low in total fat, the intake of essential fatty acids, such as *n*-6 polyunsaturated fatty acids, will be low (Appendix K). In general, with increasing intakes of carbohydrate and decreasing intakes of fat, the intake of *n*-6 polyunsaturated fatty acids decreases. Furthermore, low intakes of fat are associated with low intakes of zinc and certain B vitamins.

The digestion and absorption of fat-soluble vitamins and provitamin A carotenoids are associated with fat absorption. Jayarajan and coworkers (1980) reported that the addition of 5 or 10 g of fat to a low fat (5 g) diet

TABLE 11-4 Intervention Studies on Carbohydrate Intake and Biochemical Indicators of Diabetes

Reference	Study Design
Dunnigan et al., 1970	9 men and women 4-wk crossover 31% sucrose Sucrose-free
Rath et al., 1974	6 men 2- to 5-wk crossover 17% sucrose 52% sucrose
Reiser et al., 1979	19 men and women 6-wk crossover 30% starch 30% sucrose
Beck-Nielsen et al., 1980	7-d intervention Normal diet + 250 g glucose Normal diet + 250 g fructose
Chen et al., 1988	8 men 3- to 5-d crossover 85% carbohydrate 41% carbohydrate 30% carbohydrate
Lundgren et al., 1989	1,462 women, Prospective cohort, 12-y follow-up
Fukagawa et al., 1990	6 men 21- to 28-d intervention 40% carbohydrate 69% carbohydrate

[a,b,c] Within each study, the indicators of diabetes that are significantly different between treatment groups have a different superscript.

Results	
No diet effect on glucose tolerance and plasma insulin	
Serum insulin (μg/mL)	Serum glucose (mg/dL)
5.4[a]	87.0[a]
11.8[b]	81.1[b]
Serum insulin (μmunits/mL)	Serum glucose (mg/dL)
9.8[a]	92.5[a]
11.9[b]	94.5[a]
No significant difference in insulin concentrations	
The high fructose diet was accompanied by a significant reduction in insulin binding and insulin sensitivity	
Insulin sensitivity index	Glucose disappearance (%/min)
5.6[a]	2.2[a]
6.1[b]	2.3[b]
3.9[a,c]	1.6[a,c]
5.6[a]	2.2[a]
6.1[b]	2.3[b]
3.9[a,c]	1.6[a,c]
Carbohydrate intake of women who developed diabetes (212 g/d) was not significantly different than women who did not develop diabetes (228 g/d)	
Serum insulin (pmol/L)	Glucose disposal (μmol/kg/min)
67.4[a]	21.2[a]
50.2[b]	27.8[b]

significantly improved serum vitamin A concentrations. However, the addition of 10 g compared to 5 g did not provide any further benefit. The level of dietary fat has also been shown to improve vitamin K_2 bioavailability (Uematsu et al., 1996). Dose–response data are limited on the amount of dietary fat needed to achieve the optimal absorption of fat-soluble vitamins, but it appears that the level is quite low.

Diets High in Fiber. Most diets that are high in fiber are also high in carbohydrate. High fiber diets have the potential for reduced energy density, reduced energy intake, and poor growth. However, poor growth is unlikely in the United States where most children consume adequate energy and fiber intake is relatively low (Williams and Bollella, 1995). Miles (1992) tested the effects of daily ingestion of 64 g or 34 g of *Dietary Fiber* for 10 weeks in healthy adult males. The ingestion of 64 g/d of *Dietary Fiber* resulted in a reduction in protein utilization from 89.4 to 83.7 percent and in fat utilization from 95.5 to 92.5 percent. Total energy utilization decreased from 94.3 to 91.4 percent. Because most individuals consuming high amounts of fiber would also be consuming high amounts of energy, the slight depression in energy utilization is not significant (Miles, 1992). In other studies, ingestion of high amounts of fruit, vegetable, and cereal fiber (48.3 to 85.6 g/d) also resulted in decreases in apparent digestibilities of energy, crude protein, and fat (Göranzon et al., 1983; Wisker et al., 1988). Again, however, the *Dietary Fiber* intakes were very high, and because the recommendation for *Total Fiber* intake is related to energy intake, the high fiber consumers would also be high energy consumers.

Diets High in Added Sugars. Increased consumption of added sugars can result in decreased intakes of certain micronutrients (Table 11-5). This can occur because of the abundance of added sugars in energy-dense, nutrient-poor foods, whereas naturally occurring sugars are primarily found in fruits, milk, and dairy products that also contain essential micronutrients. Because some micronutrients (e.g., vitamin B_6, vitamin C, and folate), dietary fiber, and phytochemicals were not examined, the association between these nutrients and added sugars intakes is not known. Bowman (1999) used data from Continuing Survey of Food Intakes of Individuals (CSFII) (1994–1996) to assess the relationship between added sugars and intakes of essential nutrients in Americans' diets. The sample (n = 14,704) was divided into three groups based on the percentage of energy consumed from added sugars: (1) less than 10 percent of total energy (n = 5,058), (2) 10 to 18 percent of total energy (n = 4,488), and (3) greater than 18 percent of total energy (n = 5,158). Group 3, with a mean of 26.7 percent of energy from added sugars, had the lowest absolute mean intakes of all

the micronutrients, especially vitamin A, vitamin C, vitamin B_{12}, folate, calcium, phosphorus, magnesium, and iron. Compared with Groups 1 and 2, a decreased percentage of people in Group 3 met their Recommended Dietary Allowance (RDA) for many micronutrients. The individuals in Group 3 did not meet the 1989 RDA for vitamin E, vitamin B_6, calcium, magnesium, and zinc. In addition, the high sugar consumers (Group 3) had lower intakes of grains, fruits, vegetables, meat, poultry, and fish compared with Groups 1 and 2. At the same time, Group 3 consumed more soft drinks, fruit drinks, punches, ades, cakes, cookies, grain-based pastries, milk desserts, and candies. Similar trends were also reported by Bolton-Smith and Woodward (1995) and Forshee and Storey (2001), but were not observed by Lewis and coworkers (1992). Emmett and Heaton (1995) reported an overall deterioration in the quality of the diet in heavy users of added sugars.

Using 1990–1991 cross-sectional data, Guthrie (1996) found that women whose diets met their RDA for calcium consumed significantly more milk products, fruit, and grains, and less regular soft drinks than women who did not meet their calcium recommendations. Others have shown that intakes of soft drinks are negatively related to intakes of milk (Guenther, 1986; Harnack et al., 1999; Skinner et al., 1999).

To further look at the association between added sugars and certain micronutrient intakes, the median intakes of various micronutrients at every 5th percentile of added sugars intake was determined using data from the Third National Health and Nutrition Examination Survey (NHANES III) (Appendix J). In addition, the prevalence of subpopulations not meeting the Estimated Average Requirement (EAR) or exceeding the Adequate Intake (AI) for these micronutrients was determined. Because not all micronutrients and other nutrients, such as fiber, were evaluated, it is not known what the association is between added sugars and these nutrients. While the trends are not consistent for all age groups, reduced intakes of calcium, vitamin A, iron, and zinc were observed with increasing intakes of added sugars, particularly at intake levels exceeding 25 percent of energy. Although this approach has limitations, it gives guidance for the planning of healthy diets.

Diets High in Total Sugars. In one large dietary survey, linear reductions were observed for certain micronutrients when total sugars intakes increased (Bolton-Smith and Woodward, 1995), whereas no consistent reductions were observed in another survey (Gibney et al., 1995) (Table 11-6). Bolton-Smith (1996) reviewed the literature on the relation of sugars intake to micronutrient adequacy and concluded that, provided consumption of sugars is not excessive (defined as less than 20 percent of total energy intake), no health risks are likely to ensue due to micronutrient inadequacies.

TABLE 11-5 Survey Data on Added Sugars and Micronutrient Intake

Reference	Study Population/Survey	Diet Information
Nelson, 1991	143 children, 11–12 y	7-d weighed diet record
Rugg-Gunn et al., 1991	405 children, 11–14 y	3-d diet record
Lewis et al., 1992	Nationwide Food Consumption Survey (1977–1978)	
Bolton-Smith and Woodward, 1995	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Food frequency questionnaire
Gibson, 1997	1,675 boys and girls, 1.5–4.5 y U.K. National Diet and Nutrition Survey of Children	4-d weighed diet record
Bowman, 1999	Continuing Survey of Food Intakes by Individuals (1994–1996)	Two 24-h recalls
Forshee and Storey, 2001	Continuing Survey of Food Intakes by Individuals (1994–1996)	

Added Sugars Intake (% of energy)	Change in Micronutrient Intake
16	Decrease in nicotinic acid for girls
21	
27	
10	Decrease in vitamin D, protein
20	
Percentile of intake	
26th–75th	
> 75th	Decrease in calcium
Men: 1.0–6.2, 6.3–8.9, 9.0–13.0, 13.1–15.7, 15.8–47.9	Linear reduction in vitamin E, vitamin C, and vitamin A for both men and women
Women: 0.8–4.8, 4.9–6.3, 6.4–8.1, 8.2–11.6, 11.7–50.2	
< 12	
12–16	Decrease in zinc, calcium, riboflavin
16–20	
20–25	
> 25	Decrease in niacin, thiamin; large decrease in calcium, zinc, riboflavin
< 10	
10–18	Decrease in calcium
> 18	Decrease in vitamin A, vitamin E, vitamin C, niacin, vitamin B_6, folate, vitamin B_{12}, phosphorus, magnesium, iron, zinc, copper; large decrease in calcium
	Negative correlation between added sugar intake and intake of vitamin A, calcium, and folate

TABLE 11-6 Survey Data on Total Sugar and Micronutrient Intake

Reference	Study Population/Survey	Diet Information
Gibson, 1993	2,705 children Department of Health Survey of British School Children	7-d weighed food record
Bolton-Smith and Woodward, 1995	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Food frequency questionnaire
Gibney et al., 1995	8,296 men and women Nationwide Food Consumption Survey (1987–1988)	3-d food record
Nicklas et al., 1996	568 children, 10 y Bogalusa Heart Study	24-h dietary recall
Farris et al., 1998	568 children, 10 y Bogalusa Heart Study	24-h dietary recall

The impact of total sugar intake on the intake of micronutrients does not appear to be as great as for added sugars. Furthermore, a preliminary analysis of data from NHANES III on the intake of various micronutrients at every 5th percentile of total sugar intake did not reveal any significant associations as was observed for added sugars (Appendix J).

High Fat, Low Carbohydrate Diets of Adults

Risk of Obesity

Epidemiological Evidence. Cross-country epidemiological data of dietary fat intake and obesity have yielded mixed results (Bray and Popkin, 1998;

Total Sugar Intake (% of energy)	Change in Micronutrient Intake
< 20.7	Decrease in iron, nicotinic acid
20.7–25.2	Large decrease in iron, nicotinic acid
> 25.2	No marked changes in micronutrient intake
Men: 2.5–12.0, 12.1–14.7, 14.8–17.2, 17.3–20.7, 20.8–51.4	Linear reduction in vitamin E, retinol, and vitamin A intake
Women: 1.5–11.7, 11.8–14.1, 14.2–16.3, 16.4–19.6, 19.7–52.8	Linear reduction in vitamin E, retinol, carotene, and vitamin A intake
< 10	
10–24	Decrease in riboflavin, thiamin, calcium, iron, zinc, vitamin A
> 24	Decrease in vitamin B_6, vitamin E
18.0	
22.1	
26.4	
31.2	Decrease in percent meeting the Recommended Dietary Allowance for niacin and zinc
16.1	Linear reduction in vitamin B_6, vitamin E, thiamin, iron, zinc, and niacin intake with increasing total sugar intake
23.5	
28.2	
35.6	

Willett, 1998). In some countries, low fat, high carbohydrate diets are associated with a low prevalence of obesity, whereas in others they are not.

Within-country surveys of dietary intake and body mass index (BMI) have also yielded mixed results. Many case-control and prospective studies failed to find a strong correlation between percent of energy intake from fat and body weight (Heitmann et al., 1995; Lissner et al., 2000; Ludwig et al., 1999b; Rissanen et al., 1991; Samaras et al., 1998; Willett, 1998), whereas some did find significant associations (Bray and Popkin, 1998; Dreon et al., 1988; George et al., 1990; Klesges et al., 1992; Miller et al., 1990; Romieu et al., 1988; Tucker and Kano, 1992). Colditz and coworkers (1990) observed no association between fat intake and weight gain prospectively, but did find a positive association between previous weight

gain and high fat intake. One statistically well-designed study that included direct measurements of body fat and considered potentially confounding factors such as exercise concluded that total dietary fat was positively correlated with fat mass (adjusted for fat-free mass, $r = 0.22$, $p < 0.0001$) in adults (Larson et al., 1996). Most multiple regression studies found that about 3 percent of the total variance in body fatness was explained by diet, though some studies placed the estimate at 7 to 8 percent (Westerterp et al., 1996). Longitudinal studies generally supported dietary fat as a predictive factor in the development of obesity (Lissner and Heitmann, 1995). However, bias in subject participation, retention, and underreporting of intake may limit the power of these epidemiological studies to assess the relationship between dietary fat and obesity or weight gain (Lissner et al., 2000).

Another line of evidence often cited to indicate that dietary fat is not an important contributor to obesity is that although there has been a reduction in the percent of energy from fat consumed in the United States, there has been an increase in energy intake and a marked gain in average weight (Willett, 1998). Survey data showed an increase in total energy intake over this period (McDowell et al., 1994), so that despite the decline in percent of energy from fat, the total intake of fat (g/d) remained stable. Another study that used food supply data showed that fat intake may indeed be rising in the United States (Harnack et al., 2000).

Mechanisms for Obesity and Interventional Evidence. Several mechanisms have been proposed whereby high fat intakes could lead to excess body accumulation of fat. Foods containing high amounts of fat tend to be energy dense, and the fat is a major contributor to the excess energy consumed by persons who are overweight or obese (Prentice, 2001). The energy density of a food can be defined as the amount of metabolizable energy per unit weight or volume (Yao and Roberts, 2001); water and fat are the main determinants of dietary energy density. Energy density is an issue of interest to the extent that it influences energy intake and thus plays a role in energy regulation, weight maintenance, and the subsequent development of obesity.

Three theoretical mechanisms have been identified by which dietary energy density may affect total energy intake and hence energy regulation (Yao and Roberts, 2001). Some studies suggest that, at least in the short-term, individuals tend to eat in order to maintain a constant volume of food intake because stomach distension triggers vagal signals of fullness (Duncan et al., 1983; Lissner et al., 1987; Seagle et al., 1997; Stubbs et al., 1995a). Thus, consumption of high energy-dense foods could lead to excess energy intake due to the high energy density to small food volume ratio.

A second proposed mechanism is that high energy-dense foods are often more palatable than low energy-dense foods (Drewnowski, 1999; Drewnowski and Greenwood, 1983). A survey of American adults reported that taste is the primary influence for food choice (Glanz et al., 1998). In single-meal studies, high palatability was also associated with increased food consumption (Bobroff and Kissileff, 1986; Price and Grinker, 1973; Yeomans et al., 1997). These results suggest that high energy-dense foods may be overeaten because of effects related to their high palatability.

The third mechanism is that energy-dense foods reduce the rate of gastric emptying (Calbet and MacLean, 1997; Wisen et al., 1993). This reduction, however, does not occur proportionally to the increase in energy density. Although energy-dense foods reduce the rate at which food leaves the stomach, they actually increase the rate at which energy leaves the stomach. Thus, because energy-containing nutrients are digested more quickly, nutrient levels in the blood fall quicker and hunger returns (Friedman, 1995). While a subjective measure, highly palatable meals have also been shown to produce an increased glycemic response compared with less palatable meals that contain the same food items that are combined in different ways (Sawaya et al., 2001). This suggests a generalized link among palatability, gastric emptying, and glycemic response in the underlying mechanisms determining the effects of energy density on energy regulation. Further research on this potential link is needed.

Researchers have used instruments such as visual analogue scales to measure differences in appetite sensations (e.g., hunger and satiety) between treatments in order to examine the effects of altering nutrients that play a major role in energy density, such as dietary fat, on energy regulation (Flint et al., 2000). A number of studies have been conducted in which preloads of differing energy density were given and hunger and satiety were measured either at the subsequent meal or for the remainder of the day. In the studies that administered preloads that had constant volume but different energy content (energy density was altered by changing dietary fat content), there was no consistent difference in subsequent satiety or hunger between the various test meals (Durrant and Royston, 1979; Green et al., 1994; Hill et al., 1987; Himaya et al., 1997; Hulshof et al., 1993; Louis-Sylvestre et al., 1994; Porrini et al., 1995; Rolls et al., 1994). However, in those studies using isoenergetic preloads that differed in volume (energy density was altered by changing dietary fat content), there was consistently increased satiety and reduced hunger after consumption of the low energy-dense preload meals (i.e., those with higher volume) (Blundell et al., 1993; Holt et al., 1995; van Amelsvoort et al., 1989, 1990). It has been reported, however, that diets low in fat and high in carbohydrate may lead to more rapid return of hunger and increased snacking between meals (Ludwig et al., 1999a).

These data suggest that in the short-term, low energy-dense foods appear to increase satiety and decrease hunger compared to high energy-dense foods. Because individuals were blinded to the dietary content of the treatment diets, the results from these studies demonstrate the short-term effects of energy density after controlling for cognitive influences on food intake.

It is important that cognitive factors are taken into account during the interpretation of results of preload studies. When individuals were aware of dietary changes, they generally (Ogden and Wardle, 1990; Shide and Rolls, 1995; Wooley, 1972), but not always (Mattes, 1990; Rolls et al., 1989), compensated for changes in energy density and thus minimized changes in energy intake.

In well-controlled, short-term intervention studies lasting several days or more, high fat diets were consistently associated with higher spontaneous energy intake (Lawton et al., 1993; Proserpi et al., 1997; Thomas et al., 1992). From short- and longer-term studies, volunteers consistently consumed less dietary energy on low fat, low energy dense diets compared to high energy-dense diets (Glueck et al., 1982; Lissner et al., 1987; Poppitt and Swann, 1998; Poppitt et al., 1998; Stubbs et al., 1995b; Thomas et al., 1992; Tremblay et al., 1989, 1991). The extent to which energy intake was reduced on low energy-dense diets was similar for short- and long-term studies.

An alternative way to study the effects of energy density on energy intake in short-term studies has been to compare energy intake between diets of similar energy density that differ in dietary fat content. Using this approach, when fat content was covertly varied between 20 and 60 percent of energy, there was no significant difference in energy intake between groups (Saltzman et al., 1997; Stubbs et al., 1996; van Stratum et al., 1978). These results suggest that energy density plays a more significant role than fat per se in the short-term regulation of food intake.

During overfeeding, fat may be slightly more efficiently used than carbohydrate (Horton et al., 1995), but in one study, no difference was seen (McDevitt et al., 2000). Thus, high fat diets are not intrinsically fattening, calorie for calorie, and will not lead to obesity unless excess total energy is consumed. It is apparent, however, that with the consumption of high fat diets by the free-living population, energy intake does increase, therefore predisposing to increased weight gain and obesity if activity level is not adjusted accordingly (see Table 11-1). While many of the short-term studies showed a more dramatic effect on weight reduction with reduced fat intake, the long-term studies showed weight loss as well.

Conclusions. Epidemiological studies provide mixed results on the question of whether high fat (low carbohydrate) diets predispose to over-

weight and obesity and promote weight gain. However, a number of short-term studies suggest mechanisms whereby high fat intake could promote weight gain in the long-term. In addition, short- and long-term intervention studies provide evidence that reduced fat intake is accompanied by reduced energy intake and therefore moderate weight reduction or prevention of weight gain. For these reasons, it may be concluded that higher fat intakes are accompanied with increased energy intake and therefore increased risk for weight gain in populations that are already disposed to overweight and obesity, such as that of North America.

Risk of CHD

Epidemiological Evidence. In populations that consume very low fat diets, such as those of rural Asia and Africa, the prevalence of CHD is low (Campbell et al., 1998; Singh et al., 1995; Tao et al., 1989; Walker and Walker, 1978). This fact has led to the concept that low fat diets will protect against CHD. However, this conclusion must be drawn with caution when it is applied to societies in which dietary and exercise habits differ markedly from societies in rural Asia and Africa. In the latter societies, people are highly active and lean (Singh et al., 1995; Walker and Walker, 1978). Both of these factors independently reduce risk for CHD and could offset any potentially detrimental effects of very low fat diets. For this reason, the effects of low fat diets must be viewed in the context of current societal habits in the United States and Canada and of changing habits in developing countries. Furthermore, in more recent years it has become clear that the relationship between fat intake and CHD is related more to the quality of fat than to the quantity. The relationship is clearly shown by cross-population studies. For example, some Mediterranean populations consume diets that are high in total fat and unsaturated fatty acids but low in saturated fatty acids; in these populations, rates of CHD are relatively low (Keys et al., 1980, 1984). In contrast, in northern Europe, where intakes of saturated fatty acids are high, so are rates of CHD (Keys et al., 1980, 1984). Two epidemiological studies showed no relationship between carbohydrate intake and LDL cholesterol concentration (Fehily et al., 1988; Tillotson et al., 1997).

In several recent, long-term prospective studies of diet and chronic disease, rates of CHD did not substantially differ across populations that consumed approximately 25 to 45 percent of energy from fat (Ascherio et al., 1996; Hu et al., 1997). Men who developed CHD were shown to consume a slightly higher percentage of energy from fat (34.7 percent) compared with those who did not develop CHD (33.3 percent); however, this small difference in fat intake may not be significant since intake was based on a

24-hour recall, and the data were not adjusted for energy intake (McGee et al., 1984). Furthermore, Hawaiians, who have a higher incidence of CHD than Japanese living in Hawaii, consumed more energy from fat (35 percent) than the Japanese (31 percent) (Bassett et al., 1969). It has been reported that those who developed CHD consumed slightly less energy from carbohydrate compared to those who did not develop CHD (Kushi et al., 1985; McGee et al., 1984) (Table 11-7). Other studies showed no significant association between risk of CHD and total carbohydrate or sugar intake (Bolton-Smith and Woodward, 1994; Liu et al., 1982, 2000).

Interventional Evidence. Increasing fat intake, as a result of increased saturated fat intake, has been shown to increase LDL cholesterol concentrations (Table 11-2), and therefore risk of CHD. Intervention studies that have investigated the effect of carbohydrate intake on LDL cholesterol concentration have shown mixed results (Table 11-3). Two intervention studies agree with the findings of West and colleagues (1990) in that LDL cholesterol concentration increased when the percent of energy from carbohydrate was decreased from 55 to 31 percent (Borkman et al., 1991) and 59 to 41 percent (Marckmann et al., 2000). However, in other studies in which saturated fatty acids have remained constant, varying the percentage of total fat was found to not alter the LDL cholesterol concentration (Garg et al., 1994; Grundy et al., 1988).

Yu-Poth and colleagues (1999) conducted a meta-analysis on 37 intervention studies that evaluated the effects of the National Cholesterol Education Program's Step I and Step II dietary interventions on various cardiovascular disease risk factors. Reductions in plasma total cholesterol and LDL cholesterol concentrations were significantly correlated with reductions in percentages of total dietary fat, but these also included a decrease in saturated fatty acids. Similarly, individuals who consumed the Dietary Approaches to Stop Hypertension diet, which contains 27 percent of energy from fat and only 7 percent of energy from saturated fat, had reduced total and LDL cholesterol concentrations (Obarzanek et al., 2001b). Singh and colleagues (1992) reported that mortality from CHD and other causes was significantly lower when patients with acute myocardial infarction were fed a reduced fat diet.

The increase in LDL cholesterol concentration observed with increased fat intake is due to the strong positive association between total fat and saturated fat intake and the weak association between total fat and polyunsaturated fat intake (Masironi, 1970; Stamler, 1979). This association is also observed in Appendix Tables K-4, K-5, K-7, and K-8. As shown in many studies, saturated fatty acids raise LDL cholesterol concentrations (see Chapter 8), whereas unsaturated fatty acids do not. In fact, *n*-6 polyunsaturated fatty acids reduce serum LDL cholesterol concentrations some-

what compared with carbohydrate (Hegsted et al., 1993; Mensink and Katan, 1992). The adverse effects of saturated fats are discussed in Chapter 8.

It has been postulated that a high fat intake predisposes to a prothrombotic state, which contributes to venous thrombosis, coronary thrombosis, or thrombotic strokes (Barinagarrementeria et al., 1998; Kahn et al., 1997; Salomon et al., 1999). Consumption of diets high in fat (42 or 50 percent) have been shown to increase blood concentrations of the prothrombotic markers, blood coagulation factor VII (VIIc), and activated factor VII (VIIa) (Bladbjerg et al., 1994; Larsen et al., 1997). The concentration of factor VII is associated with increased risk of CHD (Kelleher, 1992). Furthermore, a significant and positive association was found between the level of dietary fat and factor VIIc concentration (Miller et al., 1989).

Relation of Intakes of Saturated Fatty Acids and Total Fat. When fat is consumed in typical foods it contains a mixture of saturated, polyunsaturated, and monounsaturated fatty acids. Even when the content of saturated fatty acids in consumed fats is relatively low, the intakes of these fatty acids can be high with high fat intakes. For example, if all of the dietary fats consumed were low in saturated fatty acids (e.g., 20 percent of fat energy), a total fat intake of 35 percent of total energy would yield a saturated fatty acid intake of 7 percent of total energy. Consumption of a variety of dietary fats would likely result in an even higher percentage of saturated fatty acids. Thus, in practical terms, it would be difficult to avoid high intakes of saturated fatty acids for most persons if total fat intakes exceeded 35 percent of total energy. This fact is revealed by attempts to create a variety of heart-healthy menus (National Cholesterol Education Program, 2001). Moreover, data from CSFII show that with increased fat intake, there tends to be a greater increase in saturated fatty acid intake relative to polyunsaturated fatty acid intake (Appendix Tables K-4, K-5, K-7, K-8; Masironi, 1970; Stamler, 1979). It should be pointed out, however, that when replacing saturated fatty acid intake with carbohydrate, there is no effect on the total cholesterol:HDL cholesterol ratio (Mensink and Katan, 1992).

Conclusions. A few case-control studies have shown an association between total fat intake and risk for CHD. However, a detailed evaluation of these studies shows that it is not possible to separate total fat intake from saturated fatty acid intake, which is known to raise LDL cholesterol concentrations. Unsaturated fatty acids, which do not raise LDL cholesterol concentrations compared with carbohydrate, have not been implicated in risk for CHD through adverse effects on lipids or other risk factors. Nonetheless, practical efforts to create "heart-healthy" menus reveal that intakes of total fat exceeding 35 percent of total energy result in unacceptably high intakes

TABLE 11-7 Epidemiological Studies on Total Carbohydrate and Sugar Intake and Risk of Coronary Heart Disease (CHD)

Reference	Study Design	Results		Comments
Liu et al., 1982	Multi-country bivariate analysis			No significant association between sugar intake and CHD
McGee et al., 1984	7,088 men Prospective cohort, 10-y follow-up	Mean carbohydrate intake (% of energy)		Those who developed CHD consumed less energy as carbohydrates No association between sugar intake and risk of CHD
		Non-CHD	46.5[a]	
		CHD	45.0[b]	
		Mean sugar intake (% of energy)		
		Non-CHD	8.0[a]	
		CHD	8.1[a]	
Kushi et al., 1985	1,001 men Prospective cohort, 20-y follow-up	Mean carbohydrate intake (% of energy)		Those who died from CHD consumed significantly less total carbohydrate No association between sugar intake and risk of CHD death
		No CHD death	42.7[a]	
		CHD death	41.2[b]	
		Mean sugar intake (% of energy)		
		No CHD death	17.3[a]	
		CHD death	16.9[a]	

Bolton-Smith and Woodward, 1994	11,626 men and women Cross-sectional survey	Mean sugar intake (% of energy)			No association between risk of CHD and either intrinsic or extrinsic sugar intake
		Intrinsic sugar	Men	Women	
		Control	2.06	3.31	
		CHD	1.89–2.19	3.15–3.31	
		Added sugar			
		Control	11.2	8.55	
		CHD	10.5–11.4	8.63–9.10	
Liu et al., 2000	75,521 women Prospective cohort, 10-y follow-up		Relative risk of CHD		No significant association between risk of CHD and total carbohydrate, sucrose, or fructose intake
		Quintile of intake	Carbohydrate	Sucrose	Fructose
		1	1.00	1.00	1.00
		2	1.02	1.03	0.91
		3	1.09	1.16	0.96
		4	1.03	1.02	1.11
		5	1.23	1.22	1.07

[a,b] Within each study, the mean sugar or carbohydrate intakes that are significantly different between treatment groups have a different superscript.

of saturated fatty acids. Moreover, there is the possibility that high fat intakes may enhance a prothrombotic state, although the evidence to support this mechanism for enhancing CHD risk is not strong enough alone to make solid recommendations.

Risk of Hyperinsulinemia, Glucose Intolerance, the Metabolic Syndrome, and Type 2 Diabetes

The metabolic syndrome (insulin-resistance syndrome) describes a clustering of metabolic abnormalities including insulin resistance (with or without glucose intolerance), an atherogenic lipid profile (high triacylglycerol concentration, low HDL cholesterol concentration, and high small, dense LDL), raised blood pressure, a prothrombotic state, and a proinflammatory state (Reaven, 2001). A prothrombotic state is characterized by elevations of plasminogen activator inhibitor and high fibrinogen concentrations, whereas a proinflammatory state is indicated by high c-reactive protein concentrations and other inflammatory markers. Abdominal obesity (waist circumference > 102 cm in men and 88 cm in women) is highly correlated with the presence of insulin resistance (NHLBI/NIDDK, 1998) and is considered to be one of the clinical components of the metabolic syndrome (National Cholesterol Education Program, 2001). An excess of intra-abdominal fat has been identified as being highly associated with the lipid risk factors of the metabolic syndrome (Després, 1993), although total abdominal fat appears to be even more highly predictive of the insulin resistance component of the syndrome (Abate et al., 1996; Peiris et al., 1988). Many persons with the metabolic syndrome eventually develop type 2 diabetes. Thus, both obesity and weight gain are undisputed as major risk factors for the development of type 2 diabetes (defined as fasting plasma glucose ≥ 7 mmol/L) (American Diabetes Association, 2001).

The contribution of diet per se to the development of type 2 diabetes is less clear. In some laboratory animals (e.g., some species of rodents), a high percentage of fat in the diet will induce insulin resistance (Budohoski et al., 1993; Chisholm and O'Dea, 1987). An important question is whether humans are similarly susceptible to this phenomenon independent of the effects of total fat intake on body fat content. Human studies do not provide a clear answer to this question. Thus, if higher intakes of total fat lead to obesity, this in and of itself will reduce insulin sensitivity and predispose to the metabolic syndrome and type 2 diabetes. Recent studies have demonstrated that reduced fat intake and weight loss result in improved glucose tolerance and reduced risk of type 2 diabetes (Swinburn et al., 2001; Tuomilehto et al., 2001).

Epidemiological Evidence. In several population studies, investigators have attempted to determine the contribution of total fat intake to either insulin sensitivity or diabetes. These analyses are difficult to interpret because of the multiplicity of potential confounding variables. Nevertheless, several studies have reported an association between higher fat intakes and insulin resistance as indicated by high fasting insulin concentration, impaired glucose tolerance, or impaired insulin sensitivity (Lovejoy and DiGirolamo, 1992; Marshall et al., 1991; Mayer et al., 1993), as well as to the development of type 2 diabetes (West and Kalbfleisch, 1971). A number of studies, however, have not shown this association (Coulston et al., 1983; Liu et al., 1983; Salmerón et al., 2001). In the Insulin Resistance Atherosclerosis Study, total fat intake univariately correlated with less insulin sensitivity (Mayer-Davis et al., 1997); however, in multiple regression analyses, the presence of obesity appeared to be a confounding variable. Lovejoy and DiGirolamo (1992) likewise found intercorrelations among insulin resistance, total fat intake, and obesity. In contrast, Larsson and coworkers (1999) found no evidence of independent effects of diet on insulin secretory or sensitivity among 74 postmenopausal women. Although several studies suggest an association between total fat intake and the presence of insulin resistance (Lovejoy, 1999; Vessby, 2000), the degree to which the relationship is mediated by obesity remains uncertain. Decreased physical activity is also a significant predictor of higher postprandial insulin concentrations and may confound some studies (Feskens et al., 1994; Parker et al., 1993).

Interventional Evidence. A number of metabolic and intervention studies have examined the relationships among fat intake, fasting glucose and insulin concentrations, areas under curves for plasma glucose and insulin concentrations, insulin sensitivity, glucose effectiveness, and glucose disposal rates (Table 11-8). Several studies reported that diets containing 35 percent fat were accompanied by more impaired glucose tolerance than diets containing 25 percent fat or less (Fukagawa et al., 1990; Jeppesen et al., 1997; Straznicky et al., 1999; Swinburn et al., 1991). Coulston and coworkers (1983) found that a diet containing 41 percent fat led to significantly higher concentrations of insulin in response to meals compared with a diet containing 21 percent fat, but there were no alterations in fasting concentrations. In other studies, no effect on measures of glucose tolerance were reported when diets varied in fat content from 11 to 30 (Leclerc et al., 1993) or 20 to 50 percent fat (Abbott et al., 1989; Borkman et al., 1991; Howard et al., 1991; Thomsen et al., 1999). When the diet was high in fat (50 percent of energy), the area under the curve for plasma glucose and insulin concentration was lower than when the diet had a low fat content (25 percent of energy) (Yost et al., 1998). In this study, the decreased

TABLE 11-8 Interventional Studies on the Effect of Dietary Fat on the Metabolic Parameters for Glucose and Insulin in Healthy Individuals

Reference	Study Design	Percent of Fat	Fasting Glucose	Fasting Insulin
Coulston et al., 1983	11 men and women 10-d crossover	41–21	NSC[a]	NSC
Chen et al., 1988	8 young men 3- to 5-d crossover	0		
		42	ND	ND
		55	ND	ND
	10 elderly men 3- to 5-d crossover	0–37	ND	ND
Abbott et al., 1989	9 men and women 5-wk crossover	42–21	NSC	NSC
Fukagawa et al., 1990	6 young men 21- to 28-d intervention	42–14	Decreased[b]	Decreased[b]
	6 elderly men and women 21- to 28-d intervention	38–15	Decreased[b]	Decreased[b]
Borkman et al., 1991	8 men and women 3-wk crossover	20–50	NSC	NSC
Howard et al., 1991	7 men and women 5- to 7-wk crossover	42–21	NSC	NSC
	9 men and women 3- to 5-wk longitudinal	42–21	NSC	NSC
	12 Caucasians and 12 Pima Indians 2-wk crossover	15–50	Increased[d]	NSC

Area Under the Curve for Glucose	Area Under the Curve for Insulin	Insulin Sensitivity	Glucose Effectiveness	Glucose Disposal/ Disappearance Rate
NSC	Decreased[b]	ND[c]	ND	ND
ND	ND	Decreased[b]	NSC	ND
ND	ND	Increased[b]	NSC	ND
ND	ND	Decreased[b]	NSC	ND
ND	ND	ND	ND	ND
ND	ND	ND	ND	Increased[b]
ND	ND	ND	ND	NSC
ND	ND	ND	ND	NSC
NSC	ND	ND	ND	ND
ND	ND	ND	ND	ND
Increased[e]	Increased[e]	NSC	Decreased[d]	ND

continued

TABLE 11-8 Continued

Reference	Study Design	Percent of Fat	Fasting Glucose	Fasting Insulin
Swinburn et al., 1991	24 Caucasians and Pima Indians 2-wk crossover	15–50	Increased[d]	NSC
Leclerc et al., 1993	7 men and women 7-d crossover	11–30	NSC	NSC
Jeppesen et al., 1997	10 women 3-wk crossover	25–45	ND	ND
Yost et al., 1998	25 men and women 15-d crossover	25–50	NSC	NSC
Straznicky et al., 1999	14 men 2-wk crossover	25–47	Increased[b]	NSC
Thomsen et al., 1999	16 men and women 4-wk crossover	28–42	NSC	NSC
Kasim-Karakas et al., 2000	54 postmenopausal women 4- to 12-mo crossover	15, 25, and 34	NSC	NSC

[a] NSC = no significant change.
[b] $p < 0.05$.
[c] ND = no data available.
[d] $p < 0.001$.
[e] $p < 0.01$.

fat intake was accompanied by an increased percentage of energy from carbohydrate. Garg and coworkers (1992b) reported that insulin sensitivity, indicated by insulin-mediated glucose disposal, was similar after almost a month of ingestion of either a reduced fat (25 percent of energy) or an increased fat diet (50 percent of energy). However, favorable effects of substituting a monounsaturated fat diet for a saturated fat diet on insulin sensitivity were seen at a total fat intake of up to 37 percent of energy (Vessby et al., 2001). A large, long-term intervention trial in adults showed that reducing total fat intake, in part, reduced the risk of the onset of type 2 diabetes by 58 percent (Tuomilehto et al., 2001). Similarly, the Diabetes Prevention Program Research Group reported that diet modification,

Area Under the Curve for Glucose	Area Under the Curve for Insulin	Insulin Sensitivity	Glucose Effectiveness	Glucose Disposal/ Disappearance Rate
Increased[e]	Increased[e]	NSC	Decreased[d]	ND
NSC	NSC	ND	ND	ND
NSC	Increased[d]	ND	ND	ND
Decreased[e]	Decreased[c]	ND	ND	ND
Increased[e]	NSC	Decreased[b]	ND	ND
ND	NSC	NSC	NSC	ND
ND	ND	ND	ND	ND

including a reduction of total fat intake from 34 to 27 percent of energy reduced the incidence of type 2 diabetes by 58 percent. Thus, there is no definitive evidence from metabolic and interventional studies that higher fat intakes impair insulin sensitivity in humans as they do in various laboratory animals. Any suggestive links between fat intake and either insulin secretion or sensitivity may be mediated through confounding factors, such as body-fat content, making it difficult to detect any independent contribution of total fat intake to insulin sensitivity.

Conclusions. Although high fat diets can induce insulin resistance in rodents, investigations in humans fail to confirm this effect. Moreover, an

association between dietary fat intake and risk for diabetes has been reported in some epidemiological studies, but this association is most likely confounded by various factors, such as obesity and glycemic index.

Risk of Cancer

High intakes of dietary fat have been implicated in the development of cancer, especially cancer of the lung, breast, colon, and prostate gland. Early support for this theory comes from laboratory animal and cross-cultural studies. The latter were based largely on international food disappearance data and migrant and time trend studies. In recent years, the theory that a diet high in fat predisposes to certain cancers has been weakened by additional epidemiological studies. Early cross-cultural and case-control studies reported strong associations between total fat intake and breast cancer (Howe et al., 1991; Miller et al., 1978; van't Veer et al., 1990), yet a number of epidemiological studies, most in the last 15 years, have found little or no association between fat intake and breast cancer (Hunter et al., 1996; Jones et al., 1987; Kushi et al., 1992; van den Brandt et al., 1993; Velie et al., 2000; Willett et al., 1987, 1992). A meta-analysis of 23 studies yielded a relative risk of 1.01 and 1.21 from cohort and case-control studies, respectively (Boyd et al., 1993).

Total fat intake in relation to colon cancer has strong support from animal studies (Reddy, 1992). However, evidence from epidemiological studies has been mixed (De Stefani et al., 1997b; Giovannucci et al., 1994; Willett et al., 1990). Howe and colleagues (1997) reported no association between fat intake and risk of colorectal cancer from the combined analysis of 13 case-control studies.

Epidemiological studies tend to suggest that dietary fat intake is not associated with prostate cancer (Ramon et al., 2000; Veierød et al., 1997b). Giovannucci and coworkers (1993), however, reported a positive association between total fat consumption, primarily animal fat, and risk of advanced prostate cancer. Findings on the association between fat intake and lung cancer have been mixed (De Stefani et al., 1997a; Goodman et al., 1988; Veierød et al., 1997a; Wu et al., 1994).

Risk of Nutrient Inadequacy or Excess

Diets High in Fat. With increasing intakes of carbohydrate, and therefore decreasing fat intakes, there is a trend towards reduced consumption of dietary fiber, folate, and vitamin C (Appendix K). With higher fat intakes, it is difficult to create practical high fat menus that do not contain unacceptably high amounts of saturated fatty acids (National Cholesterol Education Program, 2001).

Diets Low in Total Sugars. Micronutrient inadequacy can occur when sugars intake is very low (less than 4 percent of total energy) (Bolton-Smith and Woodward, 1995) because many foods that are abundant in micronutrients, such as fruits and dairy products, also contain naturally occurring sugars. A wide variety of foods from different food groups are needed to meet nutrient requirements. Because sugars are important for the palatability of foods, the complete omission of sugars from the diet could endanger overall nutrient adequacy by leading to low total energy intake, as well as low micronutrient intakes (Bolton-Smith, 1996). Although reduced nutrient intakes have been reported, adverse affects on health have not. Individuals with fructose intolerance, a condition caused by fructose-1-phosphate aldolase deficiency, strictly avoid foods containing fructose and sucrose and yet remain in good health (Burmeister et al., 1991).

AMDRs for Adults

When fat intakes are low and carbohydrate intakes are high, intervention studies, with the support of epidemiological studies, demonstrate a reduction in plasma HDL cholesterol concentration, an increase in the plasma total cholesterol:HDL cholesterol ratio, and an increase in plasma triacylglycerol concentration, which are all consistent with an increased risk of CHD. Conversely, many interventional studies show that when fat intake is high, many individuals consume additional energy, and therefore gain additional weight. Weight gain on high fat diets can be detrimental to individuals already susceptible to obesity and can worsen the metabolic consequences of obesity, particularly the risk of CHD. Moreover, high fat diets are usually accompanied by increased intakes of saturated fatty acids, which can raise plasma LDL cholesterol concentrations and further increase risk for CHD. Based on the apparent risk for CHD that may occur on low fat diets, and the risk for increased energy intake and therefore obesity with the consumption of high fat diets, the AMDR for fat and carbohydrate is estimated to be 20 to 35 and 45 to 65 percent of energy, respectively, for all adults. By consuming fat and carbohydrate within these ranges, the risk for obesity, as well as for CHD and diabetes, can be kept at a minimum. Furthermore, these ranges allow for sufficient intakes of essential nutrients while keeping the intake of saturated fatty acids at moderate levels.

There is no lower limit of intake and no known adverse effects with the chronic consumption of *Dietary Fiber* or *Functional Fiber* (Chapter 7). Therefore, an AMDR is not set for *Dietary, Functional,* or *Total Fiber.*

Maximal Intake Level for Added Sugars

Data from various national surveys show that increasing intakes of added sugars is associated with a decline in the consumption of certain micronutrients, thus increasing the prevalence of those consuming below the EAR or the AI. While such trends exist, it is not possible to determine a defined intake level at which inadequate micronutrient intakes occur. Furthermore, at very low or very high intakes, unusual eating habits most likely exist that allow for other factors to contribute to low micronutrient intakes. Based on the available data, no more than 25 energy from added sugars should be comsumed by adults. A daily intake of added sugars that individuals should aim for to achieve a healthy diet was not set. Total sugars intake can be lowered by consuming primarily sugars that are naturally occurring and present in micronutrient-rich foods, such as milk, dairy products, and fruits, while at the same time limiting consumption of added sugars from foods and beverages that contain minimal amounts of micronutrients, such as soft drinks, fruitades, and candies.

Low Fat, High Carbohydrate Diets of Children

Fat Oxidation

Jones and colleagues (1998) reported a significantly greater fat oxidation in children (aged 5 to 10 years, $n = 12$) than in adults (aged 20 to 30 years, $n = 6$). Breath $^{13}CO_2$ was measured in 12 children and 6 men following an oral bolus dose of [1-^{13}C]palmitic acid (10 mg/kg of body weight) consumed with a test meal. Breath $^{13}CO_2$ excretion was less in the men (35.1 percent of absorbed dose, $P = 0.005$) than in the children (57.0 percent of absorbed dose). The children exhibited greater fat oxidation in the postabsorptive state (2.43 g/h) and postprandial (11.89 g/6 h) states than the men (0.93 g/h postabsorptive, 9.86 g/6 h postprandial). The children also had greater fat oxidation compared with women studied previously by these investigators (0.53 g/h postabsorptive, 0.03 g/6 h postprandial) (Murphy et al., 1995).

Growth

Most studies have reported no effect of the level of dietary fat on growth when energy intake is adequate (Boulton and Magarey, 1995; Fomon et al., 1976; Lagström et al., 1999; Lapinleimu et al., 1995; Niinikoski et al., 1997a, 1997b; Obarzanek et al., 1997; Shea et al., 1993). Two well-controlled trials demonstrated that a diet providing less than 30 percent energy from fat does not result in adverse effects on growth in

children up to 8 years of age (Lapinleimu et al., 1995; Niinikoski et al., 1997a, 1997b). A cohort study with a 25-month follow-up showed that there was no difference in stature or growth of children aged 3 to 4 years at baseline across quintiles (27 to 38 percent) of total fat intake (Shea et al., 1993). The Special Turku Coronary Risk Factor Intervention Project showed no difference in growth of children 7 months to 5 years of age when they consumed 21 to 38 percent fat (Lagström et al., 1999). Niinikoski and coworkers (1997a) reported that 1-year-old children who consistently consumed low fat diets (less than 28 percent) grew as well as children with higher fat intakes. A cohort study showed that children aged 2 years in the lower tertile of fat intake (less than 30 percent) had a height and weight similar to that of the higher fat intake groups (Boulton and Magarey, 1995).

A few studies have observed impaired growth among hypercholsterolemic children who were advised to consume 30 percent or less of energy from fat. However, the energy intake was also reduced (Lifshitz and Moses, 1989) or not reported (Hansen et al., 1992). In a group of Canadian children 3 to 6 years of age, a fat intake of less than 30 percent of energy was associated with an odds ratio of 2.3 for weight-for-age below the 50th percentile at 6 years of age (Vobecky et al., 1995). A comprehensive evaluation of the effect of diet-related variables on the growth of children under 6 years of age from 18 Latin American countries (FAO/WHO, 1996) demonstrated that diets providing less than 22 percent energy from fat and with less than 45 percent of total fat from animal fat were related to low birth weight, underweight, and stunting (height-for-age ≤ 2 standard deviations) (Uauy et al., 2000). The dietary determinants that best explained low birth weight were energy, protein, and animal fat, suggesting that high-quality animal protein and associated nutrients are important for growth and development.

Risk of Nutrient Inadequacy or Excess

Diets High in Carbohydrate and Low in Fats. Because the diets of young children are less diversified than that of adults, the risk of inadequate micronutrient intake is increased in these children. A cohort of 500 children aged 3 to 6 years showed that those who consumed less than 30 percent of energy from fat consumed less vitamin A, vitamin D, and vitamin E compared with those who consumed higher intakes of fat (30 to 40 percent) (Vobecky et al., 1995). Calcium intakes decreased by more than 100 mg/d for 4- and 6-year-old children who consumed less than 30 percent of energy from fat (Boulton and Magarey, 1995). Lagström and coworkers (1997, 1999), however, did not observe reduced intakes of micronutrients in children with low fat intakes (26 percent).

The Dietary Intervention Study in Children (DISC), a multi-center, randomized trial of children 8 to 10 years of age, demonstrated that reducing the intake of fat to 28 percent of energy over a 3-year period increased the percentage of children not meeting the RDA for vitamin E and zinc; however, no biochemical evidence of deficiency of these nutrients was found (Obarzanek et al., 1997). Tonstad and Sivertsen (1997) observed no reduced intake of micronutrients with diets providing 25 percent of energy as fat. Nicklas and coworkers (1992) reported reduced intakes of certain micronutrients by 10-year-old children who consumed less than 30 percent of energy as fat; however, this level of fat intake was associated with marked increased intakes of candy. It has been suggested that children who consume a low fat diet can meet their micronutrient recommendation by appropriate selection of certain low fat foods (Peterson and Sigman-Grant, 1997). This is especially true for older children whose diets are typically more diverse.

The tables in Appendix K show the intakes of nutrients at various intake levels of carbohydrate. With increasing intakes of carbohydrate, and therefore decreasing intakes of fat, the intake levels of calcium and zinc markedly decreased in children 1 to 18 years of age (Appendix Tables K-1 through K-3).

Diets High in Added Sugars. Several surveys have evaluated the impact of added sugars intake on micronutrient intakes in children (Table 11-5). Gibson (1997) examined data from the U.K. National Diet and Nutrition Survey of Children Aged 1.5 to 4.5 Years (boys, $n = 848$; girls, $n = 827$) and found evidence of a nutrient dilution effect by nonmilk extrinsic sugars (NMES). Children consuming the highest concentrations of NMES (greater than 24 percent of energy) had intakes of most micronutrients that were between 6 and 20 percent below average. Gibson (1997) concluded that the inverse association of NMES with micronutrient intakes was of most significance for the 20 percent of children with the diets highest in NMES (24.9 percent of energy for boys and 24.5 percent of energy for girls).

In a study of British adolescents, reduced intakes of calcium, phosphorus, iron, vitamin A, vitamin D, and folic acid were associated with increased sugars intakes (mean added sugars intake for the high sugars consumers was 122 g/d for boys and 119 g/d for girls) (Rugg-Gunn et al., 1991). In a smaller survey ($n = 143$), added sugars intakes at levels as high as 27 percent of energy did not have a significant impact on micronutrient intakes (Nelson, 1991).

Similar to that observed for adults using data from NHANES III, increasing the added sugars intake by every 5th percentile tended to be associated with reduced intakes of certain micronutrients, including

calcium, vitamin A, iron, and zinc (Appendix Tables J-1 through J-3, J-6, and J-7). This reduction in micronutrient intake was most significant when added sugars intake levels exceeded 25 percent of energy.

From 1989 to 1995, energy intakes increased for U.S. children aged 2 to 17 years primarily due to increased carbohydrate consumption. Beverages, particularly soft drinks, were important contributors to the increased carbohydrate consumption. During this period, micronutrient intakes (except for iron) did not increase and calcium intakes decreased. This was attributed to the fact that increased energy was largely obtained from soft drinks, which do not add nutrients and displace milk in children's diets, with negative consequences for total diet quality (Morton and Guthrie, 1998).

Children who were high consumers of nondiet soft drinks had lower intakes of riboflavin, folate, vitamin A, vitamin C, calcium, and phosphorus in comparison with children who were nonconsumers of soft drinks (Harnack et al., 1999). Several of these nutrients (folate, vitamin A, and calcium) have been identified in national surveys as "shortfall" or "problem" nutrients among various age and gender groups (ARS, 1998). Ballew and colleagues (2000) demonstrated that in U.S. children, milk consumption was positively associated with the likelihood of achieving recommended vitamin A, vitamin B_{12}, folate, calcium, and magnesium intakes in all age groups. Juice (100 percent fruit or vegetable juice) consumption was positively associated with achieving vitamin C and folate recommended intakes in all age groups, as well as magnesium intake among children aged 6 years and older. Soft drink intake was negatively associated with achieving recommended vitamin A intake in all age groups, calcium in children younger than 12 years of age, and magnesium in children 6 years of age and older.

Others have shown that children who consumed milk at the noon meal had the highest daily intakes of vitamin A, vitamin E, calcium, and zinc, whereas the opposite was true for children who consumed soft drinks and tea (Johnson et al., 1998). Hence, beverages that are major contributors of the naturally occurring sugars, such as lactose and fructose, in the diet (e.g., milk and fruit juice) have been positively associated with nutrient adequacy, while beverages that are the principal source of added sugars in the diet (e.g., soft drinks) have been negatively associated with nutrient adequacy in the diets of U.S. children and adolescents (Ballew et al., 2000; Johnson et al., 1998).

Diets High in Total Sugars. The findings from three surveys on the relationship between total sugars intake and micronutrient intake in children are mixed (Table 11-6). Gibson (1993) did not observe reduced micronutrient intakes when total sugars intake exceeded 25 percent of energy. Nicklas and coworkers (1996) reported that the percent of children meeting the RDA for only niacin and zinc was significantly reduced

when the intake of total sugars exceeded 31 percent of energy. A linear reduction in several micronutrients was observed with increasing total sugars intake (Farris et al., 1998).

High Fat, Low Carbohydrate Diets of Children

Risk of Obesity

In the United States and Canada, there is evidence that children are becoming progressively overweight (Flegal, 1999; Gortmaker et al., 1987; Tremblay and Willms, 2000; Troiano et al., 1995). Furthermore, Serdula and coworkers (1993) reviewed a number of longitudinal studies with varying cut-off levels for obesity and concluded that 26 to 41 percent of obese preschool children and 42 to 63 percent of obese school-age children became obese adults. Clinical evidence of disease associated with excess body weight, reduced physical activity, or high dietary fat intakes, however, are generally absent. The evidence for a role of dietary fat intakes in promoting higher energy intakes and thus promoting obesity in young children is conflicting.

A positive trend in energy intake was associated with an increased percent of energy from fat for children up to 8 years of age (Boulton and Magarey, 1995). A positive correlation between fat intake and fat mass has been reported for boys 4 to 7 years of age (Nguyen et al., 1996). A lack of effect of dietary fat on BMI and adiposity, however, has been reported for children 1.5 to 4.5 years of age (Atkin and Davies, 2000; Davies, 1997).

The DISC trial found no difference in BMI for children 8 to 10 years of age who consumed diets containing 29 or 33 percent fat over a 3-year period (Lauer et al., 2000). However, several studies showed a positive correlation between dietary fat intake and body fatness in children 8 to 12 years of age (Maffeis et al., 1996; Obarzanek et al., 1994; Ricketts, 1997). The average fat intake of nonobese children was measured to be 31 to 34 percent for children 9 to 11 years old, whereas the average fat intake of obese children was 39 percent of energy (Gazzaniga and Burns, 1993). A positive association between fat intake and several adiposity indices were observed, but only for up to 35 percent of energy (Maillard et al., 2000). Other factors that have been associated with increased BMI include physical activity.

Risk of CHD

Clinical studies have provided some evidence that serum cholesterol concentration is modified in children the same way as in adults, with serum total, LDL, and non-HDL cholesterol concentrations being increased by

consuming diets higher in total fat (Lauer et al., 2000; Niinikoski et al., 1996; Obarzanek et al., 2001a; Shannon et al., 1994; Simell et al., 2000; Vartiainen et al., 1986). However, no significant association between dietary fat and LDL cholesterol concentration was observed for boys and girls (aged 8 to 10 years) consuming fat ranging from 10 to 50 percent of energy (R = –0.04 to 0.14) (Kwiterovich et al., 1997). Furthermore, a significant positive association between fat intake and total cholesterol concentration was observed in only two of five countries (Knuiman et al., 1983).

Another potential indicator for children's future risk of CHD is the presence of fatty streaks, which are found in the aortas of almost all children over 3 years of age in North America (Holman et al., 1958), and begin to appear in the coronary arteries about 5 to 10 years later than in the aorta (Berenson et al., 1992; McGill, 1968; Stary, 1989; Strong et al., 1992). The prevalence of aortic fatty streaks differs only slightly among children and adolescents of all populations studied, regardless of the frequency of atherosclerosis and coronary artery disease in adults of the respective population (Holman et al., 1958; McGill, 1968). The absence of a relation between aortic fatty streaks and the clinically relevant lesions of atherosclerosis in epidemiological and histological studies has thus raised questions on the clinical significance of fatty streaks in the aorta of young children (Newman et al., 1995; Olson, 2000). The Pathobiological Determinants of Atherosclerosis in Youth Study, however, has provided evidence that an unfavorable lipoprotein pattern (i.e., elevated non-HDL cholesterol and low HDL cholesterol concentrations), obesity, and hyperglycemia are associated with raised fatty streaks in the coronary artery and abdominal aorta in late teenage years (McGill et al., 2000a, 2000b). Similarly, the Bogalusa Heart Study observed a positive association between LDL cholesterol concentration and the percentage of surface with fatty streaks in the aorta (Berenson et al., 1992). These findings are consistent with the hypothesis of the progression of fatty streaks to fibrous plaques under the influence of the prevailing risk factors for coronary artery disease (McGill et al., 2000a, 2000b).

It is still unclear, however, how reduction in serum cholesterol concentration in childhood, if maintained, is associated with risk of CHD in adulthood. In addition, there are still pivotal issues that must be examined further, including the relationship between fatty streaks found in the arteries of young children and the later appearance of raised lesions associated with coronary vascular disease, the effects of dietary total fat modification on predictive risk factors in children, the safety of the diet with respect to total energy and micronutrients for the general population, and the long-term health benefit of establishing healthy dietary patterns early in childhood.

Risk of Nutrient Inadequacy or Excess

Appendix Tables K-1 through K-3 and K-6 provide data from CFSII on the intake of various nutrients based on the level of carbohydrate intake. It can been seen from these tables that as the level of carbohydrate intake decreases, and therefore the level of fat increases, certain nutrients such as folate and vitamin C markedly decrease. Furthermore, with increasing levels of fat intake, the intake of saturated fat relative to linoleic acid intake markedly increases.

AMDRs for Children

The evidence suggests that children have a higher fat oxidation rate compared to adults, and that reduced intake of certain micronutrients can occur with the consumption of low fat diets, whereas there is potential risk of obesity with high fat intakes. High intakes of fat may promote increased risk for CHD and obesity. Dietary fat provides energy, which may be important for younger children with reduced food intakes, particularly during the transition from a diet high in milk to a mixed diet. Thus, there should be a transition from the high fat intake during infancy (55 and 40 percent of energy for the 0- to 6- and 7- to 12-months age groups, respectively) (Chapter 8) to an AMDR for adults (20 to 35 percent of energy). Therefore, it is estimated that the AMDR for fat intake is approximately 30 to 40 percent of energy for children 1 to 3 years of age and 25 to 35 percent of energy for children 4 to 18 years of age. The AMDR for carbohydrate is the same as for adults (45 to 65 percent of energy). The ranges of fat intake include intakes of saturated fat that should be consumed at levels as low as possible while consuming a nutritionally adequate diet.

Maximal Intake Level for Added Sugars

As for adults, no more than 25 percent of energy from added sugars should be consumed by children to ensure adequate micronutrient intakes. For those children whose intake is above this level, added sugars intake can be reduced by consuming sugars that are primarily naturally occurring and present in foods such as milk, dairy products, and fruits, which also contain essential micronutrients.

n-9 MONOUNSATURATED FATTY ACIDS

Approximately 20 to 40 percent of fat is consumed as *n*-9 monounsaturated fatty acids, almost all of which is oleic acid (Appendix Tables E-1 and E-8). Monounsaturated fatty acids are not essential fatty acids, but they may have some benefit in the prevention of chronic disease. Although

early research pointed to this potential benefit, most attention has been given to it in the past decade.

Low n-*9 Monounsaturated Fatty Acid Diets*

Risk of CHD

Epidemiological Evidence. Population data on monounsaturated fatty acid intake and risk of coronary heart disease (CHD) are limited. However, in long-term follow-up studies of the Seven Countries Study, higher intakes of monounsaturated fatty acids were associated with decreased rates of CHD mortality (Keys et al., 1986). Other reports indicate that monounsaturated fatty acids have a neutral or beneficial effect on risk (Hu et al., 1997; Kromhout and de Lezenne Coulander, 1984; Pietinen et al., 1997).

Interventional Evidence. Much work has been conducted and is ongoing to identify the ideal substitute for saturated fat in a blood cholesterol-lowering diet. The effects of a high monounsaturated fatty acid versus a low fat, high carbohydrate diet on serum lipid and lipoprotein concentrations have been a focus of considerable scientific inquiry. Eighteen well-controlled clinical studies that compared the effects of substituting monounsaturated fatty acids versus carbohydrate for saturated fat in a blood cholesterol-lowering diet have recently been reviewed (Kris-Etherton et al., 2000). In these studies, when on both high monounsaturated fat and low fat, high carbohydrate diets, saturated fatty acids contributed to 4 to 12 percent of energy and dietary cholesterol varied from less than 100 up to 410 mg/d. Diets high in monounsaturated fatty acids provided 17 to 33 percent of energy from monounsaturated fatty acids and contained more total fat (33 to 50 percent energy) than the low fat, high carbohydrate diets (18 to 30 percent energy). The low fat, high carbohydrate diets provided 55 to 67 percent of energy from carbohydrate. Compared to baseline values, serum total cholesterol concentrations changed from –17 to +3 percent on the low fat, high carbohydrate diet, whereas it changed from –20 to –3 percent on the high monounsaturated fatty acid diet. The range of decrease in plasma low density lipoprotein (LDL) cholesterol concentration was similar (–22 to +1 percent) among individuals on the two diets. The change in serum triacylglycerol concentrations ranged from –23 to +37 percent for individuals consuming the low fat, high carbohydrate diets and from –43 to +12 percent for diets high in monounsaturated fatty acids. Changes in high density lipoprotein (HDL) cholesterol concentrations ranged from –25 to +2 percent for individuals on the low fat, high carbohydrate diets compared to a –9 to +6 percent change for individuals on diets high in monounsaturated fatty acids.

These data indicate that in weight-stable individuals, a high monounsaturated fatty acid, low saturated fatty acid diet results in a more favorable metabolic profile with respect to total cholesterol, HDL cholesterol, and triacylglycerol concentrations. Figure 11-4 shows that with increased monounsaturated fatty acid intake, there is a favorable reduction in the total cholesterol:HDL cholesterol ratio. Furthermore, a meta-analysis of feeding studies estimated that the regression coefficients for the effects of monounsaturated fatty acids on LDL and HDL cholesterol concentrations were –0.008 and +0.006, respectively, suggesting a slight positive benefit (Clarke et al., 1997).

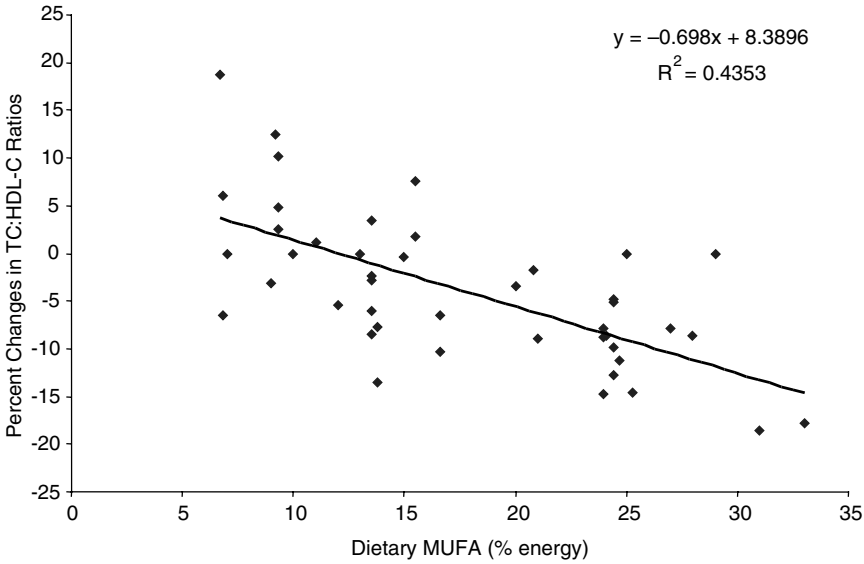

FIGURE 11-4 Relationship between monounsaturated fatty acid (MUFA) intake and total cholesterol (TC):high density lipoprotein cholesterol (HDL-C) concentration ratio. Weighted least-squares regression analyses were performed using the mixed procedure to test for differences in lipid concentrations (SAS Statistical package, version 8.00, SAS Institute, Inc., 1999).
DATA SOURCES: Berry et al. (1992); Curb et al. (2000); Garg et al. (1988, 1992a, 1994); Ginsberg et al. (1990); Grundy (1986); Grundy et al. (1988); Jansen et al. (1998); Kris-Etherton et al. (1999); Lefevre et al., unpublished; Lopez-Segura et al. (1996); Mensink and Katan (1987); Nelson et al. (1995); Parillo et al. (1992); Pelkman et al. (2001); Perez-Jimenez et al. (1995, 1999, 2001).

Risk of Diabetes

Epidemiological studies tend to suggest no association between monounsaturated fatty acid intake and risk of indicators for diabetes (Feskens et al., 1995; Marshall et al., 1997). Similarly, some intervention studies showed no effect of monounsaturated fatty acid intake on indicators for risk of diabetes (Fasching et al., 1996; Roche et al., 1998; Thomsen et al., 1999; Vessby et al., 2001). Uusitupa and coworkers (1994), however, reported a significantly lower area under the curve for plasma glucose concentration and a greater glucose disappearance rate when healthy women consumed a diet rich in monounsaturated fatty acids (19 to 20 percent) compared with a diet rich in saturated fatty acids.

Risk of Cancer

Bartsch and colleagues (1999) reported a protective effect of oleic acid on cancer of the breast, colon, and possibly the prostate. A few epidemiological studies have reported an inverse relationship between monounsaturated fatty acid intake and risk of breast cancer (Willett et al., 1992; Wolk et al., 1998), while a number of studies reported no association (Holmes et al., 1999; Hunter et al., 1996; Jones et al., 1987; Kushi et al., 1992; van den Brandt et al., 1993; van't Veer et al., 1990). Increased consumption of olive oil was associated with significantly reduced breast cancer risk (La Vecchia et al., 1995; Martin-Moreno et al., 1994; Trichopoulou et al., 1995).

A diet high in monounsaturated fatty acid-rich vegetable oils, including olive, canola, or peanut oils, has been associated with a protective effect or no risk of prostate cancer (Norrish et al., 2000; Ramon et al., 2000; Schuurman et al., 1999; Veierød et al., 1997b). Some speculate that the apparent protective effects of olive oil (and other vegetable oils) reflect constituents other than monounsaturated fatty acids including squalene (Newmark, 1999), phenolic compounds, antioxidants, and other compounds (Owen et al., 2000).

No significant association has been reported for monounsaturated fatty acid intake and risk of colorectal cancer (Giovannucci et al., 1994; Howe et al., 1997).

Risk of Nutrient Inadequacy

In the United States, monounsaturated fatty acids provide 12 to 13 percent of energy intake. About 50 percent of these fatty acids are consumed via animal products, primarily meat fat (Jonnalagadda et al., 1995). Vegetable oils that are good sources of monounsaturated fatty acids include canola

oil and olive oil. Although the major sources of monounsaturated fatty acids (animal fat and vegetable oils) are not required to supply essential nutrients, very low intakes of monounsaturated fatty acids would require increased intakes of other types of fatty acids to achieve recommended fat intakes. Consequently, intakes of saturated and *n*-6 polyunsaturated fatty acids would probably exceed a desirable level of intake (see "*n*-6 Polyunsaturated Fatty Acids" and Chapter 8).

High n-*9 Monounsaturated Fatty Acid Diets*

There are limited data on the adverse health effects from consuming high levels of *n*-9 monounsaturated fatty acids (see Chapter 8, "Tolerable Upper Intake Levels").

Acceptable Macronutrient Distribution Range

n-9 Monounsaturated fatty acids are not essential in the diet, and the evidence relating low and high intakes of monounsaturated fatty acids and chronic disease is limited. Therefore, an Acceptable Macronutrient Distribution Range (AMDR) for *n*-9 monounsaturated fatty acids is not provided. Nonetheless, practical limits on intakes of monounsaturated fatty acids will be imposed by AMDRs for total fat and other types of fatty acids.

n-6 POLYUNSATURATED FATTY ACIDS

Low n-*6 Polyunsaturated Fatty Acid Diets*

Risk of CHD

Epidemiological Evidence. Many populations of the world, such as in Crete and Japan, have low total intakes of *n*-6 polyunsaturated fatty acids (e.g., < 4 percent of total energy) without obvious health consequences (Okita et al., 1995; Renaud et al., 1995). However, high intakes of *n*-6 polyunsaturated fats have been associated with blood lipid profiles (e.g., reduced total and low density lipoprotein [LDL] cholesterol, reduced triacylglycerol, and increased high density lipoprotein [HDL] cholesterol concentrations) that are associated with low risk of coronary heart disease (CHD) (Arntzenius et al., 1985; Becker et al., 1983; Sonnenberg et al., 1996). Prospective epidemiological evidence suggests that after controlling for other components of the diet, replacing saturated fats with unsaturated fats decreases risk of CHD (Hu et al., 1997); however, the dose–response

relationship between *n*-6 fatty acids and risk of CHD was not adequately established with certainty. An inverse association between linoleic acid intake and risk of coronary death was observed in several prospective studies (Arntzenius et al., 1985; Gartside and Glueck, 1993), while Pietinen and coworkers (1997) did not observe a relationship between linoleic acid intake and risk of CHD. A cross-sectional study showed that linoleic acid was inversely related to the prevalence of CHD, and this effect was stronger with higher intakes of linolenic acid (Djoussé et al., 2001). It is difficult to provide a direct assessment of *n*-6 fatty acids on risk of CHD without taking into consideration the impact of several dietary and nondietary factors, in addition to serum cholesterol concentrations, that lead to CHD and may be modified by the intake of saturated fat and *n*-6 fatty acids.

Interventional Evidence. From the standpoint of blood lipid concentration and CHD, higher *n*-6 polyunsaturated fatty acid intake generally alters blood lipid concentration to result in a decreased risk profile (Katan et al., 1994) (Table 11-9). Controlled trials have examined the effects of substituting *n*-6 fatty acids in the diet to replace carbohydrate or saturated fatty acids (Mensink et al., 1992). In general, any fat that replaces carbohydrate in the diet raises HDL cholesterol and decreases triacylglycerol concentrations, with only small differences between individual fatty acids. *n*-6 Fatty acids decrease LDL cholesterol concentrations to a much greater degree than do saturated fatty acids (Mensink et al., 1992).

Risk of Diabetes

A number of epidemiological studies have been conducted to ascertain whether the quality of fat can affect the risk for diabetes. An inverse relationship was reported for vegetable fats and polyunsaturated fats and risk of diabetes (Colditz et al., 1992; Salmerón et al., 2001; Trevisan et al., 1990). One study reported a positive association between 2-hour glucose concentrations and polyunsaturated fatty acid intake (Mooy et al., 1995). A review of epidemiological studies on this relationship concluded that higher intakes of polyunsaturated fats could be beneficial in reducing the risk for diabetes (Hu et al., 2001).

Risk of Nutrient Inadequacy

Dietary *n*-6 polyunsaturated fatty acids have been reported to contribute approximately 5 to 7 percent of total energy intake of adults (Allison et al., 1999; Fischer et al., 1985), and range up to no more than 10 percent of energy intake (Willett et al., 1987; Appendix Tables E-1 and E-9). The

TABLE 11-9 Interventional Studies on *n*-6 Fatty Acid Intake and Blood Lipid Concentrations

Reference	Study Design	Percent of Energy from Fatty Acid[a]
Becker et al., 1983	12 men	4.3 18:2
	4-wk crossover	6.8 18:2
		18 18:2
Mattson and Grundy, 1985	20 adults	3.9 18:2
	4-wk crossover	29 18:2
McDonald et al., 1989	18 men	7.9 18:2 and 18.8 18:1
	18-d parallel	21.3 18:2 and 7.0 18:1
Zock and Katan, 1992	56 men and women	3.8 18:2 (*trans* diet)
	3-wk crossover	3.9 18:2 (18:0 diet)
		12 18:2 (18:2 diet)
Kris-Etherton et al., 1993	30 and 33 men	7.2 → 1.7 18:2
	26-d crossover	7.2 → 2.1 18:2
		7.2 → 17.8 18:2
		5.7 → 1.6 18:2
		5.7 → 1.8 18:2
		5.7 → 2.1 18:2
Howard et al., 1995	63 men and women	3.0 18:2
	6-wk crossover	4.2 18:2
		7.0 18:2
		12.8 18:2

[a] 18:2 = linoleic acid, 18:1 = oleic acid.
[b] LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol.

main sources of *n*-6 polyunsaturated fatty acids are vegetable oils (e.g., soybean oil, safflower oil, and corn oil). Linoleic acid, the predominant *n*-6 polyunsaturated fatty acid, is essential in the diet, and therefore an Adequate Intake (AI) is set (see Chapter 8). Based on the estimated energy requirement for each age group, a minimum intake of 5 percent of energy from linoleic acid would be needed to meet the AI.

Postintervention Blood Lipid Concentration (mmol/L)[b]			
LDL-C	HDL-C	Total Cholesterol	Triacylglycerol
2.11	1.03	3.44	0.81
1.83	1.12	3.28	0.84
1.68	1.17	3.17	0.79
3.70[c]	1.01[c]	5.80[c]	2.93[c]
3.10[d]	0.91[c]	4.94[d]	2.61[c]
2.52[c]	1.35[c]	3.97[c]	0.82[c]
2.03[d]	1.19[d]	3.39[d]	0.82[c]
3.07[c]	1.37[c]	4.90[c]	1.00[c]
3.00[c]	1.41[c]	4.89[c]	1.04[d]
2.83[d]	1.47[d]	4.74[d]	0.95[c]
2.92[c]	1.16[c]	4.55[c]	0.99[c]
2.66[c]	1.14[c]	4.27[d]	0.98[c]
2.15[d]	1.16[c]	3.59[e]	0.82[d]
3.23[c]	1.34[c]	4.89[c]	0.90[c]
2.79[d]	1.40[c]	4.45[c]	0.79[c]
2.82[d]	1.34[c]	4.40[c]	0.76[c]
4.14	1.16	5.92	1.43
4.14	1.16	5.89	1.41
4.11	1.14	5.87	1.37
4.03	1.16	5.79	1.34

[c,d,e] Within each study, the blood lipid concentrations that are significantly different between treatment groups have a different superscript.

High n-*6 Polyunsaturated Fatty Acid Diets*

Risk of LDL Oxidation

When exposed to oxidant stress, *n*-6 fatty acids are vulnerable to attack by free radicals and oxidation into lipid peroxides (Halliwell and Chirico, 1993). An example of lipid peroxidation is LDL oxidation, which plays an important role in the development of atherosclerosis (Steinberg et al.,

1989). Oxidation products of lipids and proteins are found in atherosclerotic plaque and in macrophage foam cells. Compared with monounsaturated fatty acids, in vitro susceptibility of LDLs to undergo oxidative modification has been shown to increase with increased linoleic acid content in LDLs as a result of increased intakes of linoleic acid (Abbey et al., 1993; Berry et al., 1991; Bonanome et al., 1992; Louheranta et al., 1996; Reaven et al., 1991, 1993, 1994).

The mechanism whereby incorporation of polyunsaturated fatty acids into LDLs enhances susceptibility of LDL oxidation has been studied extensively (Chisolm and Steinberg, 2000; Jessup and Kritharides, 2000). Nonetheless, the hypothesis suggesting that a diet rich in polyunsaturated fat increases the polyunsaturated fatty acid content of LDL particles and increases their susceptibility to oxidation, which in turn leads to atherosclerosis and CHD, still needs to be substantiated in human studies before measures of oxidation can be used as adequate indicators of chronic disease.

Risk of Inflammatory Disorders

There has been significant interest in the use of dietary *n*-6 fatty acids to modulate inflammatory response. γ-Linolenic acid (GLA, 18:3*n*-6) is the Δ6 desaturase product of linoleic acid and is elongated to dihomo-γ-linolenic acid (DGLA, 20:3*n*-6). The Δ6 desaturase enzyme is the initial step in desaturation of linoleic acid to arachidonic acid (see Figure 8-1). When given as a dietary supplement, GLA has been found to reduce symptoms of several chronic inflammatory diseases such as rheumatoid arthritis and atopic dermatitis (Andreassi et al., 1997; Leventhal et al., 1993, 1994; Lovell et al., 1981; Tate et al., 1989; Zurier et al., 1996). Even though GLA is the precursor to arachidonic acid, human neutrophils contain an elongase enzyme that converts GLA to DGLA, but they lack the Δ5 desaturase needed to form arachidonic acid. As a result, GLA supplementation results in accumulation of DGLA, but not arachidonic acid, and a reduction in leukotriene B_4 production in neutrophils (Chilton-Lopez et al., 1996; Johnson et al., 1997; Ziboh and Fletcher, 1992). However, plasma arachidonic acid concentrations increase after GLA supplementation (Johnson et al., 1997), and this could have adverse implications for other problems such as platelet aggregation (Rodier et al., 1993).

Risk of Cancer

An 8-year controlled clinical trial of 846 men demonstrated a significant increase in fatal carcinomas when the amount of *n*-6 polyunsaturated fatty acids fed was 15 percent of energy compared to 4 percent of energy

(Pearce and Dayton, 1971). Epidemiological studies, however, suggest that *n*-6 polyunsaturated fatty acids are not associated (or have an inverse relationship) with cancer. Howe and coworkers (1990) analyzed 12 case-control studies conducted prior to 1990 and determined that the relative risk of breast cancer for an increment of 45 g of polyunsaturated fat per day was only 1.25. More recent case-control and prospective studies further support the minimal effect of *n*-6 polyunsaturated fatty acids on breast cancer risk (Männistö et al., 1999; Toniolo et al., 1994). A similar relationship has been reported for linoleic acid intake and prostate cancer (Giovannucci et al., 1993; Schuurman et al., 1999). A meta-analysis of 7 cohort studies (Hunter et al., 1996) and a combined analysis of 12 case-control studies (Howe et al., 1990) consistently found no relationship between polyunsaturated fats or vegetable fats and risk of breast cancer. The range of intake of polyunsaturated fat was sufficiently large in these combined studies to comfortably conclude that the epidemiological evidence largely contradicts the animal studies; at least to date, no association between polyunsaturated fat, mainly *n*-6 fatty acids, and risk of breast cancer has been detected. Furthermore, in a review of the literature and meta-analyses of case-controlled and prospective epidemiological studies, Zock and Katan (1998) concluded that it was unlikely that high intakes of linoleic acid substantially raise the risk of breast, colorectal, or prostate cancer.

Risk of Nutrient Excess

High intakes of linoleic acid can inhibit the formation of long-chain *n*-3 polyunsaturated fatty acids from α-linolenic acid, which are precursors to the important eicosanoids (see Chapter 8).

Acceptable Macronutrient Distribution Range

Based on the median energy intakes for each age group (Appendix Table E-1), a minimum intake of 5 percent of energy from linoleic acid would be needed to meet the AI (see Chapter 8). An upper boundary of 10 percent of energy is estimated based on the following information: (1) the highest intake of *n*-6 polyunsaturated fatty acids for individuals in North America is approximately 10 percent of energy, (2) there is not a large body of epidemiological evidence that demonstrates the long-term safety of *n*-6 polyunsaturated fatty acid intakes exceeding 10 percent of energy from typical mixed diets, and (3) evidence from human studies demonstrates that enrichment of lipoproteins and cell membranes with *n*-6 polyunsaturated fatty acids contributes to a pro-oxidant state, thus

suggesting caution for recommending intakes that exceed 10 percent of energy. For these reasons, an Acceptable Macronutrient Distribution Range (AMDR) is estimated to be 5 to 10 percent of energy for children and adults.

n-3 POLYUNSATURATED FATTY ACIDS

Low n-*3 Polyunsaturated Fatty Acid Diets*

Risk of CHD and Stroke

Growing evidence suggests that dietary *n*-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) reduce the risk of coronary heart disease (CHD) and stroke. *n*-3 Polyunsaturated fatty acids may reduce CHD risk through a multitude of mechanisms by (1) preventing arrhythmias (Billman et al., 1999; Kang and Leaf, 1996; McLennan, 1993), (2) reducing atherosclerosis (von Schacky et al., 1999), (3) decreasing platelet aggregation by inhibiting the production of thromboxane A_2 (Harker et al., 1993), (4) decreasing plasma triacylglycerol concentration (Harris, 1989), (5) slightly increasing high density lipoprotein (HDL) cholesterol concentration and decreasing triacylglycerol concentration (Harris, 1989, 1997), (6) modulating endothelial function (De Caterina et al., 2000), (7) decreasing proinflammatory eicosanoids (James et al., 2000), and (8) moderately decreasing blood pressure (Morris, 1994).

Epidemiological Evidence. Many of the epidemiological studies used fish or fish oil intake as a surrogate for *n*-3 polyunsaturated fatty acid intake. The amounts of *n*-3 fatty acids vary greatly in fish, however, and unless the amounts of *n*-3 fatty acids are known, any conclusions are open to question. Furthermore, other components in fish may have effects that are similar to *n*-3 fatty acids and therefore may confound the results. Early epidemiological studies of Greenland Eskimos suggested that diets high in *n*-3 fatty acids, predominantly EPA and DHA, might protect against CHD (Bang et al., 1976; Dyerberg and Bang, 1979). Subsequent observational epidemiological studies have shown mixed results. In the Zutphen study, eating fish one or two times per week was associated with a significant reduction in CHD mortality (Kromhout et al., 1985). A similar result was found in Rotterdam that compared older people who ate fish with those who did not (Kromhout et al., 1995). In three cohorts from the Seven Countries Study, the consumption of fatty fish, but not total fish or lean fish, was associated with a 34 percent decrease in CHD mortality (Oomen et al., 2000). In the Chicago Western Electric Study, eating more than 35 g/d of fish resulted in decreased CHD mortality, mainly of the nonsudden death type (Daviglus

et al., 1997). Utilizing data from 36 countries, an inverse correlation was found between fish consumption and CHD and all-cause mortality (Zhang et al., 1999). In the Multiple Risk Factor Intervention Trial, CHD mortality and intake of *n*-3 fatty acids from fish were significantly and inversely correlated (Dolecek, 1992). In the Physicians' Health Study, eating fish once per week decreased the relative risk of sudden cardiac death by 52 percent compared with eating fish less than once per month (Albert et al., 1998). In this study, although dietary total *n*-3 fatty acid intake correlated inversely with total mortality, no effect on total myocardial infarction, nonsudden cardiac death, or total cardiovascular mortality was observed. The relative risk of sudden death was only 0.58 when 0.3 to 2.6 g/mo of total *n*-3 fatty acids were consumed. Siscovick and colleagues (1995) reported that a mean intake of 2.9 and 5.5 g/mo of long-chain *n*-3 fatty acids reduced the risk of primary cardiac arrest by 30 and 50 percent, respectively. A cross-sectional study showed that α-linolenic acid was inversely related to the prevalence of CHD; this effect was stronger with increasing intakes of linoleic acid (Djoussé et al., 2001).

In contrast to the above studies, the Health Professionals' Follow-up Study showed no significant association between fish intake and risk of CHD (Ascherio et al., 1995). In 16 cohorts from the Seven Countries Study, an inverse association between fish consumption and CHD mortality was found, but after correcting for saturated fat and flavonoid intakes and smoking, this association was not significant (Kromhout et al., 1996). Finally, in the EURAMIC study, adipose tissue biopsy from cases with first myocardial infarction and controls indicated lower α-linolenic acid intake in cases and a relative risk reduction of 58 percent comparing the highest versus lowest quintile of α-linolenic acid intake (Guallar et al., 1999). After adjustment for classical risk factors, the reduction was only 32 percent and no longer significant. In a meta-analysis of 11 prospective cohort studies of fish intake and CHD mortality, the two largest studies found no protective effect and the two smallest found an inverse relationship, with intermediate size studies showing intermediate benefits (Marckmann and Grønbaek, 1999). This analysis suggested that 40 to 60 g/d of fish provided a reduction in CHD mortality in high-risk, but not low-risk, individuals.

There are fewer data with regard to the effects of fish and *n*-3 polyunsaturated fatty acids on stroke. In the Zutphen Study, consumption of more than 20 g/d of fish was associated with a decrease in the risk of stroke (Keli et al., 1994). In the NHANES Epidemiological Follow-up Study, for white women and for black women and men, but not white men, consumption of fish more than once a week was associated with decreased age-adjusted stroke incidence (Gillum et al., 1996). In the Nurses' Health Study, higher consumption of fish and *n*-3 polyunsaturated fatty acids were associated with a reduced risk of total stroke and thrombotic infarction

but not hemorrhagic stroke (mainly among women who did not take aspirin regularly) (Iso et al., 2001). In contrast, in the Chicago Western Electric Study and the Physicians' Health Study, fish intake was not significantly associated with decreased stroke risk (Morris et al., 1995; Orencia et al., 1996).

Nonclinical Interventional Evidence. Supplementation with fish oil, which is high in EPA and DHA, reduces triacylglycerol concentrations; low density lipoprotein (LDL) and HDL cholesterol concentrations are either increased or unchanged (Ågren et al., 1996; Axelrod et al., 1994; Bhathena et al., 1991; Bønaa et al., 1992; DeLany et al., 1990; Eritsland et al., 1994a; Haglund et al., 1990; Lungershausen et al., 1994; Mori et al., 1991; Nelson et al., 1997a; Sanders and Hinds, 1992; Saynor and Gillott, 1992; Schmidt et al., 1992).

Data from studies on the effects of EPA and DHA as a percent of energy on blood lipid concentrations in healthy individuals are presented in Table 11-10. In general, EPA+DHA intake is associated with small increases in LDL and HDL cholesterol concentrations and a significant decrease in triacylglycerol concentrations (Harris, 1997).

The consumption of 3.65 to 6 g/d of *n*-3 polyunsaturated fatty acids inhibits platelet aggregation, which in turn prevents the risk of CHD (Mori et al., 1997; Tremoli et al., 1995). Some studies, however, did not show an effect on platelet aggregation after the consumption of 4.5 to 6 g/d of EPA+DHA (Nelson et al., 1997b; Turini et al., 1994).

Randomized, Controlled Clinical Trials Evidence. There are four randomized, controlled clinical trials that show a benefit of fish, fish oils, or α-linolenic acid on CHD prevention. In the Diet and Reinfarction Trial (DART), male myocardial infarction (MI) survivors were encouraged to increase their oily fish intake to 200 to 400 g/wk in order to increase EPA and DHA intake. Over a 2-year period, this resulted in a significant reduction in total mortality, with the greatest benefit in a lower rate of fatal MI (Burr et al., 1989a, 1989b). In the DART trial, of the group randomized to ingest dietary fish, a subgroup chose to ingest 1.5 g/d of fish oil capsules rather than to consume fish. The capsule group had a significant reduction in CHD death and a significant reduction in all-cause mortality, suggesting that the benefits of the fish consumption were in the fish oil fraction (Burr et al., 1994). In the Indian Experiment of Infarct Survival, MI survivors were treated with either fish oil capsules (1.08 g/d of EPA) or mustard oil (2.9 g/d of α-linolenic acid) or placebo for 1 year (Singh et al., 1997). The fish oil and mustard oil groups had decreased total cardiac events, nonfatal infarctions, arrhythmias, left ventricular enlargement, and angina

pectoris. The fish oil group, but not the mustard oil group, had decreased cardiac deaths. In the Lyon Diet Heart Study, post-MI patients were randomized into a control group or into an experimental group that received dietary counseling and a special margarine containing α-linolenic acid (de Lorgeril et al., 1994, 1999). The control and experimental groups consumed approximately 0.27 and 0.81 percent of energy as α-linolenic acid, respectively. There was a significant reduction in risk for cardiac death for the experimental group after 27 months, and a reduction after a 4-year follow-up. The extent to which these reductions in risk were due to *n*-3 fatty acids is uncertain.

In another trial, patients with recent MI were randomized to receive 300 mg of vitamin E, 850 mg of *n*-3 fatty acids (EPA+DHA), both, or neither (GISSI-Prevenzione Investigators, 1999). After 3.5 years, the *n*-3 fatty acid group experienced a 15 percent reduction in the primary endpoints of death, nonfatal myocardial infarction, and nonfatal stroke, and a 20 percent reduction in the other primary endpoints of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. This group also experienced a 20 percent reduction in all-cause mortality and a 45 percent reduction in sudden deaths compared with the control group. Vitamin E, in contrast to *n*-3 polyunsaturated fatty acids, had no beneficial effects on cardiovascular endpoints.

n-3 Polyunsaturated fatty acids have also been reported to reduce blood pressure in hypertensive individuals. A meta-analysis of 31 placebo-controlled trials estimated a mean reduction in systolic and diastolic blood pressure of 3.0 and 1.5 mm Hg, respectively (Morris et al., 1993). Furthermore, a statistically significant dose–response effect occurred with the smallest reduction observed with intakes of less than 3 g/d and the largest reduction observed with intakes at 15 g/d.

When 55 individuals were randomized to receive either 5.2 g/d of *n*-3 fatty acids or a placebo for 12 weeks, heart rate variability (naturally occurring irregular heart beats) significantly increased after supplementation with *n*-3 fatty acids (Christensen et al., 1997). Because impaired heart rate variability is associated with increased arrhythmic events (Farrell et al., 1991), this finding supports the hypothesis that *n*-3 polyunsaturated fatty acids have antiarrhythmic effects in humans (Christensen et al., 1997). A more recent study by Christensen and coworkers (1999) reported a dose–response effect on heart rate variability, suggesting antiarrhythmic effects in men but not women, given 3 g/d of EPA plus 2.9 g/d of DHA or 0.9 g/d of EPA plus 0.8 g/d of DHA for 12 weeks. However, the beneficial effect was found only in men with low initial heart rate variability.

TABLE 11-10 *n*-3 Fatty Acid (EPA and DHA)[a] Intake and Blood Lipid Concentrations

Reference	Study Design	Percent of Energy from Fatty Acid	Postintervention Blood Lipid Concentration (mmol/L)[b]		
			LDL-C	HDL-C	Triacylglycerol
Flaten et al., 1990	64 men	Control diet (0 *n*-3)		1.28[c]	1.71[c]
	6-wk parallel	Control diet + 2.2 EPA/DHA		1.15[c]	1.23[d]
Kestin et al., 1990	33 men	0.6 18:3*n*-3	4.44[c]	1.26[c]	1.62[c]
	6-wk parallel	2.7 18:3*n*-3	4.55[c]	1.16[c]	1.85[c]
		1.1 EPA/DHA	4.62[d]	1.28[c]	1.24[d]
Bhathena et al., 1991	40 men	0 EPA/DHA			1.62[c]
	10-wk crossover	2.2 EPA/DHA			1.17[d]
Bønaa et al., 1992	144 men and women	0.28 EPA/DHA/22:5	4.65	1.32	1.95
	Cross-sectional	0.30 EPA/DHA/22:5	4.71	1.31	1.49
		0.52 EPA/DHA/22:5	4.43	1.36	1.32
		0.72 EPA/DHA/22:5	4.47	1.36	1.34
Eritsland et al., 1994a	511 men and women	Control diet	5.03[c]	1.08[c]	2.08[c]
	9-mo parallel	Control diet + 1.46 EPA/DHA	5.11[c]	1.16[c]	1.57[d]
Eritsland et al., 1994b	57 men and women	Control diet	4.84[c]	1.01[c]	1.80[c]
	6-mo parallel	Control diet + 1.4 EPA/DHA	5.03[c]	0.97[c]	1.71[c]

Ågren et al., 1996	55 men	0 *n*-3	2.60[c]		1.42[c]
	15-wk parallel	0.36 *n*-3 (fish)	2.56[c]		1.16[d]
		0.60 *n*-3 (DHA oil)	2.42[c]		0.97[d]
		0.76 *n*-3 (fish oil)	2.51[c]		0.89[d]
Grimsgaard et al., 1997	224 men	0.19 *n*-3 (corn oil)	4.10[c]	1.40[c]	1.33[c]
	7-wk parallel	0.52 *n*-3 (DHA oil)	4.13[c]	1.42[d]	1.02[d]
		0.55 *n*-3 (EPA oil)	3.98[c]	1.34[c]	1.08[d]
Sanders et al., 1997	26 men	0 EPA/DHA (saturated fat diet)	2.60[c]	1.18[c]	0.93[c]
	3-wk crossover	0 EPA/DHA (*n*-6 diet)	2.29[d]	1.19[c]	0.92[c]
		1.5 EPA/DHA (*n*-3 diet)	2.30[d]	1.22[c]	0.68[d]

[a] EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.
[b] LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol.
[c,d] Within each study, the blood lipid concentrations that are significantly different between treatment groups have a different superscript.

Risk of Obesity

One study in laboratory mice suggested that diets containing *n*-3 polyunsaturated fatty acids lead to lower levels of fat accumulation compared with diets containing other fatty acids (Hun et al., 1999). Several studies have examined whether *n*-3 polyunsaturated fatty acids affect growth of adipose tissue. Parrish and colleagues (1990, 1991) found that rats given a high fat diet supplemented with fish oil had less fat in perirenal and epididymal fat pads and decreased adipocyte volumes compared with rats fed lard. Adipose tissue growth restriction appeared to be the result of limiting the amount of triacylglycerol in each adipose tissue cell rather than by limiting the number of cells. Rustan and colleagues (1993) found similar results using rats fed either lard or lard supplemented with EPA and DHA. Although body weight gain and mean energy expenditure were similar for both groups, the mean respiratory quotient was significantly higher during both fasting and fed periods in rats fed the EPA+DHA supplement. The researchers concluded that the rats supplemented with *n*-3 fatty acids demonstrated reduced oxidation of fat and increased carbohydrate utilization. Little data exist with respect to the specific effects of dietary *n*-3 polyunsaturated fatty acids on adiposity in humans; therefore, prevention of obesity cannot be considered an indicator at this time.

Risk of Diabetes

Epidemiological Evidence. While several studies have reported a negative relationship between polyunsaturated fatty acid intake and risk of diabetes (Colditz et al., 1992; Salmerón et al., 2001; Trevisan et al., 1990), fish intake has specifically been reported to have a negative association (Feskens et al., 1991b, 1995). A review of the epidemiological data on this association concluded that polyunsaturated fatty acids, and possibly long-chain *n*-3 fatty acids, could be beneficial in reducing the risk of diabetes (Hu et al., 2001).

Interventional Evidence. Studies conducted in rodents have shown that administration of fish oil results in increased insulin sensitivity (Chicco et al., 1996) and corrected hyperinsulinemia (Luo et al., 1996). Substituting a proportion of the fat in a high fat diet with fish oil prevented the development of insulin resistance in rats (Storlien et al., 1987) and normalized insulin action in rats experiencing severe insulin resistance (Storlien et al., 1991). Additionally, rats prone to spontaneous diabetes mellitus that were given EPA in doses of 0.1, 0.3, and 1.0 g/kg/d for 8 months had reduced incidences of diabetes (92, 50, and 17 percent, respectively) (Nobukata et

al., 2000). Thus, animal evidence suggests that the fatty acid composition of the diet may be an important factor in the effect of dietary fat on insulin action.

Whether a change of dietary fat composition will alter insulin sensitivity in humans remains an open question. Studies in humans have demonstrated a relationship between increased insulin sensitivity and the proportion of long-chain *n*-3 polyunsaturated fatty acids in skeletal muscle phospholipids (Borkman et al., 1993; Clore et al., 1998). Supplementation with EPA and DHA resulted in improved insulin sensitivity in diabetic individuals (Popp-Snijders et al., 1987) and increased the insulin-stimulated glucose disposal rate in patients with impaired glucose tolerance (Fasching et al., 1991). However, other studies in nondiabetic individuals (Toft et al., 1995) and individuals with type 2 diabetes (Annuzzi et al., 1991; Luo et al., 1998) reported no beneficial effect of *n*-3 fatty-acid supplementation on insulin action.

Risk of Cancer

Experimental evidence suggests several mechanisms in which *n*-3 polyunsaturated fatty acids may protect against cancer. *n*-3 Polyunsaturated fatty acids, particularly DHA and EPA, have been shown to suppress neoplastic transformation (Takahashi et al., 1992), inhibit cell growth and proliferation (Anti et al., 1992; Calviello et al., 1998; Grammatikos et al., 1994), induce apoptosis (Calviello et al., 1998; Lai et al., 1996), and inhibit angiogenesis (Rose and Connolly, 2000), which may occur by suppressing *n*-6 fatty acid eicosanoid production (see Chapter 8). Animal studies with *n*-3 fatty acid or fish-oil supplementation have shown inhibition of mammary carcinogenesis and tumor growth (Grammatikos et al., 1994; Karmali et al., 1984), colon carcinogenesis (Deschner et al., 1990; Reddy et al., 1991), and prostate tumorigenesis and tumor cell growth (Karmali et al., 1987).

Across-country epidemiological studies have shown an inverse relationship between dietary fish intake and breast cancer incidence and mortality (Kaizer et al., 1989; Sasaki et al., 1993), but the intakes of *n*-3 fatty acids in these studies are not well defined. Moreover, despite these results, most case-control and prospective studies have not reported a protective effect of fish consumption on breast cancer (Willett, 1997). Ecological studies have also shown inverse relationships between fish and fish oil intake and colorectal cancer (Caygill and Hill, 1995; Caygill et al., 1996), although some were nonsignificant (Hursting et al., 1990). Results from case-control and prospective studies have been somewhat equivocal (Boutron et al., 1991). However, Willett and colleagues (1990) found that higher fish consumption was associated with less colon cancer in women. No significant

associations were reported in the few studies that have examined fish consumption and risk of prostate cancer (Giovannucci et al., 1993; Severson et al., 1989; Talamini et al., 1992).

Risk of Nutrient Inadequacy

Vegetable oils, such as soybean oil, flaxseed oil, and canola oil, contain high amounts of α-linolenic acid. Fatty fishes and fish oils provide a mixture of biologically active EPA and DHA. *n*-3 Polyunsaturated fatty acids (α-linolenic acid) are essential in the diet and Adequate Intakes (AIs) have been set (see Chapter 8). Intakes of α-linolenic acid range from approximately 0.6 to 1.2 percent of energy (Appendix Tables E-1 and E-11). Low intakes of α-linolenic acid can result in inadequate biosynthesis of the longer-chain *n*-3 polyunsaturated fatty acids, resulting in an excessive ratio of *n*-6 polyunsaturated fatty acids (see Chapter 8).

High n-*3 Polyunsaturated Fatty Acid Diets*

There is evidence to suggest that high intakes of *n*-3 polyunsaturated fatty acids (EPA and DHA) may have adverse effects on immune function and may increase the risk of excessive bleeding and hemorrhagic stroke (see Chapter 8). High intakes of *n*-3 polyunsaturated fatty acids (α-linolenic acid) can also result in inadequate biosynthesis of long chain *n*-6 polyunsaturated fatty acids that are important for prostaglandin and eicosanoid synthesis (see Chapter 8).

Acceptable Macronutrient Distribution Range

α-Linolenic acid is essential in the diet and therefore AIs have been set (see Chapter 8). Up to 10 percent of the AI can be consumed as EPA and/or DHA. The above studies suggest that α-linolenic acid, EPA, and DHA may provide beneficial health effects when consumed at moderate levels. Based on the median energy intake by the various age groups (Appendix Table E-1), it is estimated that approximately 0.6 percent of energy from α-linolenic acid is needed to meet the AI. This level is used as the lower boundary for the Acceptable Macronutrient Distribution Range (AMDR) for α-linolenic acid. The upper boundary of the AMDR for α-linolenic acid is set at 1.2 percent of energy and represents the highest levels of α-linolenic acid consumed in the form of foods by individuals in North America. Data from interventional studies to support the benefit of even higher intakes of α-linolenic acid were not considered strong enough to justify establishing an upper boundary greater than 1.2 percent of

energy. Approximately 10 percent of the AMDR for *n*-3 fatty acids (α-linolenic acid) can be consumed as EPA and/or DHA (0.06 to 0.12 percent of energy).

SATURATED FATTY ACIDS, *TRANS* FATTY ACIDS, AND CHOLESTEROL

Low Saturated Fatty Acid, Trans *Fatty Acid, and Cholesterol Diets*

There are no known risks of chronic disease from consuming low intakes of saturated fatty acids, *trans* fatty acids, or cholesterol. In the United States, saturated fatty acids provided 11 to 12 percent of energy in adult diets and 12.2 to 13.9 percent of energy in the diets of children and adolescents (CDC, 1994). It is estimated that the intake of *trans* fatty acids is approximately 2.6 percent of energy (Allison et al., 1999). The intake of cholesterol by American adults ranges from less than 100 mg/d to just under 770 mg/d (Appendix Table E-15).

It is important to recognize that lower intakes of saturated fatty acids and cholesterol are observed for vegetarians, especially vegans (Janelle and Barr, 1995; Shultz and Leklem, 1983). Because certain micronutrients, saturated fats, and cholesterol are consumed mainly through animal foods, it is possible that diets low in saturated fat and cholesterol are associated with low intakes of these micronutrients. When the micronutrient intakes of Seventh-day Adventist vegetarians and nonvegetarians were measured, there were no significant reductions in micronutrient intakes with the lower saturated fat (7.3 versus 12.6 percent of energy) and cholesterol intakes (186 versus 404 mg/d) of vegetarian compared to nonvegetarian men (12.6 percent of energy and 404 mg/d) (Shultz and Leklem, 1983). Similarly, the intakes of most micronutrients were not significantly lower for vegans, except for vitamin B_{12} (0.51 versus 3.79 mg/d), riboflavin (1.32 versus 1.72 mg/d), and calcium (578 versus 950 mg/d). Vegans had significantly lower intakes of saturated fat (6.9 versus 10.6 percent of energy) and cholesterol (94 versus 231 mg/d) than nonvegetarians (Janelle and Barr, 1995).

Analysis of nutritionally adequate menus indicates that there is a minimum amount of saturated fat that can be consumed so that sufficient levels of linoleic and α-linolenic acid are consumed (as an example see Appendix Tables G-1 and G-2). Other than soy products that are high in *n*-6 and *n*-3 fatty acids, many vegetable-based fat sources are also high in saturated fatty acids, and these differences should be considered in planning menus.

High Saturated Fatty Acid, Trans *Fatty Acid, and Cholesterol Diets*

There is a body of evidence suggesting that saturated and *trans* fatty acids and cholesterol increase blood total and low density lipoprotein cholesterol concentrations, and therefore the risk of coronary heart disease (CHD) (see Chapters 8 and 9). Because the intake of each of these three nutrients and risk of CHD is a positive linear trend, even very low intakes of each may increase risk.

To minimize saturated fatty acid intake requires decreased intake of animal fats (e.g., meat fat and butter fat) and certain oils, such as coconut and palm kernel oil. Saturated fatty acids can be reduced by choosing lean cuts of meat, trimming away visible fat on meats, and eating smaller portions. The amount of butter that is added to foods can be minimized or replaced with vegetable oils or nonhydrogenated vegetable oil spreads. Vegetable oils, such as canola and safflower oil, can be used to replace more saturated oils such as coconut and palm oil. Such changes can reduce saturated fat intake without altering the intake of essential nutrients.

A reduction in the frequency of intake or serving size of certain foods such as liver (375 mg/3 oz slice) and eggs (250 mg/egg) can help reduce the intake of cholesterol, as well as foods that contain eggs, such as cheesecake (170 mg/slice) and custard pie (170 mg/slice). There are a number of meats and dairy products that contain low amounts of cholesterol (e.g., lean meats [30 mg/2 slices] and 2 percent milk [18 mg/cup]). Therefore, there are a variety of foods that are low in saturated fat and cholesterol and also abundant in essential nutrients such as iron, zinc, and calcium.

Trans fatty acids are high in stick margarine and those foods containing vegetable shortenings that have been subjected to hydrogenation. Examples of foods that contain relatively high levels of *trans* fatty acids include cakes, pastries, doughnuts, and french fries (Litin and Sacks, 1993). Therefore, the intake of *trans* fatty acids can be reduced without limiting the intake of most essential nutrients by decreasing the serving size and frequency of intake of these foods, or by using unhardened oil.

CONJUGATED LINOLEIC ACID

Conjugated linoleic acid (CLA) has been shown to play a role in the alteration of body composition in animals (Park et al., 1997), the inhibition of tumor cell growth (Whigham et al., 2000), and the inhibition of experimental atherosclerosis in animals (Lee et al., 1994). The *trans*-10,*cis*-12 CLA isomer appears to be the isomer primarily responsible for the induction of changes in body composition (de Deckere et al., 1999; Park et al., 1999). Several studies suggest that these changes are primarily due to a reduction in lipid uptake by adipocytes (Pariza et al., 2001), which results

from the action of CLA on the activities of stearoyl-coenzyme A desaturase (Choi et al., 2000; Lee et al., 1998) and lipoprotein lipase (Park et al., 1997, 1999). The *trans*-10,*cis*-12 CLA isomer has also been reported to inhibit proliferation and differentiation in cultured mouse adipocytes (Brodie et al., 1999) and to induce apoptosis in vivo in the adipose tissue of mice (Tsuboyama-Kasaoka et al., 2000). In addition to body fat reduction, dietary CLA may increase whole body protein accretion in animals, suggesting the enhancement of lean body mass (Ostrowska et al., 1999; Park et al., 1997; Stangl, 2000).

Research on the effects of CLA on body composition in humans has provided conflicting results. Blankson and coworkers (2000) conducted a study in overweight and obese men and women given either placebo or 1.7, 3.4, 5.1, or 6.8 g/d of a CLA preparation consisting of equal parts of the *cis*-9,*trans*-11 and *trans*-10,*cis*-12 isomers. After 12 weeks, none of the groups exhibited significant reductions in body weight or body mass index. However, the groups given 1.7, 3.4, and 6.8 g/d of CLA showed significant decreases in body fat mass compared to the placebo group. No differences in lean body mass were observed. Zambell and coworkers (2000) studied the effects of CLA supplementation in healthy adult women given either placebo or 3 g/d of CLA for 64 days. They found no significant changes in fat-free mass, fat mass, body weight, or percentage of body fat with CLA supplementation.

CLA has been studied for its potential anticancer benefits in numerous animal and in vitro models. CLA mixtures have been shown to exhibit anticarcinogenic properties in skin, lung, forestomach, colorectal, prostate, and mammary tissues (Cesano et al., 1998; Ha et al., 1990; Liew et al., 1995; Schønberg and Krokan, 1995; Shultz et al., 1992), although the majority of the research has been conducted with breast cancer. Ip and Scimeca (1997) conducted a study in female rats chemically induced for mammary tumors and fed a diet containing either 2 percent or 12 percent linoleic acid. The rats were also supplemented with 0, 0.5, 1, 1.5, or 2 percent CLA. The researchers found that increasing CLA from 0.5 to 1 percent resulted in a dose-dependent decrease in both tumor incidence and total number of tumors. No further protection was observed in the groups receiving 1.5 or 2 percent CLA. In addition to inhibiting tumor growth, CLA eliminated the spread of breast cancer cells to the lungs, peripheral bone, and bone marrow of mice supplemented with 1 percent CLA (Visonneau et al., 1997).

Although the exact mechanisms of the anticarcinogenic effects of CLA are not fully understood, several explanations have been offered. It has been suggested that growth inhibition of cancer cells may be due to the ability of CLA to inhibit protein and nucleotide biosynthesis (Ip et al., 1999; Shultz et al., 1992) and to induce cell apoptosis (Ip et al., 1999,

2000). Antioxidant activity of CLA has also been suggested (Ha et al., 1990; Ip et al., 1991); however, this theory has been contradicted by studies showing that CLA does not decrease lipid peroxide formation (Cunningham et al., 1997; van den Berg et al., 1995). Another possible mechanism of cancer cell growth inhibition by CLA includes alteration of eicosanoid metabolism. CLA may compete with linoleic acid in its conversion to arachidonic acid, thereby reducing the biosynthesis of eicosanoids (Banni et al., 1999), which have been associated with the proliferation of cultured breast cancer cells (Karmali, 1986; Noguchi et al., 1995). CLA has been shown to reduce leukotriene B_4 and prostaglandin E_2 levels in animals (Kavanaugh et al., 1999; Sugano et al., 1998). To date, there are insufficient data in humans to recommended a level of CLA at which beneficial health effects may occur.

DIETARY FIBER AND FUNCTIONAL FIBER

Low Fiber Diets

A low fiber diet is often attributed to the intake of a low carbohydrate diet. A number of adverse clinical effects, including impaired laxation and increased risk of cancer, obesity, heart disease, and type 2 diabetes, have been associated with the chronic consumption of low amounts of *Dietary Fiber* or *Functional Fiber*. The studies to support a beneficial role of these fibers are reviewed in Chapter 7.

Certain animal studies have shown that some fibers can actually enhance mineral absorption (Demigné et al., 1989; Levrat et al., 1991a, 1991b). There are several potential mechanisms by which ingestion of *Dietary Fiber* may actually enhance mineral status. For example, a more acidic pH in the colon is produced with fiber fermentation, and this results in more ionized calcium, which is better absorbed (Rémésy et al., 1992). *Dietary Fiber* in the colon can also stimulate bacterial fermentation, which has been associated with increases in calcium, magnesium, and potassium absorption (Demigné et al., 1989; Levrat et al., 1991a). Many fiber sources, such as karaya gum, sugar beet fiber, and coarse bran, are also excellent sources of minerals (Behall et al., 1987; Fairweather-Tait and Wright, 1990; Van Dokkum et al., 1982).

Several investigators have shown that inulin and fructooligosaccharides actually enhance calcium and magnesium absorption (Coudray et al., 1997; Delzenne et al., 1995; Levrat et al., 1991b; Ohta et al., 1995). There is also indirect evidence of this same enhancement with calcium in humans (Trinidad et al., 1993, 1996). A direct effect of fiber on mineral absorption has also been reported in humans where inulin increased the apparent absorption and balance of calcium (Coudray et al., 1997).

High Fiber Diets

There is limited data to suggest that chronic consumption of high fiber diets results in adverse health effects (see Chapter 7). Gastrointestinal distress can occur with the consumption of high fiber diets, but this often subsides with time.

DIETARY PROTEIN

Low Protein Diets

Although uncommon in North America, protein–energy malnutrition (PEM) is one of the most common nutritional diseases in developing countries (Torun and Chew, 1999). The etiology of PEM is complex as there are a number of factors that are attributed to its onset, including insufficient food intake or intake of low protein-containing foods, which in turn is attributed to poverty, unsanitary conditions, and food insecurity. Because PEM is attributed to insufficient food intake, not only are protein and energy limited, but the micronutrients that are often present in protein-containing foods are also limited. Epidemiological analysis from 53 developing countries indicated that 56 percent of deaths in young children were due to the potentiating effects of malnutrition in infectious diseases (Pelletier et al., 1995). The increased duration or susceptibility to infectious diseases such as respiratory infections and diarrhea are due, in part, to the involvement of protein in immune function.

Impaired Immune Function

Chandra (1972) showed that in individuals with PEM, a variety of immune responses were impaired. The major defects observed with severe PEM involve T lymphocytes and the complement system. With PEM, the number of lymphocytes is markedly reduced and delayed cutaneous hypersensitivity responses to both recall and new antigens are depressed (Chandra, 1991), as is the production of several components of the complement system (Keusch et al., 1984). Furthermore, antibody affinity (Chandra et al., 1984) and lysozyme concentrations (Chandra and Newberne, 1977) are decreased.

Impaired Growth

Low protein intake during pregnancy is correlated with a higher incidence of low birth weight (King, 2000). Furthermore, in children, diets low in protein and energy are most frequently associated with a deficit in

weight-for-height (wasting) and height-for-age (stunting) (Waterlow, 1976). These deficits can be corrected by the provision of a high protein diet (Badaloo et al., 1999) and with an adequate energy intake to permit catch-up growth. For these reasons, various anthropometric measures are used for diagnosis and monitoring the treatment of PEM.

Low Birth Weight

Rush and coworkers (1980) found decreases in both gestational length and birth weight and increases in very early premature births and mortality with high density protein supplementation (additional 40 g/d) in poor, black pregnant women at risk of having low birth weight infants. In contrast, Adams and coworkers (1978) reported no differences from the controls in mean birth weights of infants of mothers at risk of having a low birth weight infant when these women were supplemented with 40 g/d of protein. No reports were found of protein toxicity in healthy pregnant or lactating women that were not at risk of having a low birth weight infant. Thus, at the present time, low birth weight cannot be utilized to set a Tolerable Upper Intake Level (UL) for protein for women.

Risk of Nutritional Inadequacy

High quality protein is typically consumed via animal products, and therefore vegetarians may consume less high quality protein than omnivores. Because animal foods are the primary sources of certain nutrients, such as calcium, vitamin B_{12}, and bioavailable iron and zinc, low protein intakes may result in inadequate intakes of these micronutrients. As an example, Janelle and Barr (1995) reported significantly lower intakes of riboflavin, vitamin B_{12}, and calcium by vegans who also consumed lower amounts of protein (10 versus 15 percent of energy) compared with nonvegetarians.

Vegetable protein has been shown to decrease plasma cholesterol concentrations in experimental animals and humans (Nagata et al., 1998; Nicolosi and Wilson, 1997; Terpstra et al., 1991). When the ratio of casein:soybean protein in the diet was decreased, there was a reduction in total and non-high density lipoprotein cholesterol concentrations (Fernandez et al., 1999; Teixeira et al., 2000). In laboratory animals, it was shown that the onset of atherosclerosis was significantly reduced when animals were fed a textured vegetable protein diet compared to a beef protein diet (Kritchevsky et al., 1981).

High Protein Diets

Osteoporosis

There is a substantial amount of literature that documents the increase in urinary excretion of calcium with increasing protein intake (Allen et al., 1979; Heaney, 1993; Lemann, 1999). The magnitude of this effect for a doubling of the protein intake, in the absence of change in any other nutrient, is a 50 percent increase in urinary calcium (Heaney, 1993). This has two potential detrimental consequences: loss of bone calcium and increased risk of renal calcium stone formation. Loss of calcium from bone is thought to occur because of bone mineral resorption that provides the buffer for the acid produced by the oxidation of the sulfur amino acids of protein (Barzel and Massey, 1998). However, although increased resorption of bone with increased protein intake has been shown (Kerstetter et al., 1999; Whiting et al., 1997), whether this in practice leads to bone loss and osteoporosis is controversial (Barzel and Massey, 1998; Heaney, 1998). It has recently been concluded that there may be no need to restrain dietary protein intake. Poor protein status itself leads to bone loss, whereas increased protein intake may lead to increased calcium intake, and bone loss does not occur if calcium intake is adequate (Heaney, 1998). In a recent prospective study of men and women aged 55 to 92 years, consumption of animal protein was positively associated with bone mineral density in women, but not in men (Promislow et al., 2002). In contrast, Dawson-Hughes and Harris (2002) reported no association between protein intake and bone mineral density in 342 healthy men and women aged 65 years and older. However, when the individuals were given calcium citrate malate and vitamin D in addition to the high protein intake, there was a favorable change in bone mineral density.

Kidney Stones

It has been estimated that 12 percent of the population in the United States will suffer from a kidney stone at some time (Sierakowski et al., 1978). The most common form of kidney stone is composed of calcium oxalate, and its formation is promoted by high concentrations of calcium and oxalate in the urine. A high animal protein intake in healthy humans increases urinary calcium and oxalate and the overall probability of forming kidney stones by 250 percent (Robertson et al., 1979). Conversely, restricting protein intake improved the lithogenic profile in hypercalciuric patients (Giannini et al., 1999). Also, the incidence of calcium oxalate stones has been shown to be associated with consumption of animal protein (Curhan et al., 1996; Robertson and Peacock, 1982). In contrast, the

only long-term prospective trial (4.5 years) of the effect of animal protein restriction on stone formation in newly diagnosed patients with calcium stones gave a negative result (Hiatt et al., 1996). The relative risk factor for recurrent stone formation was 5.6 (confidence interval 1.2–26.1), suggesting that the dietary advice was detrimental. In this study, 50 patients were given low animal protein (56 to 64 g/d) and high fiber, plus adequate fluid and calcium, whereas 49 control patients were only instructed to take adequate water and calcium. However, as protein intake was not the only variable, and in view of the data described above suggesting benefits from lower protein intake, further investigation is necessary.

Renal Failure

Restriction of dietary protein intake is known to lessen the symptoms of chronic renal insufficiency (Walser, 1992). This raises two related, but distinct questions: Do high protein diets have some role in the development of chronic renal failure? Do high protein intakes accelerate the progression of chronic renal failure? The concept that protein restriction might delay the deterioration of the kidney with age was based on studies in rats in which low energy or low protein diets attenuated the development of chronic renal failure (Anderson and Brenner, 1986, 1987). Walser (1992) has argued that this mechanism is unlikely to operate in humans. In particular, the decline in kidney function in the rat is mostly due to glomerulosclerosis, whereas in humans it is due mostly to a decline in filtration by nonsclerotic nephrons. Also, when creatinine clearance was measured in men at 10- to 18-year intervals, the decline with age did not correlate with dietary protein intake (Tobin and Spector, 1986). Correlation of creatinine clearance with protein intake showed a linear relationship with a positive gradient (Lew and Bosch, 1991), suggesting that the low protein intake itself decreased renal function. These factors point to the conclusion that the protein content of the diet is not responsible for the progressive decline in kidney function with age.

Coronary Artery Disease

It is well documented that high dietary protein in rabbits induces hypercholesterolemia and arteriosclerosis (Czarnecki and Kritchevsky, 1993). However, this effect has not been consistently shown in either swine (Luhman and Beitz, 1993; Pfeuffer et al., 1988) or humans. In humans, analysis of data from the Nurses' Health Study showed an inverse relationship between protein intake and risk of cardiovascular disease (Hu et al., 1999). The association was weak but suggests that high protein intake does not increase the risk of cardiovascular disease. Similar conclusions have

been reached in observational studies showing an inverse relationship between protein intake and blood pressure (Obarzanek et al., 1996) and that replacement of carbohydrate with protein resulted in lower very low density cholesterol, low density cholesterol, and triglycerides (Wolfe and Piché, 1999).

Obesity

A number of short-term studies indicate that protein intake exerts a more powerful effect on satiety than either carbohydrate or fat (Hill and Blundell, 1990; Rolls et al., 1988; Stubbs et al., 1996). However, some epidemiological studies have shown a positive correlation between protein intake and body fatness, body mass index, and subscapular skinfold (Buemann et al., 1995; Rolland-Cachera et al., 1995). In contrast, a 6-month randomized trial demonstrated that the replacement of some dietary carbohydrate by protein improved weight loss as part of a reduced fat diet (Skov et al., 1999).

Cancer

The fact that the growth of tumor cells in culture is often increased by high amino acid concentrations (Breillout et al., 1990; Collins et al., 1998) raises concern that high dietary protein intake might enhance the incidence or the progression of cancer. Reviews of the literature on colon cancer have concluded that high meat intake may be associated with increased risk, but that high total protein intake is not (Clinton, 1993; Giovannucci and Willett, 1994; Parnaud and Corpet, 1997). A lack of correlation with total protein intake has been found in a case-control study (Slattery et al., 1997), but other studies have reported both increased (Slattery et al., 1994) and decreased (Kato et al., 1997) risk.

For breast cancer, the geographical distribution of incidence is correlated with the availability of dietary protein, especially animal protein (Clinton, 1993). Furthermore, migration to an area with typically higher protein intakes is associated with increased risk of breast cancer (Buell, 1973; Buell and Dunn, 1965). In accord with this, several studies have indicated an association among breast cancer and the intakes of animal protein and fat (Hislop et al., 1986; Lubin et al., 1981, 1986). However, others showed a relationship with fat, but not protein intake (Miller et al., 1978; Phillips, 1975). More recently, a case-control study on 2,569 patients and 2,588 controls showed a slightly negative relationship between total protein and breast cancer (Decarli et al., 1997). Another case-control study on 180 breast-cancer patients and 829 controls also showed no relation-

ship with total protein intake, but there was an increased risk ratio for meat consumption (Toniolo et al., 1994).

For other types of tumors, there also is no clear indication of greater risk with higher protein intakes. Total protein intake was not associated with increased risk of lung cancer (Lei et al., 1996), prostate cancer (Schuurman et al., 1999), endometrial cancer (Barbone et al., 1993; Shu et al., 1993), oral and pharynx cancer (Franceschi et al., 1999), esophogeal cancer (Gao et al., 1994), and non-Hodgkin's lymphoma (Chiu et al., 1996; Ward et al., 1994), although some studies detected a positive relationship with animal protein (Chiu et al., 1996; Shu et al., 1993) or cured meat consumption (Schuurman et al., 1999). Moreover, in some of these studies, there was an inverse relationship with total protein intake (Barbone et al., 1993; Franceschi et al., 1999; Gao et al., 1994). On the other hand, higher protein intake was associated with an increased risk of cancer of the upper digestive tract (De Stefani et al., 1999) and kidney (Chow et al., 1994).

Overall, despite the demonstration of a positive influence of dietary fat and total energy, as well as meat (especially red meat), on some types of tumors, no clear role for total protein has yet emerged. The current state of the literature, therefore, does not permit any recommendation of an upper limit to be made on the basis of cancer risk.

Acceptable Macronutrient Distribution Range

There is no evidence to suggest that the Acceptable Macronutrient Distribution Range (AMDR) for protein should be at levels below the Recommended Dietary Allowance (RDA) for protein (about 10 percent of energy) for adults. There was insufficient evidence to suggest a UL for protein (see Chapter 10) and insufficient data to suggest an upper limit for an AMDR for protein. To complement the AMDRs for fat (20 to 35 percent energy) and carbohydrate (45 to 65 percent energy) for adults, protein intakes may range from 10 to 35 percent of energy intake to ensure a nutritionally adequate diet. For young and older children, the RDA is approximately 5 and 10 percent of energy, respectively. To complement the AMDR for fat (30 to 40 percent of energy) and carbohydrate (45 to 65 percent of energy) for young children and for older children (25 to 35 percent of energy from fat and 45 to 65 percent of energy from carbohydrate), protein intakes may range from 5 to 20 percent for young children and 10 to 30 percent for older children.

REFERENCES

Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. 1996. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes* 45:1684–1693.

Abbey M, Belling GB, Noakes M, Hirata F, Nestel PJ. 1993. Oxidation of low-density lipoproteins: Intraindividual variability and the effect of dietary linoleate supplementation. *Am J Clin Nutr* 57:391–398.

Abbott WGH, Boyce VL, Grundy SM, Howard BV. 1989. Effects of replacing saturated fat with complex carbohydrate in diets of subjects with NIDDM. *Diabetes Care* 12:102–107.

Adams SO, Barr GD, Huenemann RL. 1978. Effect of nutritional supplementation in pregnancy. I. Outcome of pregnancy. *J Am Diet Assoc* 72:144–147.

Ågren JJ, Hänninen O, Julkunen A, Fogelholm L, Vidgren H, Schwab U, Pynnönen O, Uusitupa M. 1996. Fish diet, fish oil and docosahexaenoic acid rich oil lower fasting and postprandial plasma lipid levels. *Eur J Clin Nutr* 50:765–771.

Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN, Manson JE. 1998. Fish consumption and risk of sudden cardiac death. *J Am Med Assoc* 279:23–28.

Allen LH, Oddoye EA, Margen S. 1979. Protein-induced calciuria: A longer term study. *Am J Clin Nutr* 32:741–749.

Allison DB, Egan K, Barraj LM, Caughman C, Infante M, Heimbach J. 1999. Estimated intakes of *trans* fatty and other fatty acids in the US population. *J Am Diet Assoc* 99:166–174.

American Diabetes Association. 2001. Screening for diabetes. *Diabetes Care* 24:S21–S24.

Anderson S, Brenner BM. 1986. Effects of aging on the renal glomerulus. *Am J Med* 80:435–442.

Anderson S, Brenner BM. 1987. The aging kidney: Structure, function, mechanisms, and therapeutic implications. *J Am Geriatr Soc* 35:590–593.

Andreassi M, Forleo P, Di Lorio A, Masci S, Abate G, Amerio P. 1997. Efficacy of γ-linolenic acid in the treatment of patients with atopic dermatitis. *J Int Med Res* 25:266–274.

Annuzzi G, Rivellese A, Capaldo B, Di Marino L, Iovine C, Marotta G, Riccardi G. 1991. A controlled study on the effects of *n*-3 fatty acids on lipid and glucose metabolism in non-insulin-dependent diabetic patients. *Atherosclerosis* 87:65–73.

Anti M, Marra G, Armelao F, Bartoli GM, Ficarelli R, Percesepe A, De Vitis I, Maria G, Sofo L, Rapaccini GL. 1992. Effect of omega-3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. *Gastroenterology* 103:883–891.

Arntzenius AC, Kromhout D, Barth JD, Reiber JHC, Bruschke AVG, Buis B, van Gent CM, Kempen-Voogd N, Strikwerda S, van der Velde EA. 1985. Diet, lipoproteins, and the progression of coronary atherosclerosis. The Leiden Intervention Trial. *N Engl J Med* 312:805–811.

ARS (Agricultural Research Service). 1998. *Food and Nutrient Intakes by Individuals in the United States, by Sex and Age, 1994–96*. Washington, DC: U.S. Department of Agriculture.

Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. 1995. Dietary intake of marine *n*-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med* 332:977–982.

Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. 1996. Dietary fat and risk of coronary heart disease in men: Cohort follow up study in the United States. *Br Med J* 313:84–90.

Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO. 2000. The role of low-fat diets in body weight control: A meta-analysis of ad libitum dietary intervention studies. *Int J Obes Relat Metab Disord* 24:1545–1552.

Atkin L-M, Davies PSW. 2000. Diet composition and body composition in preschool children. *Am J Clin Nutr* 72:15–21.

Austin MA, King MC, Vranizan KM, Krauss RM. 1990. Atherogenic lipoprotein phenotype: A proposed genetic marker for coronary heart disease risk. *Circulation* 82:495–506.

Axelrod L, Camuso J, Williams E, Kleinman K, Briones E, Schoenfeld D. 1994. Effects of a small quantity of ω-3 fatty acids on cardiovascular risk factors in NIDDM. *Diabetes Care* 17:37–44.

Badaloo A, Boyne M, Reid M, Persaud C, Forrester T, Millward DJ, Jackson AA. 1999. Dietary protein, growth and urea kinetics in severely malnourished children and during recovery. *J Nutr* 129:969–979.

Baer JT. 1993. Improved plasma cholesterol levels in men after a nutrition education program at the worksite. *J Am Diet Assoc* 93:658–663.

Ballew C, Kuester S, Gillespie C. 2000. Beverage choices affect adequacy of children's nutrient intakes. *Arch Pediatr Adolesc Med* 154:1148–1152.

Bang HO, Dyerberg J, Hjørne N. 1976. The composition of food consumed by Greenland Eskimos. *Acta Med Scand* 200:69–73.

Banni S, Angioni E, Casu V, Melis MP, Carta G, Corongiu FP, Thompson H, Ip C. 1999. Decrease in linoleic acid metabolites as a potential mechanism in cancer risk reduction by conjugated linoleic acid. *Carcinogenesis* 20:1019–1024.

Barbone F, Austin H, Partridge EE. 1993. Diet and endometrial cancer: A case-control study. *Am J Epidemiol* 137:393–403.

Barinagarrementeria F, González-Duarte A, Cantú-Brito C. 1998. Prothrombic states and cerebral ischemia. *Rev Neurol* 26:85–91.

Bartsch H, Nair J, Owen RW. 1999. Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: Emerging evidence for their role as risk modifiers. *Carcinogenesis* 20:2209–2218.

Barzel US, Massey LK. 1998. Excess dietary protein can adversely affect bone. *J Nutr* 128:1051–1053.

Bassett DR, Abel M, Moellering RC, Rosenblatt G, Stokes J. 1969. Coronary heart disease in Hawaii: Dietary intake, depot fat, "stress," smoking, and energy balance in Hawaiian and Japanese men. *Am J Clin Nutr* 22:1483–1503.

Becker N, Illingworth R, Alaupovic P, Connor WE, Sundberg EE. 1983. Effects of saturated, monounsaturated, and ω-6 polyunsaturated fatty acids on plasma lipids, lipoproteins, and apoproteins in humans. *Am J Clin Nutr* 37:355–360.

Beck-Nielsen H, Pedersen O, Lindskov HO. 1980. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. *Am J Clin Nutr* 33:273–278.

Behall KM, Scholfield DJ, Lee K, Powell AS, Moser PB. 1987. Mineral balance in adult men: Effect of four refined fibers. *Am J Clin Nutr* 46:307–314.

Bennett PH, Knowler WC, Baird HR, Butler WJ, Pettitt DJ, Reid JM. 1984. Diet and the development of noninsulin-dependent diabetes mellitus: An epidemiological perspective. In: Pozza G, ed. *Diet, Diabetes, and Atherosclerosis.* New York: Raven Press. Pp. 109–119.

Berenson GS, Wattigney WA, Tracy RE, Newman WP, Srinivasan SR, Webber LS, Dalferes ER, Strong JP. 1992. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *Am J Cardiol* 70:851–858.

Berry EM, Eisenberg S, Haratz D, Friedlander Y, Norman Y, Kaufmann NA, Stein Y. 1991. Effects of diets rich in monounsaturated fatty acids on plasma lipoproteins—The Jerusalem Nutrition Study: High MUFAs vs high PUFAs. *Am J Clin Nutr* 53:899–907.

Berry EM, Eisenberg S, Friedlander Y, Harats D, Kaufmann NA, Norman Y, Stein Y. 1992. Effects of diets rich in monounsaturated fatty acids on plasma lipoproteins—The Jerusalem Nutrition Study. II. Monounsaturated fatty acids vs carbohydrates. *Am J Clin Nutr* 56:394–403.

Bhathena SJ, Berlin E, Judd JT, Kim YC, Law JS, Bhagavan HN, Ballard-Barbash R, Nair PP. 1991. Effects of ω3 fatty acids and vitamin E on hormones involved in carbohydrate and lipid metabolism in men. *Am J Clin Nutr* 54:684–688.

Billman GE, Kang JX, Leaf A. 1999. Prevention of sudden cardiac death by dietary pure ω-3 polyunsaturated fatty acids in dogs. *Circulation* 99:2452–2457.

Black HS, Herd JA, Goldberg LH, Wolf JE, Thornby JI, Rosen T, Bruce S, Tschen JA, Foreyt JP, Scott LW, Jaax S, Andrews K. 1994. Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med* 330:1272–1275.

Bladbjerg EM, Marckmann P, Sandström B, Jespersen J. 1994. Non-fasting factor VII coagulant activity (FVII:C) increased by high fat diet. *Thromb Haemost* 71:755–758.

Blankson H, Stakkestad JA, Fagertun H, Thom E, Wadstein J, Gudmundsen O. 2000. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. *J Nutr* 130:2943–2948.

Bloemberg BPM, Kromhout D, Goddijn HE, Jansen A, Obermann-de Boer GL. 1991. The impact of the Guidelines for a Healthy Diet of the Netherlands Nutrition Council on total and high density lipoprotein cholesterol in hypercholesterolemic free-living men. *Am J Epidemiol* 134:39–48.

Blundell JE, Burley VJ, Cotton JR, Lawton CL. 1993. Dietary fat and the control of energy intake: Evaluating the effects of fat on meal size and postmeal satiety. *Am J Clin Nutr* 57:772S–778S.

Bobroff EM, Kissileff HR. 1986. Effects of changes in palatability on food intake and the cumulative food intake curve in man. *Appetite* 7:85–96.

Bolton-Smith C. 1996. Intake of sugars in relation to fatness and micronutrient adequacy. *Int J Obes Relat Metab Disord* 20:S31–S33.

Bolton-Smith C, Woodward M. 1994. Coronary heart disease: Prevalence and dietary sugars in Scotland. *J Epidemiol Community Health* 48:119–122.

Bolton-Smith C, Woodward M. 1995. Antioxidant vitamin adequacy in relation to consumption of sugars. *Eur J Clin Nutr* 49:124–133.

Bønaa KH, Bjerve KS, Nordøy A. 1992. Habitual fish consumption, plasma phospholipid fatty acids, and serum lipids: The Tromsø Study. *Am J Clin Nutr* 55:1126–1134.

Bonanome A, Pagnan A, Biffanti S, Opportuno A, Sorgato F, Dorella M, Maiorino M, Ursini F. 1992. Effect of dietary monounsaturated and polyunsaturated fatty acids on the susceptibility of plasma low density lipoproteins to oxidative modification. *Arterioscler Thromb* 12:529–533.

Borkman M, Campbell LV, Chisholm DJ, Storlien LH. 1991. Comparison of the effects on insulin sensitivity of high carbohydrate and high fat diets in normal subjects. *J Clin Endocrinol Metab* 72:432–437.

Borkman M, Storlien LH, Pan DA, Jenkins AB, Chisholm DJ, Campbell LV. 1993. The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. *N Engl J Med* 328:238–244.

Boulton TJC, Magarey AM. 1995. Effects of differences in dietary fat on growth, energy and nutrient intake from infancy to eight years of age. *Acta Paediatr* 84:146–150.

Boutron MC, Wilpart M, Faivre J. 1991. Diet and colorectal cancer. *Eur J Cancer Prev* 1:13–20.

Bowman MP, Van Doren J, Taper LJ, Thye FW, Ritchey SJ. 1988. Effect of dietary fat and cholesterol on plasma lipids and lipoprotein fractions in normolipidemic men. *J Nutr* 118:555–560.

Bowman SA. 1999. Diets of individuals based on energy intakes from added sugars. *Fam Econ Nutr Rev* 12:31–38.

Boyar AP, Rose DP, Loughridge JR, Engle A, Palgi A, Laakso K, Kinne D, Wynder EL. 1988. Response to a diet low in total fat in women with postmenopausal breast cancer: A pilot study. *Nutr Cancer* 11:93–99.

Boyd NF, Cousins M, Beaton M, Kriukov V, Lockwood G, Tritchler D. 1990. Quantitative changes in dietary fat intake and serum cholesterol in women: Results from a randomized, controlled trial. *Am J Clin Nutr* 52:470–476.

Boyd NF, Martin LJ, Noffel M, Lockwood GA, Tritchler DL. 1993. A meta-analysis of studies of dietary fat and breast cancer risk. *Br J Cancer* 68:627–636.

Bray GA, Popkin BM. 1998. Dietary fat intake does affect obesity! *Am J Clin Nutr* 68:1157–1173.

Breillout F, Antoine E, Poupon MF. 1990. Methionine dependency of malignant tumors: A possible approach for therapy. *J Natl Cancer Inst* 82:1628–1632.

Brodie AE, Manning VA, Ferguson KR, Jewell DE, Hu CY. 1999. Conjugated linoleic acid inhibits differentiation of pre- and post-confluent 3T3-L1 preadipocytes but inhibits cell proliferation only in preconfluent cells. *J Nutr* 129:602–606.

Brussaard JH, Katan MB, Groot PHE, Havekes LM, Hautvast JGAJ. 1982. Serum lipoproteins of healthy persons fed a low-fat diet or a polyunsaturated fat diet for three months. A comparison of two cholesterol-lowering diets. *Atherosclerosis* 42:205–219.

Budohoski L, Panczenko-Kresowska B, Langfort J, Ż̇ernicka E, Dubaniewicz A, Ziemlan´ski S´, Challiss RAJ, Newsholme WA. 1993. Effects of saturated and polyunsaturated fat enriched diet on the skeletal muscle insulin sensitivity in young rats. *J Physiol Pharmacol* 44:391–398.

Buell P. 1973. Changing incidence of breast cancer in Japanese-American women. *J Natl Cancer Inst* 51:1479–1483.

Buell P, Dunn JE. 1965. Cancer mortality among Japanese Issei and Nisei of California. *Cancer* 18:656–664.

Buemann B, Tremblay A, Bouchard C. 1995. Social class interacts with the association between macronutrient intake and subcutaneous fat. *Int J Obes Relat Metab Disord* 19:770–775.

Burmeister LA, Valdivia T, Nuttal FQ. 1991. Adult hereditary fructose intolerance. *Arch Intern Med* 151:773–776.

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. 1989a. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet* 2:757–761.

Burr ML, Fehily AM, Rogers S, Welsby E, King S, Sandham S. 1989b. Diet and Reinfarction Trial (DART): Design, recruitment, and compliance. *Eur Heart J* 10:558–567.

Burr ML, Sweetnam PM, Fehily AM. 1994. Diet and reinfarction. *Eur Heart J* 15:1152–1153.

Buzzard IM, Asp EH, Chlebowski RT, Boyar AP, Jeffery RW, Nixon DW, Blackburn GL, Jochimsen PR, Scanlon EF, Insull W, Elashoff RM, Butram R, Wynder EL. 1990. Diet intervention methods to reduce fat intake: Nutrient and food group composition of self-selected low-fat diets. *J Am Diet Assoc* 90:42–50, 53.

Calbet JA, MacLean DA. 1997. Role of caloric content on gastric emptying in humans. *J Physiol* 498:553–559.

Calviello G, Palozza P, Piccioni E, Maggiano N, Frattucci A, Franceschelli P, Baroli GM. 1998. Dietary supplementation with eicosapentaenoic and docosahexaenoic acid inhibits growth of Morris hepatocarcinoma 3924A in rats: Effects on proliferation and apoptosis. *Int J Cancer* 75:699–705.

Campbell TC, Parpia B, Chen J. 1998. Diet, lifestyle, and the etiology of coronary artery disease: The Cornell China Study. *Am J Cardiol* 82:18T–21T.

Castelli WP, Anderson K, Wilson PWF, Levy D. 1992. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol* 2:23–28.

Caygill CPJ, Hill MJ. 1995. Fish, *n*-3 fatty acids and human colorectal and breast cancer mortality. *Eur J Cancer Prev* 4:329–332.

Caygill CPJ, Charlett A, Hill MJ. 1996. Fat, fish, fish oil and cancer. *Br J Cancer* 74:159–164.

CDC (Centers for Disease Control and Prevention). 1994. Daily dietary fat and total food-energy intakes—Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. *Morb Mortal Wkly Rep* 43:116–117, 123–125.

Cesano A, Visonneau S, Scimeca JA, Kritchevsky D, Santoli D. 1998. Opposite effects of linoleic acid and conjugated linoleic acid on human prostatic cancer in SCID mice. *Anticancer Res* 18:833–838.

Chandra RK. 1972. Immunocompetence in undernutrition. *J Pediatr* 81:1194–1200.

Chandra RK. 1991. 1990 McCollum Award lecture. Nutrition and immunity: Lessons from the past and new insights into the future. *Am J Clin Nutr* 53:1087–1101.

Chandra RK, Newberne PM. 1977. *Nutrition, Immunity, and Infection: Mechanisms of Interactions.* New York: Plenum Press.

Chandra RK, Chandra S, Gupta S. 1984. Antibody affinity and immune complexes after immunization with tetanus toxoid in protein-energy malnutrition. *Am J Clin Nutr* 40:131–134.

Chen M, Bergman RN, Porte D. 1988. Insulin resistance and β-cell dysfunction in aging: The importance of dietary carbohydrate. *J Clin Endocrinol Metab* 67:951–957.

Chicco A, D'Alessandro ME, Karabatas L, Gutman R, Lombardo YB. 1996. Effect of moderate levels of dietary fish oil on insulin secretion and sensitivity, and pancreas insulin content in normal rats. *Ann Nutr Metab* 40:61–70.

Chilton-Lopez T, Surette ME, Swan DD, Fonteh AN, Johnson MM, Chilton FH. 1996. Metabolism of gammalinolenic acid in human neutrophils. *J Immunol* 156:2941–2947.

Chisholm KW, O'Dea K. 1987. Effect of short-term consumption of a high fat diet on glucose tolerance and insulin sensitivity in the rat. *J Nutr Sci Vitaminol* 3:377–390.

Chisolm GM, Steinberg D. 2000. The oxidative modification hypothesis of atherogenesis: An overview. *Free Radic Biol Med* 28:1815–1826.

Chiu BC, Cerhan JR, Folsom AR, Sellers TA, Kushi LH, Wallace RB, Zheng W, Potter JD. 1996. Diet and risk of non-Hodgkin lymphoma in older women. *J Am Med Assoc* 275:1315–1321.

Choi Y, Kim Y-C, Han Y-B, Park Y, Pariza M, Ntambi JM. 2000. The *trans*-10,*cis*-12 isomer of conjugated linoleic acid downregulates stearoyl-CoA desaturase 1 gene expression in 3T3-L1 adipocytes. *J Nutr* 130:1920–1924.

Chow WH, Gridley G, McLaughlin JK, Mandel JS, Wacholder S, Blot WJ, Niwa S, Fraumeni JF. 1994. Protein intake and risk of renal cell cancer. *J Natl Cancer Inst* 86:1131–1139.

Christensen JH, Gustenhoff P, Korup E, Aarøe J, Møller JM, Rasmussen K, Dyerberg J, Schmidt EB. 1997. *n*-3 Polyunsaturated fatty acids, heart rate variability and ventricular arrhythmias in patients with previous myocardial infarcts. *Ugeskr Laeger* 159:5525–5529.

Christensen JH, Christensen MS, Dyerberg J, Schmidt EB. 1999. Heart rate variability and fatty acid content of blood cell membranes: A dose-response study with *n*-3 fatty acids. *Am J Clin Nutr* 70:331–337.

Clarke R, Frost C, Collins R, Appleby P, Peto R. 1997. Dietary lipids and blood cholesterol: Quantitative meta-analysis of metabolic ward studies. *Br Med J* 314:112–117.

Clinton SK. 1993. Dietary protein and the origins of human cancer. In: Liepa GU, Beitz DC, Beynen AC, Gorman MA, eds. *Dietary Proteins: How They Alleviate Disease and Promote Better Health.* Champaign, IL: American Oil Chemists' Society. Pp. 84–122.

Clore JN, Li J, Gill R, Gupta S, Spencer R, Azzam A, Zuelzer W, Rizzo WB, Blackard WG. 1998. Skeletal muscle phosphatidylcholine fatty acids and insulin sensitivity in normal humans. *Am J Physiol* 275:E665–E670.

Colditz GA, Willett WC, Stampfer MJ, London SJ, Segal MR, Speizer FE. 1990. Patterns of weight change and their relation to diet in a cohort of healthy women. *Am J Clin Nutr* 51:1100–1105.

Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. 1992. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023.

Collins CL, Wasa M, Souba WW, Abcouwer SF. 1998. Determinants of glutamine dependence and utilization by normal and tumor-derived breast cell lines. *J Cell Physiol* 176:166–178.

Coudray C, Bellanger J, Castiglia-Delavaud C, Rémésy C, Vermorel M, Rayssignuier Y. 1997. Effect of soluble or partly soluble dietary fibres supplementation on absorption and balance of calcium, magnesium, iron and zinc in healthy young men. *Eur J Clin Nutr* 51:375–380.

Coulston AM, Liu GC, Reaven GM. 1983. Plasma glucose, insulin and lipid responses to high-carbohydrate low-fat diets in normal humans. *Metabolism* 32:52–56.

Coulston AM, Hollenbeck CB, Swislocki AL, Chen YD, Reaven GM. 1987. Deleterious metabolic effects of high-carbohydrate, sucrose-containing diets in patients with non-insulin-dependent diabetes mellitus. *Am J Med* 82:213–220.

Cunningham DC, Harrison LY, Shultz TD. 1997. Proliferative responses of normal human mammary and MCF-7 breast cancer cells to linoleic acid, conjugated linoleic acid and eicosanoid synthesis inhibitors in culture. *Anticancer Res* 17:197–204.

Curb JD, Wergowske G, Dobbs JC, Abbott RD, Huang B. 2000. Serum lipid effects of a high-monounsaturated fat diet based on macadamia nuts. *Arch Intern Med* 160:1154–1158.

Curhan GC, Willet WC, Rimm EB, Stampfer MJ. 1996. A prospective study of dietary calcium and other nutrients and the risk of kidney stones in men: 8 Year follow-up. In: Pak CY, Resnick MI, Preminger GM, eds. *Urolithiasis.* Dallas, TX: Millet. Pp. 164–166.

Czarnecki SK, Kritchevsky D. 1993. Dietary protein and atherosclerosis. In: Liepa GU, Beitz DC, Beynen AC, Gorman MA, eds. *Dietary Proteins: How They Alleviate Disease and Promote Better Health.* Champaign, IL: American Oil Chemists' Society. Pp. 42–56.

Davies PS. 1997. Diet composition and body mass index in pre-school children. *Eur J Clin Nutr* 51:443–448.

Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB. 1997. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 336:1046–1053.

Dawson-Hughes B, Harris SS. 2002. Calcium intake influences the association of protein intake with rates of bones loss in elderly men and women. *Am J Clin Nutr* 75:773–779.

Decarli A, Favero A, La Vecchia C, Russo A, Ferraroni M, Negri E, Franceschi S. 1997. Macronutrients, energy intake, and breast cancer risk: Implications from different models. *Epidemiology* 8:425–428.

De Caterina R, Liao JK, Libby P. 2000. Fatty acid modulation of endothelial activation. *Am J Clin Nutr* 71:213–223.

de Deckere EAM, van Amelsvoort JMM, McNeill GP, Jones P. 1999. Effects of conjugated linoleic acid (CLA) isomers on lipid levels and peroxisome proliferation in the hamster. *Br J Nutr* 82:309–317.

DeLany JP, Vivian VM, Snook JT, Anderson PA. 1990. Effects of fish oil on serum lipids in men during a controlled feeding trial. *Am J Clin Nutr* 52:477–485.

de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin J-L, Monjaud I, Guidollet J, Touboul P, Delaye J. 1994. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 343:1454–1459.

de Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. 1999. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction. Final report of the Lyon Diet Heart Study. *Circulation* 99:779–785.

Delzenne N, Aertssens J, Verplaetse H, Roccaro M, Roberfroid M. 1995. Effect of fermentable fructo-oligosaccharides on mineral, nitrogen and energy digestive balance in the rat. *Life Sci* 57:1579–1587.

Demigné C, Levrat M-A, Rémésy C. 1989. Effects of feeding fermentable carbohydrates on the cecal concentrations of minerals and their fluxes between the cecum and blood plasma in the rat. *J Nutr* 119:1625–1630.

Deschner EE, Lytle JS, Wong G, Ruperto JF, Newmark HL. 1990. The effect of dietary omega-3 fatty acids (fish oil) on azoxymethanol-induced focal areas of dysplasia and colon tumor incidence. *Cancer* 66:2350–2356.

Després J-P. 1993. Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition* 9:452–459.

De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Carzoglio JC, Ronco A. 1997a. Dietary fat and lung cancer: A case-control study in Uruguay. *Cancer Causes Control* 8:913–921.

De Stefani E, Mendilaharsu M, Deneo-Pellegrini H, Ronco A. 1997b. Influence of dietary levels of fat, cholesterol, and calcium on colorectal cancer. *Nutr Cancer* 29:83–89.

De Stefani E, Ronco A, Mendilaharsu M, Deneo-Pellegrini H. 1999. Diet and risk of cancer of the upper aerodigestive tract. II. Nutrients. *Oral Oncol* 35:22–26.

Djoussé L, Pankow JS, Eckfeldt JH, Folsom AR, Hopkins PN, Province MA, Hong Y, Ellison RC. 2001. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Clin Nutr* 74:612–619.

Dolecek TA. 1992. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial. *Proc Soc Exp Med Biol* 200:177–182.

Dreon DM, Frey-Hewitt B, Ellsworth N, Williams PT, Terry RB, Wood PD. 1988. Dietary fat:carbohydrate ratio and obesity in middle-aged men. *Am J Clin Nutr* 47:995–1000.

Drewnowski A. 1999. Intense sweeteners and energy density of foods: Implications for weight control. *Eur J Clin Nutr* 53:757–763.

Drewnowski A, Greenwood MR. 1983. Cream and sugar: Human preferences for high-fat foods. *Physiol Behav* 30:629–633.

Duncan KH, Bacon JA, Weinsier RL. 1983. The effects of high and low energy density diets on satiety, energy intake, and eating time of obese and nonobese subjects. *Am J Clin Nutr* 37:763–767.

Dunnigan MG, Fyfe T, McKiddie MT, Crosbie SM. 1970. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. *Clin Sci* 38:1–9.

Durrant M, Royston P. 1979. Short-term effects of energy density on salivation, hunger and appetite in obese subjects. *Int J Obes* 3:335–347.

Dyerberg J, Bang HO. 1979. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. *Lancet* 2:433–435.

Emmett PM, Heaton KW. 1995. Is extrinsic sugar a vehicle for dietary fat? *Lancet* 345:1537–1540.

Eritsland J, Arnesen H, Seljeflot I, Høstmark AT. 1994a. Long-term metabolic effects of *n*-3 polyunsaturated fatty acids in patients with coronary artery disease. *Am J Clin Nutr* 61:831–836.

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H, Torjesen PA. 1994b. Long-term effects of *n*-3 fatty acids on serum lipids and glycaemic control. *Scand J Clin Lab Invest* 54:273–280.

Ernst N, Fisher M, Smith W, Gordon T, Rifkind BM, Little JA, Mishkel MA, Williams OD. 1980. The association of plasma high-density lipoprotein cholesterol with dietary intake and alcohol consumption. The Lipid Research Clinics Program Prevalence Study. *Circulation* 62:IV41–IV52.

Fairweather-Tait SM, Wright AJA. 1990. The effects of sugar-beet fibre and wheat bran on iron and zinc absorption in rats. *Br J Nutr* 64:547–552.

FAO/WHO (Food and Agricultural Organization/World Health Organization). 1996. *Sixth World Food and Nutrition Survey*. Rome: FAO.

Farrell TG, Bashir Y, Cripps T, Malik M, Poloniecki J, Bennett ED, Ward DE, Camm AJ. 1991. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 18:687–697.

Farris RP, Nicklas TA, Myers L, Berenson GS. 1998. Nutrient intake and food group consumption of 10-year-olds by sugar intake level: The Bogalusa Heart Study. *J Am Coll Nutr* 17:579–585.

Fasching P, Ratheiser K, Waldhäusl W, Rohac M, Osterrode W, Nowotny P, Vierhapper H. 1991. Metabolic effects of fish-oil supplementation in patients with impaired glucose tolerance. *Diabetes* 40:583–589.

Fasching P, Ratheiser K, Schneeweiss B, Rohac M, Nowotny P, Waldhausl W. 1996. No effect of short-term dietary supplementation of saturated and poly- and monounsaturated fatty acids on insulin secretion and sensitivity in healthy men. *Ann Nutr Metab* 40:116–122.

Fehily AM, Yarnell JWG, Bolton CH, Butland BK. 1988. Dietary determinants of plasma lipids and lipoproteins: The Caerphilly Study. *Eur J Clin Nutr* 42:405–413.

Fernandez ML, Wilson TA, Conde K, Vergara-Jimenez M, Nicolosi RJ. 1999. Hamsters and guinea pigs differ in their plasma lipoprotein cholesterol distribution when fed diets varying in animal protein, soluble fiber, or cholesterol content. *J Nutr* 129:1323–1332.

Feskens EJM, Bowles CH, Kromhout D. 1991a. Carbohydrate intake and body mass index in relation to the risk of glucose tolerance in an elderly population. *Am J Clin Nutr* 54:136–140.

Feskens EJ, Bowles CH, Kromhout D. 1991b. Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. *Diabetes Care* 14:935–941.

Feskens EJM, Loeber JG, Kromhout D. 1994. Diet and physical activity as determinants of hyperinsulinemia: The Zutphen Elderly Study. *Am J Epidemiol* 140:350–360.

Feskens EJM, Virtanen SM, Räsänen L, Tuomilehto J, Stengard J, Pekkanen J, Nissinen A, Kromhout D. 1995. Dietary factors determining diabetes and impaired glucose tolerance: A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes Care* 18:1104–1112.

Fischer DR, Morgan KJ, Zabik ME. 1985. Cholesterol, saturated fatty acids, polyunsaturated fatty acids, sodium, and potassium intakes of the United States population. *J Am Coll Nutr* 4:207–224.

Flaten H, Høstmark AT, Kierulf P, Lystad E, Trygg K, Bjerkedal T, Osland A. 1990. Fish-oil concentrate: Effects on variables related to cardiovascular disease. *Am J Clin Nutr* 52:300–306.

Flegal KM. 1999. The obesity epidemic in children and adults: Current evidence and research issues. *Med Sci Sports Exerc* 31:S509–S514.

Flint A, Raben A, Blundell JE, Astrup A. 2000. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord* 24:3–48.

Fomon SJ, Thomas LN, Filer LJ, Anderson TA, Nelson SE. 1976. Influence of fat and carbohydrate content of diet on food intake and growth of male infants. *Acta Paediatr Scand* 65:136–144.

Forshee RA, Storey ML. 2001. The role of added sugars in the diet quality of children and adolescents. *J Am Coll Nutr* 20:32–43.

Franceschi S, Levi F, Conti E, Talamini R, Negri E, Dal Maso L, Boyle P, Decarli A, La Vecchia C. 1999. Energy intake and dietary pattern in cancer of the oral cavity and pharynx. *Cancer Causes Control* 10:439–444.

Friedman MI. 1995. Control of energy intake by energy metabolism. *Am J Clin Nutr* 62:1096S–1100S.

Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL. 1990. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. *Am J Clin Nutr* 52:524–528.

Gao YT, McLaughlin JK, Gridley G, Blot WJ, Ji BT, Dai Q, Fraumeni JF. 1994. Risk factors for esophageal cancer in Shanghai, China. II. Role of diet and nutrients. *Int J Cancer* 58:197–202.

Garg A, Bonanome A, Grundy SM, Zhang Z-J, Unger RH. 1988. Comparison of a high-carbohydrate diet with a high-monounsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 319:829–834.

Garg A, Grundy SM, Koffler M. 1992a. Effect of high carbohydrate intake on hyperglycemia, islet function, and plasma lipoproteins in NIDDM. *Diabetes Care* 15:1572–1580.

Garg A, Grundy SM, Unger RH. 1992b. Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. *Diabetes* 41:1278–1285.

Garg A, Bantle JP, Henry RR, Coulston AM, Griver KA, Raatz SK, Brinkley L, Chen Y-DI, Grundy SM, Huet BA, Reaven GM. 1994. Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. *J Am Med Assoc* 271:1421–1428.

Gartside PS, Glueck CJ. 1993. Relationship of dietary intake to hospital admission for coronary heart and vascular disease: The NHANES II National Probability Study. *J Am Coll Nutr* 6:676–684.

Gazzaniga JM, Burns TL. 1993. Relationship between diet composition and body fatness, with adjustment for resting energy expenditure and physical activity, in preadolescent children. *Am J Clin Nutr* 58:21–28.

George V, Tremblay A, Després JP, Leblanc C, Bouchard C. 1990. Effect of dietary fat content on total and regional adiposity in men and women. *Int J Obes* 14:1085–1094.

Gerhard GT, Connor SL, Wander RC, Connor WE. 2000. Plasma lipid and lipoprotein responsiveness to dietary fat and cholesterol in premenopausal African American and white women. *Am J Clin Nutr* 72:56–63.

Giannini S, Nobile M, Sartori L, Dalle Carbonare L, Ciuffreda M, Corro P, D'Angelo A, Calo L, Crepaldi G. 1999. Acute effects of moderate dietary protein restriction in patients with idiopathic hypercalciuria and calcium nephrolithiasis. *Am J Clin Nutr* 69:267–271.

Gibney M, Sigman-Grant M, Stanton JL, Keast DR. 1995. Consumption of sugars. *Am J Clin Nutr* 62:178S–194S.

Gibson SA. 1993. Consumption and sources of sugars in the diets of British schoolchildren: Are high-sugar diets nutritionally inferior? *J Hum Nutr Diet* 6:355–371.

Gibson SA. 1997. Non-milk extrinsic sugars in the diets of pre-school children: Association with intakes of micronutrients, energy, fat and NSP. *Br J Nutr* 78:367–378.

Gillum RF, Mussolino ME, Madans JH. 1996. The relationship between fish consumption and stroke incidence. The NHANES I epidemiologic follow-up study. *Arch Intern Med* 156:537–542.

Ginsberg HN, Barr SL, Gilbert A, Karmally W, Deckelbaum R, Kaplan K, Ramakrishnan R, Holleran S, Dell RB. 1990. Reduction of plasma cholesterol levels in normal men on an American Heart Association Step 1 diet or a Step 1 diet with added monounsaturated fat. *N Engl J Med* 322:574–579.

Giovannucci E, Willet WC. 1994. Dietary factors and risk of colon cancer. *Ann Med* 26:443–452.

Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. 1993. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 85:1571–1579.

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. 1994. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54:2390–2397.

GISSI-Prevenzione Investigators. 1999. Dietary supplementation with *n*-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. *Lancet* 354:447–455.

Glanz K, Basil M, Maibach E, Goldberg J, Snyder D. 1998. Why Americans eat what they do: Taste, nutrition, cost, convenience, and weight control concerns as influences on food consumption. *J Am Diet Assoc* 98:1118–1126.

Glueck CJ, Hastings MM, Allen C, Hogg E, Baehler L, Gartside PS, Phillips D, Jones M, Hollenbach EJ, Braun B, Anastasia JV. 1982. Sucrose polyester and covert caloric dilution. *Am J Clin Nutr* 35:1352–1359.

Goodman MT, Kolonel LN, Yoshizawa CN, Hankin JH. 1988. The effect of dietary cholesterol and fat on the risk of lung cancer in Hawaii. *Am J Epidemiol* 128:1241–1255.

Göranzon H, Forsum E, Thilén M. 1983. Calculation and determination of metabolizable energy in mixed diets to humans. *Am J Clin Nutr* 38:954–963.

Gortmaker SL, Dietz WH, Sobol AM, Wehler CA. 1987. Increasing pediatric obesity in the United States. *Am J Dis Child* 141:535–540.

Grammatikos SI, Subbaiah PV, Victor TA, Miller WM. 1994. *n*-3 and *n*-6 Fatty acid processing and growth effects in neoplastic and non-cancerous human mammary epithelial cell lines. *Br J Cancer* 70:219–227.

Green SM, Burley VJ, Blundell JE. 1994. Effect of fat- and sucrose-containing foods on the size of eating episodes and energy intake in lean males: Potential for causing overconsumption. *Eur J Clin Nutr* 48:547–555.

Grill V, Björklund A. 2001. Overstimulation and beta-cell function. *Diabetes* 50:S122–S124.

Grimsgaard S, Bønaa KH, Hansen J-B, Nordøy A. 1997. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *Am J Clin Nutr* 66:649–659.

Grundy SM. 1986. Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. *N Engl J Med* 314:745–748.

Grundy SM, Florentin L, Nix D, Whelan MF. 1988. Comparison of monounsaturated fatty acids and carbohydrates for reducing raised levels of plasma cholesterol in man. *Am J Clin Nutr* 47:965–969.

Guallar E, Aro A, Jiménez FJ, Martín-Moreno JM, Salminen I, van't Veer P, Kardinaal AFM, Gómez-Aracena J, Martin BC, Kohlmeier L, Kark JD, Mazaev VP, Ringstad J, Guillén J, Riemersma RA, Huttunen JK, Thamm M, Kok FJ. 1999. Omega-3 fatty acids in adipose tissue and risk of myocardial infarction. The EURAMIC Study. *Arterioscler Thromb Vasc Biol* 19:1111–1118.

Guenther PM. 1986. Beverages in the diets of American teenagers. *J Am Diet Assoc* 86:493–499.

Guthrie JF. 1996. Dietary patterns and personal characteristics of women consuming recommended amounts of calcium. *Fam Econ Nutr Rev* 9:33–49.

Guthrie JF, Derby B. 1998. Changes in consumers' knowledge of food guide recommendations, 1990–91 versus 1994–95. *Fam Econ Nutr Rev* 11:42–48.

Ha YL, Storkson J, Pariza MW. 1990. Inhibition of benzo(*a*)pyrene-induced mouse forestomach neoplasia by conjugated dienoic derivatives of linoleic acid. *Cancer Res* 50:1097–1101.

Haglund O, Wallin R, Luostarinen R, Saldeen T. 1990. Effects of a new fluid fish oil concentrate, ESKIMO-3, on triglycerides, cholesterol, fibrinogen and blood pressure. *J Intern Med* 227:347–353.

Halliwell B, Chirico S. 1993. Lipid peroxidation: Its mechanism, measurement, and significance. *Am J Clin Nutr* 57:715S–725S.

Hansen D, Michaelsen KF, Skovby F. 1992. Growth during treatment of familial hypercholesterolemia. *Acta Paediatr* 81:1023–1025.

Harker LA, Kelly AB, Hanson SR, Krupski W, Bass A, Osterud B, Fitzgerald GA, Goodnight SH, Connor WE. 1993. Interruption of vascular thrombus formation and vascular lesion formation by dietary *n*-3 fatty acids in fish oil in nonhuman primates. *Circulation* 87:1017–1029.

Harnack L, Stang J, Story M. 1999. Soft drink consumption among US children and adolescents: Nutritional consequences. *J Am Diet Assoc* 99:436–441.

Harnack LJ, Jeffery RW, Boutelle KN. 2000. Temporal trends in energy intake in the United States: An ecologic perspective. *Am J Clin Nutr* 71:1478–1484.

Harris WS. 1989. Fish oils and plasma lipid and lipoprotein metabolism in humans: A critical review. *J Lipid Res* 30:785–807.

Harris WS. 1997. *n*-3 Fatty acids and serum lipoproteins: Human studies. *Am J Clin Nutr* 65:1645S–1654S.

Health Canada. 1997. *Canada's Food Guide to Healthy Eating*. Ottawa: Minister of Public Works and Government Services Canada.

Heaney RP. 1993. Protein intake and the calcium economy. *J Am Diet Assoc* 93:1259–1260.

Heaney RP. 1998. Excess dietary protein may not adversely affect bone. *J Nutr* 128:1054–1057.

Hegsted DM, Ausman LM, Johnson JA, Dallal GE. 1993. Dietary fat and serum lipids: An evaluation of the experimental data. *Am J Clin Nutr* 57:875–883.

Heitmann BL, Lissner L, Sørensen TIA, Bengtsson C. 1995. Dietary fat intake and weight gain in women genetically predisposed for obesity. *Am J Clin Nutr* 61:1213–1217.

Hiatt RA, Ettinger B, Caan B, Quesenberry CP, Duncan D, Citron JT. 1996. Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *Am J Epidemiol* 144:25–33.

Hill AJ, Blundell JE. 1990. Sensitivity of the appetite control system in obese subjects to nutritional and serotoninergic challenges. *Int J Obes* 14:219–233.

Hill AJ, Leathwood PD, Blundell JE. 1987. Some evidence for short-term caloric compensation in normal weight human subjects: The effects of high- and low-energy meals on hunger, food preference and food intake. *Hum Nutr Appl Nutr* 41:244–257.

Hill JO, Peters JC, Reed GW, Schlundt DG, Sharp T, Greene HL. 1991. Nutrient balance in humans: Effects of diet composition. *Am J Clin Nutr* 54:10–17.

Hill JO, Melanson EL, Wyatt HT. 2000. Dietary fat intake and regulation of energy balance: Implications for obesity. *J Nutr* 130:284S–288S.

Himaya A, Fantino M, Antoine JM, Bronel L, Louis-Sylvestre J. 1997. Satiety power of dietary fat: A new appraisal. *Am J Clin Nutr* 65:1410–1418.

Hislop TG, Coldman AJ, Elwood JM, Brauer G, Kan L. 1986. Childhood and recent eating patterns and risk of breast cancer. *Cancer Detect Prev* 9:47–58.

Holman RL, McGill HC, Strong JP, Greer JC. 1958. The natural history of atherosclerosis. The early aortic lesions as seen in New Orleans in the middle of the 20th century. *Am J Pathol* 34:209–235.

Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, Hankinson SE, Speizer FE, Rosner B, Willett WC. 1999. Association of dietary intake of fat and fatty acids with risk of breast cancer. *J Am Med Assoc* 281:914–920.

Holt SH, Miller JC, Petocz P, Farmakalidid E. 1995. A satiety index of common foods. *Eur J Clin Nutr* 49:675–690.

Höppener JWM, Ahrén B, Lips CJM. 2000. Islet amyloid and type 2 diabetes mellitus. *N Engl J Med* 343:411–419.

Horton TJ, Drougas H, Brachey A, Reed GW, Peters JC, Hill JO. 1995. Fat and carbohydrate overfeeding in humans: Different effects on energy storage. *Am J Clin Nutr* 62:19–29.

Horvath PJ, Eagen CK, Fisher NM, Leddy JJ, Pendergast DR. 2000. The effects of varying dietary fat on performance and metabolism in trained male and female runners. *J Am Coll Nutr* 19:52–60.

Howard BV, Abbott WGH, Swinburn BA. 1991. Evaluation of metabolic effects of substitution of complex carbohydrates for saturated fat in individuals with obesity and NIDDM. *Diabetes Care* 14:786–795.

Howard BV, Hannah JS, Heiser CC, Jablonski KA, Paidi MC, Alarif L, Robbins DC, Howard WJ. 1995. Polyunsaturated fatty acids result in greater cholesterol lowering and less triacylglycerol elevation than do monounsaturated fatty acids in a dose–response comparison in a multiracial study group. *Am J Clin Nutr* 62:392–402.

Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan J-M, Katsouyanni K, Lubin F, Marubini E, Modan B, Rohan T, Toniolo P, Shunzhang Y. 1990. Dietary factors and risk of breast cancer: Combined analysis of 12 case-control studies. *J Natl Cancer Inst* 82:561–569.

Howe GR, Friedenreich CM, Jain M, Miller AB. 1991. A cohort study of fat intake and risk of breast cancer. *J Natl Cancer Inst* 83:336–340.

Howe GR, Aronson KJ, Benito E, Castelleto R, Cornée J, Duffy S, Gallagher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA, Kune S, Lee HP, Lee M, Miller AB, Peters RK, Potter JD, Riboli E, Slattery ML, Trichopoulos D, Tuyns A, Tzonou A, Watson LF, Whittemore AS, Wu-Willimas AH, Shu Z. 1997. The relationship between dietary fat intake and risk of colorectal cancer: Evidence from the combined analysis of 13 case-control studies. *Cancer Causes Control* 8:215–228.

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. 1997. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 337:1491–1499.

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Speizer FE, Hennekens CH, Willett WC. 1999. Dietary protein and risk of ischemic heart disease in women. *Am J Clin Nutr* 70:221–227.

Hu FB, van Dam RM, Liu S. 2001. Diet and risk of type II diabetes: The role of types of fat and carbohydrate. *Diabetologia* 44:805–817.

Hulshof T, De Graaf C, Weststrate JA. 1993. The effects of preloads varying in physical state and fat content on satiety and energy intake. *Appetite* 21:273–286.

Hun CS, Hasegawa K, Kawabata T, Kato M, Shimokawa T, Kagawa Y. 1999. Increased uncoupling protein2 mRNA in white adipose tissue, and decrease in leptin, visceral fat, blood glucose, and cholesterol in KK-A^y mice fed with eicosapentaenoic and docosahexaenoic acids in addition to linolenic acid. *Biochem Biophys Res Comm* 259:85–90.

Hunter DJ, Spiegelman D, Adami H-O, Beeson L, van den Brandt PA, Folsom AR, Fraser GE, Goldbohn A, Graham S, Howe GR, Kushi LH, Marshall JR, McDermott A, Miller AB, Speizer FE, Wolk A, Yaun S-S, Willett W. 1996. Cohort studies of fat intake and the risk of breast cancer—A pooled analysis. *N Engl J Med* 334:356–361.

Hursting SD, Thornquist M, Henderson MM. 1990. Types of dietary fat and the incidence of cancer at five sites. *Prev Med* 19:242–253.

Ip C, Scimeca JA. 1997. Conjugated linoleic acid and linoleic acid are distinctive modulators of mammary carcinogenesis. *Nutr Cancer* 27:131–135.

Ip C, Chin SF, Scimeca JA, Pariza MW. 1991. Mammary cancer prevention by conjugated dienoic derivative of linoleic acid. *Cancer Res* 51:6118–6124.

Ip C, Ip MM, Loftus T, Shoemaker S, Shea-Eaton W. 2000. Induction of apoptosis by conjugated linoleic acid in cultured mammary tumor cells and premalignant lesions of the rat mammary gland. *Cancer Epidemiol Biomarkers Prev* 9:689–696.

Ip MM, Masso-Welch PA, Shoemaker SF, Shea-Eaton WK, Ip C. 1999. Conjugated linoleic acid inhibits proliferation and induces apoptosis of normal rat mammary epithelial cells in primary culture. *Exp Cell Res* 250:22–34.

Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Hennekens CH, Willett WC. 2001. Intake of fish and omega-3 fatty acids and risk of stroke in women. *J Am Med Assoc* 285:304–312.

James MJ, Gibson RA, Cleland LG. 2000. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 71:343S–348S.

Janelle KC, Barr SI. 1995. Nutrient intakes and eating behavior scores of vegetarian and nonvegetarian women. *J Am Diet Assoc* 95:180–196.

Jansen S, Lopez-Miranda J, Salas J, Castro P, Paniagua JA, Lopez-Segura F, Ordovas JM, Jimenez-Pereperez JA, Blanco A, Perez-Jimenez F. 1998. Plasma lipid response to hypolipidemic diets in young healthy non-obese men varies with body mass index. *J Nutr* 128:1144–1149.

Jayarajan P, Reddy V, Mohanram M. 1980. Effect of dietary fat on absorption of β carotene from green leafy vegetables in children. *Indian J Med Res* 71:53–56.

Jeppesen J, Schaaf P, Jones C, Zhou M-Y, Chen Y-DI, Reaven GM. 1997. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. *Am J Clin Nutr* 65:1027–1033.

Jéquier E. 1999. Response to and range of acceptable fat intake in adults. *Eur J Clin Nutr* 53:S84–S93.

Jessup W, Kritharides L. 2000. Metabolism of oxidized LDL by macrophages. *Curr Opin Lipidol* 11:473–481.

Johnson MM, Swan DD, Surette ME, Stegner J, Chilton T, Fonteh AN, Chilton FH. 1997. Dietary supplementation with γ-linolenic acid alters fatty acid content and eicosanoid production in healthy humans. *J Nutr* 127:1435–1444.

Johnson RK, Panely C, Wang MQ. 1998. The association between noon beverage consumption and the diet quality of school-age children. *J Child Nutr Manage* 22:95–100.

Jones AE, Murphy JL, Stolinski M, Wootton SA. 1998. The effect of age and gender on the metabolic disposal of [1-^{13}C]palmitic acid. *Eur J Clin Nutr* 52:22–28.

Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, Hoover R, Taylor PR. 1987. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey. I. Epidemiologic follow-up study. *J Natl Cancer Inst* 79:465–471.

Jonnalagadda SS, Egan SK, Heimbach JT, Harris SS, Kris-Etherton PM. 1995. Fatty acid consumption pattern of Americans: 1987–1988 USDA Nationwide Food Consumption Survey. *Nutr Res* 15:1767–1781.

Kahn SR, Solymoss S, Flegel KM. 1997. Nonvalvular atrial fibrillation: Evidence for a prothrombic state. *Can Med Assoc J* 157:673–681.

Kaizer L, Boyd NF, Kriukov V, Tritchler D. 1989. Fish consumption and breast cancer risk: An ecologic study. *Nutr Cancer* 12:61–68.

Kang JX, Leaf A. 1996. Antiarrhythmic effects of polyunsaturated fatty acids: Recent studies. *Circulation* 94:1774–1780.

Kannel WB. 2000. The Framingham Study: Its 50-year legacy and future promise. *J Atheroscler Thromb* 6:60–66.

Karmali RA. 1986. Eicosanoids and cancer. *Prog Clin Biol Res* 222:687–697.

Karmali RA, Marsh J, Fuchs C. 1984. Effect of omega-3 fatty acids on growth of a rat mammary tumor. *J Natl Cancer Inst* 73:457–461.

Karmali RA, Reichel P, Cohen LA, Terano T, Hirai A, Tamura Y, Yoshida S. 1987. The effects of dietary omega-3 fatty acids on the DU-145 transplantable human prostatic tumor. *Anticancer Res* 7:1173–1179.

Kasim SE, Martino S, Kim P-N, Khilnani S, Boomer A, Depper J, Reading BA, Heilbrun LK. 1993. Dietary and anthropometric determinants of plasma lipoproteins during a long-term low-fat diet in healthy women. *Am J Clin Nutr* 57:146–153.

Kasim-Karakas SE, Lane E, Almario R, Mueller W, Walzem R. 1997. Effects of dietary fat restriction on particle size of plasma lipoproteins in postmenopausal women. *Metabolism* 46:431–436.

Kasim-Karakas SE, Almario RU, Mueller WM, Peerson J. 2000. Changes in plasma lipoproteins during low-fat, high-carbohydrate diets: Effects of energy intake. *Am J Clin Nutr* 71:1439–1447.

Katan MB, Zock PL, Mensink RP. 1994. Effects of fats and fatty acids on blood lipids in humans: An overview. *Am J Clin Nutr* 60:1017S–1022S.

Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E. 1997. Prospective study of diet and female colorectal cancer: The New York University Women's Health Study. *Nutr Cancer* 28:276–281.

Kavanaugh CJ, Liu K-L, Belury MA. 1999. Effect of dietary conjugated linoleic acid on phorbol ester-induced PGE_2 production and hyperplasia in mouse epidermis. *Nutr Cancer* 33:132–138.

Keli SO, Feskens EJ, Kromhout D. 1994. Fish consumption and risk of stroke. The Zutphen Study. *Stroke* 25:328–332.

Kelleher CC. 1992. Plasma fibrinogen and factor VII as risk factors for cardiovascular disease. *Eur J Epidemiol* 8:79–82.

Kendall A, Levitsky DA, Strupp BJ, Lissner L. 1991. Weight loss on a low-fat diet: Consequence of the imprecision of the control of food intake in humans. *Am J Clin Nutr* 53:1124–1129.

Kerstetter JE, Mitnick ME, Gundberg CM, Caseria DM, Ellison AF, Carpenter TO, Insogna KL. 1999. Changes in bone turnover in young women consuming different levels of dietary protein. *J Clin Endocrinol Metab* 84:1052–1055.

Kestin M, Clifton P, Belling GB, Nestel PJ. 1990. *n*-3 Fatty acids of marine origin lower systolic blood pressure and triglycerides but raise LDL cholesterol compared with *n*-3 and *n*-6 fatty acids from plants. *Am J Clin Nutr* 51:1028–1034.

Keusch GT, Torun B, Johnson RB, Urrutia JJ. 1984. Impairment of hemolytic complement activation by both classical and alternative pathways in serum from patients with kwashiorkor. *J Pediatr* 105:434–436.

Keys A, Aravanis C, Blackburn H, Buzina R, Djordević BS, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, Menotti A, Mohaček I, Nedeljković S, Puddu V, Punsar S, Taylor HL, van Buchem FSP. 1980. *Seven Countries. A Multivariate Analysis of Death and Coronary Heart Disease.* Cambridge, MA: Harvard University Press.

Keys A, Menotti A, Aravanis C, Blackburn H, Djordević BS, Buzinz R, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, Mohaček I, Nedeljković S, Puddu V, Punsar S, Taylor HL, Conti S, Kromhout D, Toshima H. 1984. The Seven Countries Study: 2,289 deaths in 15 years. *Prev Med* 13:141–154.

Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjević BS, Dontas AS, Fidanza F, Keys MH. 1986. The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol* 124:903–915.

King JC. 2000. Physiology of pregnancy and nutrient metabolism. *Am J Clin Nutr* 71:1218S–1225S.

Klesges RC, Klesges LM, Haddock CK, Eck LH. 1992. A longitudinal analysis of the impact of dietary intake and physical activity on weight change in adults. *Am J Clin Nutr* 55:818–822.

Knopp RH, Walden CE, Retzlaff BM, McCann BS, Dowdy AA, Albers JJ, Gey GO, Cooper MN. 1997. Long-term cholesterol-lowering effects of 4 fat-restricted diets in hypercholesterolemic and combined hyperlipidemic men. *J Am Med Assoc* 278:1509–1515.

Knuiman JT, Westenbrink S, van der Heyden L, West CE, Burema J, De Boer J, Hautvast JGAJ, Räsänen L, Virkkunen L, Viikari J, Lokko P, Pobee JOM, Ferro-Luzzi A, Ferrini AM, Scaccini C, Sette S, Villavieja GM, Bulatao-Jayme J. 1983. Determinants of total and high density lipoprotein cholesterol in boys from Finland, the Netherlands, Italy, the Philippines and Ghana with special reference to diet. *Hum Nutr Clin Nutr* 37:237–254.

Knuiman JT, West CE, Katan MB, Hautvast JGAJ. 1987. Total cholesterol and high density lipoprotein cholesterol levels in populations differing in fat and carbohydrate intake. *Arteriosclerosis* 7:612–619.

Krauss RM. 2001. Atherogenic lipoprotein phenotype and diet-gene interactions. *J Nutr* 131:340S–343S.

Krauss RM, Dreon DM. 1995. Low-density-lipoprotein subclasses and response to a low-fat diet in healthy men. *Am J Clin Nutr* 62:478S–487S.

Kris-Etherton PM (for the DELTA Investigators). 1996. Effects of replacing saturated fat (SFA) with monounsaturated fat (MUFA) or carbohydrate (CHO) on plasma lipids and lipoproteins in individuals with markers for insulin resistance. *FASEB J* 10:2666.

Kris-Etherton PM, Derr J, Mitchell DC, Mustad VA, Russell ME, McDonnell ET, Salabsky D, Pearson TA. 1993. The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: I. Effects of whole food diets high in cocoa butter, olive oil, soybean oil, dairy butter, and milk chocolate on the plasma lipids of young men. *Metabolism* 42:121–129.

Kris-Etherton PM, Pearson TA, Wan Y, Hargrove RL, Moriarty K, Fishell V, Etherton TD. 1999. High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. *Am J Clin Nutr* 70:1009–1015.

Kris-Etherton PM, Zhao G, Pelkman CL, Fishell VK, Coval SM. 2000. Beneficial effects of a diet high in monounsaturated fatty acids on risk factors for cardiovascular disease. *Nutr Clin Care* 3:153–162.

Kritchevsky D, Tepper SA, Czarnecki SK, Klurfeld DM, Story JA. 1981. Experimental atherosclerosis in rabbits fed cholesterol-free diets. Part 9. Beef protein and textured vegetable protein. *Atherosclerosis* 39:169–175.

Kromhout D, de Lezenne Coulander C. 1984. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men. *Am J Epidemiol* 119:733–741.

Kromhout D, Bosschieter EB, de Lezenne Coulander C. 1985. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 312:1205–1209.

Kromhout D, Feskens EJM, Bowles CH. 1995. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *Int J Epidemiol* 24:340–345.

Kromhout D, Bloemberg BPM, Feskens EJM, Hertog MGL, Menotti A, Blackburn H. 1996. Alcohol, fish, fibre and antioxidant vitamins intake do not explain population differences in coronary heart disease mortality. *Int J Epidemiol* 25:753–759.

Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. 1985. Diet and 20-year mortality from coronary heart disease. The Ireland–Boston Diet–Heart Study. *N Engl J Med* 312:811–888.

Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, Folsom AR. 1992. Dietary fat and postmenopausal breast cancer. *J Natl Cancer Inst* 84:1092–1099.

Kwiterovich PO, Barton BA, McMahon RP, Obarzanek E, Hunsberger S, Simons-Morton D, Kimm SYS, Friedman LA, Lasser N, Robson A, Lauer R, Stevens V, Van Horn L, Gidding S, Snetselaar L, Hartmuller VW, Greenlick M, Franklin F. 1997. Effects of diet and sexual maturation on low-density lipoprotein cholesterol during puberty. The Dietary Intervention Study in Children (DISC). *Circulation* 96:2526–2533.

Lagström H, Jokinen E, Seppänen R, Rönnemaa T, Viikari J, Välimäki I, Venetoklis J, Myyrinmaa A, Niinikoski H, Lapinleimu H, Simell O. 1997. Nutrient intakes by young children in a prospective randomized trial of a low-saturated fat, low-cholesterol diet. The STRIP Baby Project. *Arch Pediatr Adolesc Med* 151:181–188.

Lagström H, Seppänen R, Jokinen E, Niinikoski H, Rönnemaa T, Viikari J, Simell O. 1999. Influence of dietary fat on the nutrient intake and growth of children from 1 to 5 y of age: The Special Turku Coronary Risk Factor Intervention Project. *Am J Clin Nutr* 69:516–523.

Lai PBS, Ross JA, Fearson KCH, Anderson JD, Carter DC. 1996. Cell cycle arrest and induction of apoptosis in pancreatic cancer cells exposed to eicosapentaenoic acid in vitro. *Br J Cancer* 74:1375–1383.

Lapinleimu H, Viikari J, Jokinen E, Salo P, Routi T, Leino A, Rönnemaa R, Seppänen R, Välimäki I, Simell O. 1995. Prospective randomised trial in 1062 infants of diet low in saturated fat and cholesterol. *Lancet* 345:471–476.

Larsen LF, Bladbjerg E-M, Jespersen J, Marckmann P. 1997. Effects of dietary fat quality and quantity on postprandial activation of blood coagulation factor VII. *Arterioscler Thromb Vasc Biol* 17:2904–2909.

Larson DE, Hunter GR, Williams MJ, Kekes-Szabo T, Nyikos I, Goran MI. 1996. Dietary fat in relation to body fat and intraabdominal adipose tissue: A cross-sectional analysis. *Am J Clin Nutr* 64:677–684.

Larsson H, Elmståhl S, Berglund G, Ahrén B. 1999. Habitual dietary intake versus glucose tolerance, insulin sensitivity and insulin secretion in postmenopausal women. *J Intern Med* 245:581–591.

Lauer RM, Obarzanek E, Hunsberger SA, Van Horn L, Hartmuller VW, Barton BA, Stevens VJ, Kwiterovich PO, Franklin FA, Kimm SYS, Lasser NL, Simons-Morton DG. 2000. Efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol in children with elevated LDL cholesterol: The Dietary Intervention Study in Children. *Am J Clin Nutr* 72:1332S–1342S.

La Vecchia C, Negri E, Franceschi S, Decarli A, Giacosa A, Lipworth L. 1995. Olive oil, other dietary fats, and the risk of breast cancer (Italy). *Cancer Causes Control* 6:545–550.

Lawton CL, Burley VJ, Wales JK, Blundell JE. 1993. Dietary fat and appetite control in obese subjects: Weak effects on satiation and satiety. *Int J Obes Relat Metab Disord* 17:409–416.

Leclerc I, Davignon I, Lopez D, Garrel DR. 1993. No change in glucose tolerance and substrate oxidation after a high-carbohydrate, low-fat diet. *Metabolism* 42:365–370.

Lee KN, Kritchevsky D, Pariza MW. 1994. Conjugated linoleic acid and atherosclerosis in rabbits. *Atherosclerosis* 108:19–25.

Lee KN, Pariza MW, Ntambi JM. 1998. Conjugated linoleic acid decreases hepatic stearoyl-CoA desaturase mRNA expression. *Biochem Biophys Res Comm* 248:817–821.

Lee-Han H, Cousins M, Beaton M, McGuire V, Kriukov V, Chipman M, Boyd N. 1988. Compliance in a randomized clinical trial of dietary fat reduction in patients with breast dysplasia. *Am J Clin Nutr* 48:575–586.

Lei YX, Cai WC, Chen YZ, Du YX. 1996. Some lifestyle factors in human lung cancer: A case control study of 792 lung cancer cases. *Lung Cancer* 14:S121–S136.

Leibel RL, Hirsch J, Appel BE, Checani GC. 1992. Energy intake required to maintain body weight is not affected by wide variation in diet composition. *Am J Clin Nutr* 55:350–355.

Lemann J. 1999. Relationship between urinary calcium and net acid excretion as determined by dietary protein and potassium: A review. *Nephron* 81:18–25.

Leventhal LJ, Boyce EG, Zurier RB. 1993. Treatment of rheumatoid arthritis with gammalinolenic acid. *Ann Intern Med* 119:867–873.

Leventhal LJ, Boyce EG, Zurier RB. 1994. Treatment of rheumatoid arthritis with blackcurrant seed oil. *Br J Rheumatol* 33:847–852.

Levrat M-A, Behr SR, Rémésy C, Demigné C. 1991a. Effects of soybean fiber on cecal digestion in rats previously adapted to a fiber-free diet. *J Nutr* 121:672–678.

Levrat M-A, Rémésy C, Demigné C. 1991b. High propionic acid fermentations and mineral accumulation in the cecum of rats adapted to different levels of inulin. *J Nutr* 121:1730–1737.

Lew SQ, Bosch JP. 1991 Effect of diet on creatinine clearance and excretion in young and elderly healthy subjects and in patients with renal disease. *J Am Soc Nephrol* 2:856–865.

Lewis CL, Park YK, Dexter PB, Yetley EA. 1992. Nutrient intakes and body weights of persons consuming high and moderate levels of added sugars. *J Am Diet Assoc* 92:708–713.

Liew C, Schut HAJ, Chin SF, Pariza MW, Dashwood RH. 1995. Protection of conjugated linoleic acids against 2-amino-3-methylimidazo[4,5-*f*]quinoline-induced colon carcinogenesis in the F344 rat: A study of inhibitory mechanisms. *Carcinogenesis* 16:3037–3043.

Lifshitz F, Moses N. 1989. Growth failure. A complication of dietary treatment of hypercholesterolemia. *Am J Dis Child* 143:537–542.

Lissner L, Heitmann BL. 1995. Dietary fat and obesity: Evidence from epidemiology. *Eur J Clin Nutr* 49:79–90.

Lissner L, Levitsky DA, Strupp BJ, Kalkwarf HJ, Roe DA. 1987. Dietary fat and the regulation of energy intake in human subjects. *Am J Clin Nutr* 46:886–892.

Lissner L, Heitmann BL, Bengtsson C. 2000. Population studies of diet and obesity. *Br J Nutr* 83:S21–S24.

Litin L, Sacks F. 1993. Trans-fatty-acid content of common foods. *N Engl J Med* 329:1969–1970.

Liu GC, Coulston AM, Reaven GM. 1983. Effect of high-carbohydrate-low-fat diets on plasma glucose, insulin and lipid responses in hypertriglyceridemic humans. *Metabolism* 32:750–753.

Liu K, Stamler J, Trevisan M, Moss D. 1982. Dietary lipids, sugar, fiber, and mortality from coronary heart disease. Bivariate analysis of international data. *Arteriosclerosis* 2:221–227.

Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. 2000. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 71:1455–1461.

Lopes-Virella MF, Virella G. 1996. Modified lipoproteins, cytokines and macrovascular disease in non-insulin-dependent diabetes mellitus. *Ann Med* 28:347–354.

Lopez-Segura F, Velasco F, Lopez-Miranda J, Castro P, Lopez-Pedrera R, Blanco A, Jimenez-Pereperez J, Torres A, Trujillo J, Ordovas JM, Perez-Jiminez F. 1996. Monounsaturated fatty acid-enriched diet decreases plasma plasminogen activator inhibitor type 1. *Ateriosclerosis Thromb Vasc Biol* 16:82–88.

Louheranta AM, Porkkala-Sarataho EK, Nyyssonen MK, Salonen RM, Salonen JT. 1996. Linoleic acid intake and susceptibility of very-low-density and low density lipoproteins to oxidation in men. *Am J Clin Nutr* 63:698–703.

Louis-Sylvestre J, Tournier A, Chapelot D, Chabert M. 1994. Effect of a fat-reduced dish in a meal on 24-h energy and macronutrient intake. *Appetite* 22:165–172.

Lovejoy JC. 1999. Dietary fatty acids and insulin resistance. *Curr Atheroscler Rep* 1:215–220.

Lovejoy J, DiGirolamo M. 1992. Habitual dietary intake and insulin sensitivity in lean and obese adults. *Am J Clin Nutr* 55:1174–1179.

Lovell CR, Burton JL, Horrobin DF. 1981. Treatment of atopic eczema with evening primrose oil. *Lancet* 1:278.

Lubin F, Wax Y, Modan B. 1986. Role of fat, animal protein, and dietary fiber in breast cancer etiology: A case-control study. *J Natl Cancer Inst* 77:605–612.

Lubin JH, Burns PE, Blot WJ, Ziegler RG, Lees AW, Fraumeni JF. 1981. Dietary factors and breast cancer risk. *Int J Cancer* 28:685–689.

Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. 1999a. High glycemic index foods, overeating, and obesity. *Pediatrics* 103:E26.

Ludwig DS, Pereira MA, Kroenke CH, Hilner JE, Van Horn L, Slattery ML, Jacobs DR. 1999b. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *J Am Med Assoc* 282:1539–1546.

Luhman CM, Beitz DC. 1993. Dietary protein and blood cholesterol homeostasis. In: Liepa GU, Beitz DC, Beynen AC, Gorman MA, eds. *Dietary Proteins: How They Alleviate Disease and Promote Better Health.* Champaign, IL: American Oil Chemists' Society. Pp. 57–76.

Lundgren H, Bengtsson C, Blohmé G, Isaksson B, Lapidus L, Lenner RA, Saaek A, Winther E. 1989. Dietary habits and incidence of noninsulin-dependent diabetes mellitus in a population study of women in Gothenburg, Sweden. *Am J Clin Nutr* 49:708–712.

Lungershausen YK, Abbey M, Nestel PJ, Howe PRC. 1994. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. *J Hypertens* 12:1041–1045.

Luo J, Rizkalla SW, Boillot J, Alamowitch C, Chaib H, Bruzzo F, Desplanque N, Dalix A-M, Durand G, Slama G. 1996. Dietary (*n*-3) polyunsaturated fatty acids improve adipocyte insulin action and glucose metabolism in insulin-resistant rats: Relation to membrane fatty acids. *J Nutr* 126:1951–1958.

Luo J, Rizkalla SW, Vidal H, Oppert J-M, Colas C, Boussari A, Guerre-Millo M, Chapuis A-S, Chevalier A, Durand G, Slama G. 1998. Moderate intake of *n*-3 fatty acids for 2 months has no detrimental effect on glucose metabolism and could ameliorate the lipid profile in type 2 diabetic men: Results of a controlled study. *Diabetes Care* 21:717–724.

Maffeis C, Pinelli L, Schutz Y. 1996. Fat intake and adiposity in 8 to 11-year-old obese children. *Int J Obes Relat Metab Disord* 20:170–174.

Maillard G, Charles MA, Lafay L, Thibult N, Vray M, Borys J-M, Basdevant A, Eschwège E, Romon M. 2000. Macronutrient energy intake and adiposity in non obese prepubertal children aged 5–11 y (the Fleurbaix Laventie Ville Santé Study). *Int J Obes Relat Metab Disord* 24:1608–1617.

Männistö S, Pietinen P, Virtanen M, Kataja V, Uusitupa M. 1999. Diet and the risk of breast cancer in a case-control study: Does the threat of disease have an influence on recall bias? *J Clin Epidemiol* 52:429–439.

Marckmann P, Grønbaek M. 1999. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. *Eur J Clin Nutr* 53:585–590.

Marckmann P, Raben A, Astrup A. 2000. Ad libitum intake of low-fat diets rich in either starchy foods or sucrose: Effects on blood lipids, factor VII coagulant activity, and fibrinogen. *Metabolism* 49:731–735.

Marshall JA, Hamman RF, Baxter J. 1991. High-fat, low-carbohydrate diet and the etiology of non-insulin-dependent diabetes mellitus: The San Luis Valley Diabetes Study. *Am J Epidemiol* 134:590–603.

Marshall JA, Bessesen DH, Hamman RF. 1997. High saturated fat and low starch and fibre are associated with hyperinsulinemia in a non-diabetic population: The San Luis Valley Diabetes Study. *Diabetologia* 40:430–438.

Martin-Moreno JM, Willett WC, Gorgojo L, Banegas JR, Rodriguez-Artalejo F, Fernandez-Rodriguez JC, Maisonneuve P, Boyle P. 1994. Dietary fat, olive oil intake and breast cancer risk. *Int J Cancer* 58:774–780.

Masironi R. 1970. Dietary factors and coronary heart disease. *Bull World Health Organ* 42:103–114.

Mattes R. 1990. Effects of aspartame and sucrose on hunger and energy intake in humans. *Physiol Behav* 47:1037–1044.

Mattson FH, Grundy SM. 1985. Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. *J Lipid Res* 26:194–202.

Mayer EJ, Newman B, Quesenberry CP, Selby JV. 1993. Usual dietary fat intake and insulin concentrations in healthy women twins. *Diabetes Care* 16:1459–1469.

Mayer-Davis EJ, Monaco JH, Hoen HM, Carmichael S, Vitolins MZ, Rewers MJ, Haffner SM, Ayad MF, Bergman RN, Karter AJ. 1997. Dietary fat and insulin sensitivity in a triethnic population: The role of obesity. The Insulin Resistance Atheroscelrosis Study (IRAS). *Am J Clin Nutr* 65:79–87.

McDevitt RM, Poppitt SD, Murgatroyd PR, Prentice AM. 2000. Macronutrient disposal during controlled overfeeding with glucose, fructose, sucrose, or fat in lean and obese women. *Am J Clin Nutr* 72:369–377.

McDonald BE, Gerrard JM, Bruce VM, Corner EJ. 1989. Comparison of the effect of canola oil and sunflower oil on plasma lipids and lipoproteins and on in vivo thromboxane A_2 and prostacyclin production in healthy young men. *Am J Clin Nutr* 50:1382–1388.

McDowell MA, Briefel RR, Alaimo K, Bischof AM, Caughman CR, Carroll MD, Loria CM, Johnson CL. 1994. Energy and macronutrient intakes of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. *Adv Data* 255:1–24.

McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. 1984. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. *Am J Epidemiol* 119:667–676.

McGill HC. 1968. Fatty streaks in the coronary arteries and aorta. *Lab Invest* 18:100–104.

McGill HC, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, Malcom GT, Tracy RE, Oalmann MC, Strong JP. 2000a. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. *Arterioscler Thromb Vasc Biol* 20:1998–2004.

McGill HC, McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, Strong JP. 2000b. Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation* 102:374–379.

McLennan PL. 1993. Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats. *Am J Clin Nutr* 57:207–212.

Mensink RP, Katan MB. 1987. Effect of monounsaturated fatty acids versus complex carbohydrates on high-density lipoproteins in healthy men and women. *Lancet* 1:122–125.

Mensink RP, Katan MB. 1992. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler Thromb* 12:911–919.

Mensink RP, Zock PL, Katan MB, Hornstra G. 1992. Effect of dietary *cis* and *trans* fatty acids on serum lipoprotein[a] levels in humans. *J Lipid Res* 33:1493–1501.

Meyer KA, Kushi LH, Jacobs DR, Slavin J, Sellers TA, Folsom AR. 2000. Carbohydrates, dietary fiber, and incident of type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930.

Miles CW. 1992. The metabolizable energy of diets differing in dietary fat and fiber measured in humans. *J Nutr* 122:306–311.

Miller AB, Kelly A, Choi NW, Matthews V, Morgan RW, Munan L, Burch JD, Feather J, Howe GR, Jain M. 1978. A study of diet and breast cancer. *Am J Epidemiol* 107:499–509.

Miller GJ, Cruickshank JK, Ellis LJ, Thompson RL, Wilkes HC, Stirling Y, Mitropoulos KA, Allison JV, Fox TE, Walker AO. 1989. Fat consumption and factor VII coagulant activity in middle-aged men. An association between a dietary and thrombogenic coronary risk factor. *Atherosclerosis* 78:19–24.

Miller WC, Lindeman AK, Wallace J, Niederpruem M. 1990. Diet composition, energy intake, and exercise in relation to body fat in men and women. *Am J Clin Nutr* 52:426–430.

Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, Heine RJ. 1995. Prevalence and determinants of glucose intolerance in a Dutch Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270–1273.

Mori TA, Vandongen R, Masarei JRL, Rouse IL, Dunbar D. 1991. Comparison of diets supplemented with fish oil or olive oil on plasma lipoproteins in insulin-dependent diabetics. *Metabolism* 40:241–246.

Mori TA, Beilin LJ, Burke V, Morris J, Ritchie J. 1997. Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease. *Arterioscler Thromb Vasc Biol* 17:279–286.

Morris MC. 1994. Dietary fats and blood pressure. *J Cardiovasc Risk* 1:21–30.

Morris MC, Sacks F, Rosner B. 1993. Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation* 88:523–533.

Morris MC, Manson JE, Rosner B, Buring JE, Willett WC, Hennekens CH. 1995. Fish consumption and cardiovascular disease in the Physicians' Health Study: A prospective study. *Am J Epidemiol* 142:166–175.

Morton JF, Guthrie JF. 1998. Changes in children's total fat intakes and their food group sources of fat, 1989–91 versus 1994–95: Implications for diet quality. *Fam Econ Nutr Rev* 11:44–57.

Murphy JL, Jones A, Brookes S, Wootton SA. 1995. The gastrointestinal handling and metabolism of [1-^{13}C]palmitic acid in healthy women. *Lipids* 30:291–298.

Nagata C, Takatsuka N, Kurisu Y, Shimizu H. 1998. Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women. *J Nutr* 128:209–213.

National Cholesterol Education Program. 2001. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).* NIH Publication No. 01-3670. Bethesda, MD: National Institutes of Health.

Nelson GJ, Schmidt PC, Kelly DS. 1995. Low-fat diets do not lower plasma cholesterol levels in healthy men compared to high-fat diets with similar fatty acid composition at constant caloric intake. *Lipids* 30:969–976.

Nelson GJ, Schmidt PC, Bartolini GL, Kelley DS, Kyle D. 1997a. The effect of dietary docosahexaenoic acid on plasma lipoproteins and tissue fatty acid composition in humans. *Lipids* 32:1137–1146.

Nelson GJ, Schmidt PS, Bartolini GL, Kelley DS, Kyle D. 1997b. The effect of dietary docosahexaenoic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. *Lipids* 32:1129–1136.

Nelson M. 1991. Food, vitamins and IQ. *Proc Nutr Soc* 50:29–35.

Newman TB, Garber AM, Holtzman NA, Hulley SB. 1995. Problems with the report of the Expert Panel on blood cholesterol levels in children and adolescents. *Arch Pediatr Adolesc Med* 149:241–247.

Newmark HL. 1999. Squalene, olive oil, and cancer risk: Review and hypothesis. *Ann NY Acad Sci* 889:193–203.

Nguyen VT, Larson DE, Johnson RK, Goran MI. 1996. Fat intake and adiposity in children of lean and obese parents. *Am J Clin Nutr* 63:507–513.

NHLBI/NIDDK (National Heart, Lung, and Blood Institute/National Institute of Diabetes and Digestive and Kidney Diseases). 1998. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report.* NIH Publication No. 98-4083. Bethesda, MD: National Institutes of Health.

Nicklas TA, Webber LS, Koschak M, Berenson GS. 1992. Nutrient adequacy of low fat intakes for children: The Bogalusa Heart Study. *Pediatrics* 89:221–228.

Nicklas TA, Myers L, Farris RP, Srinivasan SR, Berenson GS. 1996. Nutritional quality of a high carbohydrate diet as consumed by children: The Bogalusa Heart Study. *J Nutr* 126:1382–1388.

Nicolosi RJ, Wilson TA. 1997. The anti-atherogenic effect of dietary soybean protein concentrate in hamsters. *Nutr Res* 17:1457–1467.

Niinikoski H, Viikari J, Rönnemaa T, Lapinleimu H, Jokinen E, Salo P, Seppänen R, Leino A, Tuominen J, Välimäki I, Simell O. 1996. Prospective randomized trial of low-saturated-fat, low-cholesterol diet during the first 3 years of life. The STRIP Baby Project. *Circulation* 94:1386–1393.

Niinikoski H, Lapinleimu H, Viikari J, Rönnemaa T, Jokinen E, Seppänen R, Terho P, Tuominen J, Välimäki I, Simell O. 1997a. Growth until 3 years of age in a prospective, randomized trial of a diet with reduced saturated fat and cholesterol. *Pediatrics* 99:687–694.

Niinikoski H, Viikari J, Rönnemaa T, Helenius H, Jokinen E, Lapinleimu H, Routi T, Lagström H, Seppänen R, Välimäki I, Simell O. 1997b. Regulation of growth of 7- to 36-month-old children by energy and fat intake in the prospective, randomized STRIP baby trial. *Pediatrics* 100:810–816.

Nobukata H, Ishikawa T, Obata M, Shibutani Y. 2000. Long-term administration of highly purified eicosapentaenoic acid ethyl ester prevents diabetes and abnormalities of blood coagulation in male WBN/Kob rats. *Metabolism* 49:912–919.

Noguchi M, Rose DP, Earashi M, Miyazaki I. 1995. The role of fatty acids and eicosanoid synthesis inhibitors in breast carcinoma. *Oncology* 52:265–271.

Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM. 2000. Men who consume vegetable oils rich in monounsaturated fat: Their patterns and risk of prostate cancer (New Zealand). *Cancer Causes Control* 11:609–615.

Obarzanek E, Schreiber GB, Crawford PB, Goldman SR, Barrier PM, Frederick MM, Lakatos E. 1994. Energy intake and physical activity in relation to indexes of body fat: The National Heart, Lung, and Blood Institute Growth and Health Study. *Am J Clin Nutr* 60:15–22.

Obarzanek E, Velletri PA, Cutler JA. 1996. Dietary protein and blood pressure. *J Am Med Assoc* 275:1598–1603.

Obarzanek E, Hunsberger SA, Van Horn L, Hartmuller VV, Barton BA, Stevens VJ, Kwiterovich PO, Franklin FA, Kimm SYS, Lasser NL, Simons-Morton DG, Lauer RM. 1997. Safety of a fat-reduced diet: The Dietary Intervention Study in Children (DISC). *Pediatrics* 100:51–59.

Obarzanek E, Kimm SYS, Barton BA, Van Horn L, Kwiterovich PO, Simons-Morton DG, Hunsberger SA, Lasser NL, Robson AM, Franklin FA, Lauer RM, Stevens VJ, Friedman LA, Dorgan JF, Greenlick MR. 2001a. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: Seven-year results of the Dietary Intervention Study in Children (DISC). *Pediatrics* 107:256–264.

Obarzanek E, Sacks FM, Vollmer WM, Bray GA, Miller ER, Lin P-H, Karanja NM, Most-Windhauser MM, Moore TJ, Swain JF, Bales CW, Proschan MA. 2001b. Effects on blood lipids of a blood pressure-lowering diet: The Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr* 74:80–89.

Ogden J, Wardle J. 1990. Cognitive restraint and sensitivity to cues for hunger and satiety. *Physiol Behav* 47:477–481.

O'Hanesian MA, Rosner B, Bishop LM, Sacks FM. 1996. Effects of inherent responsiveness to diet and day-to-day diet variation on plasma lipoprotein concentrations. *Am J Clin Nutr* 64:53–59.

Ohta A, Ohtsuki M, Baba S, Adachi T, Sakata T, Sakaguchi E. 1995. Calcium and magnesium absorption from the colon and rectum are increased in rats fed fructooligosaccharides. *J Nutr* 125:2417–2424.

Okita M, Yoshida S, Yamamoto J, Suzuki K, Kaneyuki T, Kubota M, Sasagawa T. 1995. *n*-3 and *n*-6 Fatty acid intake and serum phospholipid fatty acid composition in middle-aged women living in rural and urban areas in Okayama Prefecture. *J Nutr Sci Vitaminol* 41:313–323.

Olson RE. 2000. Is it wise to restrict fat in the diets of children? *J Am Diet Assoc* 100:28–32.

Oomen CM, Feskens EJM, Räsänen L, Fidanza F, Nissinen AM, Menotti A, Kok FJ, Kromhout D. 2000. Fish consumption and coronary heart disease mortality in Finland, Italy, and the Netherlands. *Am J Epidemiol* 151:999–1006.

Orencia AJ, Daviglus ML, Dyer AR, Shekelle RB, Stamler J. 1996. Fish consumption and stroke in men. 30-Year findings of the Chicago Western Electric Study. *Stroke* 27:204–209.

Ostrowska E, Muralitharan M, Cross RF, Bauman DE, Dunshea FR. 1999. Dietary conjugated linoleic acids increase lean tissue and decrease fat deposition in growing pigs. *J Nutr* 129:2037–2042.

Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H. 2000. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. *Eur J Cancer* 36:1235–1247.

Parillo M, Rivellese AA, Ciardullo AV, Capaldo B, Giacco A, Genovese S, Riccardi G. 1992. A high-monounsaturated-fat/low-carbohydrate diet improves peripheral insulin sensitivity in non-insulin-dependent diabetic patients. *Metabolism* 41:1373–1378.

Pariza MW, Park Y, Cook ME. 2001. The biologically active isomers of conjugated linoleic acid. *Prog Lipid Res* 40:283–298.

Park Y, Albright KJ, Liu W, Storkson JM, Cook ME, Pariza MW. 1997. Effect of conjugated linoleic acid on body composition in mice. *Lipids* 32:853–858.

Park Y, Storkson JM, Albright KJ, Liu W, Pariza MW. 1999. Evidence that the *trans*-10,*cis*-12 isomer of conjugated linoleic acid induces body composition changes in mice. *Lipids* 34:235–241.

Parker DR, Weiss ST, Troisi R, Cassano PA, Vokonas PS, Landsberg L. 1993. Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations: The Normative Aging Study. *Am J Clin Nutr* 58:129–136.

Parnaud G, Corpet DE. 1997. Colorectal cancer: Controversial role of meat consumption. *Bull Cancer* 84:899–911.

Parrish CC, Pathy DA, Angel A. 1990. Dietary fish oils limit adipose tissue hypertrophy in rats. *Metabolism* 39:217–219.

Parrish CC, Pathy DA, Parkes JG, Angel A. 1991. Dietary fish oils modify adipocyte structure and function. *J Cell Physiol* 148:493–502.

Pearce ML, Dayton S. 1971. Incidence of cancer in men on a diet high in polyunsaturated fat. *Lancet* 1:464–467.

Peiris AN, Struve MF, Mueller RA, Lee MB, Kissebah AH. 1988. Glucose metabolism in obesity: Influence of body fat distribution. *J Clin Endocrinol Metab* 67:760–767.

Pelkman CL, Coval SM, Mauger DT, Zhao G, Kris-Etherton PM. 2001. A meta-analysis of low-fat versus high-MUFA diets. *FASEB J* 15:394.

Pelletier DL, Frongillo EA, Schroeder DG, Habicht J-P. 1995. The effects of malnutrition on child mortality in developing countries. *Bull World Health Organ* 73:443–448.

Perez-Jimenez F, Espino A, Lopez-Segura F, Blanco J, Ruiz-Gutierrez V, Prada JL, Lopez-Miranda J, Jimenez-Pereperez J, Ordovas JM. 1995. Lipoprotein concentrations in normolipidemic males consuming oleic acid-rich diets from two different sources: Olive oil and oleic acid-rich sunflower oil. *Am J Clin Nutr* 62:769–775.

Perez-Jimenez F, Catrso P, Lopez-Miranda J, Paz-Rojas E, Blanco A, Lopez-Segura F, Velasco F, Marin C, Fuentes F, Ordovas JM. 1999. Circulating levels of endothelial function are modulated by dietary monounsaturated fat. *Atherosclerosis* 145:351–358.

Perez-Jimenez F, Lopez-Miranda J, Pinillos MD, Gomez P, Pas-Rojas E, Montilla P, Marin C, Velasco MJ, Blanco-Molina A, Jimenez Pereperez JA, Ordovas JM. 2001. A Mediterranean and a high-carbohydrate diet improves glucose metabolism in healthy young persons. *Diabetologica* 44:2038–2043.

Peterson S, Sigman-Grant M. 1997. Impact of adopting lower-fat food choices on nutrient intake of American children. *Pediatrics* 100:E4.

Pfeuffer M, Ahrens F, Hagemeister H, Barth CA. 1988. Influence of casein versus soy protein isolate on lipid metabolism of minipigs. *Ann Nutr Metab* 32:83–89.

Phillips RL. 1975. Role of life-style and dietary habits in risk of cancer among Seventh-Day Adventists. *Cancer Res* 35:3513–3522.

Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. 1997. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol* 145:876–887.

Poppitt SD, Swann DL. 1998. Dietary manipulation and energy compensation: Does the intermittent use of low-fat items in the diet reduce total energy intake in free-feeding lean men? *Int J Obes Relat Metab Disord* 22:1024–1031.

Poppitt SD, Swann DL, Murgatroyd PR, Elia M, McDevitt RM, Prentice AM. 1998. Effect of dietary manipulation on substrate flux and energy balance in obese women taking the appetite suppressant dexfenfluramine. *Am J Clin Nutr* 68:1012–1021.

Popp-Snijders C, Schouten JA, Heine RJ, van der Meer J, van der Veen EA. 1987. Dietary supplementation of omega-3 polyunsaturated fatty acids improves insulin sensitivity in non-insulin-dependent diabetes. *Diabetes Res* 4:141–147.

Porrini M, Crovetti R, Riso P, Santangelo A, Testolin G. 1995. Effects of physical and chemical characteristics of food on specific and general satiety. *Physiol Behav* 57:461–468.

Prentice AM. 2001. Overeating: The health risks. *Obes Res* 9:234S–238S.

Price JM, Grinker J. 1973. Effects of degree of obesity, food deprivation, and palatability on eating behavior of humans. *J Comp Physiol Psychol* 85:265–271.

Promislow JHE, Goodman-Gruen D, Slymen DJ, Barrett-Conner E. 2002. Protein consumption and bone mineral density in the elderly. The Rancho Bernardo Study. *Am J Epidemiol* 155:636–644.

Proserpi C, Sparti A, Schutz Y, Di Vetta V, Milon H, Jéquier E. 1997. Ad libitum intake of a high-carbohydrate or high-fat diet in young men: Effects on nutrient balances. *Am J Clin Nutr* 66:539–545.

Raben A, Macdonald I, Astrup A. 1997. Replacement of dietary fat by sucrose or starch: Effects on 14 d ad libitum energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. *Int J Obes Relat Metab Disord* 21:846–859.

Ramon JM, Bou R, Romea S, Alkiza ME, Jacas M, Ribes J, Oromi J. 2000. Dietary fat intake and prostate cancer risk: A case-control study in Spain. *Cancer Causes Control* 11:679–685.

Rath R, Mašek J, Kujalová V, Slabochová Z. 1974. Effect of a high sugar intake on some metabolic and regulatory indicators in young men. *Nahrung* 18:343–353.

Reaven GM. 1988. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37:1595–1607.

Reaven GM. 1995. Pathophysiology of insulin resistance in human disease. *Physiol Rev* 75:473–486.

Reaven GM. 2001. Insulin resistance, compensatory hyperinsulinemia, and coronary heart disease: Syndrome X revisited. In: Jefferson LS, Cherrington AD, Goodman HM, eds. *Handbook of Physiology. Section 7: The Endocrine System. Volume II: The Endocrine Pancreas and Regulation of Metabolism.* Oxford: Oxford University Press. Pp. 1169–1197.

Reaven P, Parthasarathy S, Grasse BJ, Miller E, Almazan F, Mattson FH, Khoo JC, Steinberg D, Witztum JL. 1991. Feasibility of using an oleate-rich diet to reduce the susceptibility of low-density lipoprotein to oxidative modification in humans. *Am J Clin Nutr* 54:701–706.

Reaven P, Parthasarathy S, Grasse BJ, Miller E, Steinberg D, Witztum JL. 1993. Effects of oleate-rich and linoleate-rich diets on the susceptibility of low density lipoprotein to oxidative modification in mildly hypercholesterolemic subjects. *J Clin Invest* 91:668–676.

Reaven PD, Grasse BJ, Tribble DL. 1994. Effects of linoleate-enriched and oleate-enriched diets in combination with alpha-tocopherol on the susceptibility of LDL and LDL subfractions to oxidative modification in humans. *Arterioscler Thromb* 14:557–566.

Reddy BS. 1992. Dietary fat and colon cancer: Animal model studies. *Lipids* 27:807–813.

Reddy BS, Burill C, Rigotty J. 1991. Effect of diets high in ω-3 and ω-6 fatty acids on initiation and postinitiation stages of colon carcinogenesis. *Cancer Res* 51:487–491.

Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OE, Prather ES. 1979. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. *Am J Clin Nutr* 32:2206–2216.

Rémésy C, Behr SR, Levrat M-A, Demigné C. 1992. Fiber fermentability in the rat cecum and its physiological consequences. *Nutr Res* 12:1235–1244.

Renaud S, de Lorgeril M, Delaye J, Guidollet J, Jacquard F, Mamelle N, Martin JL, Monjaud I, Salen P, Toubol P. 1995. Creten Mediterranean diet for prevention of coronary heart disease. *Am J Clin Nutr* 61:1360S–1367S.

Ricketts CD. 1997. Fat preferences, dietary fat intake and body composition in children. *Eur J Clin Nutr* 51:778–781.

Rissanen AM, Heliövaara M, Knekt P, Reunanen A, Aromaa A. 1991. Determinants of weight gain and overweight in adult Finns. *Eur J Clin Nutr* 45:419–430.

Robertson WG, Peacock M. 1982. The pattern of urinary stone disease in Leeds and in the United Kingdom in relation to animal protein intake during the period 1960–1980. *Urol Int* 37:394–399.

Robertson WG, Heyburn PJ, Peacock M, Hanes FA, Swaminathan R. 1979. The effect of high animal protein intake on the risk of calcium stone-formation in the urinary tract. *Clin Sci* 57:285–288.

Roche HM, Zampelas A, Jackson KG, Williams CM, Gibney MJ. 1998. The effect of test meal monounsaturated fatty acid:saturated fatty acid ratio on postprandial lipid metabolism. *Br J Nutr* 79:419–424.

Rodier M, Colette C, Crastes de Paulet P, Crastes de Paulet A, Monnier L. 1993. Relationships between serum lipids, platelet membrane fatty acid composition and platelet aggregation in type 2 diabetes mellitus. *Diabete Metab* 19:560–565.

Rolland-Cachera MF, Deheeger M, Akrout M, Bellisle F. 1995. Influence of macronutrients on adiposity development: A follow up study of nutrition and growth from 10 months to 8 years of age. *Int J Obes Relat Metab Disord* 19:573–578.

Rolls BJ, Hetherington M, Burley VJ. 1988. The specificity of satiety: The influence of foods of different macronutrient content on the development of satiety. *Physiol Behav* 43:145–153.

Rolls BJ, Laster LJ, Summerfelt A. 1989. Hunger and food intake following consumption of low-calorie foods. *Appetite* 13:115–127.

Rolls BJ, Kim-Harris S, Fischman MW, Foltin RW, Moran TH, Stoner SA. 1994. Satiety after preloads with different amounts of fat and carbohydrate: Implications for obesity. *Am J Clin Nutr* 60:476–487.

Romieu I, Willett WC, Stampfer MJ, Colditz GA, Sampson L, Rosner B, Hennekens CH, Speizer FE. 1988. Energy intake and other determinants of relative weight. *Am J Clin Nutr* 47:406–412.

Rose DP, Connolly JM. 2000. Regulation of tumor angiogenesis by dietary fatty acids and eicosanoids. *Nutr Cancer* 37:119–127.

Rugg-Gunn AJ, Hackett AF, Jenkins GN, Appleton DR. 1991. Empty calories? Nutrient intake in relation to sugar intake in English adolescents. *J Hum Nutr Diet* 4:101–111.

Rush D, Stein Z, Susser M. 1980. A randomized controlled trial of prenatal nutrition supplementation in New York City. *Pediatrics* 65:683–697.

Rustan AC, Hustvedt B-E, Drevon CA. 1993. Dietary supplementation of very long-chain *n*-3 fatty acids decreases whole body lipid utilization in the rat. *J Lipid Res* 34:1299–1309.

Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. 1997. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *J Am Med Assoc* 277:472–477.

Salmerón J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. 2001. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr* 73:1019–1026.

Salomon O, Steinberg DM, Zivelin A, Gitel S, Dardik R, Rosenberg N, Berliner S, Inbal A, Many A, Lubetsky A, Varon D, Martinowitz U, Seligsohn U. 1999. Single and combined prothrombic factors in patients with idiopathic venous thromboembolism. Prevalence and risk assessment. *Arterioscler Thromb Vasc Biol* 19:511–518.

Saltzman E, Dallal GE, Roberts SB. 1997. Effect of high-fat and low-fat diets on voluntary energy intake and substrate oxidation: Studies in identical twins consuming diets matched for energy density, fiber, and palatability. *Am J Clin Nutr* 66:1332–1339.

Samaras K, Kelly PJ, Chiano MN, Arden N, Spector TD, Campbell LV. 1998. Genes versus environment. The relationship between dietary fat and total and central abdominal fat. *Diabetes Care* 21:2069–2076.

Sanders TAB, Hinds A. 1992. The influence of a fish oil high in docosahexaenoic acid on plasma lipoprotein and vitamin E concentrations and haemostatic function in healthy male volunteers. *Br J Nutr* 68:163–173.

Sanders TAB, Oakley FR, Miller GJ, Mitropoulos KA, Crook D, Oliver MF. 1997. Influence of *n*-6 versus *n*-3 polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors. *Arterioscler Thromb Vasc Biol* 17:3449–3460.

Saris WHM, Astrup A, Prentice AM, Zunft HJF, Formiguera X, Verboeket-van de Venne WPHG, Raben A, Poppitt SD, Seppelt B, Johnston S, Vasilaras TH, Keogh GF. 2000. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs complex carbohydrates on body weight and blood lipids: The CARMEN study. *Int J Obes Relat Metab Disord* 24:1310–1318.

Sasaki S, Horacsek M, Kesteloot H. 1993. An ecological study of the relationship between dietary fat intake and breast cancer mortality. *Prev Med* 22:187–202.

Sawaya AL, Fuss PJ, Dallal GE, Tsay R, McCrory MA, Young V, Roberts SB. 2001. Meal palatability, substrate oxidation and blood glucose in young and older men. *Physiol Behav* 72:5–12.

Saynor R, Gillott T. 1992. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of *n*-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. *Lipids* 27:533–538.

Schmidt EB, Lervang H-H, Varming K, Madsen P, Dyerberg J. 1992. Long-term supplementation with *n*-3 fatty acids. I: Effect on blood lipids, haemostasis and blood pressure. *Scand J Clin Lab Invest* 52:221–228.

Schønberg S, Krokan HE. 1995. The inhibitory effect of conjugated dienoic derivates (CLA) of linoleic acid on the growth of human tumor cell lines is in part due to increased lipid peroxidation. *Anticancer Res* 15:1241–1246.

Schuurman AG, van den Brandt PA, Dorant E, Brants HAM, Goldbohm RA. 1999. Association of energy and fat intake with prostate carcinoma risk. Results from the Netherlands Cohort Study. *Cancer* 86:1019–1027.

Seagle HM, Davy BM, Grunwald G, Hill JO. 1997. Energy density of self-reported food intake: Variation and relationship to other food components. *Obes Res* 5:78S.

Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers TE. 1993. Do obese children become obese adults? A review of the literature. *Prev Med* 22:167–177.

Severson RK, Nomura AMY, Grove JS, Stemmermann GN. 1989. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res* 49:1857–1860.

Shannon BM, Tershakovec AM, Martel JK, Achterberg CL, Cortner JA, Smiciklas-Wright HS, Stallings VA, Stolley PD. 1994. Reduction of elevated LDL-cholesterol levels of 4- to 10-year-old children through home-based dietary education. *Pediatrics* 94:923–927.

Shea S, Basch CE, Stein AD, Contento IR, Irigoyen M, Zybert P. 1993. Is there a relationship between dietary fat and stature or growth in children three to five years of age? *Pediatrics* 92:579–586.

Sheppard L, Kristal AR, Kushi LH. 1991. Weight loss in women participating in a randomized trial of low-fat diets. *Am J Clin Nutr* 54:821–828.

Shetty PS, Prentice AM, Goldberg GR, Murgatroyd PR, McKenna APM, Stubbs RJ, Volschenk PA. 1994. Alterations in fuel selection and voluntary food intake in response to isoenergetic manipulation of glycogen stores in humans. *Am J Clin Nutr* 60:534–543.

Shide DJ, Rolls BJ. 1995. Information about the fat content of preloads influences energy intake in healthy women. *J Am Diet Assoc* 95:993–998.

Shu XO, Zheng W, Potischman N, Brinton LA, Hatch MC, Gao YT, Fraumeni JF. 1993. A population-based case-control study of dietary factors and endometrial cancer in Shanghai, People's Republic of China. *Am J Epidemiol* 137:155–165.

Shultz TD, Leklem JE. 1983. Dietary status of Seventh-day Adventists and non-vegetarians. *J Am Diet Assoc* 83:27–33.

Shultz TD, Chew BP, Seaman WR, Luedecke LO. 1992. Inhibitory effect of conjugated dienoic derivates of linoleic acid and β-carotene on the in vitro growth of human cancer cells. *Cancer Lett* 63:125–133.

Sierakowski R, Finlayson B, Landes RR, Finlayson CD, Sierakowski N. 1978. The frequency of urolithiasis in hospital discharge diagnoses in the United States. *Invest Urol* 15:438–441.

Simell O, Niinikoski H, Rönnemaa T, Lapinleimu H, Routi T, Lagström H, Salo P, Jokinen E, Viikari J. 2000. Special Turku Coronary Risk Factor Intervention Project for Babies (STRIP). *Am J Clin Nutr* 72:1316S–1331S.

Singh RB, Rastogi SS, Verma R, Laxmi B, Singh R, Ghosh S, Niaz MA. 1992. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: Results of one year follow up. *Br Med J* 304:1015–1019.

Singh RB, Ghosh S, Niaz AM, Gupta S, Bishnoi I, Sharma JP, Agarwal P, Rastogi SS, Beegum R, Chibo H. 1995. Epidemiologic study of diet and coronary risk factors in relation to central obesity and insulin levels in rural and urban populations of north India. *Int J Cardiol* 47:245–255.

Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. 1997. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: The Indian Experiment of Infarct Survival—4. *Cardiovasc Drugs Ther* 11:485–491.

Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, Bovbjerg V, Arbogast P, Smith H, Kushi LH, Cobb LA, Copass MK, Psaty BM, Lemaitre R, Retzlaff B, Childs M, Knopp RH. 1995. Dietary intake and cell membrane levels of long-chain *n*-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *J Am Med Assoc* 274:1363–1367.

Skinner JD, Carruth BR, Moran J, Houck K, Coletta F. 1999. Fruit juice intake is not related to children's growth. *Pediatrics* 103:58–64.

Skov AR, Toubro S, Ronn B, Holm L, Astrup A. 1999. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. *Int J Obes Relat Metab Disord* 23:528–536.

Slattery ML, Potter JD, Sorenson AW. 1994. Age and risk factors for colon cancer (United States and Australia): Are there implications for understanding differences in case-control and cohort studies? *Cancer Causes Control* 5:557–563.

Slattery ML, Caan BJ, Potter JD, Berry TD, Coates A, Duncan D, Edwards SL. 1997. Dietary energy sources and colon cancer risk. *Am J Epidemiol* 145:199–210.

Sonko BJ, Prentice AM, Poppitt SD, Prentice A, Jequier E, Whitehead RG. 1994. Could dietary fat intake be an important determinant of seasonal weight changes in a rural subsistence farming community in The Gambia? In: *Nestlé Foundation for the Study of the Problems of Nutrition in the World. Annual Report 1994.* Lausanne, Switzerland: Nestlé Foundation. Pp. 74–87.

Sonnenberg LM, Quatromoni PA, Gagnon DR, Cupples LA, Franz MM, Ordovas JM, Wilson PWF, Schaefer EJ, Millen BE. 1996. Diet and plasma lipids in women. II. Macronutrients and plasma triglycerides, high-density lipoprotein, and the ratio of total to high-density lipoprotein cholesterol in women: The Framingham Nutrition Studies. *J Clin Epidemiol* 49:665–672.

Stamler J. 1979. Population studies. In: Levy R, Rifkind B, Dennis B, Ernst N, eds. *Nutrition, Lipids, and Coronary Heart Disease.* New York: Raven Press. Pp. 25–88.

Stangl GI. 2000. Conjugated linoleic acids exhibit a strong fat-to-lean partitioning effect, reduce serum VLDL lipids and redistribute tissue lipids in food-restricted rats. *J Nutr* 130:1140–1146.

Stary HC. 1989. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. *Arteriosclerosis* 9:I19–I32.

Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD. 1998. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *N Engl J Med* 339:12–20.

Steinberg D, Parthawarathy S, Carew TE, Khoo JC, Witztum JL. 1989. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 320:915–924.

Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS. 1987. Fish oil prevents insulin resistance induced by high-fat feeding. *Science* 237:885–888.

Storlien LH, Jenkins AB, Chisholm DJ, Pascoe WS, Khouri S, Kraegen EW. 1991. Influence of dietary fat composition on development of insulin resistance in rats. Relationship to muscle triglyceride and ω-3 fatty acids in muscle phospholipid. *Diabetes* 40:280–289.

Straznicky NE, O'Callaghan CJ, Barrington VE, Louis WJ. 1999. Hypotensive effect of low-fat, high-carbohydrate diet can be independent of changes in plasma insulin concentrations. *Hypertension* 34:580–585.

Strong JP, Malcom GT, Newman WP, Oalmann MC. 1992. Early lesions of atherosclerosis in childhood and youth: Natural history and risk factors. *J Am Coll Nutr* 11:51S–54S.

Stubbs RJ, Harbron CG, Murgatroyd PR, Prentice AM. 1995a. Covert manipulation of dietary fat and energy density: Effect on substrate flux and food intake in men eating ad libitum. *Am J Clin Nutr* 62:316–329.

Stubbs RJ, Ritz P, Coward WA, Prentice AM. 1995b. Covert manipulation of the ratio of dietary fat to carbohydrate and energy density: Effect on food intake and energy balance in free-living men eating ad libitum. *Am J Clin Nutr* 62:330–337.

Stubbs RJ, Harbron CG, Prentice AM. 1996. Covert manipulation of the dietary fat to carbohydrate ratio of isoenergetically dense diets: Effect on food intake in feeding men ad libitum. *Int J Obes Relat Metab Disord* 20:651–660.

Sugano M, Tsujita A, Yamasaki M, Noguchi M, Yamada K. 1998. Conjugated linoleic acid modulates tissue levels of chemical mediators and immunoglobulins in rats. *Lipids* 33:521–527.

Swinburn BA, Boyce VL, Bergman RN, Howard BV, Bogardus C. 1991. Deterioration in carbohydrate metabolism and lipoprotein changes induced by modern, high fat diet in Pima Indians and Caucasians. *J Clin Endocrinol Metab* 73:156–165.

Swinburn BA, Metcalf PA, Ley SJ. 2001. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care* 24:619–624.

Takahashi M, Przetakiewicz M, Ong A, Borek C, Lowenstein JM. 1992. Effect of omega 3 and omega 6 fatty acids on transformation of cultured cells by irradiation and transfection. *Cancer Res* 52:154–162.

Talamini R, Franceschi S, La Vecchia C, Serraino D, Barra S, Negri E. 1992. Diet and prostatic cancer: A case-control study in Northern Italy. *Nutr Cancer* 18:277–286.

Tao SC, Huang ZD, Wu XG, Zhou BF, Xiao ZK, Hao JS, Li YH, Cen RC, Rao XX. 1989. CHD and its risk factors in the People's Republic of China. *Int J Epidemiol* 18:S159–S163.

Tate G, Mandell BF, Laposata M, Ohliger D, Baker DG, Schumacher HR, Zurier RB. 1989. Suppression of acute and chronic inflammation by dietary gamma linolenic acid. *J Rheumatol* 16:729–733.

Teixeira SR, Potter SM, Weigel R, Hannum S, Erdman JW, Hasler CM. 2000. Effects of feeding 4 levels of soy protein for 3 and 6 wk on blood lipids and apolipoproteins in moderately hypercholesterolemic men. *Am J Clin Nutr* 71:1077–1084.

Terpstra AHM, Holmes JC, Nicolosi RJ. 1991. The hypocholesterolemic effect of dietary soybean protein vs. casein in hamsters fed cholesterol-free or cholesterol-enriched semipurified diets. *J Nutr* 121:944–947.

Thomas CD, Peters JC, Reed GW, Abumrad NN, Sun M, Hill JO. 1992. Nutrient balance and energy expenditure during ad libitum feeding of high-fat and high-carbohydrate diets in humans. *Am J Clin Nutr* 55:934–942.

Thomsen C, Rasmussen O, Christiansen C, Pedersen E, Vesterlund M, Storm H, Ingerslev J, Hermansen K. 1999. Comparison of the effects of a monounsaturated fat diet and a high carbohydrate diet on cardiovascular risk factors in first degree relatives to type-2 diabetic subjects. *Eur J Clin Nutr* 52:818–823.

Tillotson JL, Grandits GA, Bartsch GE, Stamler J. 1997. Relation of dietary carbohydrates to blood lipids in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr* 65:314S–326S.

Tobin J, Spector D. 1986. Dietary protein has no effect on future creatinine clearance (Ccr). *Gerontologist* 26:59A.

Toft I, Bønaa KH, Ingebretsen OC, Nordøy A, Jenssen T. 1995. Effects of *n*-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension. A randomized, controlled trial. *Ann Intern Med* 123:911–918.

Toniolo P, Riboli E, Shore RE, Pasternack BS. 1994. Consumption of meat, animal products, protein, and fat and risk of breast cancer: A prospective cohort study in New York. *Epidemiology* 5:391–397.

Tonstad S, Sivertsen M. 1997. Relation between dietary fat and energy and micronutrient intakes. *Arch Dis Child* 76:416–420.

Torun B, Chew F. 1999. Protein-energy malnutrition. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*, 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 963–988.

Tremblay A, Plourde G, Despres J-P, Bouchard C. 1989. Impact of dietary fat content and fat oxidation on energy intake in humans. *Am J Clin Nutr* 49:799–805.

Tremblay A, Lavallee N, Almeras N, Allard L, Despres J-P, Bouchard C. 1991. Nutritional determinants of the increase in energy intake associated with a high-fat diet. *Am J Clin Nutr* 53:1134–1137.

Tremblay MS, Willms JD. 2000. Secular trends in the body mass index of Canadian children. *Can Med Assoc J* 163:1429–1433.

Tremoli E, Maderna P, Marangoni F, Colli S, Eligini S, Catalano I, Angeli MT, Pazzucconi F, Gainfranceschi G, Davi G, Stragliotto E, Sirtori CR, Galli C. 1995. Prolonged inhibition of platelet aggregation after *n*-3 fatty acid ethyl ester ingestion by healthy volunteers. *Am J Clin Nutr* 61:607–613.

Trevisan M, Krogh V, Freudenheim J, Blake A, Muti P, Panico S, Farinaro E, Mancini M, Menotti A, Ricci G. 1990. Consumption of olive oil, butter, and vegetable oils and coronary heart disease risk factors. The Research Group ATS-RF2 of the Italian National Research Council. *J Am Med Assoc* 263:688–692.

Trichopoulou A, Katsouyanni K, Stuver S, Tzala L, Gnardellis C, Rimm E, Trichopoulos D. 1995. Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *J Natl Cancer Inst* 87:110–116.

Trinidad TP, Wolever TMS, Thompson LU. 1993. Interactive effects of Ca and SCFA on absorption in the distal colon of men. *Nutr Res* 13:417–425.

Trinidad TP, Wolever TMS, Thompson LU. 1996. Effect of acetate and propionate on calcium absorption from the rectum and distal colon of humans. *Am J Clin Nutr* 63:574–578.

Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. 1995. Overweight prevalence and trend for children and adolescents: The National Health and Nutrition Examination Surveys, 1963 to 1991. *Arch Pediatr Adolesc Med* 149:1085–1091.

Tsuboyama-Kasaoka N, Takahashi M, Tanemura K, Kim H-J, Tange T, Okuyama H, Kasai M, Ikemoto S, Ezaki O. 2000. Conjugated linoleic acid supplementation reduces adipose tissue by apoptosis and develops lipodystrophy in mice. *Diabetes* 49:1534–1542.

Tucker LA, Kano MJ. 1992. Dietary fat and body fat: A multivariate study of 205 adult females. *Am J Clin Nutr* 56:616–622.

Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Eng J Med* 344:1343–1350.

Turini ME, Powell WS, Behr SR, Holub BJ. 1994. Effects of a fish-oil and vegetable-oil formula on aggregation and ethanolamine-containing lysophospholipid generation in activated human platelets and on leukotriene production in stimulated neutrophils. *Am J Clin Nutr* 60:717–724.

Turner NC, Clapham JC. 1998. Insulin resistance, impaired glucose tolerance and non-insulin-dependent diabetes, pathologic mechanisms and treatment: Current status and therapeutic possibilities. *Prog Drug Res* 51:33–94.

Uauy R, Mize CE, Castillo-Duran C. 2000. Fat intake during childhood: Metabolic responses and effects on growth. *Am J Clin Nutr* 72:1354S–1360S.

Uematsu T, Nagashima S, Niwa M, Kohno K, Sassa T, Ishii M, Tomono Y, Yamato C, Kanamaru M. 1996. Effect of dietary fat content on oral bioavailability of menatetrenone in humans. *J Pharm Sci* 85:1012–1016.

USDA (U.S. Department of Agriculture). 1996. *The Food Guide Pyramid*. Home and Garden Bulletin No. 252. Washington, DC: U.S. Government Printing Office.

Uusitupa M, Schwab U, Mäkimattila S, Karhapää P, Sarkkinen E, Maliranta H, Ågren J, Penttilä I. 1994. Effects of two high-fat diets with different fatty acid compositions on glucose and lipid metabolism in healthy young women. *Am J Clin Nutr* 59:1310–1316.

van Amelsvoort JM, van Stratum P, Kraal JH, Lussenburg RN, Houtsmuller UMT. 1989. Effects of varying the carbohydrate:fat ratio in a hot lunch on postprandial variables in male volunteers. *Br J Nutr* 61:267–283.

van Amelsvoort JM, van Stratum P, Dubbelman GP, Lussenburg RN. 1990. Effects of meal size reduction on postprandial variables in male volunteers. *Ann Nutr Metab* 34:163–174.

van den Berg JJM, Cook NE, Tribble DL. 1995. Reinvestigation of the antioxidant properties of conjugated linoleic acid. *Lipids* 30:599–605.

van den Brandt PA, van't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJJ, Sturmans F. 1993. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. *Cancer Res* 53:75–82.

Van Dokkum W, Wesstra A, Schippers FA. 1982. Physiological effects of fibre-rich types of bread. 1. The effect of dietary fibre from bread on the mineral balance of young men. *Br J Nutr* 47:451–460.

van Stratum P, Lussenburg RN, van Wezel LA, Vergroesen AJ, Cremer HD. 1978. The effect of dietary carbohydrate:fat ratio on energy intake by adult women. *Am J Clin Nutr* 31:206–212.

van't Veer P, Kok FJ, Brants HAM, Ockhuizen T, Sturmans F, Hermus RJJ. 1990. Dietary fat and the risk of breast cancer. *Int J Epidemiol* 19:12–18.

Vartiainen E, Puska P, Pietinen P, Nissinen A, Leino U, Uusitalo U. 1986. Effects of dietary fat modifications on serum lipids and blood pressure in children. *Acta Paediatr Scand* 75:396–401.

Veierød MB, Laake P, Thelle DS. 1997a. Dietary fat intake and risk of lung cancer: A prospective study of 51,452 Norwegian men and women. *Eur J Cancer Prev* 6:540–549.

Veierød MB, Laake P, Thelle DS. 1997b. Dietary fat intake and risk of prostate cancer: A prospective study of 25,708 Norwegian men. *Int J Cancer* 73:634–638.

Velie E, Kulldorff M, Schairer C, Block G, Albanes D, Schatzkin A. 2000. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: A prospective cohort study. *J Natl Cancer Inst* 92:833–839.

Vessby B. 2000. Dietary fat and insulin action in humans. *Br J Nutr* 83:S91–S96.

Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nälsén C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson I-B, Storlien LH. 2001. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. *Diabetologia* 44:312–319.

Visonneau S, Cesano A, Tepper SA, Scimeca JA, Santoli D, Kritchevsky D. 1997. Conjugated linoleic acid suppresses the growth of human breast adenocarcinoma cells in SCID mice. *Anticancer Res* 17:969–974.

Vobecky JS, Vobecky J, Normand L. 1995. Risk and benefit of low fat intake in childhood. *Ann Nutr Metab* 39:124–133.

von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. 1999. The effect of dietary ω-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 130:554–562.

Walker AR, Walker BF. 1978. High high-density-lipoprotein cholesterol in African children and adults in a population free of coronary heart disease. *Br Med J* 2:1336–1337.

Walser M. 1992. The relationship of dietary protein to kidney disease. In: Liepa GU, Beitz DC, Beynen AC, Gorman MA, eds. *Dietary Proteins: How They Alleviate Disease and Promote Better Health.* Champaign, IL: American Oil Chemists' Society. Pp. 168–178.

Ward MH, Zahm SH, Weisenburger DD, Gridley G, Cantor KP, Saal RC, Blair A. 1994. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). *Cancer Causes Control* 5:422–432.

Waterlow JC. 1976. Classification and definition of protein-energy malnutrition. *Monogr Ser World Health Organ* 62:530–555.

Weisburger JH. 1988. Comparison of nutrition as customary in the Western World, the Orient, and northern populations (Eskimos) in relation to specific disease risk. *Arctic Med Res* 47:110–120.

West CE, Sullivan DR, Katan MB, Halferkamps IL, van der Torre HW. 1990. Boys from populations with high-carbohydrate intake have higher fasting triglyceride levels than boys from populations with high-fat intake. *Am J Epidemiol* 131:271–282.

West KM, Kalbfleisch JM. 1971. Influence of nutritional factors on prevalence of diabetes. *Diabetes* 20:99–108.

Westerterp KR, Verboeket-van de Venne WPHG, Westerterp-Plantenga MS, Velthuis-te Wierik EJM, de Graaf C, Weststrate JA. 1996. Dietary fat and body fat: An intervention study. *Int J Obes Relat Metab Disord* 20:1022–1026.

Whigham LD, Cook ME, Atkinson RL. 2000. Conjugated linoleic acid: Implications for human health. *Pharmacol Res* 42:503–510.

Whiting SJ, Anderson DJ, Weeks SJ. 1997. Calciuric effects of protein and potassium bicarbonate but not of sodium chloride or phosphate can be detected acutely in adult women and men. *Am J Clin Nutr* 65:1465–1472.

Willett WC. 1997. Specific fatty acids and risks of breast and prostate cancer: Dietary intake. *Am J Clin Nutr* 66:1557S–1563S.

Willett WC. 1998. Is dietary fat a major determinant of body fat? *Am J Clin Nutr* 67:556S–562S.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. 1987. Dietary fat and the risk of breast cancer. *N Engl J Med* 316:22–28.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. 1990. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 323:1664–1672.

Willett WC, Hunter DJ, Stampfer MJ, Colditz G, Manson JE, Spiegelman D, Rosner B, Hennekens CH, Speizer FE. 1992. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. *J Am Med Assoc* 268:2037–2044.

Williams CL, Bollella M. 1995. Is a high-fiber diet safe for children? *Pediatrics* 96:1014–1019.

Wisen O, Hellstrom PM, Johansson C. 1993. Meal energy density as a determinant of postprandial gastrointestinal adaptation in man. *Scand J Gastroenterol* 28:737–743.

Wisker E, Maltz A, Feldheim W. 1988. Metabolizable energy of diets low or high in dietary fiber from cereals when eaten by humans. *J Nutr* 118:945–952.

Wolfe BMJ, Piché LA. 1999. Replacement of carbohydrate by protein in a conventional-fat diet reduced cholesterol and triglyceride concentrations in healthy normolipidemic subjects. *Clin Invest Med* 22:140–148.

Wolk A, Bergström R, Hunter D, Willett W, Ljung H, Holmberg L, Bergkvist L, Bruce Å, Adami H-O. 1998. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. *Arch Intern Med* 158:41–45.

Wooley SC. 1972. Physiologic versus cognitive factors in short term food regulation in the obese and nonobese. *Psychosom Med* 34:62–68.

Wu Y, Zheng W, Sellars TA, Kushi LH, Bostick RM, Potter JD. 1994. Dietary cholesterol, fat, and lung cancer incidence among older women: The Iowa Women's Health Study (United States). *Cancer Causes Control* 5:395–400.

Yao M, Roberts SB. 2001. Dietary energy density and weight regulation. *Nutr Rev* 59:247–258.

Yeomans MR, Gray RW, Mitchell CJ, True S. 1997. Independent effects of palatability and within-meal pauses on intake and appetite ratings in human volunteers. *Appetite* 29:61–76.

Yost TJ, Jensen DR, Haugen BR, Eckel RH. 1998. Effect of dietary macronutrient composition on tissue-specific lipoprotein lipase activity and insulin action in normal-weight subjects. *Am J Clin Nutr* 68:296–302.

Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM. 1999. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: A meta-analysis. *Am J Clin Nutr* 69:632–646.

Zambell KL, Keim NL, Van Loan MD, Gale B, Benito P, Kelley DS, Nelson GJ. 2000. Conjugated linoleic acid supplementation in humans: Effects of body composition and energy expenditure. *Lipids* 35:777–782.

Zhang J, Sasaki S, Amano K, Kesteloot H. 1999. Fish consumption and mortality from all causes, ischemic heart disease, and stroke: An ecological study. *Prev Med* 28:520–529.

Ziboh VA, Fletcher MP. 1992. Dose-response effects of dietary γ-linolenic acid-enriched oils on human polymorphonuclear-neutrophil biosynthesis of leukotriene B_4. *Am J Clin Nutr* 55:39–45.

Zock PL, Katan MB. 1992. Hydrogenation alternatives: Effects of *trans* fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res* 33:399–410.

Zock PL, Katan MB. 1998. Linoleic acid intake and cancer risk: A review and meta-analysis. *Am J Clin Nutr* 68:142–153.

Zurier RB, Rossetti RG, Jacobson EW, DeMarco DM, Liu NY, Temming JE, White BM, Laposata M. 1996. Gamma-linolenic acid treatment of rheumatoid arthritis. A randomized, placebo-controlled trial. *Arthritis Rheum* 39:1808–1817.

12
Physical Activity

SUMMARY

Physical activity promotes health and vigor. Cross-sectional data from a doubly labeled water database were used to define a recommended level of physical activity, based on the physical activity level (PAL) associated with a normal body mass index (BMI) range of 18.5 to 25 kg/m^2. In addition to the activities identified with a sedentary lifestyle, an average of 60 minutes of daily moderate intensity physical activity (e.g., walking/jogging at 3 to 4 miles/hour) or shorter periods of more vigorous exertion (e.g., jogging for 30 minutes at 5.5 miles/hour) was associated with a normal BMI and therefore is recommended for normal-weight individuals. This amount of physical activity leads to an "active" lifestyle, corresponding to a PAL greater than 1.6 (see Chapter 5). Because the Dietary Reference Intakes are provided for the general healthy population, recommended levels of physical activity for weight loss of obese individuals are not provided.

For children, the physical activity recommendation is also an average of 60 minutes of moderate intensity daily activity. Increasing the energy expenditure of physical activity (EEPA) needs to be considered in determining the energy intake to achieve energy balance in weight stable adults, and adequate growth and development in children (Chapter 5). Body weight serves as the ultimate indicator of adequate energy intake. Increasing EEPA, or maintaining an active lifestyle provides an important means for individuals to balance food energy intake with total energy expenditure.

BACKGROUND INFORMATION

A distinction is made between physical activity[1] and exercise;[2] the latter is considered more vigorous and leads to improvements in physical fitness.[3] In qualitative terms, exercise can be defined as activity sufficiently vigorous to raise breathing to a level where conversation is labored and sweating is noticeable on temperate days. As indicated in Table 5-10, cross-sectional data indicated that the average physical activity level (PAL) among adults participating in the doubly labeled water (DLW) studies included in the DLW Database (Appendix I) was about 1.7, reflecting physical activity habits equivalent to walking 5 to 7 miles/day at 3 to 4 mph, in addition to the activities required by a sedentary lifestyle. Also regular physical activity may improve mood by reducing depression and anxiety, thereby enhancing the quality of life. The beneficial outcomes of regular physical activity and exercise appear to pertain to persons of all ages, and both women and men of diverse ethnic groups.

Throughout history, balancing dietary energy intake and total energy expenditure (TEE) has been accomplished unconsciously by most individuals because of the large component of occupation-related energy expenditure. Today, despite common knowledge that regular physical activity is healthful, more than 60 percent of Americans are not regularly physically active, and 25 percent are not active at all (HHS, 1996). It seems reasonable to anticipate continuation of the current trend for reductions in occupational physical activity and other energy expending activities of daily life. If this is to be offset by deliberately increasing voluntary physical activity, it needs to be kept in mind that in previously sedentary individuals adding periods of mild to moderate intensity exercise can unconsciously be compensated for by reducing other activities during the remainder of the day, so that TEE may be less affected than expected (Epstein and Wing, 1980; van Dale et al., 1989). Hence, to increase physical activity and to thereby facilitate weight control, recreational activities and physical training programs need to add, and not substitute for, other physical activities of daily life.

The trend for decreased activity by adults is similar to trends seen in children who are less active in and out of school (HHS, 1996). As both lack of physical activity and obesity are now recognized as risk factors for

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[1]Physical activity—Bodily movement that is produced by the contraction of muscle and that substantially increases energy expenditure (HHS, 1996).

[2]Exercise (exercise training)—Planned structured and repetitive bodily movement done to promote or maintain one or more components of physical fitness.

[3]Physical fitness—A set of attributes that people have that relates to the ability to perform physical activity.

several chronic diseases, logic requires that activity recommendations accompany dietary recommendations.

History of Physical Activity Recommendations

United States

In 1953, Kraus and Hirschland (1953) alerted health and fitness professionals, the general public, and President Dwight D. Eisenhower to the relatively poor physical condition of American youth. Their paper and other events led to the formation of the President's Council on Youth Fitness (HHS, 1996). Under President John F. Kennedy, the council was renamed the President's Council on Physical Fitness, and in 1965 it established five levels of physical fitness for adult men and women. Subsequently, the word "sports" was added to the title of the organization, making it the President's Council on Physical Fitness and Sports (HHS, 1996).

Recognizing relationships among blood lipids, diet, and physical activity, the American Heart Association (AHA) issued in 1972 the first of its handbooks and statements on the use of endurance exercise training and exercise testing for the diagnosis and prevention of heart disease (AHA, 1972). In 1978, the American College of Sports Medicine (ACSM) issued its position statement on cardio-respiratory fitness and body composition titled "The Recommended Quantity and Quality of Exercise for Developing and Maintaining Fitness in Healthy Adults" (ACSM, 1978). Subsequently, ACSM issued a series of guidelines for exercise testing and prescription (ACSM, 1980).

In 1979, agencies of the federal government became involved when the United States Department of Heath, Education, and Welfare (DHEW) issued *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention*, which recommended endurance exercise training (DHEW, 1979). In 1988, the U.S. Department of Heath and Human Services (HHS) issued *The Surgeon General's Report on Nutrition and Health*, which promoted endurance exercise as a means of weight control (HHS, 1988). Activities such as walking, jogging, and bicycling three times a week for 20 minutes were recommended.

That report was followed in 1990 by the U.S. Department of Agriculture (USDA)/Department of Health and Human Services *Dietary Guidelines for Americans*, which evaluated the role of activity in energy balance but did not offer specific exercise recommendations (USDA/HHS, 1990). In 1995, HHS issued the report *Healthy People 2000*, which listed health objectives for the nation, including an objective for physical activity and fitness (HHS, 1995). That same year, USDA and HHS updated *Dietary Guidelines for Americans* and recommended 30 minutes or more of moderate-intensity

physical activity preferably on all days of the week (USDA/HHS, 1995). In 1996 the HHS report *Physical Activity and Health: A Report of the Surgeon General* was published and offered specific recommendations for physical activity: a minimum of 30 minutes of moderate intensity on most, if not all, days of the week.

The 2000 *Dietary Guidelines for Americans* recommends that adults accumulate at least 30 minutes and children 60 minutes of moderate physical activity most days of the week, preferably daily (USDA/HHS, 2000). In addition, that report recommended combining sensible eating with regular physical activity and acknowledged that physical activity and nutrition work together for better health. Physical activity and fitness objectives of *Healthy People 2010* seek to increase the proportion of Americans that engage in daily physical activity to improve health, fitness, and quality of life (HHS, 2000).

Canada

In Canada, similar recommendations have been proposed. An early initiative was the Toronto International Conference on Physical Activity and Cardiovascular Health in 1966. Toronto was also the site of the 1988 International Consensus Conference on Exercise, Fitness and Health. In 1992, coinciding with Canada's 125th birthday, the Second International Conference on Physical Activity, Fitness, and Health was held. That meeting resulted in publication of the report, *Physical Activity, Fitness, and Health* (Bouchard et al., 1994).

Most recently, in cooperation with Health Canada and the Canadian Society of Exercise Physiology, *Canada's Physical Activity Guide to Healthy Active Living* has been published (Health Canada, 1998). This guide describes the benefits of regular physical activity and makes specific recommendations to improve fitness and achieve particular health-related outcomes such as decreasing the risk of premature death from chronic diseases (heart disease, obesity, high blood pressure, type II diabetes, osteoporosis, stroke, colon cancer, and depression). The recommendations include 60 minutes of "light effort" exercises (e.g., light walking, easy gardening), 30 to 60 minutes of "moderate effort" exercises (e.g., brisk walking, biking, swimming, water aerobics, leaf raking), or 20 to 30 minutes of "vigorous effort" exercises (e.g., aerobics, jogging, hockey, fast swimming, fast dancing, basketball). For moderate and vigorous activities, the Canadian recommendations are for 4 or more days per week and also include participation in flexibility activities (4–7 days per week) and strength activities (4–7 days per week).

PHYSICAL ACTIVITY LEVEL AND ENERGY BALANCE

Aside from dietary energy intake, energy expenditure of physical activity (EEPA) is the variable that a person can control, in contrast to age, height, and gender (Chapter 5). Energy expenditure can rise many times over resting rates during exercise, and the effects of an exercise bout on energy expenditure persist for hours, if not a day or longer (Benedict and Cathcart, 1913; Van Zant, 1992). Thus, changing activity level can have major impacts on total energy expenditure (TEE) and on energy balance. Further, exercise does not automatically increase appetite and energy intake in direct proportion to activity-related changes in energy expenditure (Blundell and King, 1998; Hubert et al., 1998; King et al., 1997). In humans and other mammals, energy intake is closely related to physical activity level when body mass is in the ideal range, but too little or too much exercise may disrupt hypothalamic and other mechanisms that regulate body mass (Mayer et al., 1954, 1956).

Impact of Physical Activity on Energy Expenditure and on PAL

Metabolic Equivalents (METs)

The impact of various physical activities is often described and compared in terms of METs (i.e., multiples of an individual's resting oxygen uptake), and one MET is defined as a rate of oxygen (O_2) consumption of 3.5 ml/kg/min in adults. Taking the oxygen energy equivalent of 5 kcal/L consumed, this corresponds to 0.0175 kcal/minute/kg (3.5 mL/min/kg × 0.005 kcal/mL). A rate of energy expenditure of 1.0 MET thus corresponds to 1.2 kcal/min in a man weighing 70 kg (0.0175 kcal/kg/minute × 70 kg) and to 1.0 kcal/minute in a woman weighing 57 kg (0.0175 kcal/kg/min × 57 kg) based on the reference body weights for adults in Table 1-1.

Knowing the intensity of a type of physical activity in terms of METs (see Table 12-1 for the METs for various activities) allows a simple assessment of its impact on the energy expended while the activity is performed (number of METs × minutes × 0.0175 kcal/kg/minute). However, as mentioned in Chapter 5, the increase in daily energy expenditure is somewhat greater because exercise induces an additional small increase in expenditure for some time after the exertion itself has been completed. This "excess post-exercise oxygen consumption" (EPOC) (Gaesser and Brooks, 1984) depends on exercise intensity and duration as well as other factors, such as the types and durations of activities in normal living; EPOC has been estimated at about 15 percent of the increment in expenditure that occurs during the exertion itself (Bahr et al., 1987). The thermic effect of food (TEF), which needs to be consumed to cover the expenditure associated

TABLE 12-1 Intensity and Impact of Various Activities on Physical Activity Level (PAL) in Adults[a]

Activity	Metabolic Equivalents (METs)[b]	ΔPAL/10 min[c]	ΔPAL/h[c]
Leisure			
Mild			
Billiards	2.4	0.013	0.08
Canoeing (leisurely)	2.5	0.014	0.09
Dancing (ballroom)	2.9	0.018	0.11
Golf (with cart)	2.5	0.014	0.09
Horseback riding (walking)	2.3	0.012	0.07
Playing			
Accordion	1.8	0.008	0.05
Cello	2.3	0.012	0.07
Flute	2.0	0.010	0.06
Piano	2.3	0.012	0.07
Violin	2.5	0.014	0.09
Volleyball (noncompetitive)	2.9	0.018	0.11
Walking (2 mph)	2.5	0.014	0.09
Moderate			
Calisthenics (no weight)	4.0	0.029	0.17
Cycling (leisurely)	3.5	0.024	0.14
Golf (without cart)	4.4	0.032	0.19
Swimming (slow)	4.5	0.033	0.20
Walking (3 mph)	3.3	0.022	0.13
Walking (4 mph)	4.5	0.033	0.20
Vigorous			
Chopping wood	4.9	0.037	0.22
Climbing hills (no load)	6.9	0.056	0.34
Climbing hills (5-kg load)	7.4	0.061	0.37
Cycling (moderately)	5.7	0.045	0.27
Dancing			
Aerobic or ballet	6.0	0.048	0.29
Ballroom (fast) or square	5.5	0.043	0.26
Jogging (10-min miles)	10.2	0.088	0.53
Rope skipping	12.0	0.105	0.63
Skating			
Ice	5.5	0.043	0.26
Roller	6.5	0.052	0.31
Skiing (water or downhill)	6.8	0.055	0.33
Squash	12.1	0.106	0.63
Surfing	6.0	0.048	0.29
Swimming	7.0	0.057	0.34
Tennis (doubles)	5.0	0.038	0.23
Walking (5 mph)	8.0	0.067	0.40

continued

TABLE 12-1 Continued

Activity	Metabolic Equivalents (METs)[b]	ΔPAL/10 min[c]	ΔPAL/h[c]
Activities of daily living			
Gardening (no lifting)	4.4	0.032	0.19
Household tasks, moderate effort	3.5	0.024	0.14
Lifting items continuously	4.0	0.029	0.17
Light activity while sitting	1.5	0.005	0.03
Loading/unloading car	3.0	0.019	0.11
Lying quietly	1.0	0.000	0.00
Mopping	3.5	0.024	0.14
Mowing lawn (power mower)	4.5	0.033	0.20
Raking lawn	4.0	0.029	0.17
Riding in a vehicle	1.0	0.000	0.00
Sitting	0.0	0.000	0.00
Taking out trash	3.0	0.019	0.11
Vacuuming	3.5	0.024	0.14
Walking the dog	3.0	0.019	0.11
Walking from house to car or bus	2.5	0.014	0.09
Watering plants	2.5	0.014	0.09

[a] PAL is the physical activity level that is the ratio of the total energy expenditure to the basal energy expenditure.
[b] METs are multiples of an individual's resting oxygen uptakes, defined as the rate of oxygen (O_2) consumption of 3.5 mL of O_2/min/kg body weight in adults.
[c] In the PAL shown here, an allowance has been made to include the delayed effect of physical activity in causing excess postexercise O_2 consumption and the dissipation of some of the food energy consumed through the thermic effect of food.
SOURCE: Adapted from Fletcher et al. (2001).

with a given activity, must also be taken into account. The TEF dissipates about 10 percent of the food energy consumed. The impact of a given activity on daily energy expenditure under conditions of energy balance thus includes the intensity of the physical activity in terms of METS, the EPOC, and the TEF and expressed as:

$$\text{\# of METs} \times \text{min} \times 0.022 \text{ kcal/kg/min} \times \text{kg body weight},$$

where 0.022 kcal/kg/min = 0.0175 kcal/kg/min × 1.15 percent (EPOC) ÷ 0.9 percent (TEF).

Bijnen and coworkers (1998) found that activities with METs greater than 4 are more effective than less intensive activities in reducing cardio-

vascular mortality. A rate of energy expenditure of 4.5 METs corresponds to the upper boundary for moderate activities (Table 12-1) and elicits an exertion that falls into the upper range of the percent of Vo_2max considered to reflect light physical activity intensity for 20- to 39-year-old adults, but falls into the lower range of moderate intensities in 40- to 64-year-old adults (Fletcher et al., 2001). A rate of exertion of 4.5 METs is reached, for example, by walking at a speed of 4 mph (Table 12-1).

Physical Activity Level (PAL)

While METs describe activity intensities relative to a resting metabolic rate (RMR), the physical activity level (PAL) is defined as the ratio of total energy expenditure (TEE) to basal energy expenditure (BEE). Thus, the actual impact on PAL depends to some extent on body size and age, as these are determinants of the BEE (Figure 12-1). The impact of these factors can be judged by examining the ratio of MET (extrapolated to 24 hours) to BEE. It is noteworthy that the errors that this introduces in the calculation of PAL values, at least over the normal range of body weights, is of minor importance in comparison to the very large uncertainties generally inherent in the assessment of the duration and intensity of physical activities in individuals and populations.

For a typical 30-year-old reference man and woman 1.77 m and 1.63 m in height and weighing 70 kg and 57 kg (Chapter 1, Table 1-1), BEEs are 1,684 and 1,312 kcal/day, respectively (calculated from the predictive BEE equations in Chapter 5. These correspond to 0.95 and 0.91 times the 1,764 and 1,436 kcal/day obtained by extrapolating a rate of 1.0 MET[4] to 24 hours for reference men and women (1,764 kcal/day = 1 MET × 1,440 min × 0.0175 kcal/kg/min × 70 kg and 1,436 kcal/day = 1 MET × 1,440 min × 0.0175 kcal/kg/min × 57 kg). The following equations, derived for reference body weights of 70 kg for men and 57 kg for women, were utilized to determine the change in PAL for each of the activities in Table 12-1.

$$\text{Men:} \quad \Delta\text{PAL} = (\text{\# of METs} - 1) \times 1.34 \times (\text{min}/1{,}440 \text{ min}),$$

where 1.34 = 1.15 percent (EPOC) ÷ 0.9 percent (TEF) ÷ 0.95 percent.[5]

$$\text{Women:} \quad \Delta\text{PAL} = (\text{\# of METs} - 1) \times 1.42 \times (\text{min}/1{,}440 \text{ min}),$$

where 1.42 = 1.15 percent (EPOC) ÷ 0.9 percent (TEF) ÷ 0.91.[5]

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[4]Defined as 0.0175 kcal/kg/min.
[5]Correction to cover EPOC and TEF.

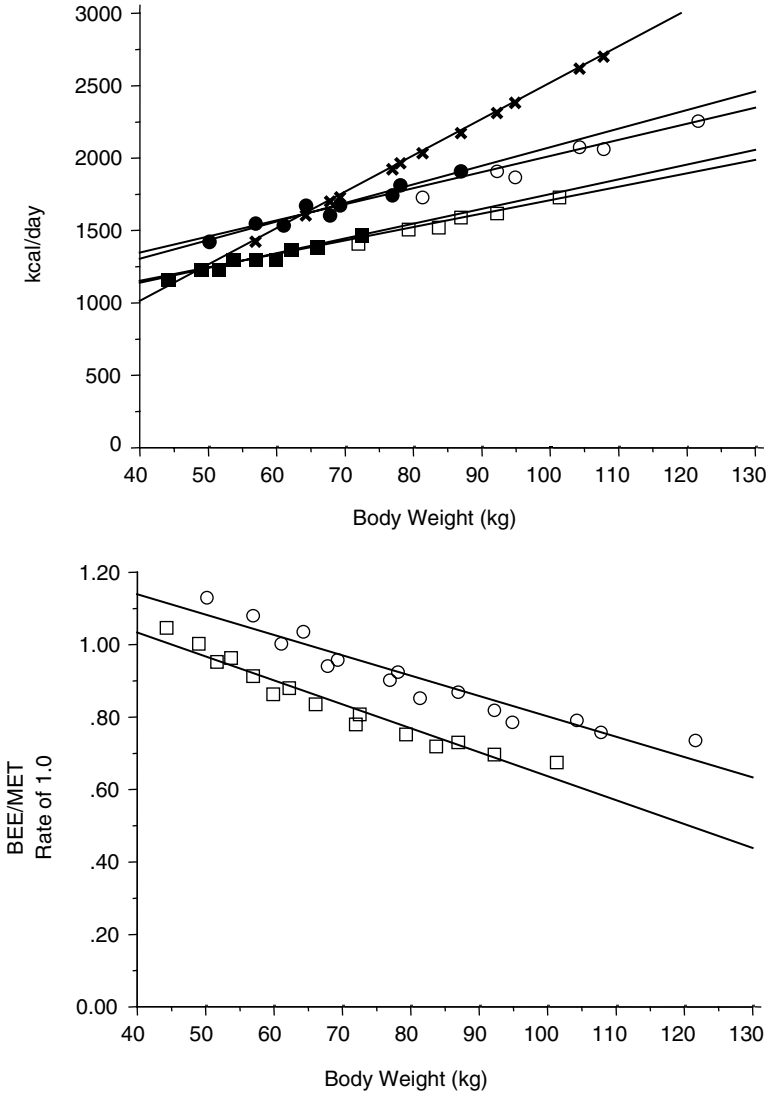

FIGURE 12-1 Relationship of basal energy expenditure (BEE), metabolic equivalents rate and body weight in 30-year-old adults. The upper panel shows the impact of body weight on BEE in men (○) and women (□) and on a MET-rate of 1.0 (×) extrapolated to 24 h. Points with body mass indexes (BMIs) from 18.5 up to 25 kg/m^2 are filled in. The lower panel shows the ratio of BEE divided by an MET rate of 1.0 for a given body weight for men (○) with reference heights of 1.75 m or reference height ± 1 standard deviation (i.e., 1.64 or 1.86 m), and for women (□) with reference heights of 1.62 m or reference height ± 1 standard deviation (i.e., 1.55 or 1.70 m), and BMI of 18.5, 22.5 (men) or 21.5 (women), 25, 30, and 35 kg/m^2.

The coefficients given in Table 12-1 can then be used to arrive at an estimate of an individual's PAL by cumulating the effects of the various activities performed on the basis of their duration and intensities (see below, "Physical Activity for Adults").

Because it is the most significant physical activity in the life of most individuals, walking/jogging is taken as the reference activity, and the impact of other activities can be considered in terms of exertions equivalent to walking/jogging, to the extent that these activities are weight bearing and hence involve costs proportional to body weight. The effect of walking/jogging on energy expenditure at various speeds is given in Table 12-1 in terms of METs and is also shown in the upper panel of Figure 12-2. The middle panel describes the energy expended in kcal/hour for walking or jogging at various speeds by individuals weighing 70 or 57 kg (the reference body weights for men and women, respectively from Table 1-1. The figure's lower panel describes the total cost of walking or jogging one mile at various speeds, including the increments in energy expenditure above the resting rate during and after walking or jogging plus a commensurate increase in TEF. The energy expended per mile walked or jogged is essentially constant at speeds ranging from 2 to 4 miles/hour (1 kcal/mile/kg for a man [70 kcal/mile/70 kg] to 1.1 kcal/mile/kg for a woman [65 kcal/mile/57 kg], or approximately 1.1 kcal/mile/kg body weight; lower panel, Figure 12-2), but increases progressively at higher speeds.

According to the formulas shown above, walking at a speed of 4 mph (4.5 METs, upper panel, Figure 12-2) for 60 minutes causes an increase in the daily ΔPAL of 0.195 ([4.5 METs – 1] × 1.34 × 60 min/1,440 min) in men and 0.204 ([4.5 METs – 1] × 1.42 × 60 min/1,440 min) in women, or a ΔPAL of approximately 0.20 as given in Table 12-1. Walking or jogging at speeds of 4.5 mph raises the metabolic rate to 6 METS (upper panel, Figure 12-2), increasing the impact on changing the daily PAL by half to 0.30 for sixty minutes (ΔPAL in men = [6 METs – 1] × 1.34 × 60 min/1,440 min = 0.279, ΔPAL in women = [6 METs – 1] × 1.42 × 60 min/1,440 min = 0.296). Indeed, walking or jogging to cover 4.5 miles in 60 minutes, at a cost of 107 kcal/mile (lower panel, Figure 12-2) or 1.53 kcal/mile/kg (107 kcal/mile ÷ 70 kg) in men, or performing some equally demanding activity for 60 minutes, will cause an increase in PAL of approximately 0.30.

Impact of Body Weight on Energy Expenditure

The impact of body weight on energy expenditure while walking at various speeds is illustrated in Figure 12-3, while Figure 12-4 describes how body weight affects the total increase in energy expenditure caused by

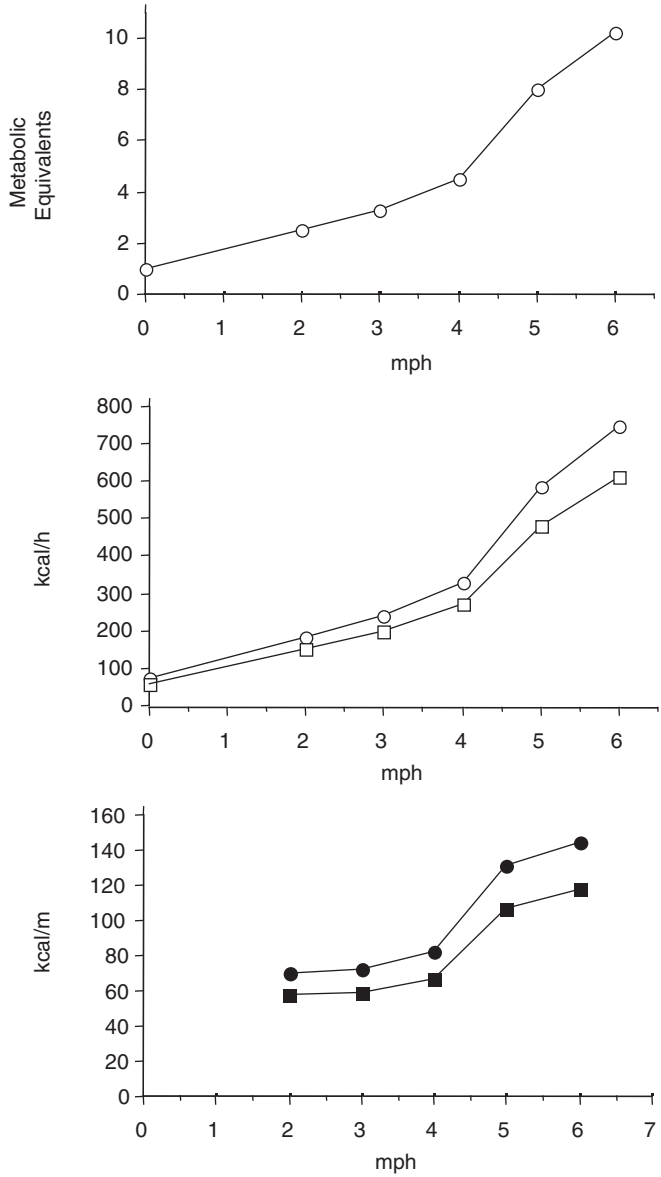

FIGURE 12-2 Relationships of energy expenditure and walking/jogging speeds. The upper panel shows the rate of energy expenditure as a function of walking/jogging speed. The middle panel shows the energy expended by a 70-kg man (○) and by a 57-kg woman (□) while walking/jogging 1 h at various speeds. The lower panel shows the increase in daily energy expenditure induced by walking/jogging 1 m at various speeds for a 70-kg man (●) and a 57-kg woman (■).

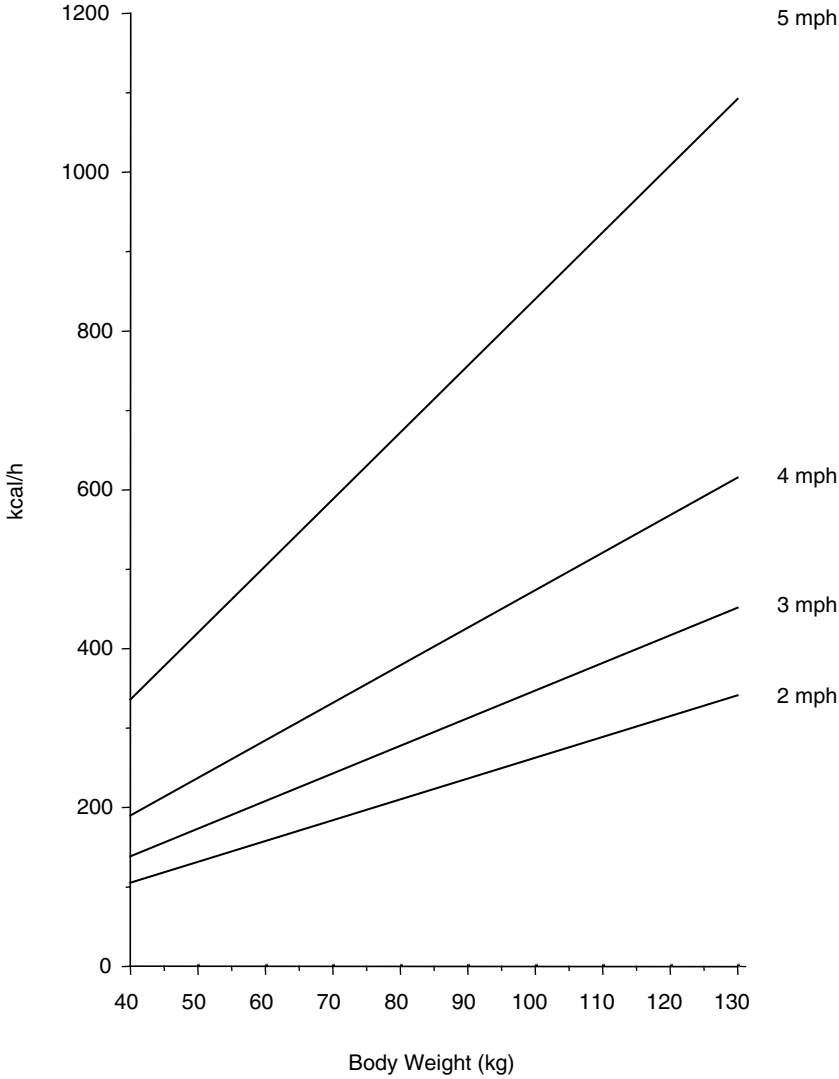

FIGURE 12-3 Impact of body weight on energy expenditure while walking at speeds of 2, 3, 4, or 5 mph.

walking one mile at various speeds. Figures 12-5 for men and 12-6 for women show how body weight influences how far and for how many minutes adults must walk at speeds of 2, 3, 4, or 5 mph (or to engage in activities rated as MET = 2.5, 3.3, 4.5, or 8.0) to raise the PAL level by 0.10. These figures also describe the effect of more demanding physical activity,

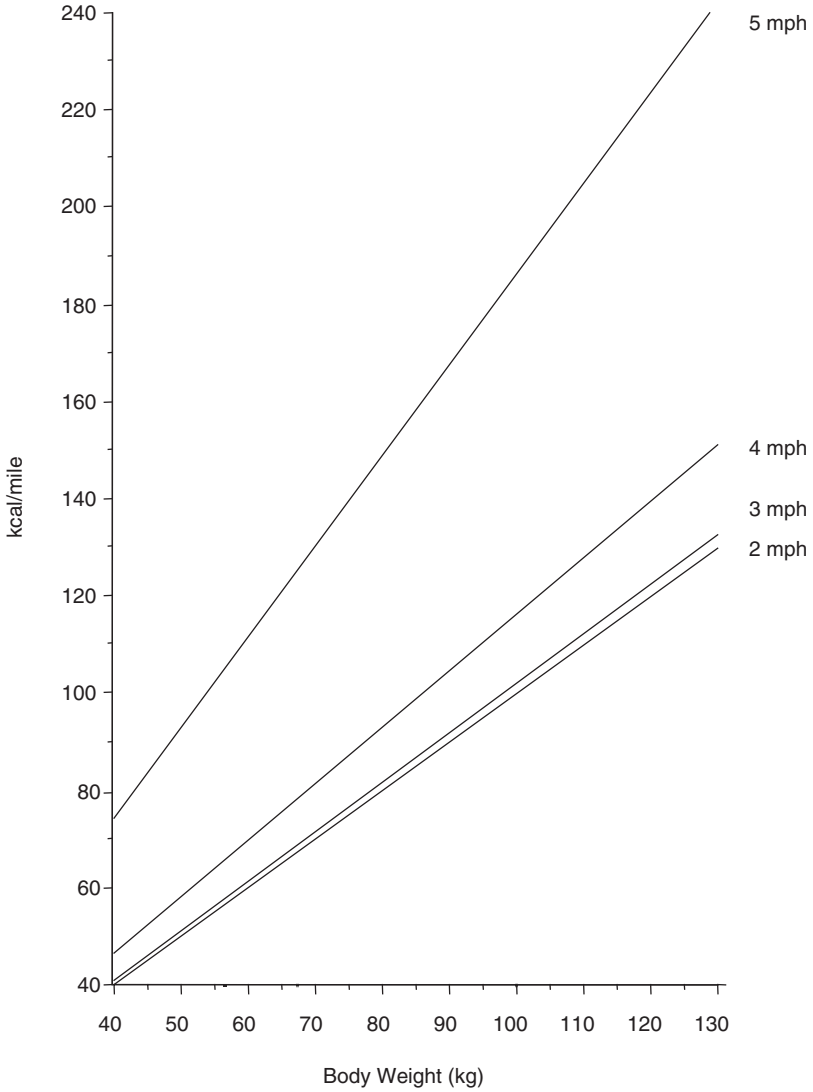

FIGURE 12-4 Impact of body weight on energy cost of walking 1 mile at speeds of 2, 3, 4, or 5 mph in men and women.

such as running at speeds of 6 or 8 mph, corresponding to exertions at 10.2 or 13.5 METs. While the effect on TEE/miles covered does not increase substantially as fast walking (5 mph) changes to jogging (6 mph) and running (8 mph) (upper panels of Figures 12-5 and 12-6), the time required for a given impact on PAL is reduced. This illustrates that high

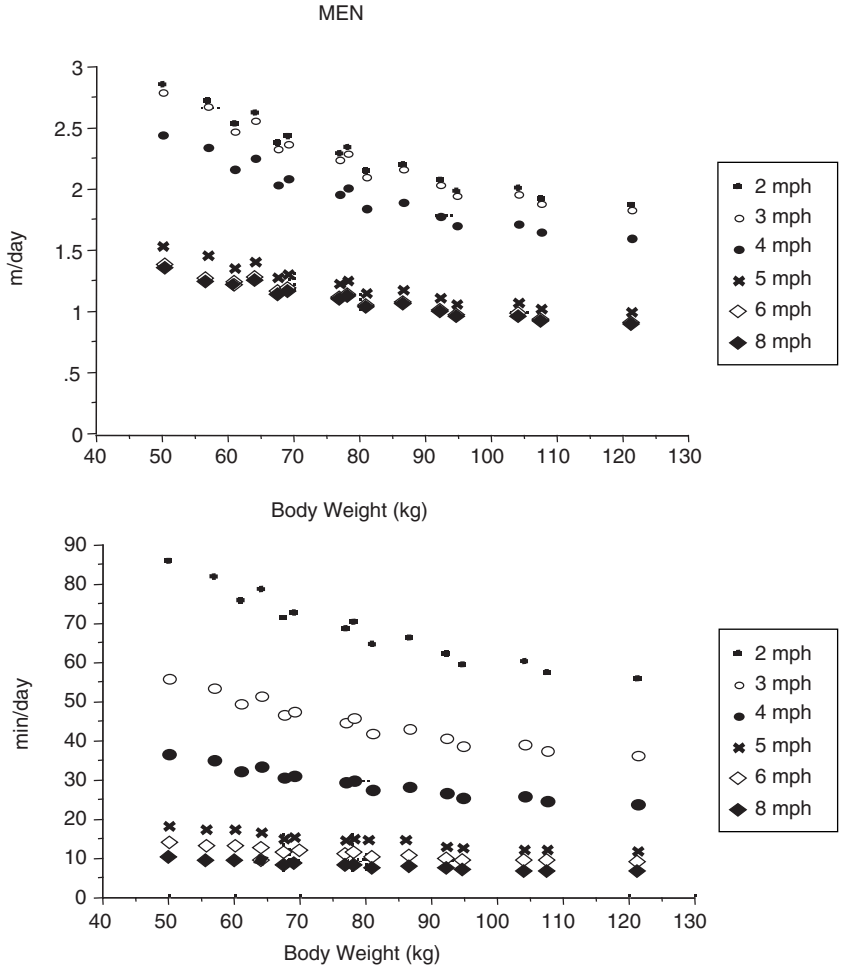

FIGURE 12-5 Distance to cover per day for men to raise physical activity level (PAL) value by 0.10 while walking or running at various speeds (upper panel) and time required to do so (lower panel). The points shown are for men with reference heights of 1.75 m or reference heights ± 1 standard deviation (i.e., 1.64 m or 1.86 m) and body mass index of 18.5, 22.5, 25, 30, or 35 kg/m^2. Energy expenditures while walking or running at speeds of 2, 3, 4, 5, or 8 mph are 2.5, 3.3, 4.5, 8.0, 10.2, and 13.5 metabolic equivalents (METs), respectively (Fletcher et al., 2001). The impact on ΔPAL was calculated as (MET – 1.0) × minutes × 1.15 ÷ 0.9 (where 1.15 accounts for excess [~15%] post-exercise oxygen consumption [Bahr et al., 1987] and 0.9 accounts for a 10% dissipation of food energy consumed by the thermic effect of food) and related to predicted basal energy expenditures for 30-year-old men calculated from the predictive basal energy expenditure equations in Chapter 5; see "Estimation of Energy Expenditure in Normal and Overweight/Obese Adults."

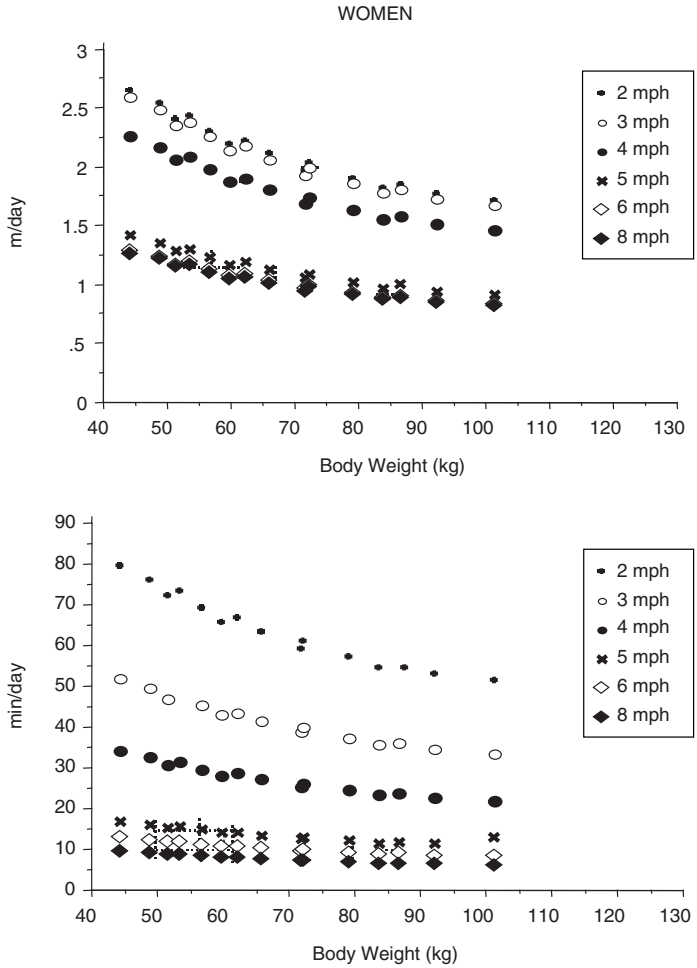

FIGURE 12-6 Distance to cover per day for women to raise physical activity level (PAL) value by 0.10 while walking or running at various speeds (upper panel) and time required to do so (lower panel). The points shown are for women with reference heights of 1.62 m or reference heights ± 1 standard deviation (i.e., 1.55 m or 1.70 m) and a body mass index of 18.5, 22.5, 25, 30, or 35 kg/m^2. Energy expenditures while walking or running at speeds of 2, 3, 4, 5, or 8 mph are 2.5, 3.3, 4.5, 8.0, 10.2, and 13.5 metabolic equivalents (METs), respectively (Fletcher et al., 2001). The impact on ΔPAL was calculated as (MET – 1.0) × minutes × 1.15 ÷ 0.9 (where 1.15 accounts for excess [~15%] post-exercise oxygen consumption [Bahr et al., 1987] and 0.9 accounts for a 10 percent dissipation of food energy consumed by the thermic effect of food) and related to predicted basal energy expenditures for 30-year-old women calculated from the predictive basal energy expenditure (BEE) equations in Chapter 5; see "Estimation of Energy Expenditure in Normal and Overweight/Obese Adults."

intensity activities must be included to achieve high PAL levels if the time spent exercising is to remain within a certain range. Cross-sectional data from a doubly labeled water database indicate that the PALs are similar for normal weight and obese individuals (Tables 5-10 and 5-11). While this is true, because energy expenditure increases with increasing body weight, there is a greater total daily energy expenditure in obese subjects (Table 5-10 and 5-11).

Physical Activity for Adults

The rationale for categorizing the cross-sectional data on adults in the doubly labeled water (DLW) database by PAL (Appendix Table I-3), as sedentary (PAL ≥ 1.0 < 1.4), low active (PAL ≥ 1.4 < 1.6), active (PAL ≥ 1.6 < 1.9), and very active (PAL ≥ 1.9 < 2.5) categories is provided in Chapter 5. Ideally, PAL of an individual can be determined from DLW studies; however, in nonexperimental situations, heart rate monitors, accelerometers, and other devices as well as activity inventories can be used. As explained earlier, the PAL coefficients in Tables 12-1 to 12-3 are based on rates of energy expenditure during physical activity reported in terms of METs, with an allowance for the EPOC induced by physical activities and the TEF that needs to be consumed to cover the overall cost of these activities.

Table 12-2 shows how adults can use the information presented in Table 12-1 to evaluate their PAL based on their daily activities. In the example shown in Table 12-2, the "sedentary" column illustrates the impact of an adult's typical daily living activities on the PAL ratio of TEE:BEE. This activity-induced increase in PAL of 0.29 is to be added to a base value of 1.1, which represents the BEE of 1.0 to which 10 percent has been added to account for the dissipation of energy due to the TEF that needs to be consumed to cover BEE. This adds up to a sedentary PAL value of 1.39, which corresponds to a sedentary lifestyle (PAL ≥ 1.0 < 1.4). Incorporating a 30 min/day walk at a speed of 4 mph raises the PAL to 1.49 ("low active" column), which corresponds to a low active lifestyle (PAL ≥ 1.4 < 1.6). If in addition to walking 30 min/day at a speed of 4 mph, an adult cycled moderately for another 25 minutes and played tennis for 40 minutes, the PAL would increase to 1.75 (the first "active" column), which reflects an active lifestyle (PAL ≥ 1.6 < 1.9). The second "active" column illustrates a mix of activities as reflected by the average time spent per day on various forms of activity and exercise. Finally, the "very active" column describes a level of activity corresponding to a PAL of 2.06, indicative of a very active lifestyle (PAL ≥ 1.9 < 2.5).

Because activities vary greatly from day to day, a person's PAL can be more accurately evaluated from a meticulous activity log maintained over a period of a week or more. The example in Table 12-3 describes an adult

TABLE 12-2 Intensity and Impact of Various Activities on Physical Activity Level (PAL) Estimations (Daily Example)

Activity	METs[a]	ΔPAL/ 10 min	ΔPAL/h
Leisure			
Mild			
Billiards	2.4	0.013	0.08
Canoeing (leisurely)	2.5	0.014	0.09
Dancing (ballroom)	2.9	0.018	0.11
Golf (with cart)	2.5	0.014	0.09
Horseback riding (walking)	2.3	0.012	0.07
Playing			
Accordion	1.8	0.008	0.05
Cello	2.3	0.012	0.07
Flute	2.0	0.01	0.06
Piano	2.3	0.012	0.07
Violin	2.5	0.014	0.09
Volleyball (noncompetitive)	2.9	0.018	0.11
Walking (2 mph)	2.5	0.014	0.09
Moderate			
Calisthenics (no weight)	4.0	0.029	0.17
Cycling (leisurely)	3.5	0.024	0.14
Golf (without cart)	4.4	0.032	0.19
Swimming (slow)	4.5	0.033	0.20
Walking (3 mph)	3.3	0.022	0.13
Walking (4 mph)	4.5	0.033	0.20
Vigorous			
Chopping wood	4.9	0.037	0.22
Climbing hills (no load)	6.9	0.056	0.34
Climbing hills (5-kg load)	7.4	0.061	0.37
Cycling (moderately)	5.7	0.045	0.27
Dancing			
Aerobic or ballet	6.0	0.048	0.29
Ballroom (fast) or square	5.5	0.043	0.26
Jogging (10-min miles)	10.2	0.088	0.53
Rope skipping	12.0	0.105	0.63
Skating			
Ice	5.5	0.043	0.26
Roller	6.5	0.052	0.31
Skiing (water or downhill)	6.8	0.055	0.33
Squash	12.1	0.106	0.63
Surfing	6.0	0.048	0.29
Swimming	7.0	0.057	0.34
Tennis (doubles)	5.0	0.038	0.23
Walking (5 mph)	8.0	0.067	0.40

Sedentary[b]		Low Active[b]		Active[b]		Active (Mix)[b]		Very Active[b]	
Min ΔPAL		Min ΔPAL		Min ΔPAL		Avg Min ΔPAL		Min ΔPAL	
						10	0.014		
						10	0.012		
						10	0.012		
						10	0.029		
						10	0.032		
						10	0.022		
		30	0.099	30	0.099	10	0.033		
				25	0.113			45	0.203
						10	0.088	15	0.132
								10	0.105
						10	0.057		
				40	0.152	20	0.076	60	0.228

continued

TABLE 12-2 Continued

Activity	METs[a]	ΔPAL/ 10 min	ΔPAL/h
Activities of daily living			
Gardening (no lifting)	4.4	0.032	0.19
Household tasks, moderate effort	3.5	0.024	0.14
Lifting items continuously	4.0	0.029	0.17
Light activity while sitting	1.5	0.005	0.03
Loading/unloading car	3.0	0.019	0.11
Lying quietly	1.0	0	0
Mopping	3.5	0.024	0.14
Mowing lawn (power mower)	4.5	0.033	0.20
Raking lawn	4.0	0.029	0.17
Riding in a vehicle	1.0	0	0
Taking out trash	3.0	0.019	0.11
Vacuuming	3.5	0.024	0.14
Walking the dog	3.0	0.019	0.11
Walking from house to car or bus	2.5	0.014	0.09
Watering plants	2.5	0.014	0.09
ΔPAL/day due to activities of daily living			
Sedentary PAL = basal energy expenditure (BEE) + thermic effect of food (0.1 × BEE) + sedentary activities =			
ΔPAL due to exercise and leisure activities		ΔPAL /day	
		PAL =	

[a] METs are multiples of an individual's resting oxygen (O_2) uptake, defined as a rate of O_2 consumption of 3.5 mL of O_2/min/kg body weight in adults.

whose activities of daily living raises energy expenditure to a sedentary PAL of 1.39 (PAL ≥ 1.0 < 1.4). If the individual recorded all additional activities over the week and added all of the ΔPALs for each of the activities performed as shown in Table 12-3, the adult would have had a mean increase in PAL of 0.65/day above basal expenditure. Thus, when added to the PAL of 1.1 (representing a base BEE value of 1.0 + 10 percent for TEF), this individual would move into the "active" category with a PAL of 1.75 (PAL ≥ 1.6 < 1.9).

A somewhat simplified approach, instead of recording all activities, would be to evaluate whether the level of daily living activities is comparable to that depicted in Tables 12-2 and 12-3. If they are, then a log of daily activities may be kept, and their average ΔPAL could be added to the PAL value (1.39) corresponding to that for a sedentary lifestyle in the example in Tables 12-2 and 12-3.

Sedentary[b]		Low Active[b]		Active[b]		Active (Mix)[b]		Very Active[b]	
Min	ΔPAL	Min	ΔPAL	Min	ΔPAL	Avg Min	ΔPAL	Min	ΔPAL
25	0.060	25	0.060	25	0.060	25	0.060	25	0.060
120	0.060	120	0.060	120	0.060	120	0.060	120	0.060
5	0.010	5	0.010	5	0.010	5	0.010	5	0.010
10	0.024	10	0.024	10	0.024	10	0.024	10	0.024
10	0.029	10	0.029	10	0.029	10	0.029	10	0.029
5	0.010	5	0.010	5	0.010	5	0.010	5	0.010
10	0.024	10	0.024	10	0.024	10	0.024	10	0.024
15	0.029	15	0.029	15	0.029	15	0.029	15	0.029
20	0.028	20	0.028	20	0.028	20	0.028	20	0.028
12	0.017	12	0.017	12	0.017	12	0.017	12	0.017
	0.29		0.29		0.29		0.29		0.29
	1.39		1.39		1.39		1.39		1.39
			0.10		0.36		0.38		0.67
	1.39		**1.49**		**1.75**		**1.77**		**2.06**

[b] PAL levels are Sedentary: PAL ≥ 1.0 < 1.4; Low Active: PAL ≥ 1.4 < 1.6; Active: PAL ≥ 1.6 < 1.9; Active (Mix): PAL ≥ 1.6 < 1.9; Very Active: PAL ≥ 1.9 < 2.5.

The factorial approach summations of various estimates of activities and durations applied in Tables 12-2 and 12-3 to evaluate energy turnover is more convenient than previous procedures inasmuch as it is applicable without making reference to body weight, as required, though often ignored, in estimating increments in energy expenditure in terms of their cost in kcal. Furthermore, the ΔPAL coefficients in Table 12-1 include an appropriate allowance for EPOC and TEF, whose effects are commonly disregarded when evaluating energy turnover. However, it must be remembered that the reliability of evaluations of overall energy expenditure and ΔPALs depends greatly on the accuracy of the activity estimates or activity logs and on whether they were obtained during a period representative of the habitual lifestyle. Because intentional and spontaneous activities are interrelated, assessing ΔPALs of individuals and populations can be more difficult. From the standpoint of energetics, any activity raises metabolic

TABLE 12-3 Weekly Activities and Their Impact on Physical Activity Level (PAL) in an Active Individual (Weekly Activity Log)

Activity	METs[a]	ΔPAL/ 10 min	ΔPAL/h
Leisure			
Mild			
Billiards	2.4	0.013	0.08
Canoeing (leisurely)	2.5	0.014	0.09
Dancing (ballroom)	2.9	0.018	0.11
Golf (with cart)	2.5	0.014	0.09
Horseback riding (walking)	2.3	0.012	0.07
Playing			
Accordion	1.8	0.008	0.05
Cello	2.3	0.012	0.07
Flute	2.0	0.010	0.06
Piano	2.3	0.012	0.07
Violin	2.5	0.014	0.09
Volleyball (noncompetitive)	2.9	0.018	0.11
Walking (2 mph)	2.5	0.014	0.09
Moderate			
Calisthenics (no weight)	4.0	0.029	0.17
Cycling (leisurely)	3.5	0.024	0.14
Golf (without cart)	4.4	0.032	0.19
Swimming (slow)	4.5	0.033	0.2
Walking (3 mph)	3.3	0.022	0.13
Walking (4 mph)	4.5	0.033	0.2
Vigorous			
Chopping wood	4.9	0.037	0.22
Climbing hills (no load)	6.9	0.056	0.34
Climbing hills (5-kg load)	7.4	0.061	0.37
Cycling (moderately)	5.7	0.045	0.27
Dancing			
Aerobic or ballet	6.0	0.048	0.29
Ballroom (fast) or square	5.5	0.043	0.26
Jogging (10-min miles)	10.2	0.088	0.53
Rope skipping	12.0	0.105	0.63
Skating			
Ice	5.5	0.043	0.26
Roller	6.5	0.052	0.31
Skiing (water or downhill)	6.8	0.055	0.33
Squash	12.1	0.106	0.63
Surfing	6.0	0.048	0.29
Swimming	7.0	0.057	0.34
Tennis (doubles)	5.0	0.038	0.23
Walking (5 mph)	8.0	0.670	0.40

Weekly Activity Log								
Day 1 (min)	Day 2 (min)	Day 3 (min)	Day 4 (min)	Day 5 (min)	Day 6 (min)	Day 7 (min)	Total Minutes	ΔPAL
				20			20	0.036
	30					60	90	0.105
15					10		25	0.030
				50			50	0.092
					80		80	0.253
60							60	0.130
		50					50	0.167
						100	100	0.617
			40				40	0.180
		20		10			30	0.265
		30					30	0.170
	60				60		120	0.460

continued

TABLE 12-3 Continued

Activity	METs[a]	ΔPAL/ 10 min	ΔPAL/h
Activities of daily living			
Gardening (no lifting)	4.4	0.032	0.19
Household tasks, moderate effort	3.5	0.024	0.14
Lifting items continuously	4.0	0.029	0.17
Light activity while sitting	1.5	0.005	0.03
Loading/unloading car	3.0	0.019	0.11
Lying quietly	1.0	0	0
Mopping	3.5	0.024	0.14
Mowing lawn (power mower)	4.5	0.033	0.2
Raking lawn	4.0	0.029	0.17
Riding in a vehicle	1.0	0	0
Taking out trash	3.0	0.019	0.11
Vacuuming	3.5	0.024	0.14
Walking the dog	3.0	0.019	0.11
Walking from house to car or bus	2.5	0.014	0.09
Watering plants	2.5	0.014	0.09
Min spent on daily living activities			
Min spent on daily leisure activities and exercise			

[a] METs are multiples of an individual's resting oxygen (O_2) uptake, defined as a rate of O_2 consumption of 3.5 mL of O_2/min/kg body weight in adults.

rate over basal and thus helps in raising energy expenditure. Some activities, such as fidgeting, are spontaneous and can have variable effects on TEE (see Chapter 5 "Spontaneous Non-Exercise Activity"). In room calorimeters, the metabolic costs of unintentional, nondirected activities can be quantified (Ravussin et al., 1986).

Physical Activity for Children

Measurements of the energy expended in various activities are much more limited in children than adults. Torun (1990) compiled the energy expenditure of several common activities in children from 28 studies and expressed the data as multiples of basal metabolic rate (BMR). The activities

Weekly Activity Log								
Day 1 (min)	Day 2 (min)	Day 3 (min)	Day 4 (min)	Day 5 (min)	Day 6 (min)	Day 7 (min)	Total Minutes	ΔPAL
10	30	20	40	10	20	20	150	0.350
160	160	180	160	160	90	90	1,000	0.500
				10	10	20	40	0.073
	20			10		10	40	0.093
			50				50	0.165
20					20		40	0.113
					20		20	0.038
30				30			60	0.140
	30			45		30	105	0.193
30	30	30	30	30	20	20	190	0.285
			30			20	50	0.075
250	270	230	310	295	180	210	1,745	2.025
75	90	100	40	80	150	160	695	2.505
				ΔPAL/week = 2.025 + 2.505 = 4.530				
				mean ΔPAL/day = 4.53/7 = 0.65				
				mean PAL = 1.1 + mean ΔPAL/day = 1.75				

were classified into 10 categories as shown in Tables 12-4 (Boys) and 12-5 (Girls). When the data are expressed as multiples of BMR, the values are similar for boys and girls. There are no age-related differences for sedentary activities (lying awake, sitting), but the values for walking and moving around increases from early childhood to adolescence. Kimm and colleagues (2002) reported a decline in physical activity in girls during adolescence. The impact of performing various activities for 10 and 60 minutes on PAL also are shown for children in Tables 12-4 and 12-5. The use of MET values for various activities measured in adults leads to errors that increase with decreasing age in children.

To classify children into PAL categories, judgment must be made on their PAL. In Tables 12-6 and 12-7, the differences in energy expenditure

TABLE 12-4 Various Activities: Intensity and Impacts on Physical Activity Level (PAL) in Children (Boys)

	Energy Expenditure (kcal/kg/min)					Energy expenditure of categories of activity at different ages expressed as multiples of BMR (Torun, 1990)				
Age (y)	1.5–6	7–12	13–14	15–16	17–19	1.5–6	7–12	13–14	15–16	17–19
Activity										
Lying awake	0.046	0.035	0.026	0.024	0.020	1.1	1.1	1.0	1.1	1.1
Sitting quietly	0.047	0.037	0.028	0.028	0.026	1.2	1.2	1.1	1.2	1.4
Standing quietly			0.029	0.033	0.027			1.3	1.5	1.5
Standing, moderate movement		0.069	0.052	0.052			2.2	2.1	2.4	
Walking, free velocity, level ground	0.078	0.078	0.066	0.066	0.053	2.1	2.9	2.8	3.3	3.1
Walking, fast, uphill or with load	0.098	0.110	0.103	0.094		2.6	3.4	3.8	4.4	
At school or light work		0.055–0.084			0.030		1.9–3.0			1.7
Light and moderate housework										
Leisure and moderate play	0.073–0.094	0.061–0.126	0.056–0.075	0.054		1.9–2.5	2.3–4.7	2.5–3.3	2.5	
Running, exercise sports			0.068–0.132	0.067	0.072–0.099			3.1–5.6	3.6	3.9–5.4

TABLE 12-5 Various Activities: Intensity and Impacts on Physical Activity Level (PAL) in Children (Girls)

	Energy Expenditure (kcal/kg/min)					Energy expenditure of categories of activity at different ages expressed as multiples of BMR (Torun, 1990)				
Age (y)	1.5–6	7–12	13–14	15–16	17–19	1.5–6	7–12	13–14	15–16	17–19
Activity										
Lying awake	0.046			0.018	0.018	1.1			1.1	1.1
Sitting quietly	0.047	0.032	0.027	0.021	0.021	1.2	1.2	1.4	1.2	1.2
Standing quietly			0.028	0.024	0.024			1.4	1.4	1.4
Standing, moderate movement										
Walking, free velocity, level ground	0.078	0.068	0.059	0.057	0.057	2.1	2.7	3.2	3.4	3.4
Walking, fast, uphill or with load	0.098					2.6				
At school or light work				0.026–0.031	0.026–0.031				1.6–1.8	1.6–1.8
Light and moderate housework				0.046–0.058	0.046–0.058				2.9–3.6	2.9–3.6
Leisure and moderate play	0.073–0.094			0.032–0.050	0.032–0.050	1.9–2.5			1.9–3.1	1.9–3.1
Running, exercise sports				0.067–0.100	0.067–0.100				3.9–5.9	3.9–5.9

ΔPAL/10 min					ΔPAL/60 min				
1.5–6	7–12	13–14	15–16	17–19	1.5–6	7–12	13–14	15–16	17–19
0.0009	0.0009	0.0000	0.0009	0.0009	0.0053	0.0053	0.0000	0.0053	0.0053
0.0018	0.0018	0.0009	0.0018	0.0036	0.0107	0.0107	0.0053	0.0107	0.0213
		0.0027	0.0044	0.0044			0.0160	0.0266	0.0266
	0.0107	0.0098	0.0124			0.0639	0.0586	0.0746	
0.0098	0.0169	0.0160	0.0204	0.0186	0.0586	0.1012	0.0959	0.1225	0.1118
0.0142	0.0213	0.0249	0.0302		0.0852	0.1278	0.1491	0.1811	
	0.008–0.018			0.0062		0.048–0.108			0.0373
0.008–0.013	0.012–0.033	0.013–0.020	0.0133		0.048–0.078	0.072–0.198	0.078–0.120	0.0799	
		0.019–0.041	0.0231	0.026–0.039			0.114–0.246	0.1385	

ΔPAL/10 min					ΔPAL/60 min				
1.5–6	7–12	13–14	15–16	17–19	1.5–6	7–12	13–14	15–16	17–19
0.0009			0.0009	0.0009	0.0053			0.0053	0.0053
0.0018	0.0018	0.0036	0.0018	0.0018	0.0107	0.0107	0.0213	0.0107	0.0107
		0.0036	0.0036	0.0036			0.0213	0.0213	0.0213
0.0098	0.0151	0.0195	0.0213	0.0213	0.0586	0.0905	0.1172	0.1278	0.1278
0.0142					0.0852				
			0.005–0.007	0.005–0.007				0.030–0.042	0.030–0.042
			0.017–0.023	0.017–0.023				0.102–0.138	0.102–0.138
0.008–0.013			0.008–0.019	0.008–0.019	0.048–0.078			0.048–0.114	0.048–0.114
			0.026–0.043	0.026–0.043				0.156-0.258	0.156-0.258

TABLE 12-6 Total Energy Expenditure (TEE) in Boys and Walking Times at Speeds of 2.5 mph to Move to the Next Higher Physical Activity Level (PAL)

						TEE (kcal/d)				PAL
Age (y)	Weight (kg)[a]	Height (m)[a]	BEE (kcal/d)[b]	BEE METs (kcal/kg/min)[c]	BEE METs (kcal/kg/hr)	Sedentary PAL[d]	Low Active PAL[d]	Active PAL[d]	Very Active PAL[d]	Low Active PAL[e]
3	14.3	0.95	889	0.043	2.59	1,142	1,304	1,465	1,663	1.47
4	16.2	1.02	935	0.040	2.40	1,195	1,370	1,546	1,763	1.47
5	18.4	1.09	985	0.037	2.23	1,255	1,446	1,638	1,874	1.47
6	20.7	1.15	1,030	0.035	2.07	1,308	1,515	1,722	1,977	1.47
7	23.1	1.22	1,084	0.033	1.95	1,373	1,597	1,820	2,095	1.47
8	25.6	1.28	1,132	0.031	1.84	1,433	1,672	1,911	2,205	1.48
9	28.6	1.34	1,187	0.029	1.73	1,505	1,762	2,018	2,334	1.48
10	31.9	1.39	1,240	0.027	1.62	1,576	1,850	2,124	2,461	1.49
11	35.9	1.44	1,303	0.025	1.51	1,666	1,960	2,254	2,615	1.50
12	40.5	1.49	1,376	0.024	1.42	1,773	2,088	2,403	2,792	1.52
13	45.6	1.56	1,471	0.022	1.34	1,910	2,251	2,593	3,013	1.53
14	51.0	1.64	1,578	0.021	1.29	2,065	2,434	2,804	3,258	1.54
15	56.3	1.70	1,669	0.021	1.23	2,198	2,593	2,988	3,474	1.55
16	60.9	1.74	1,734	0.020	1.19	2,295	2,711	3,127	3,638	1.56
17	64.6	1.75	1,764	0.019	1.14	2,341	2,771	3,201	3,729	1.57
18	67.2	1.76	1,777	0.018	1.10	2,358	2,798	3,238	3,779	1.57

[a] From Chapter 5, Table 5-8.
[b] BEE = Basal Energy Expenditure, calculated from equations in Chapter 5; see "TEE Equations for Normal-Weight Children."
[c] MET = Metabolic Equivalents as calculated from BEE/weight (kg)/1,440 minutes (1 day).
[d] From Chapter 5, Table 5-20.
[e] PAL = Physical Activity Level = TEE/BEE.

above the sedentary level for the low active, active, and very active PAL categories have been expressed in terms of minutes walking at 2.5 mph. Because the BEE and walking energy expenditure (kcal/kg/min) decrease with age differentially, the MET equivalent for walking is not constant and actually increases with age (see Tables 12-6 and 12-7). Thus, the energy cost of walking 2.5 mph decreases from 0.92–0.75 to 0.04–0.05 kcal/kg/min from early childhood to adolescence, and the corresponding MET values increase from ~2.0 to ~3.0.

Examining the number of minutes of walking that would be required to go from the sedentary to the low active (~120 minutes), active (~230 minutes), and very active (~400 minutes) categories, it is clear that children in the active and very active categories are most likely participating in moderate and vigorous activities, in addition to walking at 2.5 mph. With

		Difference in energy expenditure from sedentary level (kcal/d)			Energy cost of walking		Walking equivalent (min)[h]		
Active PAL[e]	Very Active PAL[e]	Low Active–Sedentary	Active–Sedentary	Very Active–Sedentary	2.5 mph (kcal/kg/2.5 min)[f]	METs of walking mph[g]	Low Active–Sedentary	Active–Sedentary	Very Active–Sedentary
1.65	1.87	162	323	521	0.092	2.13	123	246	396
1.65	1.89	175	351	568	0.089	2.23	121	242	392
1.66	1.90	191	383	619	0.087	2.34	119	239	387
1.67	1.92	207	414	669	0.084	2.44	118	237	383
1.68	1.93	224	447	722	0.082	2.52	118	236	381
1.69	1.95	239	478	772	0.079	2.59	118	235	380
1.70	1.97	257	513	829	0.077	2.67	117	233	377
1.71	1.98	274	548	885	0.074	2.76	115	231	373
1.73	2.01	294	588	949	0.072	2.85	114	228	367
1.75	2.03	315	630	1,019	0.069	2.94	112	224	362
1.76	2.05	341	683	1,103	0.067	2.99	112	224	361
1.78	2.06	369	739	1,193	0.064	3.00	112	225	363
1.79	2.08	395	790	1,276	0.062	3.01	113	227	366
1.80	2.10	416	832	1,343	0.059	3.01	115	230	371
1.81	2.11	430	860	1,388	0.057	3.00	117	234	377
1.82	2.13	440	880	1,421	0.054	2.96	120	241	388

[f] Determined from treadmill testing (Puyau et al., 2002; Treuth et al., 1998; Treuth et al., 2000; Treuth et al. (2003).
[g] Calculated as energy cost of walking 2.5 mph (kcal/kg/min) divided by BEE MET (kcal/kg/min).
[h] Calculated by dividing the difference in energy expenditure from sedentary level (kcal/d) by the energy cost of walking 2.5 mph (kcal/kg/min) × weight (kg).

information on the number of minutes children spend in moderate and vigorous play and work, the appropriate PAL category can be assigned.

Physical Activity for Pregnant Women

For women who have been previously physically active, continuation of physical activities during pregnancy and postpartum can be advantageous (Mottola and Wolfe, 2000). Unfortunately, too much or improper activity can be injurious to the woman and fetus. Regular exercise during pregnancy counteracts the effects of deconditioning that lead to fatigue, loss of muscle tone, poor posture, joint laxity, back pain, and muscle cramping (Brooks et al., 2000). Likewise, physical fitness improves glucose tolerance and insulin action, improves emotional well-being and helps

TABLE 12.7 Total Energy Expenditure (TEE) in Girls and Walking Times at Speeds of 2.5 mph to Move to the Next Higher Physical Activity Level (PAL)

						TEE (kcal/d)				PAL
Age (y)	Weight (kg)[a]	Height (m)[a]	BEE (kcal/d)[b]	BEE METs (kcal/kg/min)[c]	BEE METs (kcal/kg/hr)	Sedentary PAL[d]	Low Active PAL[d]	Active PAL[d]	Very Active PAL[d]	Low Active PAL[e]
3	13.9	0.94	879	0.044	2.63	1,060	1,223	1,375	1,629	1.39
4	15.8	1.01	910	0.040	2.40	1,113	1,290	1,455	1,730	1.42
5	17.9	1.08	943	0.037	2.20	1,169	1,359	1,537	1,834	1.44
6	20.2	1.15	979	0.034	2.02	1,227	1,431	1,622	1,941	1.46
7	22.8	1.21	1,014	0.031	1.85	1,278	1,495	1,699	2,038	1.47
8	25.6	1.28	1,056	0.029	1.72	1,340	1,573	1,790	2,153	1.49
9	29.0	1.33	1,094	0.026	1.57	1,390	1,635	1,865	2,248	1.49
10	32.9	1.38	1,139	0.024	1.44	1,445	1,704	1,947	2,351	1.50
11	37.2	1.44	1,193	0.022	1.34	1,513	1,788	2,046	2,475	1.50
12	41.6	1.51	1,253	0.021	1.26	1,592	1,884	2,158	2,615	1.50
13	45.8	1.57	1,306	0.020	1.19	1,659	1,967	2,256	2,737	1.51
14	49.4	1.60	1,337	0.019	1.13	1,693	2,011	2,309	2,806	1.50
15	52.0	1.62	1,351	0.018	1.08	1,706	2,032	2,337	2,845	1.50
16	53.9	1.63	1,352	0.017	1.05	1,704	2,034	2,343	2,858	1.50
17	55.1	1.63	1,340	0.017	1.01	1,685	2,017	2,328	2,846	1.51
18	56.2	1.63	1,327	0.016	0.98	1,665	1,999	2,311	2,833	1.51

[a] From Chapter 5, Table 5-9.
[b] BEE = Basal Energy Expenditure, calculated from equations in Chapter 5; see "TEE Equations for Normal-Weight Children."
[c] MET = Metabolic Equivalents as calculated from BEE/weight (kg)/1,440 minutes (1 day).
[d] From Chapter 5, Table 5-21.
[e] PAL = Physical Activity Level = TEE/BEE.

prevent excessive weight gain. Fitness promotes faster delivery, which is considered beneficial to mother and baby, and hastens recovery from pregnancy. Moreover, resumption of physical activity after pregnancy is important for restoration of normal body weight. Women who gain more than the recommended weight during pregnancy and who fail to lose this weight 6 months after giving birth are at much higher risk of being obese nearly a decade later (Rooney and Schauberger, 2002). Professional organizations such as the American College of Obstetricians and Gynecologists (ACOG) have published guidelines and specific recommendations for exercise by women before, during, and after pregnancy (ACOG, 1994).

A full description of the benefits and hazards of exercise for the pregnant woman and fetus is beyond the scope of this report. Physically active

		Difference in energy expenditure from sedentary level (kcal/d)			Energy cost of walking		Walking equivalent (min)[h]		
Active PAL[e]	Very Active PAL[e]	Low Active–Sedentary	Active–Sedentary	Very Active–Sedentary	2.5 mph (kcal/kg/2.5 min)[f]	METs of walking mph[g]	Low Active–Sedentary	Active–Sedentary	Very Active–Sedentary
1.57	1.85	163	315	569	0.095	2.16	124	239	432
1.60	1.90	177	342	617	0.091	2.28	123	237	428
1.63	1.94	190	368	665	0.088	2.40	121	234	423
1.66	1.98	204	395	714	0.085	2.51	119	231	418
1.68	2.01	217	421	760	0.081	2.63	117	228	411
1.70	2.04	233	450	813	0.078	2.72	117	226	408
1.70	2.05	245	475	858	0.074	2.84	114	220	398
1.71	2.06	259	502	906	0.071	2.96	111	215	388
1.72	2.07	275	533	962	0.068	3.04	109	212	382
1.72	2.09	292	566	1,023	0.064	3.07	109	212	383
1.73	2.10	308	597	1,078	0.061	3.07	110	214	387
1.73	2.10	318	616	1,113	0.058	3.06	112	217	392
1.73	2.11	326	631	1,139	0.054	3.00	116	224	405
1.73	2.11	330	639	1,154	0.051	2.91	121	234	422
1.74	2.12	332	643	1,161	0.047	2.81	127	246	445
1.74	2.13	334	646	1,168	0.044	2.68	135	261	472

[f] Determined from treadmill testing (Puyau et al., 2002; Treuth et al., 1998; Treuth et al., 2000; Treuth et al. (2003).

g Calculated as energy cost of walking 2.5 mph (kcal/kg/min) divided by BEE MET (kcal/kg/min).

[h] Calculated by dividing the difference in energy expenditure from sedentary level (kcal/d) by the energy cost of walking 2.5 mph (kcal/kg/min) × weight (kg).

TABLE 12-8 Target Heart Rate Zones for Healthy Pregnant Women

Age (y)	Heart Rate (beats/min)
< 20	140–155
20–29	135–150
30–39	130–145
> 40	125–140

SOURCE: Mottola and Wolfe, 2000.

and fit women should consult with their physician on how to exercise safely during pregnancy, and probably no pregnant woman should begin an exercise-training program without medical evaluation and exercise instruction. To an extent, anatomy and physiology protect the fetus from injury because the uterus provides a protective environment, the placenta can use alternative energy fuels (e.g., lactate), and fetal blood has a higher affinity of oxygen than does adult hemoglobin (Mottola and Wolfe, 2000). However, excessive exercise or incorrect exercise could compromise placental blood flow, expose the fetus to hypoxemia (low blood oxygen), hypoglycemia (low blood sugar), or hyperthermia (high body temperature), or increase risk of trauma to woman and fetus. Excessive exercise could increase the risk of preterm delivery and lower birth weight (ACOG, 1994).

Education, common sense, and the feeling of body wellness that comes from regular physical activity can be important in guiding a pregnant woman who wants to retain the health benefits of physical activity. For instance, moderate-intensity, rhythmical activities (walking, cycling, swimming, jogging, and dancing) are recommended, whereas activities such as water skiing, surfing, scuba diving, and mountaineering at high altitudes pose unknown risks to the fetus and are not recommended at any time during pregnancy (ACOG, 1995). Similarly, intense physical activity and exercising for extended periods while dehydrated, under hot environmental conditions, and while fasted may increase the risk of hyperthermia and hypoglycemia. Usually, as pregnancy progresses, women instinctively alter exercise activity patterns. Women also need be aware to change or enhance exercise equipment, such as switching from supine to upright cycling. ACOG publishes several texts (e.g., *Encyclopedia of Women's Health*) and brochures (e.g., "Wellness Exercise During Pregnancy") that provide advice for the general public and health professionals.

Historically, concern has been that intense physical activity could result in low birth weight infants and preterm delivery, but this concern needs to be balanced against the need to control body weight during pregnancy and afterward and current evidence that prudent physical activity performed at moderate intensities within current guidelines has no adverse effects on fetal development (Mottola and Wolfe, 2000). Exercise prescriptions for pregnant women are not dissimilar to those for other adults. Exercise sessions should be preceded by a 5- to 15-minute warm-up, and followed by a similar cool-down period. Training duration should be 15 to 30 minutes. Exercise frequency should be 3 to 5 times per week, and not increase in frequency during first or third trimesters because of fatigue and an evaluation of risks to benefits. Exercise intensity should be moderate and elicit 60 to 70 percent Vo_2max, which can be monitored by the maternal heart rate response as shown in Table 12-8. Alternatively, on the 20-point

Borg Rating of Perceived Exertion Scale, women should be exercising at an intensity between 12 and 14 ("somewhat hard"). And finally, intensity can be gauged by the talk test, or exercise intensity where lactic acidosis drives pulmonary minute ventilation so that the pregnant woman is out of breath and cannot carry on a conversation.

Physical Activity Level Consistent with a Normal Body Mass Index

Based on Table 12-2, 30 minutes of moderately intensive physical activity (ΔPAL = 0.099 for walking at 4 mph) would be sufficient to raise the PAL of a person doing only the activities of daily living (PAL = 1.39) from the "sedentary" category (PAL $\geq$ 1.0 < 1.4), to the "low active" category (PAL $\geq$ 1.4 < 1.6), but insufficient to raise the PAL to the "active" category (PAL $\geq$ 1.6 < 1.9), the average PAL category of normal weight adults in the DLW database with BMIs from 18.5 up to 25 kg/m^2 (Table 5-10). One hour of moderately intensive physical activity (ΔPAL = 0.2 for walking at 4 mph) would raise the PAL from 1.39 to 1.59, the upper range of the low active category (PAL $\geq$ 1.4 < 1.6). Thus on the average, an energy expenditure equivalent to at least 60 minutes of moderate intensity physical activity is required to raise the PAL from the "sedentary" to the "active" category (PAL $\geq$ 1.6 < 1.9).

Physical Activity Recommendations for Adults and Children

Cross-sectional data from the DLW database were used to define a recommended level of physical activity for adults and children, based on the PAL associated with a normal BMI range of 18.5 to 25 kg/m^2 (Chapter 5). Factors known to affect body weight were controlled for in the DLW studies, allowing for a reliable assessment of the level of physical activity consistent with a normal weight. Because an average of 60 min/day of moderate intensity physical activity provides a PAL that is associated with a normal BMI range, this is the amount of activity that is recommended for normal weight adults. As stated in Chapter 4, the Dietary Reference Intakes are provided for the apparently healthy population, therefore recommended levels of physical activity that would result in weight loss of overweight or obese individuals are not provided.

In terms of making a realistic physical activity recommendation for busy individuals to maintain their weight, it is important to recognize that exercise and activity recommendations consider "accumulated" physical activity. This involves consideration of EEPAs of both low intensity activities of daily life (e.g., taking the stairs at work) as well as participating in more vigorous activities (e.g., taking an aerobics class). Recognition of the

value of accumulated physical activity in raising TEE makes reasonable activity patterns and sedentary occupations compatible by including significant amounts of moderate intensity activity (e.g., 60 minutes/day of brisk walking) or exercises requiring high intensities (e.g., jogging or running) performed regularly (4–7 days/week).

It is difficult to determine a quantifiable recommendation for physical activity based on reduced risk of chronic disease. Meeting the 60 minute/day physical activity recommendation, however, offers additional benefits in reducing risk of chronic diseases, for example, by favorably altering blood lipid profiles, changing body composition by decreasing body fat and increasing muscle mass, or both (Eliakim et al., 1997; Schwartz et al., 1991; Wei et al., 1997; Wilbur et al., 1999).

EVIDENCE FOR HEALTHFUL EFFECTS OF PHYSICAL ACTIVITY

Epidemiological Evidence for Reduced Risk of Chronic Diseases and Mortality

Men and women with moderate to high levels of physical activity or cardio-respiratory fitness have lower mortality rates than sedentary individuals with low fitness (Blair et al., 1993; Colditz and Coakley, 1997; Myers et al., 2002; Paffenbarger et al., 1994; Sandvik et al., 1993). For instance, in a study of Harvard alumni, mortality rates for men walking on average less than 9 miles each week were 15 percent higher than in men walking more than 9 miles a week (Paffenbarger et al., 1994). Moreover, in the same study, men who took up vigorous sports activities lowered their risk of death by 23 percent compared to those who remained sedentary (Paffenbarger et al., 1993). Similar favorable effects were observed in the Aerobics Center Longitudinal Study as men in the lowest quintile of fitness who improved their fitness to a moderate level, reduced mortality risk by 44 percent, an extent comparable to that achieved by smoking cessation (Blair et al., 1995). Results from observational and experimental studies of humans and laboratory animals provide biologically plausible insights into the benefits of regular physical activity on the delayed progression of several chronic diseases. The interrelationships between physical activity and cancer, cardiovascular disease, type 2 diabetes mellitus, obesity, and skeletal health are detailed in Chapter 3.

Table 12-9 shows seven prospective studies that associated varying ranges of leisure time energy expenditure (kcal/day or kcal/week) with the risk of chronic diseases and/or associated mortality. Assuming an average of 150 kcal expended per 30 minutes of moderate physical activity (Leon et al., 1987), the amount (minutes/day) of physical activity associated with

risk was determined. The required amount of physical activity depended on the endpoint being evaluated. The minimum amount of physical activity that provided a health benefit ranged from 15 to 60 minutes/day. The amount of physical activity that provided the lowest risk of morbidity and/or mortality was 60 to greater than 90 minutes/day.

The proposed recommendation for a daily energy expenditure equivalent to that expended during 60 minutes of brisk walking is consistent with those recommendations in *Physical Activity and Health: A Report of the Surgeon General* (HHS, 1996). This recommendation is also consistent with Canada's "Physical Activity Guide to Healthy Living" (Health Canada, 1998), and the World Health Organization technical report on obesity (2000). Specifically, recommendation number 3 in Chapter 2 of the Surgeon General's report states: "Recommendations from experts agree that for better health, physical activity should be performed regularly. The most recent recommendations advise people of all ages to include a minimum of 30 minutes of physical activity of moderate intensity (such as brisk walking) on most, if not all, days of the week. It is also acknowledged that for most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or of longer duration."

Since the articulation of the HHS recommendation for a minimum 30 minutes/day of physical activity (HHS, 1996), evidence from epidemiological, observational and intervention studies continue to support the quoted statement above. Recently, the Women's Health Initiative Observational Study reported that 2.5 hours/week of vigorous exercise was associated with significantly reduced risk of cardiovascular disease in postmenopausal women (Manson et al., 2002). Moreover, they showed that more vigorous exercise was associated with an increased degree of protection. Conversely, physical inactivity, noted by prolonged sitting, was shown to be a significant risk factor for cardiovascular disease.

Similarly, reporting on treadmill evaluations of over 6,000 men studied over a 6-year period, Myers and coworkers (2002) concluded that "exercise capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease." Recently, Kraus and colleagues (2002) demonstrated favorable effects of jogging for 6 months on blood lipoprotein profiles in overweight men and women, and the extent of changes were related to the amount and intensity of exercise.

Mental Health

Regular exercise has historically been associated with physical health and vigor (HHS, 1996), but exercise may also contribute to the sense of overall well-being and improved mood state. Mental health variables have

TABLE 12-9 Prospective Studies on the Level of Physical Activity in Reducing the Risk of Chronic Disease and Mortality

Reference	Subjects	Study Design[a]
Paffenbarger et al., 1978	16,936 Harvard male alumni, 35–74 y	Questionnaire on leisure-time physical activity, 6- to 10-y follow-up on risk of first heart attack
Paffenbarger et al., 1986	16,936 Harvard male alumni, 35–74 y	Questionnaire on leisure-time physical activity, 12- to 16-y follow-up on all-cause mortality
Leon et al., 1987	12,866 men, 35–57 y	Multiple Risk Factor Intervention Trial using Minnesota questionnaire of leisure-time physical activity, 7-y follow-up on CHD, other and all-cause mortality
Slattery et al., 1989	3,043 U.S. male railroad workers	Leisure-time physical activity questionnaire, 17- to 20-y follow-up on CHD and all-cause mortality
Helmrich et al., 1991	5,990 men, 39–68 y	Questionnaire on leisure-time physical activity, 14-y follow-up on development of type 2 diabetes
Haapanen et al., 1996	1,072 Finnish men, 35–63 y	Questionnaire on leisure-time physical activity, 10-y follow-up on the incidence of all-cause mortality and CVD mortality

Findings[b]	Analysis of Findings
The *minimum* amount of time associated with a reduction in a first heart attack was > 500 kcal/wk The *maximum* reduction in risk of a first heart attack was associated with leisure-time energy expenditure of 2,000–2,999 kcal/wk	The *minimum* amount of physical activity associated with a reduction in a first heart attack was > 15 min/d The *maximum* reduction in risk of a fatal heart attack was at 60–90 min/d
All-cause mortality declined steadily as ranges of energy expenditure from physical activity increased from 500–999 to 3,000–3,500 kcal/wk, beyond which rates slightly increased	The *minimum* amount of physical activity associated with reduced mortality was 30–60 min/d The amount of physical activity associated with *maximum* reduction in mortality was 85–100 min/d The *minimum* amount of physical activity associated with reduced CHD and all-cause mortality was 30–60 min/d. The amount of physical activity associated with the *maximum* reduced CHD and all-cause mortality was 30–60 min/d
The *minimum* amount of total leisure physical activity associated with reduced CHD, CVD and all-heart mortality was 251–1,000 kcal/wk Risk from death was the lowest when total leisure-time physical activity (light to moderate) was 1,001–1,999 kcal/wk	The *minimum* amount of total leisure time physical activity associated with reduced mortality was 10–30 min/d 30–60 min/d of total leisure time physical activity was associated with the *maximum* reduced risk of mortality
The *minimum* amount of mild/moderate physical activity associated with a reduced incidence of type 2 diabetes was 1,000–1,499 kcal/wk The incidence of type 2 diabetes declined as energy expenditure increased from < 500 (rr = 1) to > 3,500 kcal/wk (rr = 0.48)	The *minimum* range of mild/moderate physical activity associated with a reduced risk of type 2 diabetes was 30–45 min/d The amount of mild/moderate physical activity associated with the *maximum* reduction in type 2 diabetes was > 90 min/d
The *minimum* amount of physical activity associated with a reduced risk of CVD and all-cause mortality was 800–1,500 kcal/wk The amount of physical activity associated with the *maximum* reduction in all-cause mortality was > 2,100 kcal/wk and 800–1,500 kcal/wk for CVD mortality	The *minimum* amount of physical activity associated with reduced mortality was 23–45 min/d The amount of physical activity associated with the *maximum* reduction in all-cause mortality was > 60 min/d and 23–45 min/d for CVD mortality

continued

TABLE 12-9 Continued

Reference	Subjects	Study Design[a]
Rockhill et al., 2001	121,701 female nurses, 30–55y	Questionnaire on physical activity, 20-y follow-up of all-cause mortality, and death from various diseases

[a] CHD = coronary heart disease, CVD = cardiovascular disease.
[b] rr = relative risk.

been related to various forms of exercise, particularly acute and chronic aerobic exercise. The research evidence now supports stronger conclusions than presented in the *Physical Activity and Health: A Report of the Surgeon General* (HHS, 1996). The vast majority of review articles have concluded that acute or chronic aerobic exercise is related to favorable changes in anxiety, depression, stress reactivity, positive mood, self-esteem, and cognitive functioning (Anthony, 1991; Craft and Landers, 1998; Landers and Arent, 2001; Mutrie, 2000; North et al., 1990; Paluska and Schwenk, 2000; Salmon, 2001). Although one reviewer (Mutrie, 2000) has argued for a causal relationship between exercise and the reduction of clinical depression, others suggest that there are not enough clinical trial studies to support a causal interpretation (Landers and Arent, 2001). Examination of the meta-analyses indicates that the overall magnitude of the effect of exercise on anxiety, depression, stress reactivity, and cognitive functioning ranges from small to moderate, but in all cases, these effects are statistically significant (Landers and Arent, 2001).

These results are encouraging, but there is still much to learn before the relationship between physical activity and mental health can be fully understood. Recent reviews on endorphins (Hoffman, 1997), serotonin (Chaouloff, 1997), and norepinephrine (Dishman, 1997) have provided experimental evidence for potential mechanisms by which exercise can produce calming effects and mood enhancements.

Findings[b]	Analysis of Findings
The *minimum* amount of physical activity associated with a reduced risk of all-cause mortality and specific causes or mortality was 1–1.9 h/wk	The *minimum* amount of physical activity associated with a reduced risk of mortality was 15–30 min/d
The *maximum* reduction in risk (rr = 0.71) of all-cause mortality was observed for those who expended > 7 h/wk of physical activity; those specific causes of death that were most affected were respiratory deaths (rr = 0.23) and noncancer, non-CVD, and nondiabetes deaths (rr = 0.46)	A minimum amount of physical activity associated with the *maximum* reduction in mortality was 60 min/d

NOTE: 150 kcal = 30 min of a combination of light, moderate, and some vigorous physical activity (Leon et al., 1987).

BALANCE OF CARBOHYDRATE AND LIPID OXIDATION DURING EXERCISE AND RECOVERY

The balance of carbohydrate and lipid used by an individual during exercise depends mainly on relative intensity, or level of effort as related to the individual's maximal rate of oxygen consumption (Vo_2max) the greatest oxygen consumption that can be attained during an all out physical effort). In general, Vo_2max is related to body muscle mass and is a relatively constant value for a given individual but it can be altered by various factors, particularly aerobic training, which will induce a change of 10 to 20 percent. Thus, on an absolute basis, bigger individuals tend to have a larger Vo_2max (measured in liters of O_2 consumed/minute) than do smaller individuals. However, Vo_2max is also related to the size of the body and the heart. Hence, for purposes of comparison, Vo_2max is frequently considered in terms of mL/kg/min. Some examples are illustrative. An unfit man of average weight (70 kg) might have an absolute Vo_2max of 2.8 L/min, corresponding to 40 mL/kg/min (2.8 L/70 kg/min). If the man's resting metabolic rate (RMR) is 250 mL/min, he would be expected to be capable of 11.5 MET (40 mL/kg/min divided by 1 MET defined as 3.5 mL O_2/kg/min). However, a heart disease patient of the same body size might be capable of only a Vo_2max of 0.50 to 0.75 L/min, corresponding to 7 mL/kg/min (0.5 L/70 kg/min) to 10 mL/kg/min (0.75 L/70 kg/min). This would be equivalent to 2 (7 mL/kg/min divided by 3.5 mL O_2/kg/min) or 3 METs (10 mL/kg/min divided by 3.5 mL O_2/kg/min), while an Olympic-class middle distance runner of the same weight may be capable of achieving a

Vo_2max of 6 L/min, which is equivalent to 85 mL O_2/kg/min (6 L/70 kg/min), or 24 METs (85 mL O_2/kg/min divided by 3.5 mL O_2/kg/min).

Lipid is the main energy source in muscle and at the whole-body level during rest and mild intensity activity (Brooks and Mercier, 1994). As intensity increases, a shift from the predominant use of lipid to carbohydrate occurs. Figure 12-7 describes this crossover concept and, as can be seen in the figure, the relative use of fat is greatest at relatively low exercise intensities, particularly when individuals are fasting. Training slightly increases the relative use of fat as the energy source during low to moderate exercise intensities, particularly in the fasted state. In regard to the amount of fat oxidized, it must be considered that the energy output for a given percent of Vo_2max is proportionally higher (in this case 50 percent) in trained rather than in untrained cyclists. However, at relatively high power outputs, substrate use crosses over to predominant use of carbohydrate energy sources regardless of training state or recent carbohydrate nutrition.

To be used for energy generation, protein must first be degraded to amino acids before the carbon-hydrogen-oxygen skeleton can be used as an energy source through the pathways of carbohydrate and lipid metabolism, while the amino acid nitrogen is transferred and eliminated, primarily in the form of urea. The rate at which amino acids contribute to energy generation is fairly constant and does not increase nearly as much as glucose and fatty acid oxidation during periods of physical exertion. While the rate of oxidation of particular amino acids (e.g., leucine) may rise significantly during exercise, not all amino acids respond in the same way, and amino acids diminish in relative importance as fuels when power output rises during exercise (Brooks et al., 2000), providing only a small percentage of the energy used during physical activity (Brooks, 1987). Indeed, using amino acids as a major energy source would be wasteful, since protein is the most limited energy yielding nutrient. Beyond the overriding effect of relative exercise intensity, other factors such as exercise duration, gender, training status, and dietary history play important, but secondary, roles in determining the pattern of substrate utilization (Brooks et al., 2000). Therefore, the same general relationships among relative exercise intensity, duration, and pattern of substrate utilization hold for most persons, including endurance athletes.

Intensity of Physical Activity

Oxidation of lipid provides most of the energy (~ 60 percent) for noncontracting skeletal muscle and overall for the body at rest in people who have not eaten for 10 to 12 hours (i.e., postabsorptive conditions) (Brooks, 1997). Glucose released from the liver into the circulation provides the remainder of the energy for the body overall, particularly the brain, kidneys,

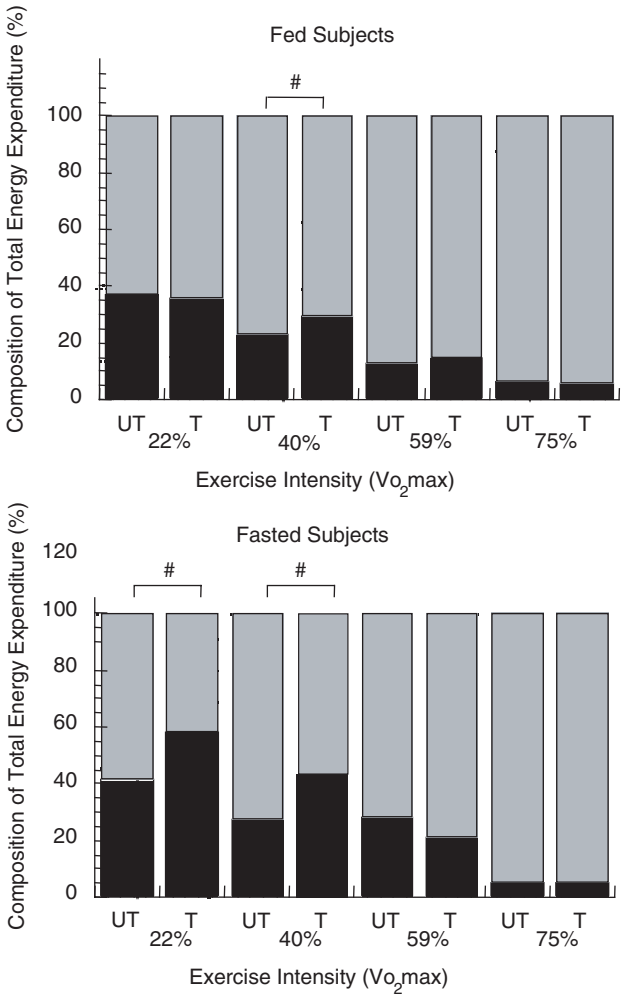

FIGURE 12-7 Illustration of the effects of relative exercise intensity, recent carbohydrate feeding, and training status on the relative use of carbohydrate (CHO) and lipid (black) energy sources as determined by indirect calorimetry. Untrained men (UT) and trained (T) male cyclists were studied after being recently fed (3–4 h after a 550-kcal meal [87% CHO, 11% protein, 2% fat]) or after an overnight (12-h) fast, during continuous cycling at graded relative exercise intensities over periods of 120 min (22% and 40% Vo_2max), 90 min (59% Vo_2max), and 45 min (75% Vo_2max). Exercise intensity expressed as a percentage of maximal oxygen consumption (Vo_2max), which averaged 39 and 58 mL of oxygen/min/kg body weight among the UT and T cyclists. $p < 0.05$ for #. Reprinted, with permission, from Bergman and Brooks (1999). Copyright 1999 by the American Physiological Society.

and blood. During mild exercise, the use of lipid increases, but if the level of effort increases, carbohydrate energy sources are used to a relatively greater extent (Figure 12-7). Peak rate of lipid oxidation is achieved at approximately 45 percent of Vo_2max. For exercises intensities greater than 50 percent of Vo_2max, the oxidation of free fatty acids declines in muscle, both as a percentage of total energy as well as on an absolute basis. In other words, there is crossover from prevalence of lipid oxidation at rest and during mild exercise to predominance of carbohydrate energy sources during moderate and greater efforts. The main carbohydrate energy source is muscle glycogen, and this is supplemented to some extent by glucose and lactate—glucose mobilized from the liver and lactate produced by muscle glycogen breakdown. If exercise persists beyond 60 to 90 minutes, lipid use will rise as carbohydrate fuel sources become depleted. In this case, the intensity of exercise must drop because of the depletion of muscle glycogen, decreasing levels of blood glucose, and other fatiguing consequences of the effort (Graham and Adamo, 1999).

Dietary carbohydrate is relatively rapidly assimilated compared to fat and protein, thus raising blood glucose and insulin levels. The increments in blood glucose and insulin in response to carbohydrate intake are less in trained than in untrained individuals (Dela et al., 1991; King et al., 1987). Still, carbohydrate feeding stimulates carbohydrate oxidation, raising the respiratory exchange ratio ($RER = R = Vco_2/Vo_2$) in all individuals. Hence, as shown in Figure 12-7 for fed individuals, crossover to predominant carbohydrate oxidation occurs already during mild (22% Vo_2max) exercise, even in trained individuals, if they have recently consumed carbohydrates.

Duration of Physical Activity

Within seconds after initiation of even mild exercise, muscle glycogen stores are mobilized to provide energy for muscle work. Over the next few minutes, as circulatory oxygen supply rises to meet demand and muscle cell energy homeostasis is restored, the use of muscle glycogen subsides and free fatty acids (FFA) as well as lipid previously stored within muscle cells (intramuscular triacylglycerol) are activated and used. After the transition period in which glycogen is primarily used, the fuel mix used during sustained mild intensity exercise returns toward the mix used at rest, in which FFA predominate. Such mild intensities correspond to easy walking and household chores. As exercise intensity increases, FFA oxidation increases, achieving a peak at about 45 percent Vo_2max; thereafter, use of carbohydrate fuel sources (i.e., muscle glycogen, blood glucose, lactate) rises exponentially and lipid oxidation declines (Figure 12-7). Depending on the person, the change from fat to carbohydrate dependence occurs at different levels of exertion. In some individuals, this may happen during

activities such as brisk walking. When labored breathing accompanies exercise, crossover to carbohydrate dependence has generally occurred.

In most cases, relationships between activity duration and intensity will be inversely related—harder intensity physical activities will necessarily be of less duration than easier ones. Extreme effort is made possible in part by the use of preformed high-energy bonds in the form of creatine-phosphate, in addition to energy generation by glycogen and glucose catabolism, with very little use of fat, leading to fatigue within seconds or minutes. Thus, the energy flux rate will be high, but total energy liberated small. In contrast, activities of mild to moderate intensity, performed over periods of hours, can result in large increments of energy expenditure with a substantial contribution coming from lipid stores (Brooks et al., 2000). Therefore, in order to use physical activity to enhance body fat utilization, sustained activity that causes substantial increases in energy expenditure is more important than the peak rate of substrate oxidation. Even in highly fit athletes, glycogen reserves will become largely depleted after maintaining high rates of exertion for several hours, so that increasing amounts of lipid will be oxidized. As a result of such physical activity, increased lipid oxidation will also take place during recovery from exercise (Chad and Quigley, 1991; Kiens and Richter, 1998).

Gender

In general, metabolic responses of women and men are similar, but women oxidize more lipid than men during exercise and when performing a task at a given level of intensity (Friedlander et al., 1998a, 1998b, 1999; Tarnopolsky et al., 1990). Paradoxically, women depend more on blood glucose and less on muscle glycogen than do men. The effects of menstrual variations on substrate utilization are under investigation, but the effects are likely to be small, because estrogen and progesterone appear to have antagonistic effects on substrate utilization (Campbell et al., 2001; Suh et al., 2002). In contrast to the effects of menstrual cycle variations in endogenous ovarian sex steroids, high levels of exogenous synthetic ovarian steroid analogs, such as contained in oral contraceptives, cause a mild insulin resistance and decrease use of blood glucose in women at rest (Yen and Vela, 1968). Consequently, men and women may possibly differ subtly in patterns of substrate utilization during physical activity, but overall patterns of carbohydrate and lipid use are similar. The effect of menopause on substrate utilization during exercise has not been studied in sufficient detail to establish if it leads to significant changes in substrate utilization. However, changes in body fat content and distribution after menopause suggest that patterns of activity and energy substrate utilization change after menopause (Poehlman et al., 1995).

Age

Maximal oxygen consumption is typically stable in the third decade of life, but then declines approximately 1 percent/year (0.5 ml/kg/min) after age 30 (Raven and Mitchell, 1980). This age-related decline is associated with the decline in muscle mass and maximal heart rate that decreases approximately 1 beat/min/year (Suominen et al., 1977). As a result, fat oxidation during physical activity is decreased and carbohydrate oxidation is increased in elderly adults (Sial et al., 1996). Recognizing that Vo_2max declines with age, any given task is likely to be accomplished at relatively greater exercise intensity, and consequently greater dependence on carbohydrate-derived energy sources. However, if relative exercise intensity is considered, many older individuals are capable of prolonged exercise at 50 to 60 percent of Vo_2max, and accordingly can oxidize significant quantities of carbohydrate and lipid (Sial et al., 1996) to favorably affect physiological systems as well as change energy balance and body composition.

Sedentary older individuals who become active through resumption of outdoor activities, gymnasium exercises, or other forms of occupational or recreational activities respond much like younger individuals (Hagberg et al., 1989; Hagerman et al., 2000). While the extent of adaptation is obviously limited in older ages, relative changes in muscle strength and aerobic capacity can be comparable or even greater than in younger adults (Hagberg et al., 1989; Hagerman et al., 2000). It must be noted that acute illness resulting in bed rest can result in a notable (~10 percent) decline in Vo_2max in 1 week, but the decline is transient and recovery occurs in a similar time frame after resumption of regular physical activities (Greenleaf and Kozlowski, 1982).

Growth and Development

In general, in children maximal oxygen consumption is higher per unit of body weight and higher in boys than girls, although the difference is small until the pubertal growth. The growth spurt usually comes earlier in girls than boys, so maximal oxygen consumption in 12- to 13-year-old girls may match or surpass that of age-matched boys. However, in boys, puberty results in much larger increments in total muscle mass, blood volume, and lung and heart size than girls. Girls acquire more fat mass than do boys and boys frequently lose body fat during the pubertal growth spurt. Consequently, puberty results in a large increment in Vo_2max whether expressed in absolute or relative terms in boys. In girls, the relative rise in Vo_2max during the pubertal growth spurt is smaller, since the absolute increase in muscle mass is less and the relative rise in fat mass (FM) is

greater than in boys. Regular endurance exercise can result in a significant increment in the Vo_2max of boys and girls (Brown et al., 1972; Mahon and Vaccaro, 1989, 1994; Vaccaro and Clarke, 1978) as well as in adults (Gallo et al., 1989; Maciel et al., 1985; Tabata et al., 1996).

It is generally assumed that the pattern of substrate utilization in children during rest and exercise is similar to that in adults. However, the data on effect of exercises of graded intensities and duration on the balance of substrate utilization in children are scarce. Compared to adults, the capacity of glycogenolysis in non–fully differentiated skeletal muscle is less in children, and they are generally less capable of speed and power-related activities (Krahenbuhl and Williams, 1992).

Physical activity levels in children vary widely, as they are capable of large amounts of spontaneous, self-directed physical activity (Blaak et al., 1992). The effects of exercise on body composition in children are likely greater than in adults, because of the much greater levels of growth hormone in children (Borer, 1995). Because growth hormone has both anabolic (tissue-building) and lipolytic (fat-mobilizing) effects (Bengtsson et al., 1990), it is not surprising that physically active children are stronger and leaner than their obese counterparts (Owens et al., 1999).

Results from the 1999 Youth Risk Behavior Study (CDC, 2000) indicate that only 29 percent of high school students attend physical education classes daily, and participation declines to 20 percent by grade 12 (Table 12-10). Furthermore, not only is there a decline in the frequency of physical education participation by high school students, but there is also a steady decline in the vigor of participation, as estimated by length of time engaging in physical activity/exercise during class.

PHYSICAL FITNESS

Endurance (Aerobic) Exercise

Traditionally, the types of activities recommended for cardiovascular fitness are those of a prolonged endurance nature, such as bicycling, hiking, jogging, and swimming. Sometimes the word "aerobic" is used as an alternative to describe such activities because integrated functions of lungs, heart, cardiovascular system, and associated muscles are involved. Because of the energy demands associated with aerobic activity, such activities have the potential to impact body fat mass (FM) (Grund et al., 2001). By decreasing FM and preserving fat free mass (FFM), prolonged mild to moderate intensity endurance exercise can change body composition.

TABLE 12-10 Percentage of Students in Grades 9 Through 12 Who Reported Enrollment in Physical Education Classes, Attendance in Physical Education Classes Daily, and Spending More Than 20 Minutes Exercising During Class, by Demographic Group[a]

Demographic Group	Enrolled in Physical Education Classes	Attended Physical Education Classes Daily	Exercised More Than 20 Min per Class[b]
Overall total	56.1 (48.9–63.3)	29.1 (19.7–38.5)	76.3 (72.6–80.0)
Gender			
Females	51.5 (43.8–59.2)	26.3 (17.3–35.3)	69.6 (65.6–73.6)
Males	60.7 (53.7–67.7)	31.9 (21.9–41.9)	82.1 (77.5–86.7)
Race/ethnicity			
White, non-Hispanic			
Total	56.1 (46.3–65.9)	28.3 (15.5–41.1)	78.7 (74.3–83.1)
Females	51.7 (40.5–62.9)	25.8 (13.3–38.3)	72.4 (67.0–77.8)
Males	60.2 (51.0–69.4)	30.8 (17.5–41.1)	83.8 (79.3–88.3)
Black, non-Hispanic			
Total	52.9 (39.1–66.7)	29.2 (19.3–39.1)	67.8 (64.3–71.3)
Females	47.1 (34.1–60.1)	25.5 (17.0–34.0)	55.8 (50.2–61.4)
Males	59.2 (43.4–75.0)	33.1 (20.4–45.8)	78.4 (74.3–82.5)
Hispanic			
Total	59.3 (52.3–66.3)	40.4 (31.5–49.3)	75.5 (70.5–80.5)
Females	53.6 (44.5–62.7)	36.2 (25.9–46.5)	70.8 (63.9–77.7)
Males	65.1 (58.1–72.1)	44.6 (35.9–53.3)	79.6 (73.5–85.7)
Grade in school			
9th			
Total	78.9 (73.0–84.8)	42.1 (29.6–54.6)	78.7 (74.5–82.9)
Females	75.6 (69.0–82.2)	40.3 (28.1–52.5)	72.5 (65.6–79.4)
Males	82.3 (76.4–88.2)	44.0 (30.8–57.2)	84.4 (80.1–88.7)
10th			
Total	60.9 (49.0–72.8)	30.4 (20.7–40.1)	75.1 (69.9–80.3)
Females	56.6 (43.1–70.1)	27.9 (17.7–38.1)	70.2 (64.6–75.8)
Males	65.3 (54.1–76.5)	32.8 (22.6–43.0)	79.4 (72.8–86.0)
11th			
Total	40.7 (31.5–49.9)	20.0 (11.7–28.3)	75.7 (70.9–80.5)
Females	36.8 (27.6–46.0)	16.6 (8.2–25.0)	68.0 (61.2–74.8)
Males	44.6 (34.5–54.7)	23.5 (15.0–32.0)	82.0 (76.0–88.0)
12th			
Total	36.6 (25.6–47.6)	20.1 (10.2–30.0)	73.4 (63.3–83.5)
Females	29.4 (17.6–41.2)	16.6 (8.5–24.7)	60.1 (51.9–68.3)
Males	43.8 (32.7–54.9)	23.6 (11.4–35.8)	82.3 (71.1–93.5)

[a] 95% confidence interval.
[b] Among students enrolled in physical education classes.
SOURCE: CDC. 2000. 1999 Youth Risk Behavior Survey.

Resistance Exercise and General Physical Fitness

Initial efforts by health professionals to reduce FM involved endurance exercise protocols mainly because of the large impact on total energy expenditure and links to coronary heart disease risk amelioration. More recent efforts using resistance exercise training, or combinations of resistance and endurance exercises, have been tried to maintain the interest of participants as well as to positively affect body composition through stimulation of anabolic stimuli (Grund et al., 2001). Practitioners of speed, power, and resistance exercises can change body composition by means of the muscle-building effects of such exertions. Moreover, exercises that strengthen muscles, bones, and joints stimulate muscle and skeletal development in children, as well as assist in balance and locomotion in the elderly, thereby minimizing the incidence of falls and associated complications of trauma and bed rest (Evans, 1999). While resistance training exercises have not yet been shown to have the same effects on risks of chronic diseases, their effects on muscle strength are an indication to include them in exercise prescriptions, in addition to activities that promote cardiovascular fitness and flexibility.

Supplementation of Water and Nutrients

As noted earlier, carbohydrate is the preferred energy source for working human muscle (Figure 12-7) and is often utilized in preference to body fat stores during exercise (Bergman and Brooks, 1999). However, over the course of a day, the individual is able to appropriately adjust the relative uses of glucose and fat, so that recommendations for nutrient selection for very active people, such as athletes and manual laborers, are generally the same as those for the population at large. With regard to the impact of activity level on energy balance, modifications in the amounts, type, and frequency of food consumption may need to be considered within the context of overall health and fitness objectives. Such distinct objectives may be as varied as: adjustment in body weight to allow peak performance in various activities, replenishment of muscle and liver glycogen reserves, accretion of muscle mass in growing children and athletes in training, or loss of body fat in overweight individuals. However, dietary considerations for active persons need to be made with the goal of assuring adequate overall nutrition.

Following the recently released joint position statement of the American College of Sports Medicine, American Dietetics Association, and Dietitians of Canada (ACSM et al., 2000), water and fluids containing carbohydrates and electrolytes may be consumed immediately prior to, during, and after physical activity. For instance, a collegiate swimmer arriving on an empty

stomach at the training site should be provided with fluids during and immediately after training as well as food after training. Similarly, following competition or training for competition, athletes should rehydrate and consume a high carbohydrate meal (ACSM, 2000). For the healthy individual, the amount and intensity of exercise recommended is unlikely to lead to glycogen depletion, dehydration, or water intoxication. Nonetheless, timing of post-exercise meals to promote restoration of glycogen reserves and other anabolic processes can benefit resumption of normal daily activities.

ADVERSE EFFECTS OF EXCESSIVE PHYSICAL ACTIVITY

Adverse Effects

Overuse Injuries

Physical exercise has the potential to cause overuse injuries to muscles, bones, and joints as well as injuries caused by accidents. Additionally, preexisting conditions can be aggravated upon initiation of a physical activity program, and chronic, repetitive activities can result in injuries. For instance, running can result in injuries to muscles and joints of the lower limbs and back, swimming can cause or irritate shoulder injuries, and cycling can cause or worsen problems to the hands, back, or buttocks. Fortunately, the recommendation in this report to accumulate a given amount of activity does not depend on any particular exercise or sports form. Hence, the activity recommendation can be implemented in spite of possible mild, localized injuries by varying the types of exercise (e.g., walking instead of jogging). Recalling the dictum of "do no harm," the physical activity recommendations in this report are intended to be healthful and invigorating. Activity-related injuries are always frustrating and often avoidable, but they do occur and need to be resolved in the interest of long-term general health and short-term physical fitness.

Dehydration and Hyperthermia

Physical activity results in conversion of the potential chemical energy in carbohydrates and fats to mechanical energy, but in this process most (~ 75 percent) of the energy released appears as heat (Brooks et al., 2000). Evaporative heat loss from sweat is the main mechanism by which humans prevent hyperthermia and heat injuries during exercise. Unfortunately, the loss of body water as sweat during exercise may be greater than what can be replaced during the activity, even if people drink ad libitum or are on a planned diet. Hence, exercise may result in dehydration that increases

the stress and relative difficulty of subsequent activity. This can be aggravated by environmental conditions that increase fluid losses, such as heat, humidity, and lack of wind (Barr, 1999). Therefore, as already described, people should consume water before, during (if possible), and after exercise (ACSM et al., 2000).

A weight loss of 1 to 2 percent of body weight on a day following exercise cannot be attributed to a loss of body fat, but reflects some degree of hypohydration that needs to be compensated for by the consumption of fluids (ACSM et al., 2000). Individuals who have lost more than 2 percent of body weight are to be considered physiologically impaired (Naghii, 2000) and should not exercise, but rehydrate.

Hypothermia

Hypothermia can result from water exposure and during winter sports. Even exposure to cool, damp environments can be dangerous to inadequately clothed and physically exhausted individuals. Accidental immersion due to capsizing of boats, poor choice of clothing during skiing, change in weather, or physical exhaustion leading to an inability to generate adequate body heat to maintain core body temperature can all lead to death, even when temperatures are above freezing. Prevention of hypothermia and its treatment are beyond this report; however, hypothermia is unlikely to accrue from attempts to fulfill the physical activity recommendation. Because water and winter sports are gaining popularity and do provide means to enjoyably follow the physical activity recommendation, safe participation in such activities needs special instruction and supervision.

Cardiac Events

While regular physical activity promotes cardiovascular fitness and reduces risks associated with cardiovascular diseases (CVD), heavy physical exertion can trigger the development of arrhythmias or myocardial infarctions (Mittleman et al., 1993; Thompson, 1982; Willich et al., 1993) or, in some instances, can lead to sudden death (Kohl et al., 1992; Koplan, 1979; Siscovick et al., 1984; Thompson, 1982). Thus, while it is true that compared to the population at large, individuals who exercise regularly have reduced risk of CVD and sudden cardiac death, there is a transient increase in risk in this group during and immediately after vigorous exercise (Kohl et al., 1992; Siscovick et al., 1984). However, Manson and colleagues (2002) recently reported that both walking and vigorous activity were associated with marked reductions in the incidence of cardiovascular events.

Female Athlete Triad

Although loading the skeleton through resistance (e.g., weight training, weight-bearing exercises) and impact activities (e.g., jumping) increases bone mineral density (BMD) (Fuchs et al., 2001; Welten et al., 1994), athletic women who undereat and/or overtrain can develop a condition, or cluster of conditions (disordered eating, amenorrhea, and osteoporosis) termed the "female athlete triad" (ACSM, 1997; Thrash and Anderson, 2000; West, 1998). In this triad, disordered eating and chronic energy deficits can disrupt the hypothalamic-pituitary axis, leading to loss of menses, osteopenia, and premature osteoporosis (Loucks et al., 1998), increasing the possibility of hip, spine, and forearm fractures. While dangerous in themselves, skeletal injuries can predispose victims to a cascade of events including thromboses, infections, and physical deconditioning.

Prevention of Adverse Effects

The possibility that exercise can result in overuse injuries, dehydration, and heart problems has been noted above. Consequently, a prudent approach to initiating physical activity or exercise by previously sedentary individuals is recommended. Men over 40 years of age and women over 50 years of age, those with pre-existing conditions, known or suspected risk factors or symptoms of cardiovascular and other chronic diseases (physical inactivity being a known risk factor) should seek medical evaluation as well as clinical exercise testing, clearance, and advice prior to initiating an exercise program (ACSM, 2000). The evaluation should include a stress electrocardiogram and blood pressure evaluation. Ideally, respiratory measurements should be performed to evaluate Vo_2max.

For all individuals initiating an exercise program, emphasis should be placed on the biological principle of stimulus followed by response. Hence, easy exercises must be performed regularly before more vigorous activities are conducted. Similarly, exercise participants need to rest and recover from previous activities prior to resuming or increasing training load. Also, as already noted, conditions of chronic soreness or acute pain and insomnia could be symptoms of over-training. Hence, activity progression should be discontinuous with adequate recovery periods to minimize chances of injury and permit physiological adaptations to occur. Those adaptations are elicited during exercise but occur during recovery. Thus, physical activity recommendations for healthful living, whether a minimum of 30 minutes for most days, as recommended in the Surgeon General's report (HHS, 1996), or 60 minutes a day, should not be construed as the starting point for an adult wishing to change from a sedentary lifestyle to a more active form of living. Depending on the individual, as little as 5 to

10 minutes a day may represent an appropriate starting point, undertaken under professional supervision for those with cardiovascular risk or orthopedic problems. Attention also needs to be given to stretching and strengthening activities as part of the physical activity core to healthful living.

RESEARCH RECOMMENDATIONS

- More information is needed on the effect of exercise (i.e., endurance, resistance, other), frequency, intensity, and duration on body fatness in young and elderly adults and children.
- More information is needed on the effects of exercise on substrate utilization and the roles of various energy depots (liver glycogen, muscle glycogen, adipose triacylglycerol, intramuscular triacylglycerol) in exercise and recovery in children, adults, and the elderly.
- Research is needed to determine whether the timing of meals and exercise can be used to optimize changes in, or to maintain favorable Body Mass Indexes and body compositions of moderately and very active individuals.
- Research is needed to determine whether there are dietary compositions that optimize accretion of lean tissue in growing children and physically active adults.
- More information is needed to identify the mechanisms by which acute and chronic physical activity alter substrate utilization and body composition.
- Efforts need to be undertaken to develop reliable, noninvasive, and clinically appropriate measurements of body composition, cardiovascular function, and physical fitness.
- Efforts should be directed at developing practical, yet reliable methods to assess habitual levels of physical activity.

REFERENCES

ACOG (American College of Obstetricians and Gynecologists).1994. Exercise during pregnancy and the postpartum period. *Tech Bull* 189. Washington DC.

ACOG (American College of Obstetricians and Gynecologists). 1995. Planning for pregnancy, birth and beyond. *Tech Bull.* Washington, DC.

ACSM (American College of Sports Medicine). 1978. The recommended quantity and quality of exercise for developing and maintaining fitness in healthy adults. *Med Sci Sports* 10:vii–x.

ACSM. 1980. *Guidelines for Graded Exercise Testing and Prescription,* 2nd ed. Philadelphia: Lea and Febiger.

ACSM. 1997. Position Stand: The female athlete triad. *Med Sci Sports Exercise* 29:I-xi.

ACSM. 2000. *ACSM's Guidelines for Exercise Testing and Prescription,* 6th ed. Philadelphia: Lippincott, Williams and Wilkins.

ACSM, American Dietetic Association, Dietitians of Canada. 2000. Joint position statement. Nutrition and athletic performance. *Med Sci Sports Exerc* 32:2130–2145.

AHA (American Heart Association). 1972. *Exercise Testing and Training of Apparently Healthy Individuals: A Handbook for Physicians.* New York: AHA.

Anthony J. 1991. Psychologic aspects of exercise. *Clin Sports Med* 10:171–180.

Bahr R, Ingnes I, Vaage O, Sejersted OM, Newsholme EA. 1987. Effect of duration of exercise on excess postexercise O_2 consumption. *J Appl Physiol* 62:485–490.

Barr SI. 1999. Effects of dehydration on exercise performance. *Can J Appl Physiol* 24:164–172.

Benedict FG, Cathcart EP. 1913. *Muscular Work: A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine.* Publication No. 187. Washington, DC: Carnegie Institution of Washington.

Bengtsson B-Å, Brummer R-J, Bosaeus I. 1990. Growth hormone and body composition. *Horm Res* 33:19–24.

Bergman B, Brooks GA. 1999. Respiratory gas-exchange ratios during graded exercise in fed and fasted trained and untrained men. *J Appl Physiol* 86:479–487.

Bijnen FCH, Caspersen CJ, Feskens EJM, Saris WHM, Mosterd WL, Kromhout D. 1998. Physical activity and 10-year mortality from cardiovascular diseases and all causes: The Zutphen Elderly Study. *Arch Intern Med* 158:1499–1505.

Blaak EE, Westerterp KR, Bar-Or R, Wouters LJM, Saris WHM. 1992. Total energy expenditure and spontaneous activity in relation to training in obese boys. *Am J Clin Nutr* 55:777–782.

Blair SN, Kohl HW, Barlow CE. 1993. Physical activity, physical fitness, and all-cause mortality in women: Do women need to be active? *J Am Coll Nutr* 12:368–371.

Blair SN, Kohl HW, Barlow CE, Paffenbarger RS, Gibbons LW, Macera CA. 1995. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *J Am Med Assoc* 273:1093–1098.

Blundell JE, King NA. 1998. Effects of exercise on appetite control: Loose coupling between energy expenditure and energy intake. *Int J Obes Relat Metab Disord* 22:S22–S29.

Borer KT. 1995. The effects of exercise on growth. *Sports Med* 26:375–397.

Bouchard C, Shephard RJ, Stephens T. 1994. *Physical Activity, Fitness, and Health: International Proceedings and Consensus Statement.* Champaign, IL: Human Kinetics.

Brooks GA. 1987. Amino acid and protein metabolism during exercise and recovery. *Med Sci Sports Exerc* 19:S150–S156.

Brooks GA. 1997. Importance of the 'crossover' concept in exercise metabolism. *Clin Exp Pharmacol Physiol* 24:889–895.

Brooks GA, Mercier J. 1994. Balance of carbohydrate and lipid utilization during exercise: The 'crossover' concept. *J Appl Physiol* 76:2253–2261.

Brooks GA, Fahey TD, White TP, Baldwin KM. 2000. *Exercise Physiology: Human Bioenergetics and Its Applications*, 3rd ed. Mountain View, CA: Mayfield Publishing.

Brown CH, Harrower JR, Deeter MF. 1972. The effects of cross-country running on pre-adolescent girls. *Med Sci Sports* 4:1–5.

Campbell SE, Angus DJ, Febbraio MA. 2001. Glucose kinetics and exercise performance during phases of the menstrual cycle: Effect of glucose ingestion. *Am J Physiol* 281:E817–E825.

CDC (Centers for Disease Control and Prevention). 2000. Youth risk behavior surveillance—United States, 1999. *Mor Mortal Wkly Rep CDC Surveill Summ* 49(SS-5):1–96.

Chad KE, Quigley BM. 1991. Exercise intensity: Effect on postexercise O_2 uptake in trained and untrained women. *J Appl Physiol* 70:1713–1719.

Chaouloff F. 1997. The serotonin hypothesis. In: Morgan WP, ed. *Physical Activity and Mental Health.* Washington, DC: Taylor and Francis. Pp. 179–198.

Colditz GA, Coakley E. 1997. Weight, weight gain, activity, and major illnesses: The Nurses' Health Study. *Int J Sports Med* 18:S162–S170.

Craft LL, Landers DM. 1998. The effect of exercise on clinical depression and depression resulting from mental illness: A meta-analysis. *J Sport Exerc Psychol* 20:339–357.

Dela F, Mikines KJ, Von Linstow M, Galbo H. 1991. Twenty-four-hour profile of plasma glucose and glucoregulatory hormones during normal living conditions in trained and untrained men. *J Clin Endocrinol Metab* 73:982–989.

DHEW (U.S. Department of Health, Education, and Welfare). 1979. *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention.* DHEW (PHS) Publication No. 79-55071. Rockville, MD: Public Health Service.

Dishman RK. 1997. The norephinephrine hypothesis. In: Morgan WP, ed. *Physical Activity and Mental Health.* Washington, DC: Taylor and Francis. Pp. 199–212.

Eliakim A, Burke GS, Cooper DM. 1997. Fitness, fatness, and the effect of training assessed by magnetic resonance imaging and skinfold-thickness measurements in healthy adolescent females. *Am J Clin Nutr* 66:223–231.

Epstein LH, Wing RR. 1980. Aerobic exercise and weight. *Addict Behav* 5:371–388.

Evans WJ. 1999. Exercise training guidelines for the elderly. *Med Sci Sports Exerc* 31:12–17.

Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R, Simons-Morton DG, Williams MA, Bazzarre T. 2001. Exercise standards for testing and training. A statement for healthcare professionals from the American Heart Association. *Circulation* 104:1694–1740.

Friedlander AL, Casazza GA, Horning MA, Buddinger TF, Brooks GA. 1998a. Effects of exercise intensity and training on lipid metabolism in young women. *Am J Physiol* 275:E853–E863.

Friedlander AL, Casazza GA, Horning MA, Huie MJ, Piacentini MF, Trimmer JK, Brooks GA. 1998b. Training-induced alterations of carbohydrate metabolism in women: Women respond differently from men. *J Appl Physiol* 85:1175–1186.

Friedlander AL, Casazza GA, Horning MA, Usaj A, Brooks GA. 1999. Endurance training increases fatty acid turnover, but not fat oxidation, in young men. *J Appl Physiol* 86:2097–2105.

Fuchs RK, Bauer JJ, Snow CM. 2001. Jumping improves hip and lumbar spine bone mass in prepubescent children: A randomized controlled trial. *J Bone Miner Res* 16:148–156.

Gaesser GA, Brooks GA. 1984. Metabolic bases of excess post-exercise oxygen consumption: A review. *Med Sci Sports Exerc* 16:29–43.

Gallo L, Maciel BC, Marin-Neto JA, Martins LEB. 1989. Sympathetic and parasympathetic changes in heart rate control during dynamic exercise induced by endurance training in man. *Braz J Med Biol Res* 22:631–643.

Graham TE, Adamo KB. 1999. Dietary carbohydrate and its effects on metabolism and substrate stores in sedentary and active individuals. *Can J Appl Physiol* 24:393–415.

Greenleaf JE, Kozlowski S. 1982. Physiological consequences of reduced physical activity during bed rest. *Exerc Sport Sci Rev* 10:84–119.

Grund A, Krause H, Kraus M, Siewers M, Rieckert H, Müller MJ. 2001. Association between different attributes of physical activity and fat mass in untrained, endurance- and resistance-trained men. *Eur J Appl Physiol* 84:310–320.

Hagberg JM, Graves JE, Limacher M, Woods DR, Leggett SH, Cononie C, Gruber JJ, Pollock ML. 1989. Cardiovascular responses of 70- to 79-yr-old men and women to exercise training. *J Appl Physiol* 66:2589–2594.

Hagerman FC, Walsh SJ, Staron RS, Hikida RS, Gilders RM, Murray TF, Toma K, Ragg KE. 2000. Effects of high-intensity resistance training on untrained older men. I. Strength, cardiovascular, and metabolic responses. *J Gerontol A Biol Sci Med Sci* 55:B336–B346.

Haapanen N, Miilunpaio S, Vuori I, Oja P, Pasanen M. 1996. Characteristics of leisure time physical activity associated with decreased risk of premature all-cause and cardiovascular disease mortality in middle-aged men. *Am J Epidemiol* 143:870-880.

Health Canada. 1998. *Canada's Physical Activity Guide to Healthy Active Living*. Ottawa, Canada: Health Canada, Canadian Society for Exercise Physiology.

Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS. 1991. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147-152.

HHS (U.S. Department of Health and Human Services). 1988. *The Surgeon General's Report on Nutrition and Health*. HHS (PHS) Publication No. 88-50210. Washington, DC: Public Health Service.

HHS. 1995. *Healthy People 2000: Midcourse Review and 1995 Revisions*. Washington, DC: Public Heath Service.

HHS. 1996. *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, GA: Centers for Disease Control and Prevention.

HHS. 2000. *Healthy People 2010: Understanding and Improving Health,* 2nd ed. Washington, DC: U.S. Department of Health and Human Services.

Hoffman P. 1997. The endorphin hypothesis. In: Morgan WP, ed. *Physical Activity and Mental Health*. Washington, DC: Taylor and Francis. Pp. 163–177.

Hubert P, King NA, Blundell JE. 1998. Uncoupling the effects of energy expenditure and energy intake: Appetite response to short-term energy deficit induced by meal omission and physical activity. *Appetite* 31:9–19.

Kiens B, Richter EA. 1998. Utilization of skeletal muscle triacylglycerol during postexercise recovery in humans. *Am J Physiol* 275:E332–E337.

Kimm SYS, Glynn NW, Kriska AM, Barton BA, Kronsberg SS, Daniels SR, Crawford PB, Sabry ZI, Liu K. 2002. Decline in physical activity in black girls and white girls during adolescence. *N Engl J Med* 347:709-715.

King DS, Dalsky GP, Staten MA, Clutter WE, Van Houten DR, Holloszy JO. 1987. Insulin action and secretion in endurance-trained and untrained humans. *J Appl Physiol* 63:2247–2252.

King NA, Lluch A, Stubbs RJ, Blundell JE. 1997. High dose exercise does not increase hunger or energy intake in free living males. *Eur J Clin Nutr* 51: 478–483.

Kohl HW, Powell KE, Gordon NF, Blair SN, Paffenbarger RS. 1992. Physical activity, physical fitness, and sudden cardiac death. *Epidemiol Rev* 14:37–58.

Koplan JP. 1979. Cardiovascular deaths while running. *J Am Med Assoc* 242:2578–2579.

Krahenbuhl GS, Williams TJ. 1992. Running economy: Changes with age during childhood and adolescence. *Med Sci Sports Exerc* 24:462–466.

Kraus H, Hirschland RP. 1953. Muscular fitness and health. *J Health Phys Ed Rec* 24:17–19.

Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. 2002. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med* 347:1483-1492.

Landers DM, Arent SM. 2001. Physical activity and mental health. In: Singer RN, Hausenblas HA, Janelle CM, eds. *Handbook of Sport Psychology,* 2nd ed. New York: John Wiley and Sons. Pp. 740–765.

Leon AS, Connett J, Jacobs DR, Rauramaa R. 1987. Leisure-time physical activity levels and risk of coronary heart disease and death. *JAMA* 258:2388-2395.

Loucks AB, Verdun M, Heath EM. 1998. Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. *J Appl Physiol* 84:37–46.

Maciel BC, Gallo L, Marin-Neto JA, Lima-Filho EC, Terra-Filho J, Manco JC. 1985. Parasympathetic contribution to bradycardia induced by endurance training in man. *Cardiovasc Res* 19:642–648.

Mahon AD, Vaccaro P. 1989. Ventilatory threshold and Vo_2max changes in children following endurance training. *Med Sci Sports Exerc* 21:425–431.

Mahon AD, Vaccaro P. 1994. Cardiovascular adaptations in 8- to 12-year-old boys following a 14-week running program. *Can J Appl Physiol* 19:139–150.

Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Moutton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. 2002. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 347:716–725.

Mayer J, Marshall NB, Vitale JJ, Christensen JH, Mashayekhi MB, Stare FJ. 1954. Exercise, food intake and body weight in normal rats and genetically obese adult mice. *Am J Physiol* 177:544–548.

Mayer J, Roy P, Mitra KP. 1956. Relation between caloric intake, body weight, and physical work: Studies in an industrial male population in West Bengal. *Am J Clin Nutr* 4:169–175.

Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. 1993. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. *N Engl J Med* 329:1677–1683.

Mottola MF, Wolfe LA. 2000. The pregnant athlete. In: Drinkwater BL, ed. *Women in Sport.* Oxford: Backwell Science. Pp. 194-207.

Mutrie N. 2000. The relationship between physical activity and clinically defined depression. In: Biddle JH, Fox KR, Boutcher SH, eds. *Physical Activity and Psychological Well-Being.* London: Routledge. Pp. 46–62.

Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. 2002. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346:793–801.

Naghii MR. 2000. The significance of water in sport and weight control. *Nutr Health* 14:127–132.

North TC, McCullagh P, Tran ZV. 1990. Effect of exercise on depression. *Exerc Sport Sci Rev* 18:379–415.

Owens S, Gutin B, Allison J. 1999. Effect of physical training on total and visceral fat in obese children. *Med Sci Sports Exerc* 31:143–148.

Paffenbarger RS, Wing AL, Hyde RT. 1978. Chronic disease in former college students. XVI. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 108:161-175.

Paffenbarger RS, Hyde RT, Wing AL, Hsieh CC. 1986. Physical activity, all-cause mortality, longevity of college alumni. *N Eng J Med* 314:605-613.

Paffenbarger RS, Hyde RT, Wing AL, Lee I-M, Jung DL, Kampert JB. 1993. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 328:538–545.

Paffenbarger RS, Kampert JB, Lee I-M, Hyde RT, Leung RW, Wing AL. 1994. Changes in physical activity and other lifeway patterns influencing longevity. *Med Sci Sports Exerc* 26:857–865.

Paluska SA, Schwenk TL. 2000. Physical activity and mental health. Current concepts. *Sports Med* 29:167–180.

Poehlman ET, Toth MJ, Gardner AW. 1995. Changes in energy balance and body composition at menopause: A controlled longitudinal study. *Ann Intern Med* 123:673–675.

Puyau MR, Adolph AL, Vohra FA, Butte NF. 2002. Validation and calibration of physical activity monitors in children. *Obes Res* 10:150–157.

Raven PB, Mitchell J. 1980. The effect of aging on the cardiovascular response to dynamic and static exercise. In: Weisfeldt ML, ed. *The Aging Heart: Its Function and Response to Stress.* New York: Raven Press. Pp. 269–296.

Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. 1986. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest* 78:1568–1578.

Rockhill B, Willett WC, Manson JE, Leitzmann MF, Stampfer MJ, Hunter DJ, Colditz GA. 2001. Physical activity and mortality: a prospective study among women. *Am J Pub Health.* 91:578-583.

Rooney BL, Schauberger, CW. 2002. Excess pregnancy weight gain and long-term obesity: One decade later. *Obstet and Gynecol* 100: 245–252.

Salmon P. 2001. Effects of physical exercise on anxiety, depression, and sensitivity to stress: A unifying theory. *Clin Psychol Rev* 21:33–61.

Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. 1993. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med* 328:533–537.

Schwartz RS, Shuman WP, Larson V, Cain KC, Fellingham GW, Beard JC, Kahn SE, Stratton JR, Cerqueira MD, Abrass IB. 1991. The effect of intensive endurance exercise training on body fat distribution in young and older men. *Metabolism* 40:545–551.

Sial S, Coggan AR, Carroll R, Goodwin J, Klein S. 1996. Fat and carbohydrate metabolism during exercise in elderly and young subjects. *Am J Physiol* 271:E983–E989.

Siscovick DS, Weiss NS, Fletcher RH, Lasky T. 1984. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med* 311:874–877.

Slattery ML, Jacobs DR, Nichman MZ. 1989. Leisure time physical activity and coronary heart disease death. The US Railroad Study. *Circulation* 79:304-311.

Suh SH, Casazza GA, Horning MA, Miller BF, Brooks GA. 2002. Luteal and follicular glucose fluxes during rest and exercise in 3-h postabsorptive women. *J Appl Physiol* 93:42–50.

Suominen H, Heikkinen E, Parkatti T, Forsberg S, Kiiskinen A. 1977. Effects of "lifelong" physical training on functional aging in men. *Scand J Soc Med Suppl* 14:225–240.

Tabata I, Nishimura K, Kouzaki M, Hirai Y, Ogita F, Miyachi M, Yamamoto K. 1996. Effects of moderate-intensity endurance and high-intensity intermittent training on anaerobic capacity and Vo_{2max}. *Med Sci Sports Exerc* 28:1327–1330.

Tarnopolsky LJ, MacDougall JD, Atkinson SA, Tarnopolsky MA, Sutton JR. 1990. Gender differences in substrate for endurance exercise. *J Appl Physiol* 68:302–308.

Thompson PD. 1982. Cardiovascular hazards of physical activity. *Exerc Sport Sci Rev* 10:208–235.

Thrash LE, Anderson JJB. 2000. The female athlete triad: Nutrition, menstrual disturbances, and low bone mass. *Nutr Today* 35:168–174.

Torun B. 1990. Energy cost of various physical activities in healthy children. In: Schurch B, Scrimshaw NS, eds. *Activity, Energy Expenditure and Energy Requirements of Infants and Children.* Switzerland: IDECG. Pp. 139–183.

Treuth MS, Adolph AL, Butte NF. 1998. Energy expenditure in children predicted from heart rate and activity calibrated against respiration calorimetry. *Am J Physiol* 275:E12–E18.

Treuth MS, Butte NF, Puyau M, Adolph A. 2000. Relations of parental obesity status to physical activity and fitness of prepubertal girls. *Pediatrics* 106:e49.

Treuth MS, Sunehag AL, Trautwein LM, Bier DM, Haymond MW, Butte NF. (2003). Metabolic adaptation to high-fat and high-carbohydrate diets in children. *Am J Clin Nutr* 77:479–489.

USDA/HHS (U.S. Department of Agriculture/Department of Health and Human Services). 1990. *Nutrition and Your Health: Dietary Guidelines for Americans*, 3rd ed. Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

USDA/HHS. 1995. *Nutrition and Your Health: Dietary Guidelines for Americans*, 4th ed. Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

USDA/HHS. 2000. *Nutrition and Your Health: Dietary Guidelines for Americans*, 5th ed. Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

Vaccaro P, Clarke DH. 1978. Cardiorespiratory alterations in 9 to 11 year old children following a season of competitive swimming. *Med Sci Sports* 10:204–207.

van Dale D, Schoffelen PFM, ten Hoor F, Saris WHM. 1989. Effects of addition of exercise to energy restriction on 24-hour energy expenditure, sleeping metabolic rate and daily physical activity. *Eur J Clin Nutr* 43:441–451.

Van Zant RS. 1992. Influence of diet and exercise on energy expenditure—A review. *Int J Sport Nutr* 2:1–19.

Wei M, Macera CA, Hornung CA, Blair SN. 1997. Changes in lipids associated with change in regular exercise in free-living men. *J Clin Epidemiol* 50:1137–1142.

Welten DC, Kemper HCG, Post GB, Van Mechelen W, Twisk J, Lips P, Teule GJ. 1994. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. *J Bone Miner Res* 9:1089–1096.

West RV. 1998. The female athlete. The triad of disordered eating, amenorrhoea and osteoporosis. *Sports Med* 26:63–71.

Wilbur J, Naftzger-Kang L, Miller AM, Chandler P, Montgomery A. 1999. Women's occupations, energy expenditure, and cardiovascular risk factors. *J Women's Health* 8:377–387.

Willich SN, Lewis M, Löwel H, Arntz H-R, Schubert F, Schröder R. 1993. Physical exertion as a trigger of acute myocardial infarction. *N Engl J Med* 329:1684–1690.

World Health Organization (WHO). 2000. *Obesity: Preventing and Managing the Global Epidemic.* Geneva:WHO.

Yen SSC, Vela P. 1968. Effects of contraceptive steroids on carbohydrate metabolism. *J Clin Endocrinol* 28:1564–1570.

13

Applications of Dietary Reference Intakes for Macronutrients

This chapter presents a general discussion of the appropriate uses of the Dietary Reference Intakes (DRIs) in the assessment and planning of diets for individuals and for groups. It also provides guidance for the use of the DRIs developed for the nutrients presented in this report, including specific examples and special considerations.

OVERVIEW

The Dietary Reference Intakes (DRIs) may be used for many purposes, most of which fall into two broad categories: assessing current nutrient intakes and planning for future nutrient intakes. Each category may be further subdivided into uses for individual diets and for group diets (Figure 13-1).

For example, the Recommended Dietary Allowance (RDA), Estimated Average Requirement (EAR), and Tolerable Upper Intake Level (UL) may be used in assessing the diet of an individual as one aspect of a nutritional status assessment. The RDA and Adequate Intake (AI) may be used as a basis for planning a diet for the same individual. Likewise, the EAR and UL are used to assess the nutrient intakes of a group, such as persons participating in dietary surveys conducted as part of the National Nutrition Monitoring System. The EAR and UL can also be used to plan nutritionally adequate diets for groups, such as people receiving meals in nursing homes, schools, prisons, and other group settings.

In the past, RDAs in the United States and Recommended Nutrient Intakes (RNIs) in Canada were the primary reference standards available

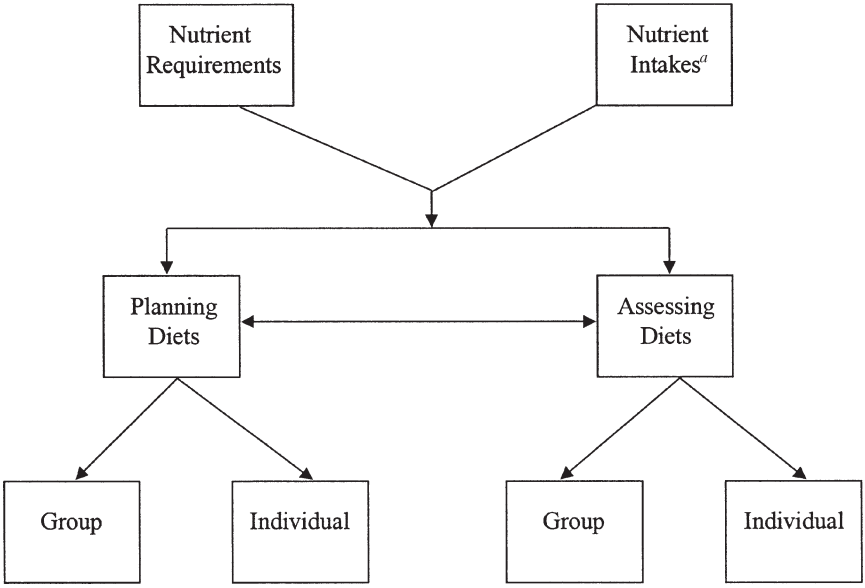

FIGURE 13-1 Conceptual framework—uses of Dietary Reference Intakes.
[a] Food plus supplements.

to health professionals for assessing and planning diets of individuals and groups and for making judgments about inadequate and excessive intake. However, neither the former RDAs nor the RNIs were ideally suited for many of these purposes (IOM, 1994). The DRIs provide a more complete set of reference values. The transition from using the former RDAs and RNIs to using all of the DRIs appropriately will require time and effort by health professionals and others.

Appropriate uses of each of the new DRIs are described briefly in this chapter and in more detail in a report on the application of the DRIs in assessment (IOM, 2000) and in a forthcoming report on their uses in planning. Included in this chapter are specific applications to the nutrients discussed in this report. Details on how the DRIs are set with reference to specific life stage and gender groups, and the primary criterion that defines adequacy for each of these nutrients are given in Chapters 5 through 10.

ASSESSING NUTRIENT INTAKES OF INDIVIDUALS

Dietary assessment methods have several inherent inaccuracies. One is that individuals underreport their intakes (Mertz et al., 1991; Schoeller,

1995; Schoeller et al., 1990), and it appears that obese individuals often do so to a greater extent than do normal-weight individuals (Heitmann and Lissner, 1995). There is no method to adjust intakes to account for under-reporting by individuals and much work is needed to develop an acceptable method. Another inherent inaccuracy is the quality of food composition databases.

Furthermore, large day-to-day variations in intake, which are exhibited by almost all individuals, mean that it often takes a prohibitively large number of days of intake measurement to approximate usual intake (Basiotis et al., 1987). As a result, caution is indicated when interpreting nutrient assessments based on self-reported dietary data covering only a few days of intake. Data on nutrient intakes should be interpreted in combination with information on typical food usage patterns to determine if the recorded intakes are representative of that individual's usual intake.

Finally, because there is considerable variation in intakes both within and between individuals, as well as variation associated with the requirement estimate, other factors must be evaluated in conjunction with the diet. The Dietary Reference Intakes (DRIs) should be used in conjunction with other data in assessing the adequacy of the diet of a specific individual. The nutritional status of an individual can be definitively determined only by a combination of dietary, anthropometric, physiological and biochemical data.

Using the Estimated Average Requirement and the Recommended Dietary Allowance

The Estimated Average Requirement (EAR) estimates the median of a distribution of requirements for a specific life stage and gender group, but it is not possible to know where an individual's requirement falls within this distribution without further anthropometric, physiological, or biochemical measures. Thus from dietary data alone, it is only possible to estimate the *likelihood* of nutrient adequacy or inadequacy. Furthermore, only rarely are precise and representative data on the usual intake of an individual available, adding additional uncertainty to the evaluation of an individual's dietary adequacy.

An approach for using data from dietary records or recalls to estimate the likelihood that an individual's nutrient intake is adequate is presented in *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000). This approach is appropriate for nutrients with symmetrical requirement distributions, which is thought to be true for all macronutrients in this report for which EARs have been established. The following data are required:

- individual's mean nutrient intake over a given number of days
- day-to-day standard deviation (SD) of intakes for each nutrient of interest, as estimated from larger data sets for the appropriate life stage and gender group
- EAR
- SD of the nutrient requirement in the individual's life stage and gender group.

From this information a ratio is computed that compares the magnitude of difference between the individual's intake and the EAR to an estimate of variability of intake and requirements. The bigger the difference between intake and EAR and the lower the variability of intakes and requirements, the greater is the degree of certainty in assessing whether the individual's nutrient intake is adequate, inadequate, or excessive. This approach is quantitative and should be used only when the data listed above are available.

However, in the more common situation where the estimate of usual intake is not based on actual 24-hour recalls or records, but on dietary history or food frequency questionnaires, a qualitative interpretation of intakes can be used. For example, many practitioners use the diet history method to construct a likely usual day's intake, but the error structure associated with this method is unknown. While the error associated with food frequency questionnaires has been evaluated (Carroll et al., 1996; Liu, 1994), use of these tools for quantitative nutrient assessment is still not possible due to lack of accurate portion size estimates and grouping of food items (IOM, 2000). Thus, a practitioner should be cautious when using this method to approximate usual intakes.

Users of the DRIs may find it useful to consider that observed intakes below the EAR probably need to be improved (because the probability of adequacy is 50 percent or less) and those between the EAR and the Recommended Dietary Allowance (RDA) probably need to be improved (because the probability of adequacy is less than 97 to 98 percent). Only if intakes have been observed for a large number of days and are at the RDA, or observed intakes for fewer days are well above the RDA, should one have a high level of confidence that the intake is adequate. Such considerations are not applicable in the case of energy intake, which should match energy expenditure in individuals maintaining desirable body weight (see later section, "Planning Nutrient Intakes of Individuals," and Chapter 5).

Using the Adequate Intake

Adequate Intakes (AIs) have been set for infants younger than 7 months of age for *n*-3 and *n*-6 polyunsaturated fatty acids and protein. By definition, infants born at term who are exclusively fed human milk by healthy

mothers consume an adequate nutrient intake. Infants who consume formulas with a nutrient profile similar to human milk (after adjustment for differences in bioavailability) are also assumed to consume adequate levels of nutrients. When an infant formula contains nutrient levels that are lower than those found in human milk, the likelihood of nutrient adequacy for infants who consume this formula cannot be determined because data on infants fed lower concentrations of nutrients are not available. AIs have also been established for infants 7 to 12 months of age for all nutrients covered in this report except protein, and for all individuals for *Total Fiber* and the *n*-3 and *n*-6 polyunsaturated fatty acids.

Equations that can be used to estimate the degree of confidence that an individual's usual intake meets or exceeds the AI are presented (IOM, 2000). The data required include the individual's reported intake over a given number of days, the AI for the age/gender group, and the day-to-day (within-person) SD for the nutrient of interest, as estimated from larger data sets for the appropriate life stage and gender group. Usual individual intakes that are equal to or above the AI can be assumed to be adequate. However, the likelihood of inadequacy of usual intakes below the AI cannot be determined.

Using the Tolerable Upper Intake Level

The Tolerable Upper Intake Level (UL) is used to examine the possibility of over-consumption of a nutrient. Equations have been developed to determine the degree of confidence that an individual's intake is below the UL (IOM, 2000). If an individual's usual nutrient intake remains below the UL, there is no risk of adverse effects from excessive intake. At intakes above the UL, the potential for risk of adverse effects increases. However, the intake at which a given individual will develop adverse effects as a result of taking large amounts of one or more nutrients is not known with certainty. No ULs were set for the macronutrients in this report. However, there is no established benefit to almost all healthy individuals who consume amounts of nutrients that exceed the RDA or AI.

Equations that can be used to estimate the degree of confidence that an individual's usual intake equals or exceeds the UL are presented in *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000). The data required include the individual's reported intake over a given number of days, the UL for the life stage and gender group, and the day-to-day (within-person) SD for the nutrient of interest, as estimated from larger data sets for the appropriate life stage and gender group.

Using the Acceptable Macronutrient Distribution Range

In addition to presenting DRIs for macronutrients, this report also presents Acceptable Macronutrient Distribution Ranges (AMDRs) for individuals as a proportion of total energy intake. The AMDRs represent intakes that minimize the potential for chronic disease over the long-term, permit essential nutrients to be consumed at adequate levels, and should be associated with adequate energy intake and physical activity to maintain energy balance. The AMDRs for adults are 20 to 35 percent of energy from fat (including 0.6 to 1.2 percent of energy from *n*-3 polyunsaturated fatty acids and 5 to 10 percent of energy from *n*-6 polyunsaturated fatty acids), 45 to 65 percent of energy from carbohydrate, and 10 to 35 percent of energy from protein. For children, the AMDRs for total fat are 30 to 40 percent between the ages of 1 and 3 years, and 25 to 35 percent between the ages of 4 and 18 years. AMDRs for protein and carbohydrate do not vary with age.

To estimate the degree of confidence that an individual's diet falls within the AMDR, the equations developed could be used to estimate the degree of confidence that the individual's intake exceeds the AI or remains below the UL (IOM, 2000). The equation for the AI could be used to determine the degree of confidence that intake is above the lower end of the AMDR, and the equation for the UL could be used to determine the degree of confidence that intake is below the upper end of the AMDR. The data required include the individual's average intake of the macronutrient of interest as a percent of energy intake over a given number of days, the boundaries of the AMDR, and the day-to-day (within-person) SD of percent energy intake, as estimated from larger data sets for the appropriate life stage and gender group.

ASSESSING NUTRIENT INTAKES OF GROUPS

The assessment of nutrient adequacy for groups of people requires unbiased, quantitative information on the intake of the nutrient of interest by individuals in the group. Care must be taken to ensure the quality of the information upon which assessments are made so that they are not underestimates or overestimates of total nutrient intake. Estimates of total nutrient intake, including amounts from supplements, should be obtained. It is also important to use appropriate food composition tables with accurate nutrient values for the foods as consumed.

Several steps must be taken to assess the intake of a group. First, the intake distribution must be adjusted to remove the effect of day-to-day variation of individual intake. This can be accomplished either by collect-

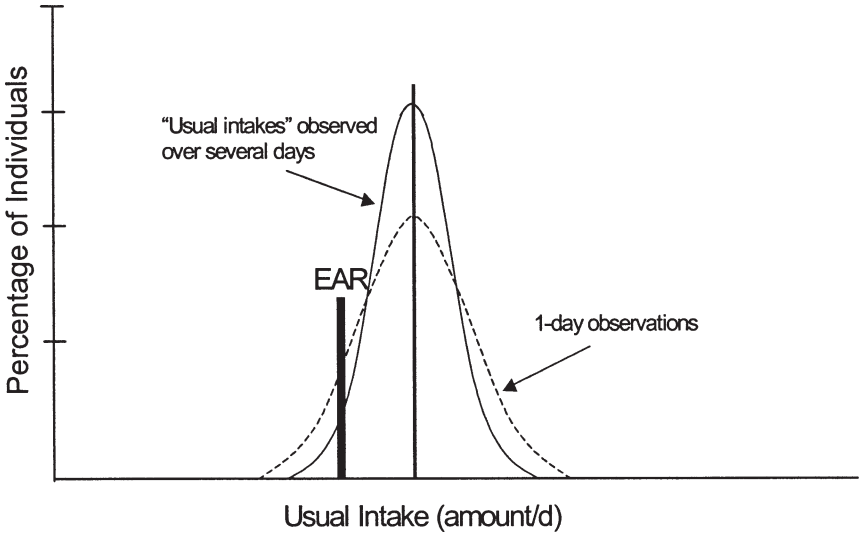

FIGURE 13-2 Comparison of 1-day and usual intakes for estimating the proportion of a group consuming below the Estimated Average Requirement (EAR).

ing dietary data for each individual over a large number of days or by statistical adjustments to the intake distribution. The statistical adjustments are based on assumptions about the day-to-day variation derived from repeat measurements of a representative subset of the group under study (Nusser et al., 1996). When this adjustment is performed and observed intakes are thus more representative of the usual diet, the intake distribution narrows, giving a more precise estimate of the proportion of the group with usual intakes below requirements (Figure 13-2). An explanation of this adjustment procedure has been presented in two previous reports (IOM, 2000; NRC, 1986).

A statistical approach is then used to combine the information on nutrient intakes with the information on nutrient requirements in order to determine the apparent percent prevalence of nutrient inadequacy in the group. Two approaches are briefly described below and in detail elsewhere (IOM, 2000; NRC, 1986).

The Probability Approach

Using the probability approach requires knowledge of both the distribution of requirements and the distribution of usual intakes for the population of interest. As described previously (IOM, 2000; NRC, 1986), the probability approach involves: (1) determining the risk of inadequacy for

each individual in the population and then (2) averaging the individual probabilities of inadequacy across the group. Appendix C of *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000) demonstrates how to carry out the necessary calculations to obtain a prevalence estimate for a group. Statistical programs (e.g., SAS or similar software) can be used to carry out these procedures.

The EAR Cut-Point Method

In most situations a cut-point method using the Estimated Average Requirement (EAR) may be used to estimate the prevalence of inadequate intakes. This cut-point method is a simplification of the full probability approach of calculating the prevalence of inadequacy described by the National Research Council (NRC, 1986). The cut-point method allows the prevalence of inadequate intakes in a population to be approximated by determining the percentage of individuals in the group whose usual intakes are less than the EAR for the nutrient of interest. This method assumes that the intake and requirement distributions are independent, an assumption that is not valid for the energy requirements addressed in this report because energy intakes are highly correlated to energy expenditure. The cut-point method further assumes that the variability of intakes among individuals within the group under study is at least as large as the variability of their requirements. This assumption is usually warranted in free-living populations. Finally, it assumes that the requirement distribution is symmetrical. This is thought to be true for all of the macronutrients discussed in this report.

Using the Estimated Average Requirement

If the assumptions for the EAR cut-point method are met, the prevalence of inadequate intakes may be estimated by the proportion of the distribution of usual intakes that falls below the EAR. An example of using the EAR cut-point method to assess the dietary carbohydrate adequacy of women aged 31 to 50 years follows. Dietary intake data are available from the 1994–1996 Continuing Survey of Food Intakes by Individuals. Estimated intakes are based on respondents' intakes, which were adjusted to remove within-person variability using the Iowa State University method (Appendix Table E-2). The EAR for women in this age group is 100 g/day. Examination of the distribution of usual carbohydrate intake reveals that intakes at the 1st and 5th percentiles are 87 and 118 g/day, respectively. Thus, fewer than 5 percent of women in this age group appear to have inadequate carbohydrate intakes.

Overestimates of the prevalence of inadequate intakes could result if the data used are based on intakes that are systematically underreported or if foods rich in the nutrient of interest are underreported. Such underreporting is common in national surveys (Briefel et al., 1997). Currently, a method for adjusting intakes to compensate for underreporting by individuals is not available, and much work is needed to develop an acceptable method. Conversely, underestimates of the prevalence of inadequacy could result if foods rich in the nutrient of interest were overreported. A more extensive discussion of potential sources of error in self-reported dietary data can be found in the report *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000).

Comparison of Assessments Using the Probability Approach and Biochemical Assessment

If requirement estimates are correct, dietary intake data are reliable estimates of true usual intake, and biochemical measures reflect the same functional criterion used to set the requirement of a nutrient for the same population, then the prevalence of apparently inadequate dietary intakes and biochemical deficiencies or indicators of inadequacy should be similar.

Using the Recommended Dietary Allowance

The Recommended Dietary Allowances are not useful in estimating the prevalence of inadequate intakes for groups. As described above, the EAR should be used for this purpose.

Using the Adequate Intake

In this report Adequate Intakes (AIs) are assigned for all nutrients for infants through the age of 6 months and reflect the average intake of infants receiving human milk. Human milk and formulas with the same nutrient composition as human milk (after adjustment for bioavailability) provide the appropriate levels of nutrients for full-term infants of healthy, well-nourished mothers. For infants ages 7 to 12 months, AIs are set for carbohydrate and *n*-3 and *n*-6 polyunsaturated fatty acids and reflect the average intakes of infants receiving human milk and complementary foods. Groups of infants consuming formulas with lower levels of nutrients than that found in human milk may be at some risk of inadequacy, although the prevalence of inadequacy cannot be quantified.

This report provides AIs for all life stage and gender groups for *Total Fiber* and *n*-3 and *n*-6 polyunsaturated fatty acids. Groups with median intakes equal to or above the AI for *Total Fiber* and *n*-3 and *n*-6 poly-

unsaturated fatty acids can be assumed to have a low prevalence of inadequacy (provided that intake variability does not exceed that of the healthy group used to establish the AI). However, when the AI is not set as a mean intake of a healthy group (e.g., fiber), confidence in this assessment should be less than it would be if the AI represents the median intake of a healthy group. It is important to note that group median intakes below the AI cannot be assumed to be inadequate.

Using the Tolerable Upper Intake Level

The proportion of the population with usual intakes below the Tolerable Upper Intake Level (UL) is likely to be at no risk of adverse effects due to overconsumption. However, the proportion of the population consuming above the UL may potentially be at some risk.

The mean intake of a population cannot be used to evaluate the prevalence of intakes above the UL. A distribution of usual intakes, including intakes from supplements, is required to assess the proportion of the population that might be at risk of over-consumption. However, if the mean or median intake is equal to or greater than the UL, it suggests that the number of individuals with excessive intake is high and warrants further investigation.

Using the Acceptable Macronutrient Distribution Range

Although primarily directed at individuals, the Acceptable Macronutrient Distribution Range (AMDR) also permits assessment of populations. By determining the proportion of the group that falls below, within, and above the AMDR, it is possible to assess population adherence to recommendations and to determine the proportion of the population that is outside the range. If significant proportions of the population fall outside the range, concern could be heightened for possible adverse consequences. Planning and public health messages can then be instituted to attempt to attain a low prevalence of intakes below or above the AMDR.

For example, the AMDR for total fat intake of children 4 to 18 years of age is 25 to 35 percent of energy. Appendix Table E-6 presents data on the usual daily intake of total fat as a percentage of energy intake and indicates that for all groups of children and adolescents, the 5th percentile of intake is at least 25 percent. Thus, fewer than 5 percent of children have intakes below the AMDR for total fat. The 75th percentiles of intake are close to 35 percent, suggesting that approximately 25 percent of children and adolescents have intakes above the AMDR for total fat. Intakes of the remaining 70 to 75 percent fall within the AMDR.

PLANNING NUTRIENT INTAKES OF INDIVIDUALS

Using the Recommended Dietary Allowance

Individuals should use the Recommended Dietary Allowance (RDA) as the target for their intakes for those nutrients for which RDAs have been established. Intakes at this level ensure that the risk to individuals of not meeting their requirements is very low (2 to 3 percent). For example, the RDA for protein for adults is 0.8 g/kg/day, or 56 and 46 g/day for reference men and women weighing 70 kg and 57 kg, respectively. For a small adult weighing 45 kg, the recommended protein intake would be 36 g/day, while for a larger adult weighing 90 kg, the RDA would be 72 g/day.

Using the Adequate Intake

Adequate Intakes (AIs) are set for infants younger than 7 months of age for all nutrients, and for all nutrients except protein and indispensable amino acids for infants 7 through 12 months of age. Human milk, by definition, supplies the AI for a nutrient for term infants; it is not necessary to plan additional sources of intake for infants exclusively fed human milk. Likewise, an infant formula with a nutrient profile similar to human milk (after adjustment for differences in bioavailability) should supply adequate nutrients for an infant.

In this report AIs are also set for children, adolescents, and adults for *Total Fiber* and *n*-3 and *n*-6 polyunsaturated fatty acids. Accordingly, individuals should use the AI as their goal for intake of these nutrients.

Using the Tolerable Upper Intake Level

Tolerable Upper Intake Levels (Uls) were not set for the macronutrients covered in this report.

Using the Acceptable Macronutrient Distribution Range

In addition to meeting the RDA or AI and remaining below the UL, an individual's intake of macronutrients should be planned so that carbohydrate, total fat, *n*-3 and *n*-6 polyunsaturated fatty acids, and protein are within their respective Acceptable Macronutrient Distribution Ranges.

PLANNING NUTRIENT INTAKES OF GROUPS

Using the Estimated Average Requirement and the Tolerable Upper Intake Level

For those nutrients with Estimated Average Requirements (EAR), the EAR may be used as a basis for planning or making recommendations for the nutrient intakes of groups. The mean intake of a group should be high enough so that only a small percentage of the group would have intakes below the EAR, thus indicating a low prevalence of dietary inadequacy. The approach to planning for a low prevalence of inadequacy differs depending on whether or not the distributions of intake and requirements are normally distributed. Additional details are provided in the forthcoming Institute of Medicine report on dietary planning.

For example, assume that the goal of planning was to target a 2 to 3 percent prevalence of inadequacy for a nutrient for which both requirement and intake distributions were statistically normal. This would be attained by planning a group mean intake equal to the EAR plus 2 standard deviations (SD) of the *intake* distribution. Because the variability of intakes generally exceeds the variability of requirements, this target group mean intake will usually exceed the Recommended Dietary Allowance (which equals the EAR plus 2 SDs of the *requirement* distribution). Prevalence of inadequacy more or less than 2 to 3 percent could also be considered. Mean intakes needed to attain the desired prevalence would be estimated by determining the number of SDs of intake added to the EAR that would result in the desired percentage prevalence below the EAR. This can be done by consulting tables that list areas under the curve of the standard normal distribution in relation to SD scores (z-scores).

When the distribution of intakes is skewed (as is true for intakes of most nutrients), a low prevalence of inadequacy can be attained by planning to position the intake distribution such that only the targeted proportion is below the EAR. Finally, when it is known that requirements for a nutrient are not normally distributed and one wants to ensure a low group prevalence of inadequacy, it is necessary to examine both the intake and requirement distributions to determine a median intake at which the proportion of individuals with intakes below requirements is likely to be low.

In addition to planning for an acceptably low group prevalence of intakes below the EAR, the planned distribution also needs to be examined to ensure that the prevalence of intakes above the Tolerable Upper Intake Level (UL) is also acceptably low.

Using the EAR and UL in planning intakes of groups involves the analysis of data and a number of key considerations such as:

- determination of the current usual nutrient intake distribution of the group of interest expressed in the same unit as the EAR (e.g., g/day, g/kg/day, percent of energy);
- selection of the degree of risk that can be tolerated when planning for the group (e.g., a 2 to 3 percent prevalence versus a higher or lower prevalence); and
- consideration of various possible interventions to shift the current distribution, if necessary, to produce an acceptably low prevalence of intakes below the EAR, as well as an acceptably low prevalence of intakes above the UL; some targeted interventions may increase the intake of only those most at risk, while other interventions (e.g., fortification of the food supply) may increase the intake, to varying degrees, of the majority of the population.

Using the Adequate Intake in Planning for Groups

As indicated previously, Adequate Intakes (AIs) have been established for some of the nutrients discussed in this report. Planning a median group intake that meets the AI should, by definition, be associated with a low prevalence of inadequacy, if the AI was set as the median intake of a healthy group and the group being planned for has similar characteristics to the group used to establish the AI. If the AI was not set as the median intake of a healthy group (e.g., the AI for *Total Fiber*), there is less confidence that the prevalence of inadequacy would be low if the group's median intake met the AI.

Using the Acceptable Macronutrient Distribution Range

In addition to ensuring that the group prevalence of intakes below the EAR or above the UL is acceptably low, an additional goal of planning is to achieve a macronutrient distribution in which the intakes of most of the group fall within the Acceptable Macronutrient Distribution Ranges (AMDRs). There may be a tendency for planners to develop menus and patterns in which the mean population intakes are at the midpoint of the AMDRs; this is one method to plan for low prevalence of intakes below or above the AMDR. For example, a meal program for a university dormitory might be planned using the midpoint of the ranges for carbohydrate and fat (for adults, these would be 55 and 28 percent of energy, respectively). The remaining 17 percent of energy would come from protein. Assessment would be needed to determine whether intakes of most members of the group fell within the AMDR, or whether interventions were required to target one end of the distribution (e.g., those with fat intakes above 35 percent). However, planning for the midpoint of a range is not the

only way that the AMDR can be used to plan for groups. Using the university dormitory example, a dietary pattern might be planned in which the mean intake from fat was 30 percent of energy. Assessment conducted following implementation of the program might reveal that actual fat intakes of the students ranged from about 25 percent to about 35 percent of energy. In other words, the prevalence of intakes outside the acceptable range is low, despite a mean fat intake that is higher than the midpoint of the range. While the AMDR can be used as a general quantitative guideline for planning and evaluating diets, qualitative considerations, such as a menu low in saturated fats, may be at least as important as these quantitative guidelines (see Chapter 11).

NUTRIENT-SPECIFIC CONSIDERATIONS

Energy

Planning Energy Intakes for Individuals

The underlying objective of planning for energy is similar to planning for nutrients—to attain an acceptably low risk of inadequacy and of excess. The approach to planning for energy, however, differs substantially from planning for other nutrients. When planning for an individual's intake of nutrient such as vitamins and minerals, the goal is a low risk of inadequacy by meeting the Recommended Dietary Allowance (RDA) or Adequate Intake (AI), and a low risk of excess by remaining below the Tolerable Upper Intake Level (UL). Even though intakes at or above the RDA or AI are almost certainly above an individual's requirement, there are no adverse effects to the individual of consuming an intake above his or her requirement, provided intake remains below the UL; however there are also no documented benefits.

The situation for energy is quite different. There are adverse effects to individuals who consume energy above their requirements—over time, weight gain will occur. This difference is reflected in the fact that there is no RDA for energy, as it would be inappropriate to recommend an intake that exceeded the requirement (and would lead to weight gain) of 97 to 98 percent of individuals. The requirement for energy for individuals of normal weight is expressed as an Estimated Energy Requirement (EER), which reflects the energy expenditure associated with an individual's sex, age, height, weight, and physical activity level.

Equations are presented to estimate an individual's energy expenditure, with separate equations for normal (body mass index [BMI] > 18.5 and < 25) and overweight (BMI ≥ 25) individuals, as well as for all individuals with BMI > 18.5 (i.e., including normal, overweight, and obese subjects).

For overweight individuals, these equations estimate Total Energy Expenditure (TEE), rather than the EER, which is reserved for normal weight individuals. In all cases, however, the equations estimate the energy expenditure associated with maintaining current body weight and activity level. They were not developed, for example, to lead to weight loss in overweight individuals. However, just as is the case with other nutrients, energy expenditures vary from one individual to another, even though their characteristics may be similar. This variability is reflected in the standard deviation (SD), which allows for estimation of the range within which the individual's energy expenditure could vary. Note that this does not imply that an individual would maintain energy balance at any intake within this range; it simply indicates how variable requirements could be among those with similar characteristics.

For example, the equation for the EER of women ages 19 years and older with a BMI > 18.5 and < 25 is:

$$\text{Energy (kcal)} = 354.1 - (6.91 \times \text{age [y]}) + \text{physical activity coefficient} \times (9.36 \times \text{weight [kg]} + 726 \times \text{height [m]})$$

The SD is 160 kcal. Therefore, the EER for a normal-weight, 33-year-old low-active woman (i.e., with a physical activity level (PAL) between 1.4 and 1.59, for whom the physical activity coefficient is 1.12), with a height of 1.63 m and a weight of 55 kg would be:

$$\text{Energy (kcal)} = 354.1 - (6.91 \times 33) + 1.12 \times (9.36 \times 55 + 726 \times 1.63) = 2{,}028$$

The 95 percent confidence interval for this equation reflects the range within which a given individual's energy expenditure likely falls, and in this example, it would be 2,028 ± (2 × 160), or between 1,708 and 2,348 kcal/day. It must be realized that considerable uncertainties are inherent in making such predictions, notably because of possible misclassification of individuals into the various PAL categories (i.e., sedentary, low active, active, and very active).

Usual energy intakes are highly correlated with expenditure when considered over periods of weeks or months. This means that most people who have access to enough food will, on average, consume amounts of energy very close to the amounts that they expend, and as a result, maintain their weight over extended periods of time. Any changes in weight that do occur usually reflect small imbalances accumulated over a long period of time. For normal individuals who are weight-stable, at a healthy weight, and performing at least the minimal recommended amount of activity, their energy requirement (and recommended intake) is their usual

energy intake. Thus, if an individual's usual energy intake were known, the plan would be to maintain it rather than use the EER (or if overweight, the TEE). In many situations, however, the usual energy intake of an individual is not known, and the estimated energy requirement equations are useful planning tools.

Using the EER (or TEE) to Maintain Body Weight. When the goal is to maintain body weight in an individual with specified characteristics (age, height, weight, and activity level), an initial estimate for energy intake is provided by the equation for the energy expenditure of an individual with those characteristics. By definition, the estimate would be expected to underestimate the true energy expenditure 50 percent of the time and to overestimate it 50 percent of the time, leading to corresponding changes in body weight. This indicates that monitoring of body weight would be required when implementing intakes based on the equations that predict individual energy requirements. For example, if subjects were enrolled in a study in which it was important to maintain body weight, each individual would be fed the amount of energy estimated to be needed based on the EER equation. Body weight would be closely monitored over time, and the amount of energy provided to each individual would be adjusted up or down from the EER (or TEE) as required to maintain body weight.

Using the EER (or TEE) to Plan to Prevent Weight Loss. In some situations the goal of planning might be to prevent weight loss in an individual with specified characteristics. In this situation, the EER or TEE equation could be used to derive the average energy expenditure for the individual, and then an amount equal to two times the SD added. This would lead to an intake that would be expected to exceed the actual energy expenditure of all but 2 to 3 percent of the individuals with similar characteristics. Using the above example for the 33-year-old, low-active woman, one would provide 2,028 + (2 × 160) kcal, or 2,348 kcal. This intake would prevent weight loss in almost all individuals with similar characteristics. Of course, this level of intake would lead to weight gain in most of these individuals.

Using the EER (or TEE) to Plan to Prevent Weight Gain. If the goal of planning is to prevent weight gain in an individual with specified characteristics, the appropriate EER equation could be used to derive the average energy expenditure for the individual, and then subtract an amount equal to two times the SD. This would lead to an intake that would be expected to fall below the actual energy requirements of all but 2.5 percent of the individuals with similar characteristics. Using the above example for the 33-year-old, low-active woman, the energy requirement would be 2,028 – (2 × 160) kcal, or 1,708 kcal. This intake would prevent

weight gain in almost all individuals with similar characteristics. Of course, this level of intake would lead to weight loss in most of these individuals.

Planning for Energy for Groups

As is true for individuals, the underlying objective in planning the energy intake of a group is similar to planning intakes for other nutrients—to attain an acceptably low prevalence of inadequacy and of potential excess. The approach to planning for energy, however, differs substantially from planning for other nutrients. When the Estimated Average Requirement (EAR) cut-point method is used to plan for a group's intake of nutrients such as vitamins and minerals, a low prevalence of inadequacy is obtained by positioning the intake distribution such that an acceptably low proportion of the group has an intake below the EAR. A low prevalence of potential risk of excess is obtained by positioning the intake distribution such that an acceptably low proportion of the group has an intake above the UL. Even though the planned distribution of intakes would exceed the actual requirements of all but the designated proportion of the group (in many cases, by a considerable margin), there are no known adverse effects to the group of consuming vitamins and minerals in amounts that exceed requirements, provided the proportion above the UL also remains low.

In the case of energy, however, there *are* adverse effects for the individuals in the group whose intakes are above their requirements, as weight gain is bound to occur over time. Therefore, the EAR cut-point method to plan for group intakes of energy is clearly inappropriate. In addition, the assumptions required to apply this method, as well as for the probability approach, do not hold for energy. Most notably, the methods assume that intakes are essentially uncorrelated with requirements. In the case of energy, however, intakes are very highly correlated with requirements.

What, then, can be done to plan for energy intakes of groups? There are two possible approaches: estimate energy requirements for the reference person or obtain an average of estimated maintenance energy needs for group members.

Estimate Energy Requirements for the Reference Person. One approach is to use the EER for the reference person who represents the group. For example, to plan for a large group of men ages 19 to 30 years, estimate the EER for the reference male with a weight of 70 kg and a height of 1.76 m and who is considered low active, and use this number (~2,700 kcal) as the target for the group. This approach would require the assumption that all members of the group were similar to the reference person, or that the reference individual accurately represented group average values for age,

height, weight, and activity level, and that these variables were symmetrically distributed. If either assumption held, the resulting EER would approximate the group mean energy requirement.

However, if the assumptions did not hold true, as is likely in many situations, the estimates would be incorrect. At a practical level, it is likely that the estimate obtained would be less than the true average energy expenditure of the group, since for most life stage and gender groups the reference person weighs less than the average person.

Obtain an Average of Estimated Maintenance Energy Needs for Group Members. The preferred approach would be to plan for an intake equal to the average energy expenditure for the group. For example, using the same group of 19- to 30-year-old men from the previous section, the energy expenditure for each individual in the group would be estimated (assuming access to data on height, weight, age, and activity level). The average of these values would be used as the planning goal for maintenance of current weight and activity level. Table 13-1 shows an example of how this is done for a small group of six healthy men with a BMI < 25. If the group included men with a BMI > 25, the equations developed to estimate the Total Energy Expenditure for overweight individuals would be used for those individuals with BMI > 25.

In this hypothetical example, the average planned intake exceeds the EER of five of the men, and is below the EER of one large, very active man (in a larger, more homogeneous group, the estimate would be expected to

TABLE 13-1 Obtaining an Average Estimated Energy Requirement (EER) for a Group

Subject	Age (y)	Height (m)	Weight (kg)	Physical Activity Level	Physical Activity Level Coefficient	EER[a] (kcal)
1	21	1.83	95	Sedentary	1.0	2,961
2	27	1.77	75	Low active	1.12	2,811
3	25	1.69	60	Active	1.27	2,794
4	19	1.80	75	Low active	1.12	2,905
5	30	1.73	80	Very active	1.45	3,575
6	25	1.75	75	Low active	1.12	2,818
Mean	24.5	1.76	76.7	—	1.18	2,977

[a] Energy (kcal) = 661.8 – 9.53 × age (y) + physical activity coefficient × [15.91 × weight (kg) + 539.6 × height (m)]. Physical activity level coefficient = 1.0 (sedentary), 1.12 (active), 1.45 (very active).

be inadequate for half the men and above the requirement for the other half). However, because intakes and expenditures are highly correlated, and assuming that all members of the group have free access to food, most members of the group will consume an amount of energy equal to their expenditure. Thus, planning for an intake that approximates the mean energy expenditure should allow the group to meet energy needs for weight maintenance and current activity levels.

Caveats. As with other planning applications, it should be emphasized that the planning goal is for energy intakes. The above approach requires the assumption that free access to food is available, that each member of the group consumes an amount of energy that approximates their individual expenditure, and that food is not wasted or spoiled. As with other planning examples, food waste and to what extent the amount of energy offered would need to exceed the target median intake need to be considered. Assessing the plan following its implementation would lead to further refinements.

Assessing Energy Intakes

As was true for planning, the approach to assessing the adequacy of energy intakes differs from that described for other nutrients. This arises in part from theoretical considerations. Perhaps more importantly though, it is related to the fact that for energy, unlike most nutrients, a readily observable, accurate biological indicator—body weight—can be used to assess the long-term adequacy of energy intake. An individual or group with a BMI above the desirable range reflects long-term excess energy intake, while the converse is true when BMI is below the desirable range.

The availability of a biological indicator to assess the adequacy of energy intake becomes particularly critical because of the effect of dietary underreporting on the assessment of adequacy. It is now widely accepted, and supported by a large body of literature, that underreporting of food intake is pervasive in dietary surveys (Black et al., 1993). Underreporters can constitute anywhere from 10 to 45 percent of the total sample, depending on the age, gender, and body composition of the sample. Underreporting tends to increase in prevalence as children age (Livingstone et al., 1992), and is greater among women than among men (Johnson et al., 1994). Both the prevalence and severity of underreporting is greater among obese individuals compared with lean individuals (Bandini et al., 1999; Lichtman et al., 1992; Prentice et al., 1986). In addition, those of low socioeconomic status (characterized by low incomes, low educational attainment, and low literacy levels) are more likely to report low energy intakes (Johnson et al., 1998; Kristal et al., 1997; Pryer et al., 1997). There-

fore, self-reported energy intakes do not reflect actual energy intakes, and other methods must be used to determine their adequacy. Relative body weight (as reflected by BMI) is a preferred indicator of energy adequacy for individuals and for groups.

Assessing Adequacy of Energy Intakes of Individuals. Theoretically, one could compare the usual energy intake of an individual to his or her requirement to maintain current weight and activity level, as estimated using the equations developed to estimate energy expenditure. However, as noted above, the EER (or TEE) equation provides an estimate that is the midpoint of the range within which the expenditure of an individual with specified characteristics could vary, and the individual's actual expenditure could be considerably above or below the midpoint. Accordingly, comparing the individual's intake to the calculated average expenditure is essentially meaningless. For example, the EER for a 33-year-old, low-active woman with a height of 1.63 m and a weight of 55 kg would be calculated at 2,028 kcal, but expenditure for a woman with these characteristics could vary between 1,708 and 2,348 kcal. If the woman's actual energy intake averaged 2,200 kcal, her actual intake could be inadequate, adequate, or excessive.

BMI, in contrast, provides a useful indicator of the adequacy of usual energy intake in relation to usual energy expenditure. If the woman in the above example had a BMI of 22 (i.e., within the healthy range of > 18.5 and < 25), her usual energy intake would be assessed as adequate relative to her usual expenditure. If her BMI was 17 (below the healthy range), then she would be assessed as having an inadequate energy intake; if it was 33 (above the healthy range), her intake would be assessed as excessive.

Assessing Adequacy of Energy Intakes of Groups. Instead of assessing the adequacy of energy intake by comparing reported intakes (which are almost always affected by considerable underreporting) to estimated expenditure, relying on BMI as a biological indicator is preferable. The distribution of BMI within a population group can be assessed, and the proportions of the group with BMI below, within, and above the desirable range would reflect the proportions with inadequate, adequate, and excessive energy intakes. When this approach is applied to body-weight data of adults ages 19 to 50 years obtained in the Continuing Survey of Food Intakes by Individuals, 59 percent of men and 44 percent of women are found to have a BMI ≥ 25, reflecting excessive energy intake; 40 percent of men and 52 percent of women have a BMI within the ideal range, reflecting adequacy; and 0.9 percent of men and 4.6 percent of women have a BMI below 18.5, reflecting inadequacy.

Although the above discussion refers to the adequacy of energy intake, it should be reiterated that intake is just one component of energy balance. Excessive intake must be interpreted as being excessive *in relation to energy expenditure*. In many cases, intake may not be excessive in absolute terms; instead, inadequate energy expenditure may be the primary factor in contributing to long-term positive energy balance. This has important implications for how this issue is best addressed at the population level. There are a number of reasons why increased energy expenditure may be a more appropriate solution than decreased energy intake to long-term positive energy balance (i.e., overweight). First, restricting energy intake also decreases the ability to meet requirements of many nutrients. Second, evidence exists to support the concept that much of the health risk attributed to an increased BMI is associated with poor fitness. Increasing physical activity, thereby improving fitness, improves health outcomes of overweight individuals irrespective of changes in relative weight (Blair et al., 1993, 1995).

Implications of Underreporting for Other Macronutrients. In addition to the major impact of underreporting on assessment of the adequacy of energy intake, it also has potential implications for other macronutrients. If it is assumed that underreporting of macronutrients occurs in proportion to underreporting of energy intake, macronutrients expressed as a percentage of energy would be relatively accurate. Accordingly, there would be little impact on the estimated proportions of those whose intakes fall outside the Acceptable Macronutrient Distribution Ranges (AMDRs) for carbohydrate, protein, total fat, and *n*-3 and *n*-6 polyunsaturated fatty acids. Underreporting would, however, overestimate the prevalence of dietary inadequacy for protein, indispensable amino acids, and carbohydrate. Conversely, it has been suggested that underreporting of nutrients may not occur in proportion to underreporting of energy (IOM, 2000). If, for example, fat intake is preferentially underreported, this would lead to an underestimate of the proportion of those whose intakes are above the upper end of the AMDRs for total fat and for *n*-3 and *n*-6 polyunsaturated fatty acids. It could also lead to an overestimate of the percentage of energy derived from carbohydrate.

Total Carbohydrate

The Dietary Reference Intakes (DRIs) for total carbohydrate (starches and sugars) are set in this report as EARs and RDAs, expressed as absolute amounts (g/day) that support brain glucose utilization. The RDA for carbohydrate (130 g/day) is an average minimum requirement and is lower than what most North Americans consume (Appendix Table E-2). A UL is not established for total carbohydrate. Most people can meet their

requirement for carbohydrate without difficulty by consuming a varied diet containing breads, rice, other grain products, potatoes, fruits, vegetables, milk products, and (in moderate amounts) starch- or sugar-based snack foods.

As discussed in Chapter 11, to achieve a healthful balance of the macronutrients that supply energy, the AMDR for total carbohydrate is 45 to 65 percent of energy. This range allows for intakes of carbohydrate that exceeds the RDA of 130 g/day. The carbohydrate content of most U.S. diets is either less than or within this range (see Appendix Table E-3), but it is more likely to be within this range if food selections emphasize grains, fruits, and vegetables prepared with minimal or modest amounts of fat.

Added Sugars

Added sugars are defined as sugars and syrups that are added to foods during processing or preparation. Major sources of added sugars include soft drinks, cakes, cookies, pies, fruitades, fruit punch, dairy desserts, and candy (USDA/HHS, 2000). Specifically, added sugars include white sugar, brown sugar, raw sugar, corn syrup, corn-syrup solids, high-fructose corn syrup, malt syrup, maple syrup, pancake syrup, fructose sweetener, anhydrous dextrose, and crystal dextrose. Since added sugars provide only energy when eaten alone and lower nutrient density when added to foods, it is suggested that added sugars in the diet should not exceed 25 percent of total energy intake. Usual intakes above this level place an individual at potential risk of not meeting micronutrient requirements. Nutrient data on added sugars has only recently become available in the U.S. Department of Agriculture's (USDA) Pyramid Servings Database, which includes data on added sugars for over 7,000 foods. Appendix Table D-1 describes the Third National Health and Nutrition Examination Survey (NHANES III) results on the distribution of intakes of added sugar.

To assess the sugar intakes of groups requires knowledge of the distribution of usual added sugar intake as a percent of energy intake. Once this is determined, the percentage of the population exceeding the maximum suggested level can be evaluated. Because the criterion for the suggested maximum intake level of added sugars is the risk of associated inadequate intakes of micronutrients, such an evaluation would be complemented by assessing micronutrient intakes, as described in the DRI report for those nutrients (IOM, 2001) and the report on dietary assessment (IOM, 2000).

Dietary, Functional, and Total Fiber

Dietary Fiber is defined in this report as nondigestible carbohydrates and lignin that are intrinsic and intact in plants. *Functional Fiber* is defined

as isolated, nondigestible carbohydrates that have beneficial physiological effects in humans. *Total Fiber* is the sum of *Dietary Fiber* and *Functional Fiber*. Fiber includes viscous forms that lower serum cholesterol concentrations (i.e., soluble fiber: oat bran, beans) and the bulking agents that improve laxation (i.e., insoluble fiber: wheat bran). The AI for *Total Fiber* is 38 and 25 g/day for 19- to 50-year-old men and women, respectively, based on a reduced risk of coronary heart disease for those within the highest quintiles of dietary fiber consumption (g/1,000 kcal) in several epidemiological studies and the median energy intake (Appendix Table E-1). Unlike the AI for some nutrients, this AI does not describe the median *Total Fiber* intake of a healthy population. Instead, it is based on health benefits associated with consuming foods that are rich in fiber. Based on CSFII data (Appendix Table E-4), the median *Dietary Fiber* intakes are 16.5 to 17.9 g/day for men and 12.1 to 13.3 g/day for women. Thus, it is evident that to meet the AI, most people will need to substantially increase their *Total Fiber* intake. Usual intakes that meet or exceed the AI can be assumed adequate, but the likelihood of inadequacy of usual intakes below the AI cannot be determined.

Fiber consumption can be increased by substituting whole grain or products with added cereal bran for more refined bakery, cereal, pasta, and rice products; by choosing whole fruits instead of fruit juices; by consuming fruits and vegetables without removing edible membranes or peels; and by eating more legumes, nuts, and seeds. For example, whole wheat bread contains three times as much *Dietary Fiber* as white bread, and the fiber content of a potato doubles if the peel is consumed. The soluble and insoluble fiber components of 228 U.S. foods have been published by Marlett and Cheung (1997).

Dietary fiber data are listed for a wide range of foods in the USDA Nutrient Database for Standard Reference (USDA, 2001). The dietary fiber values in the USDA database represent *Total Fiber* (including both dietary and functional fiber) as defined in this report. For most diets (those that have not been fortified with *Functional Fiber* that was isolated and added for health purposes), the contribution of *Functional Fiber* is minor relative to the naturally occurring *Dietary Fiber*. For example, the *Functional Fiber* content for foods such as fat-free yogurts and ice creams that contain added guar gums and carrageenan is so low that the USDA database generally indicates zero dietary fiber for these foods. Although the AI is set for *Total Fiber*, this AI is generally based upon the fibers present in foods, and until these terms are further incorporated into nutrient databases, it is appropriate to apply the *Dietary Fiber* data from the USDA database to the AI for *Total Fiber*.

Because there is insufficient evidence of deleterious effects of high *Dietary Fiber* as part of an overall healthy diet, a Tolerable Upper Intake Level has not been established.

Total Fat and n-*3 and* n-*6 Polyunsaturated Fatty Acids*

Total Fat

No RDAs or AIs are set for total fat, but an AMDR of 20 to 35 percent of energy is recommended for adults (Chapter 11). Thus, when planning diets for individuals, it is necessary to first calculate the individual's estimated energy expenditure, determine 20 and 35 percent of this number in kilocalories, and then divide by 9 kcal/g to get the range of fat intake in grams per day. For example, a person whose energy expenditure was 2,300 kcal/day should aim for an energy intake from fat of 460 to 805 kcal/day. In grams of total fat, intake should be between 51 and 89 g/day.

Likewise, when assessing fat intakes of individuals, the goal is to determine if usual energy intake from total fat is between 20 and 35 percent. As illustrated above, this is a relatively simple calculation assuming both usual fat intake and usual energy intake are known. However, because dietary data are typically based on a small number of days of records or recalls, it may not be possible to state with confidence that a diet is within this range. As explained in the DRI dietary assessment report (IOM, 2000), an adjustment can be made for the likelihood that these are not representative days, based on the day-to-day variation in fat intake and the number of days of dietary data.

When planning fat intakes for groups, the goal is to minimize the intakes of total fat that are outside the AMDR of 20 to 35 percent of energy from fat. If planning is for a confined population, a procedure similar to the one described for individuals may be used: determine the necessary energy intake from the planned meals and plan for a fat intake that provides between 20 and 35 percent of this value. If the group is not confined, then planning intakes is more complex and ideally begins with knowledge of the distribution of usual energy intake from fat. Then the distribution can be examined, and feeding and education programs designed to either increase, or more likely, decrease the percent of energy from fat.

Assessing the fat intake of a group requires knowledge of the distribution of usual fat intake as a percent of energy intake. Once the distribution is described, the percent of the population outside the AMDR can be calculated. For example, Appendix Table E-6 shows that in the CSFII, less than 1 percent of the population was below 20 percent of energy from fat, while over 50 percent consumed greater than 35 percent of energy from fat.

n-*3 and* n-*6 Polyunsaturated Fatty Acids*

n-3 and *n*-6 Polyunsaturated fatty acids have an AI based on median intakes of linoleic acid and α-linolenic acid from CFSII, respectively. In addition to an AI, an AMDR is provided for *n*-3 and *n*-6 fatty acids. The

suggested range is 0.6 to 1.2 percent of energy from *n*-3 fatty acids and 5 to 10 percent of energy from *n*-6 fatty acids. Thus, there are several considerations when planning and evaluating *n*-3 and *n*-6 fatty acid intakes. Usual intakes that meet or exceed the AI can be assumed adequate, but the likelihood of inadequacy of usual intakes below the AI cannot be determined. Assessing *n*-3 and *n*-6 fatty acid intakes of groups against the AMDR requires knowledge of the distribution of usual fatty acid intake as a percentage of energy intake. Once the distribution is described, the percentage of the population outside the AMDR can be calculated.

Saturated Fatty Acids, Trans *Fatty Acids, and Cholesterol*

No RDAs, AIs, or AMDRs are provided for saturated fatty acids, *trans* fatty acids, and cholesterol. However, with increasing intakes of either of these three nutrients, there is an increased risk of coronary heart disease. Chapter 11 provides some dietary guidance on ways to reduce the intake of saturated fatty acids, *trans* fatty acids, and cholesterol. For example, when planning diets, it is desirable to replace saturated fat with either monounsaturated or polyunsaturated fats to the greatest extent possible.

Protein and Amino Acids

The EARs and RDAs for protein and amino acids have been expressed as grams per kilogram per day, the first DRIs to be expressed in this way. This implies that requirements and recommended intakes vary among individuals of different sizes, and should be individualized when used for dietary assessment or planning. The potential implications of this are discussed below.

Dietary Assessment

For most nutrients for which EARs have been defined, the prevalence of inadequate intakes can be estimated as the proportion of the distribution of usual intakes that falls below the EAR using the EAR cut-point method (IOM, 2000). However, this method requires a number of assumptions, including that the individual requirement for the nutrient in question has a symmetric distribution. As described in Chapter 10, the distribution of the individual requirement for protein for adults is skewed, however, this skewing appears to be slight and the EAR cut-point method is expected to provide a good approximation to prevalence.

However, if more accuracy is needed, the "probability approach" can be used. This approach has been described elsewhere (IOM, 2000; NRC, 1986), and its application for assessing the prevalence of inadequacy of

iron intakes has been illustrated (IOM, 2002). The probability approach for assessing the adequacy of protein intakes is identical to that outlined for iron, with the simplification that percentiles of protein requirement can be explicitly calculated from the formula given in Chapter 10 ("RDA Summary, Ages 19–50 Years").

Planning the Diet

When planning a diet for an individual, recommended intakes can be determined on the basis of the individual's body weight. Although the RDA for the reference adult male is 56 g/day of protein (based on 0.8 g/kg/day for a 70-kg person), the recommended intakes for men weighing 60 kg and 90 kg would be 48 and 72 g/day, respectively.

It should be noted that the DRIs are intended to apply to healthy individuals. Thus, determining a recommended protein intake based on current body weight may not be appropriate for those who are significantly underweight or overweight. For example, a medical professional might choose to specify a protein intake for a malnourished, underweight patient based on what the patient's body weight would be if he were healthy. A patient weighing 40 kg, whose body weight when healthy was 55 kg, could thus have a recommended protein intake of 44 g/day (55 kg × 0.8 g/kg), rather than the 32 g/day that would be determined based on current weight. Conversely, protein intakes recommended for individuals who are morbidly obese could be based on the amounts recommended for those with more normal body weights.

Are Planning and Assessing Intakes of Indispensable Amino Acids Necessary?

The previous RDAs and Recommended Nutrient Intakes did not include recommended intakes for indispensable amino acids; it was assumed that individuals consuming a mixed diet with recommended amounts of protein would obtain required amounts of indispensable amino acids. In other words, it was not necessary to assess or plan for intakes of indispensable amino acids. Now that EARs and RDAs have been provided for indispensable amino acids, it is important to re-examine the question: Is it necessary to consider indispensable amino acids when conducting dietary planning and assessment, or is it sufficient to consider only total protein?

The simplest scenario for answering this question relates to dietary planning for individuals. When planning for individuals, the objective is to meet the RDA, as doing so ensures a very low risk of inadequacy. Thus, do diets that provide the RDA for protein also provide the RDAs for indispensable amino acids? It appears that this may not necessarily occur, at

least for the amino acid lysine. Data in Table 13-2 suggest that although most protein sources provide recommended amounts of threonine, tryptophan, and sulfur-containing amino acids, this is not true for lysine. Animal protein sources provide recommended intakes of lysine, but it is clear that individuals who do not consume animal protein sources, or who consume limited amounts, would be unlikely to obtain the recommended amounts of lysine when total protein intake is equal to the RDA, unless their diets were usually high in beans or other legumes. Even then, diets could be marginal, as the data in Table 13-2 regarding amino acid composition do not account for the apparent lower digestibility of some plant protein sources. Beans, for example, have a digestibility of 82 percent relative to milk and meat. Thus, it appears that, in addition to assessing and planning total protein intakes, it is also necessary to assess and plan for intakes of the amino acid lysine in individuals consuming proteins with low levels of lysine.

TABLE 13-2 Selected Indispensable Amino Acid Content of Protein Sources Compared with Recommended Levels

	Indispensable Amino Acid (mg/g protein)			
	Lysine	Threonine	Tryptophan	Sulfur Amino Acids
Scoring pattern, adult	47	24	6	23
FNB/IOM Recommended Protein Scoring Pattern (Child 1–3 y)	51	27	7	25
Canadian diet, 1984	61	38	12	34
U.S. diet, 1977	68	39	12	35
Wheat bread	28[a]	30	13	39
Garbanzo beans	67	37	10	26[a]
Beef	83	44	11	37
Cheddar cheese	76	33	12	29
Tofu	66	41	16	27
Brown rice	38[a]	37	13	35
Almonds	29[a]	32	15	25[a]
Peanut butter	36[a]	34	10	33
Cornmeal	28[a]	38	7	39

[a] The amino acid content in these foods is lower than the proportion recommended for the proper balance of indispensable amino acids in the total diet, based on the FNB/IOM Recommended Protein Scoring Pattern (Table 10-26). Thus a mixed diet containing a variety of protein sources is recommended.

As alluded to above, the need to plan and assess intakes of lysine is likely of greatest importance for individuals whose diets emphasize plant foods and are relatively low in total protein. For example, consider a woman who weighs 57 kg and follows a plant-based diet that provides the RDA for total protein (in her case, 57 × 0.8 g/kg = 45 g/day). She would be unlikely to meet her RDA for lysine (2.2 g/day) unless 50 percent or more of her dietary protein was provided from beans or tofu (rich sources of lysine). To be specific, 23 g of protein from beans and tofu would provide about 1.5 g of lysine, and 22 grams of protein from other sources, such as wheat, rice and nuts, would provide about 0.7 g of lysine. However, if her total protein intake was higher, (e.g., about 63 g/day, close to the median protein intake of women reported in the CSFII survey [Appendix Table E-16]), she could meet her RDA for lysine with much smaller amounts of beans and tofu.

INTEGRATED EXAMPLE

The preceding discussion illustrates that there are many considerations involved in dietary assessment and planning for energy and macronutrients. The example that follows illustrates how these considerations might be addressed in planning the macronutrient intake of an individual. Let us assume that the individual is a 35-year-old woman, 1.68 m in height, and weighing 69 kg. Her job is not physically active, and she does little planned exercise, so it might appear that activity level would be classified as sedentary. However, to provide a more reliable indication of her activity level, she keeps a 7-day record of her activities using a chart similar to that provided in Chapter 12 (Table 12-3), and this also confirms that she is sedentary.

Energy

Because recommended intakes of at least some nutrients relate to energy requirements, the first step would be to estimate her energy expenditure. Her BMI is 24.4, so the equation for normal-weight adults would be used. Assuming it was appropriate to maintain her current weight and activity level, the Estimated Energy Requirement for a woman with her characteristics would be about 2,000 kcal/day. Of course, her individual energy expenditure could be above or below this amount, but it provides a starting point. An additional consideration would be that her current activity level is less than the recommended of "active." If her energy needs were estimated based on being "active," the estimate would be 2,150 kcal, and other values listed below would change proportionally.

Fatty Acids

The AI for *n*-3 polyunsaturated fatty acid (α-linolenic acid) is 1.1 g/day, and the AI for *n*-6 polyunsaturated fatty acid (linoleic acid) is 12 g/day. Therefore, her diet should provide these levels of fatty acids, which would provide 9.9 and 108 kcal/day from *n*-3 and *n*-6 fatty acids, respectively, toward her total energy intake. Longer-chain polyunsaturated *n*-3 (approximately 10 percent) and *n*-6 fatty acids can contribute toward this AI.

Protein

The RDA for protein is 0.8 g/kg/day, so her recommended intake would be 55 g/day (69 kg × 0.8 g/kg), which would provide 220 kcal/day. In addition, she would need to meet recommended intakes of indispensable amino acids, of which lysine is most likely to be limiting. Her recommended lysine intake would be 38 mg/kg/day, or approximately 2.6 g/day.

Carbohydrate and Total Fiber

The RDA for carbohydrate for adult women is 120 g/day, which is equivalent to 480 kcal/day. More than 120 g/day will probably be needed to assure adequate energy consumption within the AMDR for carbohydrate. The AI for *Total Fiber* is 25 g/day and her diet should be planned to provide for this level of intake. The contribution of *Total Fiber* to energy (kcal/g) intake is still unclear.

Energy Distribution

The amount of energy provided by the recommended intakes of essential fatty acids, protein, and carbohydrate totals only 818 kcal/day, yet her estimated requirement is approximately 2,000 kcal/day. Her energy intake might be allocated among macronutrients as shown in Table 13-3 for an overall healthy diet.

Because the estimated energy expenditure of 2,000 kcal/day may differ from actual energy expenditure (and lead to changes in weight that may not be desirable), her weight should be monitored over time and energy intake adjusted as appropriate.

SUMMARY

The Dietary Reference Intakes (DRIs) may be used to assess nutrient intakes as well as to plan nutrient intakes. Box 13-1 summarizes the appropriate uses of the DRIs for individuals and groups.

TABLE 13-3 Example of Macronutrients in a 2,000 kcal Diet

Nutrient	AMDR[a] (%)	Range for 2,000 kcal (g)	Selected Amount (% of energy)	Amount for 2,000 kcal (g)	Energy for 2,000 kcal
Fat	20–35%	44–78	30	67 g	600 kcal
n-3 PUFA[b] (as part of total fat)	0.6–1.2%	1.3–2.7	0.8	1.8 g	16 kcal (as part of total fat)
n-6 PUFA (as part of total fat)	5–10%	11–22	7	16 g	144 kcal (as part of total fat)
Protein	10–35%	50–175	15	75 g	300 kcal
Carbohydrate	45–65%	225–325	55	275 g	1,100 kcal

[a] AMDR = Acceptable Macronutrient Distribution Range.
[b] PUFA = polyunsaturated fatty acid.

REFERENCES

Bandini LG, Vu D, Must A, Cyr H, Goldberg A, Dietz WH. 1999. Comparison of high-calorie, low-nutrient-dense food consumption among obese and non-obese adolescents. *Obes Res* 7:438–443.

Basiotis PP, Welsh SO, Cronin FJ, Kelsay JL, Mertz W. 1987. Number of days of food intake records required to estimate individual and group nutrient intakes with defined confidence. *J Nutr* 117:1638–1641.

Black AE, Prentice AM, Goldberg GR, Jebb SA, Bingham SA, Livingstone MBE, Coward WA. 1993. Measurements of total energy expenditure provide insights into the validity of dietary measurements of energy intake. *J Am Diet Assoc* 93:572–579.

Blair SN, Kohl HW, Barlow CE. 1993. Physical activity, physical fitness, and all-cause mortality in women: Do women need to be active? *J Am Coll Nutr* 12:368–371.

Blair SN, Kohl HW, Barlow CE, Paffenbarger RS, Gibbons LW, Macera CA. 1995. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *J Am Med Assoc* 273:1093–1098.

Briefel RR, Sempos CT, McDowell MA, Chien S, Alaimo K. 1997. Dietary methods research in the Third National Health and Nutrition Examination Survey: Underreporting of energy intake. *Am J Clin Nutr* 65:1203S–1209S.

Carroll RJ, Freedman LS, Hartman AM. 1996. Use of semiquantitative food frequency questionnaires to estimate the distribution of usual intake. *Am J Epidemiol* 143:392–404.

Heitmann BL, Lissner L. 1995. Dietary underreporting by obese individuals—Is it specific or non-specific? *Br Med J* 311:986–989.

IOM (Institute of Medicine). 1994. *How Should the Recommended Dietary Allowances Be Revised?* Washington, DC: National Academy Press.

IOM. 2000. *Dietary Reference Intakes: Applications in Dietary Assessment.* Washington, DC: National Academy Press.

BOX 13-1
Uses of Dietary Reference Intakes for Healthy Individuals and Groups

Type of Use	*For the Individual*[a]	*For a Group*[b]
Assessment	**EAR**[c]**:** Use to examine the probability that usual intake is inadequate.	**EAR:** Use to estimate the prevalence of inadequate intakes within a group.
	RDA: Usual intake at or above this level has a low probability of inadequacy.	**RDA:** Do not use to assess intakes of groups
	AI[d]**:** Usual intake at or above this level has a low probability of inadequacy.	**AI**[d]**:** Mean usual intake at this level implies a low prevalence of inadequate intakes.
	UL: Intake above this level has a potential risk of adverse effects.	**UL:** Use to estimate the percentage of the population at potential risk of adverse effects from excess nutrient intake.
Planning	**RDA**[e]**:** Aim for this intake.	**EAR**[c]**:** Use to plan an intake distribution with a low prevalence of inadequate intakes.
	AI[d]**:** Aim for this intake.	**AI**[d]**:** Use to plan mean intakes.
	UL: Use as a guide to limit intake; chronic intake of higher amounts may increase the potential risk of adverse effects.	**UL:** Use to plan intake distributions with a low prevalence of intakes potentially at risk of adverse effects.

[a] Requires accurate measure of usual intake. Evaluation of true status requires clinical, biochemical, and anthropometric data.
[b] Requires statistically valid approximation of distribution of usual intakes.
[c] Requires information on the variability of day-to-day intake and the variability of the requirement.
[d] For the nutrients in this report, AIs are set for infants for all nutrients, and for other age groups for *Total Fiber* and for *n*-3 and *n*-6 polyunsaturated fatty acids. The AI may be used as a guide for infants as it reflects the average intake from human milk. Infants consuming formulas with the same nutrient composition as human milk consume an adequate amount after adjustments are made for differences in bioavailability. In the context of assessing groups, when the AI for a nutrient is not based on mean intakes of a healthy population, this assessment is made with less confidence.
[e] In the case of energy, an Estimated Energy Requirement (EER) is provided; it is the dietary energy intake that is predicted (with variance) to maintain energy balance in a healthy adult of defined age, gender, weight, height, and level of physical activity, consistent with good health. In children and pregnant and lactating women, the EER is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health. For individuals, the EER represents the midpoint of a range within which an individual's energy requirement is likely to vary. As such, it is below the needs of half the individuals with specified characteristics and exceeds the needs of the other half. Body weight should be monitored and energy intake adjusted accordingly.

NOTE: RDA = Recommended Dietary Allowance, EAR = Estimated Average Requirement, AI = Adequate Intake, UL = Tolerable Upper Intake Level.

IOM. 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academy Press.

Johnson RK, Goran MI, Poehlman ET. 1994. Correlates of over- and underreporting of energy intake in healthy older men and women. *Am J Clin Nutr* 59:1286–1290.

Johnson RK, Soultanakis RP, Matthews DE. 1998. Literacy and body fatness are associated with underreporting of energy intake in US low-income women using the multiple-pass 24-hour recall: A doubly labeled water study. *J Am Diet Assoc* 98:1136–1140.

Kristal AR, Feng Z, Coates RJ, Oberman A, George V. 1997. Associations of race/ethnicity, education, and dietary intervention with the validity and reliability of a food frequency questionnaire: The Women's Health Trial Feasibility Study in Minority Populations. *Am J Epidemiol* 146:856–869.

Lichtman SW, Pisarska K, Berman ER, Pestone M, Dowling H, Offenbacher E, Weisel H, Heshka S, Matthews DE, Heymsfield SB. 1992. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med* 327:1893–1898.

Liu K. 1994. Statistical issues related to semiquantitative food-frequency questionnaires. *Am J Clin Nutr* 59:262S–265S.

Livingstone MB, Prentice AM, Coward WA, Strain JJ, Black AE, Davies PS, Stewart CM, McKenna PG, Whitehead RG. 1992. Validation of estimates of energy intake by weighed dietary record and diet history in children and adolescents. *Am J Clin Nutr* 56:29–35.

Marlett JA, Cheung TF. 1997. Database and quick methods of assessing typical dietary fiber intakes using data for 228 commonly consumed foods. *J Am Diet Assoc* 97:1139–1148.

Mertz W, Tsui JC, Judd JT, Reiser S, Hallfrisch J, Morris ER, Steele PD, Lashley E. 1991. What are people really eating? The relation between energy intake derived from estimated diet records and intake determined to maintain body weight. *Am J Clin Nutr* 54:291–295.

NRC (National Research Council). 1986. *Nutrient Adequacy. Assessment Using Food Consumption Surveys.* Washington, DC: National Academy Press.

Nusser SM, Carriquiry AL, Dodd KW, Fuller WA. 1996. A semiparametric transformation approach to estimating usual daily intake distributions. *J Am Stat Assoc* 91:1440–1449.

Prentice AM, Black AE, Coward WA, Davies HL, Goldberg GR, Murgatroyd PR, Ashford J, Sawyer M, Whitehead RG. 1986. High levels of energy expenditure in obese women. *Br Med J* 292:983–987.

Pryer JA, Vrijheid M, Nichols R, Kiggins M, Elliott P. 1997. Who are the 'low energy reporters' in the dietary and nutritional survey of British adults? *Int J Epidemiol* 26:146–154.

Schoeller DA. 1995. Limitations in the assessment of dietary energy by self-report. *Metabolism* 44:18–22.

Schoeller DA, Bandini LG, Dietz WH. 1990. Inaccuracies in self-reported intake identified by comparison with the doubly labelled water method. *Can J Physiol Pharmacol* 68:941–949.

USDA (U.S. Department of Agriculture). 2001. *USDA Nutrient Database for Standard Reference, Release 14.* Online. Nutrient Data Laboratory. Available at http://www.nal.usda.gov/fnic/foodcomp. Accessed April 2, 2002.

USDA/HHS (U.S. Department of Health and Human Services). 2000. *Nutrition and Your Health: Dietary Guidelines for Americans.* Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.

14
A Research Agenda

The Panel on Macronutrients and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes were charged with developing a research agenda to provide a basis for public-policy decisions related to recommended intakes of energy, fat, carbohydrate, and protein. This chapter describes the approach used to develop the research agenda, briefly summarizes gaps in knowledge, and presents a prioritized research agenda. Sections at the end of Chapters 5 through 10 and Chapter 12 presented prioritized lists of research topics.

APPROACH

The following approach resulted in the research agenda identified in this chapter.

1. Identify gaps in knowledge to understand the role of macronutrients in human health, functional and biochemical indicators to assess macronutrient requirements, methodological problems related to the assessment of intake of these macronutrients and to the assessment of adequacy of intake, relationships of nutrient intake to chronic disease, and adverse effects of macronutrients.
2. Examine data to identify major discrepancies between intake and recommended intakes and consider possible reasons for such discrepancies.
3. Consider the need to protect individuals with extreme or distinct vulnerabilities due to genetic predisposition or disease conditions.
4. Weigh the alternatives and set priorities based on expert judgment.

MAJOR KNOWLEDGE GAPS

Requirements

To derive an Estimated Average Requirement (EAR), the criterion must be known for a particular status indicator or combination of indicators that is consistent with impaired status as defined by some clinical consequence. For some of the macronutrients considered in this report, such as *n*-6 and *n*-3 polyunsaturated fatty acids, there is a dearth of information on the biochemical values that reflect abnormal function. A priority should be to determine if there is a correlation between existing status indicators and clinical endpoints in the same subjects. For some macronutrients, such as indispensable amino acids, more data are needed using clinical endpoints or intermediate endpoints of impaired function to determine their requirements in regard to long-term health. For determining energy requirements, more information is needed on the form, frequency, intensity, and duration of exercise that is consistent with a healthy body weight for all age groups. The number of doubly labeled water studies for the determination of total energy expenditure in certain life stage and gender categories is limited and should be expanded.

For many of the essential macronutrients, useful data are seriously lacking for setting requirements for infants, children, adolescents, pregnant and lactating women, and the elderly. As an example, more information is needed on the role of *n*-3 polyunsaturated fatty acids in the neurodevelopment of term infants. Studies should use graded levels of nutrient intake and a combination of response indexes, and they should consider other points raised above. For some of the macronutrients, studies should examine whether the requirement varies substantially by trimester of pregnancy. Data are lacking about gender issues with respect to metabolism and requirements of macronutrients.

Methodology

For some macronutrients, serious limitations exist in the methods available to analyze laboratory values indicative of energy balance and macronutrient status. For instance, biological markers of risk of excess weight gain in children and young adults are needed, as are the standardization and validation of indicators in relation to functional outcome. As an example, to better understand the relationship between fiber and colon cancer, there needs to be increased validation of intermediate markers such as polyp recurrence and the assessment of functional markers (e.g., fecal bulk) of fiber intake. These methodological limitations have slowed progress in conducting or interpreting studies of energy and macronutrient requirements.

Potential sources of error in self-reported intake data include underreporting of portion sizes and frequency of intake, omission of foods, and inaccuracies related to the use of food composition tables. It is not possible to adjust intakes based on underreporting, and much work is needed to develop an acceptable method to do so. Reliable methods to track dietary energy intakes of populations need to be developed. Furthermore, expansion and revision of food composition tables are needed to allow for further understanding of the relationship between macronutrient intake and health. As an example, a comprehensive database for the *trans* fatty acid content and glycemic index of foods consumed in North America is needed.

Relationships of Intake to Chronic Disease

There are major gaps in knowledge linking the intake of some macronutrients and the prevention and retardation of certain chronic diseases common in North America. Because the relationship between macronutrient intake and risk of chronic disease is a trend, it is difficult to ascertain the optimal range of intake for each macronutrient. Long-term, multi-dose clinical trials are needed to ascertain, for instance, the optimal range of total, saturated, and unsaturated fatty acids intake to best prevent chronic diseases such as coronary heart disease, obesity, cancer, and diabetes. Dose–response studies are also needed to determine the intake level of fiber to promote optimum laxation. To resolve whether or not fiber is protective against colon cancer in individuals or a subset of individuals, genotyping and phenotyping of individuals in fiber/colon cancer trials is needed. Long-term clinical trials are needed to further understand the role of glycemic index in the prevention of chronic disease.

Adverse Effects

There is a body of evidence to suggest that high intakes of total fat, saturated fatty acids, *trans* fatty acids, and cholesterol increase the risk of adverse health effects (e.g., elevated low-density lipoprotein [LDL] cholesterol concentration); however, a Tolerable Upper Intake Level could not be established for any of the fats or cholesterol because of the linear trend that often exists between intake and degree of adverse effect. Therefore, more clinical research is needed to ascertain clearly defined intake levels at which significant risk can occur for adverse health effects. In addition, further information is needed on the various factors that contribute to the wide inter-individual variation in LDL cholesterol response to dietary cholesterol. There is some animal data to suggest that high intakes of *n*-6 polyunsaturated fatty acids can increase the risk of certain types of cancer.

This information is lacking in humans and is much needed. Research is needed to identify intake levels at which adverse effects begin to occur with the chronic consumption of high levels of protein and of the long-chain *n*-3 polyunsaturated fatty acids: eicosapentaenoic acid and docosahexaenoic acid.

THE RESEARCH AGENDA

Four major types of information gaps were noted: (1) a lack of data designed specifically to estimate average requirements in presumably healthy humans, (2) a lack of data on the nutrient needs of infants, children, adolescents, the elderly, and pregnant women, (3) a lack of multidose, long-term studies to determine the role of macronutrients in reducing the risk of certain chronic diseases, and (4) a lack of studies designed to detect adverse effects of chronic high intakes of these nutrients.

Highest priority is given to research that has the potential to prevent or retard human disease processes and to prevent deficiencies with functional consequences. The following five areas for research were assigned the highest priority (other research recommendations are found at the ends of Chapters 5 through 10 and Chapter 12):

- Dose–response studies to help identify the requirements of macronutrients that are essential in the diet (e.g., indispensable amino acids and *n*-6 and *n*-3 polyunsaturated fatty acids) for all life-stage and gender groups. It is recognized that it is not possible to identify a defined intake level of fat for optimal health; however, it is recognized that further information is needed to identify acceptable ranges of intake for fat, as well as for protein and carbohydrate based on prevention of chronic disease and optimal nutrition;
- Studies to further understand the beneficial roles of *Dietary* and *Functional Fibers* in human health;
- Information on the form, frequency, intensity, and duration of exercise that is successful in managing body weight in children and adults;
- Long-term studies on the role of glycemic index in preventing chronic diseases, such as diabetes and coronary heart disease, in healthy individuals, and;
- Studies to investigate the levels at which adverse effects occur with chronic high intakes of carbohydrate, fiber, fat, and protein. For nutrients such as saturated fatty acids, *trans* fatty acids, and cholesterol, biochemical indicators of adverse effects can occur at very low intakes. Thus, more information is needed to ascertain defined levels of intakes at which relevant health risks may occur.

A
Glossary and Acronyms

AAP	American Academy of Pediatrics
Accommodation	An adaptative response that allows survival, but at the expense of some more or less serious consequences on health or physiological function
Action	Demonstrated effects in various biological systems that may or may not have physiological significance
Adaptation	Maintenance of essentially unchanged functional capacity despite some alterations in steady-state conditions
Adverse effect	Any significant alteration in the structure or function of the human organism, or any impairment of a physiologically important function, that could lead to an adverse health effect
AI	Adequate Intake
AMDR	Acceptable Macronutrient Distribution Range
Association	Potential interaction derived from epidemiological studies of the relationship between a specific nutrient and chronic disease
BEE	Basal energy expenditure
Bioavailability	Accessibility of a nutrient to participate in unspecified metabolic or physiological processes

BMI	Body mass index
BMR	Basal metabolic rate
CHD	Coronary heart disease
CSFII	Continuing Survey of Food Intakes by Individuals—a survey conducted by the Agricultural Research Service, U.S. Department of Agriculture
CV	Coefficient of variation—standard deviation divided by the square root of n, where n is the sample size
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DLW	Doubly labeled water
Dose–response assessment	Second step in a risk assessment, in which the realtionship between nutrient intake and adverse effect (in terms of incidence or severity of the effect) is determined
DRI	Dietary Reference Intake
EAR	Estimated Average Requirement
EEPA	Energy expenditure of physical activity
EER	Estimated energy requirement
EPA	Eicosapentaenoic acid
EPOC	Excess post-exercise oxygen consumption
Erythrocyte	A red blood cell
FAO	Food and Agriculture Organization of the United Nations
FASEB	Federation of American Societies for Experimental Biology
FDA	Food and Drug Administration
FFA	Free fatty acids
FFM	Fat-free mass
FM	Fat mass
FNB	Food and Nutrition Board
FQ	Food quotient

Function	Role played by a nutrient in growth, development, and maturation
Hazard identification	First step in a risk assessment, which is concerned with the collection, organization, and evaluation of all information pertaining to the toxic properties of a nutrient
HDL	High density lipoprotein
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
IM	Intramuscular
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety
Lacto-ovo-vegetarian	A person who consumes milk (lacto), eggs (ovo), and plant foods and products, but no meat
LBM	Lean body mass
LDL	Low density lipoprotein
LOAEL	Lowest-observed-adverse-effect level—the lowest intake (or experimental dose) of a nutrient at which an adverse effect has been identified
LSRO	Life Sciences Research Office
MET	Metabolic equivalent—a rate of energy expenditure sustained by a rate of oxygen consumption of 3.5 ml/kg of body weight/min
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey—a survey conducted periodically by the National Center for Health Statistics, Centers for Disease Control and Prevention
NOAEL	No-observed-adverse-effect level—the highest intake (or experimental dose) of a nutrient at which no adverse effect has been observed
NRC	National Research Council
OTA	Office of Technology Assessment

PAI	Physical activity index
PAL	Physical activity level
RDA	Recommended Dietary Allowance
REE	Resting energy expenditure
Risk assessment	Organized framework for evaluating scientific information, which has as its objective a characterization of the nature and likelihood of harm resulting from excess human exposure to an environmental agent (in this case, a nutrient); it includes the development of both qualitative and quantitative expressions of risk
Risk characterization	Final step in a risk assessment, which summarizes the conclusions from steps 1 through 3 of the assessment (hazard identification, dose–response, and estimate of exposure) and evaluates the risk; this step also includes a characterization of the degree of scientific confidence that can be placed in the Tolerable Upper Intake Level
Risk management	Process by which risk assessment results are integrated with other information to make decisions about the need for, method of, and extent of risk reduction; in addition, risk management considers such issues as the public health significance of the risk, the technical feasibility of achieving various degrees of risk control, and the economic and social costs of this control
RMR	Resting metabolic rate
RNA	Ribonucleic acid
RNI	Recommended Nutrient Intake
RQ	Respiratory quotient
SD	Standard deviation
SDA	Specific dynamic action
SE	Standard error
SEM	Standard error of the mean
SMR	Sleeping metabolic rate
TEE	Total energy expenditure

TEF	Thermic effect of food
UF	Uncertainty factor—the number by which the no-observed-adverse-effect level (or lowest-observed-adverse-effect level) is divided to obtain the Tolerable Upper Intake Level; the size of the UF varies depending on the confidence in the data and the nature of the adverse effect
UL	Tolerable Upper Intake Level
USDA	U.S. Department of Agriculture
VLDL	Very low density lipoprotein
WHO	World Health Organization

B

Origin and Framework of the Development of Dietary Reference Intakes

This report is the sixth in a series of publications resulting from the comprehensive effort being undertaken by the Food and Nutrition Board's (FNB) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) and its panels and subcommittees.

ORIGIN

This initiative began in June 1993, when FNB organized a symposium and public hearing entitled, "Should the Recommended Dietary Allowances Be Revised?" Shortly thereafter, to continue its collaboration with the larger nutrition community on the future of the Recommended Dietary Allowances (RDAs), FNB took two major steps: (1) It prepared, published, and disseminated the concept paper, "How Should the Recommended Dietary Allowances Be Revised?" (IOM, 1994), which invited comments regarding the proposed concept, and (2) It held several symposia at nutrition-focused professional meetings to discuss FNB's tentative plans and to receive responses to the initial concept paper. Many aspects of the conceptual framework of the DRIs came from the United Kingdom's report, *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom* (COMA, 1991).

The five general conclusions presented in FNB's 1994 concept paper were:

1. Sufficient new information has accumulated to support a reassessment of the RDAs.

2. Where sufficient data for efficacy and safety exist, reduction in the risk of chronic degenerative disease is a concept that should be included in the formulation of future recommendations.

3. Upper levels of intake should be established where data exist regarding risk of toxicity.

4. Components of food that may benefit health, although not meeting the traditional concept of a nutrient, should be reviewed, and if adequate data exist, reference intakes should be established.

5. Serious consideration must be given to developing a new format for presenting future recommendations.

Subsequent to the symposium and the release of the concept paper, FNB held workshops at which invited experts discussed many issues related to the development of nutrient-based reference values. (FNB members have continued to provide updates and engage in discussions at professional meetings.) In addition, FNB gave attention to the international uses of the earlier RDAs and the expectation that the scientific review of nutrient requirements should be similar for comparable populations.

Concurrently, Health Canada and Canadian scientists were reviewing the need for revision of the *Recommended Nutrient Intakes* (RNIs) (Health Canada, 1990). Consensus following a symposium for Canadian scientists, cosponsored by the Canadian National Institute of Nutrition and Health Canada in April 1995, was that the Canadian government should pursue the extent to which involvement with the developing FNB process would benefit both Canada and the United States in leading toward harmonization.

Based on extensive input and deliberations, FNB initiated action to provide a framework for the development and possible international harmonization of nutrient-based recommendations that would serve, where warranted, for all of North America. To this end, in December 1995, FNB began a close collaboration with the government of Canada and took action to establish the DRI Committee. It is hoped that representatives from Mexico will join in future deliberations.

THE CHARGE TO THE COMMITTEE

In 1995, the DRI Committee was appointed to oversee and conduct this project. It devised a plan involving the work of seven or more expert nutrient group panels and two overarching subcommittees (Figure B-1). The process described below for this report is expected to be used for subsequent reports.

The Panel on Dietary Reference Intakes for Macronutrients (Macronutrients Panel) was to (1) review the scientific literature regarding dietary macronutrients (protein, amino acids, fat and individual fatty acids,

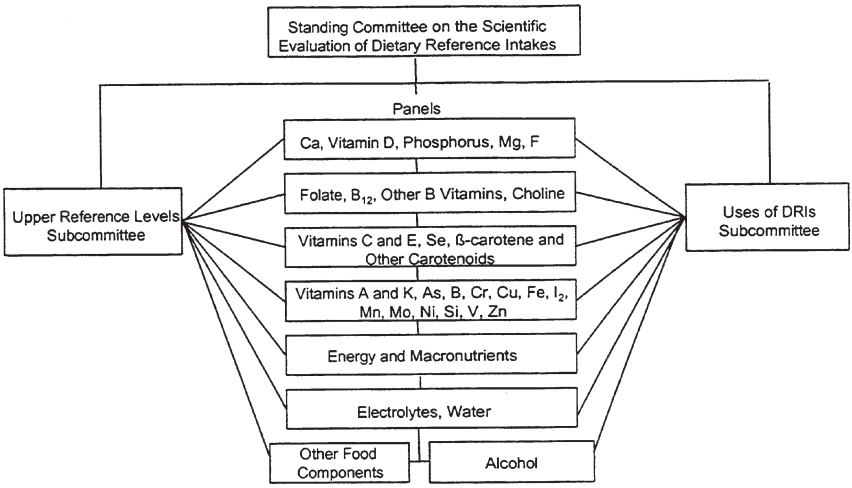

FIGURE B-1 Dietary Reference Intakes project structure.

phospholipids, cholesterol, complex carbohydrates, simple sugars, dietary fiber, energy intake, and energy expenditure) to determine the roles, if any, they play in health; (2) review selected components of food that may influence the bioavailability of these compounds; (3) develop estimates of dietary intake of these compounds that are compatible with good nutrition throughout the lifespan and that may decrease risk of chronic disease where data indicate they play a role; (4) determine Tolerable Upper Intake Levels (ULs) for each compound where scientific data are available in specific population subgroups; and (5) identify research needed to improve the knowledge of the role of macronutrients in health. This was in coordination with a separate panel that was formed to review existing and proposed definitions of dietary fiber and propose a definition that could be of use in regulatory and other areas, and could serve as a basis for the review of dietary fiber by the Macronutrients Panel.

The Macronutrients Panel was charged with analyzing the literature, evaluating possible criteria or indicators of adequacy, and providing substantive rationales for their choices of each criterion. Using the criterion chosen for each stage of the lifespan, the panel estimated the average requirement for each nutrient or food component reviewed, assuming that adequate data were available. As the panel members reviewed data on ULs, they also interacted with the Subcommittee on Upper Reference Levels of Nutrients (UL Subcommittee), which assisted the panel in applying the risk assessment model to each selected nutrient. The DRI values in

this report are a product of the joint efforts of the DRI Committee, the Macronutrients Panel, the UL Subcommittee, and the Subcommittee on Interpretation and Uses of Dietary Reference Intakes.

ISSUES OF RELEVANCE FROM PAST DIETARY REFERENCE INTAKE REPORTS

Methodology to Develop Estimated Average Requirements and Recommended Dietary Allowances When Requirements for Nutrients Are Not Normally Distributed

For most of the nutrients for which Estimated Average Requirements (EARs) have been established, the required assumption of distribution of requirements is that of symmetry about the mean. In the case of iron, a nutrient of concern in many subgroups in the population in the United States, Canada, and other areas, requirements are known to follow a non-normal distribution. Thus, a different method was needed to determine the intake of iron at which half of the individuals would be expected to be inadequate in the criterion used to establish adequacy (the EAR), and also to construct an intake level at which only a small percentage of the population would be inadequate (the Recommended Dietary Allowance [RDA]).

If the requirement of a nutrient is not normally distributed but can be transformed to normality, its EAR and RDA can be estimated by transforming the data, calculating the 50th and 97.5th percentiles, and transforming these percentiles back into the original units. In this case, the difference between the EAR and the RDA cannot be used to obtain an estimate of the standard deviation of the coefficient of variation because skewing is usually present.

Where factorial modeling is used to estimate the distribution of requirement from the distributions of the individual components of requirement, as was done in the case of iron recommendations (IOM, 2001), it is necessary to add the individual distributions (convolutions). This is easy to do given that the average requirement is simply the sum of the averages of the individual component distributions, and a standard deviation of the combined distribution can be estimated by standard statistical techniques. The 97.5th percentile can then be estimated (for a further elaboration of this method, see Chapter 9 and Appendix I of *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* [IOM, 2001]).

If normality cannot be assumed for all of the components of requirement, then Monte Carlo simulation is used for the summation of the components. This approach models the distributions of the individual distributions and randomly assigns values to a large simulated population.

The total requirement is then calculated for each individual and the median and the 97.5th percentile are calculated directly. As was the case for iron (IOM, 2001), the underlying joint distribution is approximated and a large number of individuals (100,000) are randomly generated. Information about the distribution of values for the requirement components is modeled on the basis of known physiology. Monte Carlo approaches may be used in the simulation of the distribution of components; where large data sets exist for similar populations (data sets such as growth rates in infants), estimates of relative variability may be transferred to the component in the simulated population (Gentle, 1998). At each step, the goal is to achieve distribution values for the component that not only reflect known physiology or known direct observations, but also can be transformed into a distribution that can be modeled and used in selecting random members to contribute to the final requirement distribution. When the final distribution representing the convolution of components has been derived, then the median and 97.5th percentiles of the distribution can be directly estimated. It is recognized that in its simplest form, the Monte Carlo approach ignores possible correlation among components. In the case of iron, however, expected correlation is built into the modeling of requirement where components are linked to a common variable (e.g., growth rate) so that not all sources of correlation are neglected.

Reference Heights and Weights Used in Extrapolating Dietary Reference Intakes for Vitamins and Elements

The most up-to-date data providing heights and weights of individuals in the United States and Canada when the DRI process was initiated in 1995 were limited to anthropometric data from the 1988–1994 Third National Health and Nutrition Examination Survey (NHANES III) in the United States, and older data from Canada. Reference values derived from the NHANES III data and used in previous reports are given in Table B-1. Given the increasing prevalence of overweight and obesity in both adults and children (HHS, 1996), use of such population data is of concern. Thus, recent data providing heights and ideal body mass indexes (BMIs) for adults (Kuczmarski et al., 2000) and new growth charts for infants and children have allowed the development of new reference heights and weights in this report that should more closely approximate ideal weights based on low risk of chronic disease and adequate growth for children. These new values are used in this report when reference values are needed and are discussed in Chapter 1 (see Table 1-1).

The earlier values were obtained as follows: the median heights for the life stage and gender groups through age 30 years were identified, and the median weights for these heights were based on reported median BMIs

TABLE B-1 Reference Heights and Weights for Children and Adults in the United States Used in the Vitamin and Element Dietary Reference Intake Reports[a]

Sex	Age	Median Body Mass Index (kg/m^2)	Reference Height, cm (in)	Reference Weight[b] kg (lb)
Male, female	2–6 mo	—	64 (25)	7 (16)
	7–12 mo	—	72 (28)	9 (20)
	1–3 y	—	91 (36)	13 (29)
	4–8 y	15.8	118 (46)	22 (48)
Male	9–13 y	18.5	147 (58)	40 (88)
	14–18 y	21.3	174 (68)	64 (142)
	19–30 y	24.4	176 (69)	76 (166)
Female	9–13 y	18.3	148 (58)	40 (88)
	14–18 y	21.3	163 (64)	57 (125)
	19–30 y	22.8	163 (64)	61 (133)

[a] IOM (1997, 1998, 2000a, 2000b, 2001). Adapted from the Third National Health and Nutrition Examination Survey, 1988–1994.
[b] Calculated from body mass index and height for ages 4 through 8 years and older.

for the same individuals. Since there is no evidence that weight should change as adults age if activity is maintained, the reference weights for adults ages 19 through 30 years were applied to all adult age groups.

The most recent nationally representative data available for Canadians (from the 1970–1972 Nutrition Canada Survey [Demirjian, 1980]) were also reviewed. In general, median heights of children from 1 year of age in the United States were greater by 3 to 8 cm (1 to 2.5 in) than those of children of the same age in Canada measured two decades earlier (Demirjian, 1980). This difference could be partly explained by approximations necessary to compare the two data sets, but more likely by a continuation of the secular trend of increased heights for age noted in the Nutrition Canada Survey when it compared data from that survey with an earlier (1953) national Canadian survey (Pett and Ogilvie, 1956).

Similarly, median weights beyond age 1 year derived from the recent survey in the United States (NHANES III, 1988–1994) were also greater than those obtained from the older Canadian survey (Demirjian, 1980). Differences were greatest during adolescence, ranging from 10 to 17 percent higher. The differences probably reflect the secular trend of earlier onset of puberty (Herman-Giddens et al., 1997), rather than differences in populations. Calculations of BMI for young adults (e.g., a median of 22.6 for Canadian women compared with 22.8 for U.S. women) resulted in

similar values, thus indicating greater concordance between the two surveys by adulthood.

The reference weights used in the previous DRI reports (IOM, 1997, 1998, 2000a, 2000b, 2001) were thus based on the most recent data set available from either country, with recognition that earlier surveys in Canada indicated shorter stature and lower weights during adolescence than did surveys in the United States.

REFERENCES

COMA (Committee on Medical Aspects of Food Policy). 1991. *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom.* Report on Health and Social Subjects, No. 41. London: HMSO.

Demirjian A. 1980. *Anthropometry Report. Height, Weight, and Body Dimensions: A Report from Nutrition Canada.* Ottawa: Minister of National Health and Welfare, Health and Promotion Directorate, Health Services and Promotion Branch.

Gentle JE. 1998. *Random Number Generation and Monte Carlo Methods.* New York: Springer-Verlag.

Health Canada. 1990. *Nutrition Recommendations. The Report of the Scientific Review Committee 1990.* Ottawa: Canadian Government Publishing Centre.

Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. 1997. Secondary sexual characteristics and menses in young girls seen in office practice: A study from the Pediatric Research in Office Settings Network. *Pediatrics* 99:505–512.

HHS (U.S. Department of Health and Human Services). 1996. *Physical Activity and Health: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion.

IOM (Institute of Medicine). 1994. *How Should the Recommended Dietary Allowances Be Revised?* Washington, DC: National Academy Press.

IOM. 1997. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academy Press.

IOM. 1998. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline.* Washington, DC: National Academy Press.

IOM. 2000a. *Dietary Reference Intakes: Applications in Dietary Assessment.* Washington, DC: National Academy Press.

IOM. 2000b. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.* Washington, DC: National Academy Press.

IOM. 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academy Press.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. 2000. CDC growth charts: United States. *Adv Data* 314:1–28.

Pett LB, Ogilvie GH. 1956. The Canadian Weight-Height Survey. *Hum Biol* 28:177–188.

C
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ORGANIZATIONS

American Dietetic Association
American Heart Association
American Oil Chemists' Society
American Society for Clinical Nutrition
American Society for Nutritional Sciences
Canadian Society for Nutritional Sciences
Center for Science in the Public Interest
Federation for American Scientists for Experimental Biology
F. Hoffmann-La Roche
International Food Information Council
International Life Sciences Institute
International Society for Food Technologists
Nabisco
Nutrition Coordinating Center, University of Minnesota
Procter and Gamble Company

D

Dietary Intake Data from the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

TABLE D-1 Mean and Percentiles for Usual Daily Intake of Added Sugars (tsp), United States, NHANES III (1988–1994)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–3 y	2,174	13.2	0.4	1.8	3.4
Both sexes, 4–8 y	3,448	19.3	9.3	11.7	13.1
Standard error		0.4	2.2	1.9	1.6
M, 9–13 y	1,219	28.6	16.8	19.7	21.4
Standard error		0.9	0.6	0.7	0.7
M, 14–18 y	909	36.9	15.5	20.5	23.4
Standard error		1.4	13.8	11.1	9.3
M, 19–30 y	1,902	31.5	10.7	15.3	18.1
Standard error		0.8	2.6	2.4	2.1
M, 31–50 y	2,533	25.4	3.5	6.9	9.5
Standard error		0.7	0.6	0.7	0.8
M, 51–70 y	1,942	18.0	3.1	5.5	7.2
Standard error		0.6	0.6	0.6	0.6
M, 71+ y	1,255	14.3	3.9	5.8	7.1
Standard error		0.5	0.8	0.8	0.8
F, 9–13 y	1,216	21.9	9.3	12.1	13.8
Standard error		0.7	1.7	1.5	1.3
F, 14–18 y	949	25.4	9.0	12.6	14.8
Standard error		1.2	5.5	4.8	4.2
F, 19–30 y	1,901	22.3	4.8	8.0	10.2
Standard error		0.7	1.4	1.6	1.4

25th	50th	75th	90th	95th	99th
6.8	10.9	17.7	25.3	30.9	45.5
15.6	18.9	22.4	26.0	28.3	33.0
1.1	0.4	0.9	2.0	2.7	4.3
24.5	28.2	32.3	36.3	38.9	44.1
0.8	0.9	1.1	1.2	1.4	1.7
28.9	35.7	43.5	51.8	57.3	69.1
6.0	1.9	4.5	10.6	14.9	24.4
23.5	30.3	38.1	46.4	51.9	63.6
1.6	0.9	1.4	2.9	4.1	7.0
15.0	22.8	33.0	44.2	52.2	70.9
0.7	0.7	0.9	1.6	2.3	4.6
10.8	16.2	23.2	31.2	36.8	49.2
0.6	0.6	0.7	1.1	1.5	2.9
9.7	13.3	17.8	22.7	26.0	33.1
0.6	0.4	0.7	1.5	2.1	3.5
17.0	21.1	25.9	30.9	34.3	41.6
1.1	0.8	1.1	1.8	2.5	4.2
18.9	24.3	30.6	37.3	41.8	51.4
2.9	1.4	2.5	5.5	7.8	13.3
14.6	20.8	28.4	36.6	42.1	53.9
1.1	0.7	1.1	2.0	2.9	4.8

continued

TABLE D-1 Continued

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
F, 31–50 y	2,939	17.3	2.6	4.9	6.6
Standard error		0.5	0.3	0.5	0.4
F, 51–70 y	2,065	12.8	2.5	4.2	5.3
Standard error		0.7	0.4	0.5	0.5
F, 71+ y	1,368	10.5	2.1	3.5	4.5
Standard error		0.3	0.3	0.3	0.3
Pregnant	346	21.0	5.5	8.6	10.6
Standard error		1.1	3.5	3.3	3.0
Lactating	99	19.7	12.0	14.0	15.1
Standard error		2.7	1.8	2.0	2.0
Pregnant/lactating	440	21.2	4.9	8.1	10.2
Standard error		1.0	3.6	3.5	3.2
All individuals	25,820	21.1	4.0	6.9	8.9
Standard error		0.3	0.2	0.3	0.3
All individuals (+P/L)	26,260	21.1	4.0	6.9	8.9
Standard error		0.3	0.3	0.3	0.3

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distribution for children 2–3 years of age is unadjusted. The mean and percentiles for this group were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who

25th	50th	75th	90th	95th	99th
10.4	15.7	22.5	29.8	34.9	47.0
0.4	0.5	0.6	0.8	1.0	2.9
7.8	11.5	16.3	21.7	25.3	34.4
0.4	0.6	1.3	1.8	1.5	3.3
6.6	9.7	13.4	17.6	20.6	27.5
0.3	0.3	0.4	0.8	1.1	2.1
14.5	19.7	26.1	33.1	38.0	48.4
2.2	1.2	2.2	4.5	6.4	10.8
17.2	19.5	22.0	24.4	25.8	28.7
2.2	2.6	3.2	4.0	4.7	6.2
14.3	19.8	26.6	34.1	39.2	50.5
2.4	1.4	1.9	4.4	6.6	12.1
13.1	19.2	27.0	35.8	41.9	55.3
0.3	0.3	0.4	0.6	0.8	1.3
13.1	19.1	27.0	35.8	42.0	55.4
0.3	0.3	0.4	0.6	0.8	1.3

were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics and National Cancer Institute's Pyramid Servings Database for NHANES III.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-2 Mean and Percentiles for Usual Daily Intake of Alanine (g), United States, NHANES III (1988–1994)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	793	0.72	0.20	0.30	0.40
Both sexes, 7–12 mo	827	1.32	0.40	0.50	0.60
Both sexes, 1–3 y	3,309	2.19	0.50	0.90	1.10
Both sexes, 4–8 y	3,448	2.82	1.75	2.01	2.16
Standard error		0.04	0.60	0.47	0.39
M, 9–13 y	1,219	3.73	1.90	2.34	2.59
Standard error		0.08	0.24	0.20	0.17
M, 14–18 y	909	4.68	2.25	2.81	3.15
Standard error		0.13	0.70	0.59	0.51
M, 19–30 y	1,902	5.27	2.94	3.50	3.82
Standard error		0.13	0.11	0.14	0.15
M, 31–50 y	2,533	4.88	2.54	3.10	3.43
Standard error		0.09	0.26	0.24	0.22
M, 51–70 y	1,942	4.24	1.75	2.33	2.67
Standard error		0.08	0.12	0.11	0.10
M, 71+ y	1,255	3.49	1.51	1.97	2.24
Standard error		0.06	0.14	0.12	0.11
F, 9–13 y	1,216	2.99	2.04	2.29	2.43
Standard error		0.07	0.60	0.47	0.39
F, 14–18 y	949	2.91	0.96	1.40	1.67
Standard error		0.09	0.17	0.15	0.13
F, 19–30 y	1,901	3.16	1.63	1.99	2.20
Standard error		0.08	0.26	0.22	0.19
F, 31–50 y	2,939	3.23	1.78	2.14	2.34
Standard error		0.05	0.21	0.18	0.15
F, 51–70 y	2,065	2.92	1.37	1.74	1.95
Standard error		0.04	0.10	0.09	0.08
F, 71+ y	1,368	2.62	1.19	1.53	1.73
Standard error		0.05	0.14	0.12	0.10
Pregnant	346	3.76	2.18	2.57	2.79
Standard error		0.18	0.14	0.17	0.18
Lactating	99	4.40	3.07	3.43	3.63
Standard error		0.25	0.19	0.21	0.22
Pregnant/lactating	440	3.91	2.29	2.70	2.94
Standard error		0.15	0.12	0.13	0.13
All individuals	28,575	3.63	1.30	1.79	2.08
Standard error		0.04	0.05	0.05	0.04
All individuals (+P/L)	29,015	3.64	1.32	1.81	2.10
Standard error		0.04	0.05	0.05	0.04

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.50	0.60	0.80	1.20	1.40	2.10
0.80	1.20	1.70	2.10	2.60	3.40
1.50	2.00	2.70	3.40	3.90	5.10
2.44	2.78	3.15	3.52	3.75	4.23
0.24	0.06	0.20	0.44	0.59	0.92
3.05	3.63	4.29	5.00	5.48	6.52
0.12	0.09	0.13	0.23	0.32	0.62
3.77	4.56	5.45	6.35	6.94	8.15
0.34	0.15	0.30	0.65	0.90	1.46
4.42	5.17	6.00	6.84	7.38	8.49
0.14	0.12	0.13	0.15	0.16	0.23
4.03	4.77	5.61	6.47	7.05	8.30
0.19	0.10	0.17	0.28	0.36	0.61
3.29	4.06	4.98	6.04	6.80	8.51
0.09	0.08	0.10	0.16	0.22	0.40
2.73	3.34	4.08	4.91	5.50	6.84
0.09	0.07	0.07	0.14	0.21	0.39
2.67	2.97	3.28	3.59	3.78	4.16
0.24	0.08	0.21	0.44	0.60	0.93
2.16	2.78	3.51	4.30	4.86	6.05
0.10	0.09	0.14	0.25	0.34	0.59
2.59	3.09	3.66	4.21	4.57	5.37
0.14	0.08	0.15	0.27	0.36	0.63
2.71	3.17	3.68	4.19	4.53	5.25
0.11	0.06	0.08	0.16	0.23	0.41
2.35	2.84	3.40	3.99	4.39	5.23
0.06	0.05	0.06	0.10	0.14	0.24
2.09	2.54	3.06	3.61	3.98	4.77
0.08	0.05	0.07	0.15	0.22	0.40
3.20	3.70	4.25	4.80	5.16	5.87
0.16	0.18	0.31	0.40	0.41	0.35
3.97	4.38	4.80	5.20	5.45	5.93
0.25	0.27	0.28	0.29	0.30	0.34
3.36	3.87	4.42	4.95	5.28	5.95
0.14	0.16	0.17	0.18	0.19	0.20
2.65	3.42	4.37	5.44	6.20	7.94
0.04	0.04	0.04	0.06	0.09	0.16
2.66	3.44	4.38	5.44	6.19	7.88
0.04	0.04	0.05	0.07	0.11	0.19

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-3 Mean and Percentiles for Usual Daily Intake of Arginine (g), United States, NHANES III (1988–1994)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	793	0.87	0.20	0.40	0.40
Both sexes, 7–12 mo	827	1.53	0.40	0.60	0.70
Both sexes, 1–3 y	3,309	2.52	0.60	1.00	1.30
Both sexes, 4–8 y	3,448	3.25	2.17	2.43	2.58
Standard error		0.06	0.42	0.34	0.29
M, 9–13 y	1,219	4.34	2.32	2.80	3.08
Standard error		0.16	0.42	0.39	0.36
M, 14–18 y	909	5.33	2.77	3.38	3.74
Standard error		0.14	0.93	0.77	0.67
M, 19–30 y	1,902	6.04	3.36	4.00	4.38
Standard error		0.14	0.11	0.14	0.15
M, 31–50 y	2,533	5.61	2.70	3.40	3.80
Standard error		0.10	0.26	0.23	0.23
M, 51–70 y	1,942	4.88	1.91	2.58	2.98
Standard error		0.10	0.12	0.11	0.11
M, 71+ y	1,255	4.01	1.79	2.29	2.59
Standard error		0.07	0.15	0.13	0.12
F, 9–13 y	1,216	3.46	2.60	2.83	2.96
Standard error		0.08	1.13	0.87	0.71
F, 14–18 y	949	3.39	1.26	1.75	2.04
Standard error		0.10	0.22	0.18	0.16
F, 19–30 y	1,901	3.65	1.78	2.21	2.45
Standard error		0.11	0.24	0.20	0.18
F, 31–50 y	2,939	3.71	2.19	2.57	2.79
Standard error		0.05	0.25	0.21	0.18
F, 51–70 y	2,065	3.33	1.59	2.01	2.25
Standard error		0.05	0.11	0.09	0.08
F, 71+ y	1,368	2.97	1.45	1.81	2.02
Standard error		0.05	0.15	0.13	0.12
Pregnant	346	4.31	2.51	2.96	3.22
Standard error		0.21	0.33	0.44	0.43
Lactating	99	5.08	3.56	3.99	4.23
Standard error		0.27	0.27	0.30	0.30
Pregnant/lactating	440	4.48	2.64	3.12	3.39
Standard error		0.17	0.15	0.15	0.15
All individuals	28,575	4.17	1.51	2.07	2.40
Standard error		0.04	0.06	0.05	0.05
All individuals (+P/L)	29,015	4.18	1.54	2.09	2.42
Standard error		0.04	0.06	0.06	0.05

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.50	0.70	1.10	1.60	1.90	2.80
1.00	1.40	1.90	2.50	2.90	4.30
1.70	2.30	3.10	3.90	4.60	5.80
2.86	3.21	3.60	3.97	4.20	4.66
0.20	0.07	0.17	0.34	0.45	0.69
3.60	4.23	4.96	5.72	6.25	7.38
0.27	0.19	0.32	0.52	0.70	1.24
4.40	5.22	6.14	7.07	7.66	8.88
0.45	0.18	0.35	0.79	1.10	1.78
5.07	5.92	6.88	7.84	8.46	9.72
0.15	0.15	0.16	0.18	0.20	0.26
4.50	5.50	6.50	7.60	8.30	10.00
0.24	0.11	0.24	0.29	0.36	0.63
3.72	4.64	5.77	7.07	8.01	10.13
0.10	0.10	0.12	0.17	0.22	0.38
3.13	3.83	4.68	5.64	6.33	7.89
0.09	0.07	0.09	0.17	0.24	0.45
3.18	3.45	3.73	3.99	4.15	4.48
0.43	0.11	0.34	0.74	1.00	1.53
2.58	3.25	4.04	4.90	5.49	6.76
0.12	0.10	0.15	0.27	0.38	0.64
2.92	3.54	4.26	4.96	5.43	6.53
0.13	0.09	0.20	0.32	0.42	0.77
3.18	3.65	4.18	4.70	5.04	5.76
0.12	0.06	0.09	0.19	0.27	0.45
2.69	3.24	3.86	4.52	4.96	5.90
0.07	0.05	0.06	0.11	0.15	0.26
2.41	2.91	3.46	4.02	4.37	5.11
0.09	0.05	0.09	0.17	0.22	0.34
3.68	4.25	4.88	5.49	5.89	6.68
0.32	0.25	0.42	0.55	0.56	0.44
4.62	5.07	5.53	5.94	6.19	6.66
0.28	0.28	0.33	0.37	0.39	0.39
3.86	4.43	5.05	5.64	6.01	6.74
0.16	0.18	0.20	0.21	0.22	0.25
3.04	3.93	5.02	6.25	7.11	9.10
0.04	0.04	0.05	0.07	0.10	0.18
3.06	3.95	5.03	6.25	7.10	9.04
0.05	0.04	0.05	0.08	0.11	0.20

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-4 Mean and Percentiles for Usual Daily Intake of Aspartic Acid (g), United States, NHANES III (1988–1994)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	793	1.61	0.50	0.70	0.90
Both sexes, 7–12 mo	827	2.69	0.80	1.10	1.40
Both sexes, 1–3 y	3,309	4.08	1.00	1.70	2.20
Both sexes, 4–8 y	3,448	5.15	3.40	3.84	4.10
Standard error		0.07	0.53	0.42	0.36
M, 9–13 y	1,219	6.76	3.50	4.30	4.80
Standard error		0.16	0.42	0.34	0.29
M, 14–18 y	909	8.34	4.50	5.40	6.00
Standard error		0.22	1.16	0.97	0.84
M, 19–30 y	1,902	9.31	5.30	6.30	6.80
Standard error		0.19	0.16	0.17	0.17
M, 31–50 y	2,533	8.67	4.20	5.20	5.90
Standard error		0.16	0.41	0.36	0.33
M, 51–70 y	1,942	7.58	3.20	4.20	4.80
Standard error		0.14	0.22	0.20	0.19
M, 71+ y	1,255	6.32	2.80	3.60	4.10
Standard error		0.10	0.25	0.21	0.18
F, 9–13 y	1,216	5.47	3.14	3.72	4.06
Standard error		0.13	0.09	0.09	0.09
F, 14–18 y	949	5.32	2.00	2.80	3.30
Standard error		0.15	0.28	0.23	0.20
F, 19–30 y	1,901	5.69	3.04	3.67	4.03
Standard error		0.14	0.46	0.37	0.32
F, 31–50 y	2,939	5.79	3.30	3.92	4.28
Standard error		0.08	0.37	0.30	0.26
F, 51–70 y	2,065	5.27	2.51	3.17	3.55
Standard error		0.07	0.14	0.13	0.12
F, 71+ y	1,368	4.75	2.13	2.77	3.14
Standard error		0.09	0.17	0.14	0.13
Pregnant	346	6.81	4.00	4.70	5.10
Standard error		0.28	0.39	0.39	0.35
Lactating	99	8.09	5.65	6.34	6.71
Standard error		0.45	0.52	0.56	0.55
Pregnant/lactating	440	7.12	4.23	4.97	5.40
Standard error		0.26	0.22	0.22	0.23
All individuals	28,575	6.52	2.50	3.30	3.90
Standard error		0.06	0.09	0.08	0.08
All individuals (+P/L)	29,015	6.54	2.50	3.40	3.90
Standard error		0.06	0.10	0.09	0.08

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
1.10	1.40	1.90	2.60	3.10	4.30
1.70	2.40	3.40	4.30	5.10	7.00
2.90	3.90	5.00	6.20	7.20	9.40
4.55	5.10	5.69	6.27	6.63	7.36
0.23	0.09	0.17	0.38	0.52	0.81
5.60	6.60	7.70	9.00	9.80	11.60
0.22	0.16	0.22	0.37	0.51	0.89
7.00	8.20	9.50	10.90	11.70	13.50
0.57	0.26	0.45	0.97	1.33	2.13
7.90	9.20	10.60	12.00	12.90	14.70
0.18	0.19	0.21	0.24	0.26	0.32
7.00	8.50	10.10	11.70	12.90	15.40
0.25	0.18	0.20	0.37	0.53	0.95
5.90	7.30	8.90	10.80	12.10	15.10
0.17	0.15	0.17	0.27	0.37	0.66
5.00	6.10	7.40	8.80	9.80	12.10
0.14	0.10	0.13	0.25	0.37	0.67
4.66	5.40	6.20	6.99	7.49	8.49
0.11	0.15	0.16	0.16	0.17	0.20
4.10	5.10	6.30	7.60	8.50	10.30
0.16	0.15	0.21	0.35	0.48	0.79
4.70	5.58	6.56	7.47	8.06	9.36
0.23	0.14	0.25	0.44	0.60	1.07
4.92	5.70	6.56	7.42	7.98	9.18
0.18	0.08	0.13	0.27	0.39	0.68
4.25	5.12	6.12	7.16	7.86	9.33
0.10	0.08	0.09	0.13	0.18	0.30
3.80	4.62	5.55	6.52	7.18	8.58
0.10	0.07	0.11	0.21	0.31	0.59
5.83	6.72	7.69	8.65	9.26	10.48
0.29	0.31	0.48	0.63	0.67	0.65
7.35	8.07	8.82	9.50	9.92	10.71
0.51	0.47	0.50	0.56	0.57	0.55
6.14	7.04	8.01	8.93	9.52	10.67
0.25	0.27	0.29	0.31	0.32	0.36
4.80	6.20	7.80	9.60	10.90	13.70
0.07	0.06	0.06	0.10	0.14	0.26
4.90	6.20	7.80	9.60	10.90	13.70
0.08	0.06	0.07	0.11	0.16	0.30

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-5 Mean and Percentiles for Usual Daily Intake of Cysteine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.21	0.10	0.10	0.10
Both sexes, 7–12 mo	827	0.39	0.10	0.10	0.20
Both sexes, 1–3 y	3,309	0.64	0.10	0.30	0.30
Both sexes, 4–8 y	3,448	0.82	0.43	0.53	0.58
Standard error		0.01	0.13	0.10	0.08
M, 9–13 y	1,219	1.09	0.61	0.73	0.80
Standard error		0.05	0.12	0.12	0.12
M, 14–18 y	909	1.30	0.64	0.80	0.89
Standard error		0.04	0.13	0.11	0.09
M, 19–30 y	1,902	1.43	0.83	0.99	1.08
Standard error		0.03	0.03	0.03	0.03
M, 31–50 y	2,533	1.33	0.71	0.86	0.95
Standard error		0.02	0.10	0.09	0.07
M, 51–70 y	1,942	1.16	0.49	0.65	0.74
Standard error		0.02	0.03	0.03	0.03
M, 71+ y	1,255	0.98	0.45	0.57	0.65
Standard error		0.01	0.03	0.03	0.02
F, 9–13 y	1,216	0.86	0.60	0.67	0.71
Standard error		0.02	0.14	0.11	0.09
F, 14–18 y	949	0.83	0.30	0.43	0.50
Standard error		0.03	0.06	0.05	0.04
F, 19–30 y	1,901	0.89	0.53	0.62	0.67
Standard error		0.02	0.12	0.10	0.08
F, 31–50 y	2,939	0.89	0.52	0.61	0.67
Standard error		0.01	0.05	0.04	0.04
F, 51–70 y	2,065	0.81	0.40	0.50	0.56
Standard error		0.01	0.03	0.02	0.02
F, 71+ y	1,368	0.74	0.34	0.44	0.50
Standard error		0.01	0.03	0.03	0.02
Pregnant	346	1.06	0.64	0.75	0.81
Standard error		0.04	0.05	0.06	0.06
Lactating	99	1.27	0.90	1.01	1.07
Standard error		0.08	0.11	0.11	0.11
Pregnant/lactating	440	1.11	0.68	0.79	0.86
Standard error		0.04	0.04	0.05	0.04
All individuals	28,575	1.01	0.39	0.52	0.60
Standard error		0.01	0.02	0.02	0.01
All individuals (+P/L)	29,015	1.01	0.40	0.53	0.61
Standard error		0.01	0.02	0.02	0.02

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.10	0.20	0.30	0.40	0.40	0.70
0.30	0.40	0.50	0.70	0.80	1.00
0.50	0.60	0.80	1.00	1.10	1.50
0.68	0.80	0.94	1.08	1.17	1.36
0.06	0.02	0.05	0.11	0.15	0.24
0.92	1.06	1.24	1.42	1.52	1.76
0.09	0.04	0.08	0.13	0.16	0.32
1.06	1.27	1.51	1.75	1.90	2.22
0.07	0.04	0.06	0.11	0.15	0.25
1.23	1.41	1.60	1.81	1.94	2.23
0.03	0.03	0.03	0.04	0.04	0.05
1.11	1.30	1.51	1.73	1.87	2.17
0.05	0.02	0.04	0.09	0.13	0.20
0.91	1.12	1.36	1.63	1.82	2.24
0.03	0.02	0.02	0.04	0.05	0.10
0.78	0.95	1.14	1.35	1.49	1.80
0.02	0.01	0.02	0.03	0.04	0.10
0.78	0.86	0.94	1.02	1.07	1.17
0.05	0.02	0.05	0.10	0.13	0.21
0.63	0.80	0.99	1.20	1.34	1.64
0.03	0.03	0.04	0.07	0.09	0.15
0.76	0.88	1.01	1.13	1.21	1.38
0.05	0.02	0.05	0.09	0.13	0.21
0.76	0.88	1.00	1.13	1.21	1.38
0.03	0.01	0.02	0.04	0.05	0.09
0.66	0.79	0.93	1.08	1.17	1.38
0.02	0.01	0.01	0.02	0.03	0.05
0.60	0.72	0.86	1.00	1.09	1.27
0.02	0.01	0.01	0.03	0.04	0.07
0.92	1.05	1.19	1.34	1.43	1.61
0.05	0.04	0.07	0.09	0.10	0.08
1.17	1.27	1.38	1.48	1.54	1.65
0.09	0.08	0.09	0.10	0.11	0.11
0.97	1.10	1.25	1.38	1.47	1.64
0.05	0.05	0.05	0.08	0.10	0.06
0.76	0.96	1.21	1.47	1.64	2.01
0.01	0.01	0.01	0.02	0.03	0.04
0.76	0.97	1.21	1.47	1.64	2.00
0.01	0.01	0.01	0.02	0.03	0.05

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-6 Mean and Percentiles for Usual Daily Intake of Glutamic Acid (g), United States, NHANES III (1988–1994)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	793	3.54	1.20	1.80	2.00
Both sexes, 7–12 mo	827	6.38	1.80	2.60	3.10
Both sexes, 1–3 y	3,309	10.16	2.70	4.50	5.60
Both sexes, 4–8 y	3,448	12.99	8.30	9.50	10.20
Standard error		0.19	0.16	0.16	0.16
M, 9–13 y	1,219	17.04	9.60	11.30	12.30
Standard error		0.40	1.98	1.63	1.40
M, 14–18 y	909	20.10	10.40	12.80	14.10
Standard error		0.53	2.57	2.15	1.87
M, 19–30 y	1,902	21.43	12.50	14.70	16.00
Standard error		0.43	0.44	0.45	0.40
M, 31–50 y	2,533	19.60	9.80	12.20	13.60
Standard error		0.29	0.80	0.69	0.61
M, 51–70 y	1,942	17.11	7.30	9.70	11.00
Standard error		0.27	0.56	0.53	0.42
M, 71+ y	1,255	14.34	6.40	8.20	9.20
Standard error		0.21	0.50	0.43	0.48
F, 9–13 y	1,216	13.54	8.40	9.80	10.50
Standard error		0.22	0.22	0.23	0.23
F, 14–18 y	949	12.94	6.30	8.00	8.90
Standard error		0.38	1.34	1.09	0.93
F, 19–30 y	1,901	13.42	7.20	8.70	9.60
Standard error		0.25	1.03	0.82	0.70
F, 31–50 y	2,939	13.29	6.80	8.50	9.40
Standard error		0.17	0.53	0.45	0.39
F, 51–70 y	2,065	12.07	5.70	7.20	8.10
Standard error		0.15	0.32	0.28	0.26
F, 71+ y	1,368	10.97	5.10	6.50	7.30
Standard error		0.17	0.72	0.61	0.54
Pregnant	346	16.65	10.20	11.90	12.80
Standard error		0.69	0.64	0.59	0.59
Lactating	99	20.10	14.30	16.00	17.00
Standard error		1.21	1.47	1.55	1.47
Pregnant/lactating	440	17.38	10.80	12.50	13.50
Standard error		0.57	0.57	0.55	0.54
All individuals	28,575	15.22	5.90	8.00	9.20
Standard error		0.12	0.18	0.16	0.15
All individuals (+P/L)	29,015	15.27	6.00	8.00	9.30
Standard error		0.12	0.20	0.16	0.18

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
2.60	3.20	4.10	5.30	6.50	9.70
4.10	5.50	8.10	10.80	12.50	15.60
7.40	9.60	12.40	15.10	17.40	23.50
11.40	12.80	14.50	16.00	17.00	19.00
0.17	0.19	0.23	0.28	0.32	0.44
14.30	16.70	19.40	22.20	24.00	27.80
0.92	0.39	0.90	1.90	2.63	4.26
16.60	19.70	23.20	26.50	28.70	33.10
1.30	0.64	0.95	2.01	2.78	4.44
18.30	21.10	24.20	27.20	29.20	33.10
0.38	0.52	0.58	0.56	0.56	0.71
16.10	19.10	22.50	26.10	28.50	33.70
0.45	0.30	0.39	0.74	1.04	1.74
13.40	16.50	20.10	23.90	26.60	32.80
0.47	0.30	0.46	0.59	0.89	1.58
11.30	13.90	16.90	20.10	22.20	26.50
0.35	0.25	0.50	0.57	0.71	1.58
11.90	13.40	15.10	16.70	17.70	19.90
0.22	0.22	0.25	0.28	0.30	0.33
10.60	12.70	15.00	17.30	18.90	22.10
0.65	0.40	0.61	1.18	1.62	2.63
11.20	13.20	15.40	17.60	19.00	22.10
0.48	0.26	0.46	0.84	1.16	2.04
11.00	13.00	15.20	17.50	19.00	22.10
0.28	0.18	0.21	0.39	0.54	0.97
9.80	11.80	14.00	16.40	17.90	21.30
0.21	0.16	0.18	0.25	0.33	0.64
8.90	10.70	12.80	14.90	16.20	18.90
0.37	0.19	0.32	0.66	0.91	1.45
14.50	16.50	18.60	20.70	22.00	24.50
0.63	0.71	0.79	0.86	0.91	1.01
18.50	20.20	21.70	23.10	23.90	25.40
1.33	1.26	1.41	1.53	1.51	1.39
15.20	17.30	19.40	21.40	22.60	25.00
0.56	0.59	0.62	0.66	0.69	0.76
11.50	14.50	18.10	22.20	25.00	31.30
0.13	0.12	0.13	0.21	0.30	0.53
11.50	14.60	18.20	22.20	25.00	31.10
0.15	0.13	0.13	0.20	0.33	0.58

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-7 Mean and Percentiles for Usual Daily Intake of Glycine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.53	0.10	0.20	0.20
Both sexes, 7–12 mo	827	1.03	0.30	0.40	0.50
Both sexes, 1–3 y	3,309	1.83	0.40	0.70	0.90
Both sexes, 4–8 y	3,448	2.43	1.44	1.67	1.80
Standard error		0.04	0.34	0.28	0.24
M, 9–13 y	1,219	3.24	1.77	2.11	2.31
Standard error		0.09	0.43	0.36	0.31
M, 14–18 y	909	4.13	2.22	2.68	2.95
Standard error		0.11	0.58	0.49	0.42
M, 19–30 y	1,902	4.73	2.59	3.11	3.41
Standard error		0.12	0.10	0.12	0.13
M, 31–50 y	2,533	4.36	2.31	2.79	3.08
Standard error		0.08	0.28	0.24	0.21
M, 51–70 y	1,942	3.76	1.59	2.09	2.39
Standard error		0.08	0.13	0.12	0.11
M, 71+ y	1,255	3.05	1.31	1.71	1.95
Standard error		0.05	0.13	0.11	0.10
F, 9–13 y	1,216	2.61	1.71	1.93	2.06
Standard error		0.06	0.54	0.43	0.37
F, 14–18 y	949	2.58	0.82	1.21	1.45
Standard error		0.08	0.14	0.12	0.11
F, 19–30 y	1,901	2.79	1.35	1.67	1.87
Standard error		0.08	0.18	0.15	0.14
F, 31–50 y	2,939	2.86	1.60	1.90	2.08
Standard error		0.04	0.20	0.17	0.15
F, 51–70 y	2,065	2.55	1.19	1.51	1.70
Standard error		0.04	0.11	0.10	0.09
F, 71+ y	1,368	2.27	1.15	1.42	1.58
Standard error		0.04	0.20	0.17	0.15
Pregnant	346	3.28	1.89	2.23	2.43
Standard error		0.19	0.31	0.47	0.49
Lactating	99	3.66	2.53	2.84	3.01
Standard error		0.22	0.17	0.19	0.20
Pregnant/lactating	440	3.37	1.97	2.32	2.53
Standard error		0.13	0.11	0.11	0.11
All individuals	28,575	3.20	1.09	1.52	1.79
Standard error		0.03	0.04	0.04	0.04
All individuals (+P/L)	29,015	3.21	1.11	1.53	1.80
Standard error		0.03	0.04	0.04	0.04

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who

25th	50th	75th	90th	95th	99th
0.30	0.40	0.70	1.00	1.20	1.80
0.60	0.90	1.30	1.80	2.10	3.20
1.20	1.70	2.30	3.00	3.40	4.40
2.05	2.38	2.75	3.11	3.34	3.81
0.16	0.05	0.14	0.29	0.39	0.61
2.69	3.17	3.71	4.27	4.64	5.40
0.21	0.10	0.20	0.43	0.62	1.12
3.44	4.05	4.73	5.41	5.85	6.74
0.29	0.13	0.24	0.51	0.71	1.14
3.96	4.63	5.39	6.17	6.69	7.80
0.12	0.12	0.12	0.14	0.16	0.22
3.61	4.26	5.00	5.76	6.27	7.36
0.16	0.09	0.12	0.25	0.35	0.61
2.93	3.60	4.41	5.31	5.96	7.39
0.10	0.08	0.09	0.15	0.21	0.37
2.38	2.92	3.57	4.31	4.83	5.99
0.08	0.06	0.07	0.13	0.20	0.37
2.30	2.58	2.89	3.19	3.38	3.76
0.24	0.08	0.18	0.41	0.56	0.89
1.89	2.44	3.11	3.87	4.41	5.58
0.09	0.08	0.12	0.20	0.27	0.46
2.23	2.70	3.25	3.81	4.18	5.02
0.11	0.07	0.13	0.23	0.31	0.55
2.40	2.80	3.25	3.70	4.00	4.64
0.10	0.05	0.07	0.15	0.22	0.39
2.04	2.47	2.97	3.50	3.87	4.65
0.07	0.04	0.05	0.11	0.16	0.28
1.86	2.22	2.63	3.03	3.29	3.83
0.10	0.04	0.09	0.20	0.27	0.45
2.79	3.23	3.72	4.21	4.52	5.14
0.39	0.22	0.35	0.50	0.50	0.34
3.31	3.64	3.99	4.32	4.51	4.89
0.21	0.23	0.25	0.28	0.30	0.35
2.89	3.33	3.81	4.27	4.57	5.15
0.12	0.13	0.15	0.16	0.18	0.20
2.29	3.00	3.88	4.88	5.59	7.25
0.03	0.04	0.04	0.06	0.08	0.15
2.30	3.01	3.88	4.87	5.59	7.20
0.03	0.04	0.05	0.06	0.08	0.16

responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.
DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-8 Mean and Percentiles for Usual Daily Intake of Histidine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.47	0.10	0.20	0.30
Both sexes, 7–12 mo	827	0.85	0.20	0.30	0.40
Both sexes, 1–3 y	3,309	1.38	0.30	0.60	0.70
Both sexes, 4–8 y	3,448	1.77	1.15	1.31	1.40
Standard error		0.03	0.51	0.39	0.31
M, 9–13 y	1,219	2.36	1.37	1.61	1.75
Standard error		0.06	0.20	0.17	0.15
M, 14–18 y	909	2.93	1.48	1.83	2.03
Standard error		0.08	0.35	0.30	0.26
M, 19–30 y	1,902	3.19	1.78	2.12	2.32
Standard error		0.07	0.07	0.10	0.10
M, 31–50 y	2,533	2.90	1.41	1.76	1.97
Standard error		0.05	0.13	0.12	0.11
M, 51–70 y	1,942	2.50	0.95	1.30	1.51
Standard error		0.05	0.06	0.06	0.05
M, 71+ y	1,255	2.03	0.85	1.13	1.29
Standard error		0.03	0.07	0.06	0.06
F, 9–13 y	1,216	1.89	1.10	1.30	1.42
Standard error		0.04	0.04	0.05	0.06
F, 14–18 y	949	1.80	0.70	0.96	1.12
Standard error		0.05	0.14	0.11	0.10
F, 19–30 y	1,901	1.91	1.00	1.22	1.35
Standard error		0.04	0.16	0.13	0.11
F, 31–50 y	2,939	1.92	1.09	1.30	1.41
Standard error		0.03	0.12	0.10	0.09
F, 51–70 y	2,065	1.72	0.84	1.05	1.17
Standard error		0.02	0.06	0.05	0.05
F, 71+ y	1,368	1.54	0.67	0.88	1.00
Standard error		0.03	0.09	0.06	0.05
Pregnant	346	2.32	1.38	1.62	1.75
Standard error		0.11	0.25	0.28	0.27
Lactating	99	2.72	1.91	2.14	2.26
Standard error		0.13	0.12	0.13	0.13
Pregnant/lactating	440	2.42	1.45	1.70	1.85
Standard error		0.09	0.08	0.08	0.08
All individuals	28,575	2.19	0.82	1.10	1.28
Standard error		0.02	0.03	0.03	0.03
All individuals (+P/L)	29,015	2.20	0.83	1.11	1.29
Standard error		0.02	0.03	0.03	0.03

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and

25th	50th	75th	90th	95th	99th
0.30	0.40	0.50	0.70	0.90	1.30
0.50	0.70	1.10	1.40	1.70	2.30
1.00	1.30	1.70	2.10	2.50	3.10
1.56	1.75	1.96	2.17	2.30	2.56
0.18	0.05	0.17	0.34	0.46	0.69
2.00	2.32	2.67	3.02	3.24	3.71
0.11	0.06	0.10	0.18	0.24	0.38
2.40	2.86	3.39	3.91	4.25	4.94
0.18	0.10	0.14	0.30	0.41	0.67
2.68	3.13	3.63	4.12	4.44	5.09
0.09	0.07	0.08	0.09	0.10	0.13
2.35	2.83	3.36	3.91	4.28	5.11
0.09	0.06	0.08	0.14	0.20	0.34
1.89	2.38	2.96	3.63	4.11	5.19
0.05	0.05	0.06	0.10	0.14	0.25
1.58	1.95	2.39	2.88	3.22	3.98
0.05	0.04	0.04	0.08	0.12	0.21
1.62	1.86	2.13	2.39	2.56	2.90
0.05	0.04	0.05	0.07	0.07	0.06
1.40	1.74	2.14	2.56	2.84	3.43
0.07	0.05	0.08	0.15	0.20	0.32
1.58	1.87	2.20	2.51	2.72	3.15
0.08	0.05	0.07	0.13	0.18	0.32
1.63	1.89	2.17	2.46	2.65	3.04
0.06	0.03	0.05	0.10	0.14	0.23
1.40	1.68	2.00	2.32	2.52	2.94
0.04	0.03	0.03	0.05	0.07	0.11
1.22	1.49	1.81	2.13	2.34	2.80
0.04	0.03	0.04	0.08	0.12	0.27
2.00	2.29	2.62	2.94	3.14	3.56
0.22	0.14	0.20	0.25	0.25	0.22
2.47	2.71	2.96	3.18	3.32	3.58
0.13	0.14	0.17	0.19	0.19	0.19
2.10	2.40	2.72	3.03	3.22	3.60
0.08	0.09	0.10	0.11	0.11	0.13
1.62	2.07	2.63	3.25	3.69	4.65
0.02	0.02	0.02	0.04	0.05	0.10
1.62	2.08	2.64	3.25	3.68	4.63
0.02	0.02	0.02	0.04	0.06	0.11

females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.
DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-9 Mean and Percentiles for Usual Daily Intake of Isoleucine (g), United States, NHANES III (1988–1994)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	793	0.98	0.40	0.50	0.60
Both sexes, 7–12 mo	827	1.63	0.50	0.70	0.80
Both sexes, 1–3 y	3,309	2.40	0.50	1.00	1.30
Both sexes, 4–8 y	3,448	2.98	1.77	2.07	2.25
Standard error		0.04	0.42	0.34	0.28
M, 9–13 y	1,219	3.84	2.19	2.59	2.82
Standard error		0.09	0.28	0.23	0.21
M, 14–18 y	909	4.60	2.15	2.73	3.07
Standard error		0.13	0.44	0.38	0.33
M, 19–30 y	1,902	5.01	2.88	3.42	3.72
Standard error		0.11	0.21	0.23	0.19
M, 31–50 y	2,533	4.59	2.29	2.85	3.18
Standard error		0.08	0.22	0.20	0.17
M, 51–70 y	1,942	4.03	1.61	2.17	2.50
Standard error		0.07	0.11	0.10	0.09
M, 71+ y	1,255	3.36	1.34	1.81	2.08
Standard error		0.05	0.12	0.09	0.07
F, 9–13 y	1,216	3.09	1.81	2.13	2.32
Standard error		0.06	0.05	0.05	0.05
F, 14–18 y	949	2.94	1.19	1.61	1.85
Standard error		0.08	0.20	0.16	0.14
F, 19–30 y	1,901	3.09	1.52	1.90	2.11
Standard error		0.07	0.21	0.17	0.15
F, 31–50 y	2,939	3.12	1.70	2.05	2.25
Standard error		0.04	0.17	0.14	0.12
F, 51–70 y	2,065	2.83	1.31	1.67	1.88
Standard error		0.04	0.08	0.07	0.07
F, 71+ y	1,368	2.58	1.15	1.49	1.69
Standard error		0.05	0.14	0.12	0.11
Pregnant	346	3.78	2.37	2.76	2.95
Standard error		0.26	0.40	0.39	0.27
Lactating	99	4.70	3.30	3.69	3.90
Standard error		0.28	0.24	0.26	0.26
Pregnant/lactating	440	4.03	2.40	2.82	3.06
Standard error		0.15	0.13	0.13	0.14
All individuals	28,575	3.55	1.38	1.84	2.13
Standard error		0.03	0.05	0.04	0.04
All individuals (+P/L)	29,015	3.55	1.42	1.87	2.15
Standard error		0.03	0.06	0.05	0.05

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.70	0.90	1.10	1.50	1.80	2.60
1.00	1.40	2.00	2.70	3.20	4.00
1.70	2.30	2.90	3.70	4.20	5.50
2.56	2.94	3.35	3.76	4.02	4.53
0.17	0.05	0.15	0.32	0.44	0.68
3.24	3.77	4.35	4.93	5.31	6.07
0.15	0.09	0.14	0.25	0.35	0.64
3.70	4.49	5.38	6.26	6.83	7.99
0.25	0.15	0.20	0.38	0.52	0.85
4.25	4.91	5.66	6.42	6.92	7.94
0.12	0.16	0.17	0.14	0.14	0.25
3.76	4.47	5.29	6.13	6.70	7.89
0.13	0.08	0.11	0.21	0.28	0.47
3.11	3.86	4.75	5.76	6.49	8.15
0.08	0.08	0.08	0.13	0.18	0.33
2.58	3.21	3.97	4.83	5.44	6.80
0.06	0.05	0.07	0.12	0.17	0.32
2.65	3.05	3.48	3.90	4.17	4.69
0.05	0.06	0.06	0.07	0.08	0.09
2.30	2.85	3.48	4.13	4.57	5.48
0.11	0.09	0.13	0.21	0.30	0.53
2.51	3.01	3.59	4.15	4.52	5.33
0.11	0.07	0.11	0.20	0.27	0.49
2.61	3.06	3.55	4.04	4.37	5.05
0.08	0.04	0.07	0.14	0.19	0.33
2.27	2.75	3.30	3.87	4.24	5.02
0.05	0.04	0.05	0.08	0.11	0.21
2.06	2.52	3.04	3.56	3.90	4.58
0.08	0.05	0.07	0.14	0.19	0.31
3.26	3.66	4.20	4.78	5.16	5.91
0.23	0.46	0.45	0.32	0.28	0.31
4.27	4.69	5.12	5.51	5.76	6.22
0.28	0.30	0.30	0.31	0.32	0.36
3.48	3.98	4.53	5.06	5.39	6.05
0.15	0.16	0.17	0.18	0.18	0.20
2.67	3.38	4.24	5.17	5.83	7.28
0.04	0.03	0.04	0.06	0.07	0.14
2.69	3.40	4.25	5.14	5.74	7.01
0.04	0.03	0.04	0.07	0.09	0.15

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-10 Mean and Percentiles for Usual Daily Intake of Leucine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	1.63	0.60	0.80	1.00
Both sexes, 7–12 mo	827	2.72	0.90	1.10	1.30
Both sexes, 1–3 y	3,309	4.07	0.90	1.80	2.20
Both sexes, 4–8 y	3,448	5.11	3.21	3.70	3.97
Standard error		0.07	1.36	1.04	0.85
M, 9–13 y	1,219	6.66	4.01	4.69	5.07
Standard error		0.17	0.65	0.50	0.42
M, 14–18 y	909	8.00	3.90	4.90	5.50
Standard error		0.22	0.75	0.65	0.58
M, 19–30 y	1,902	8.64	5.00	5.90	6.40
Standard error		0.17	0.15	0.15	0.15
M, 31–50 y	2,533	7.91	3.90	4.90	5.40
Standard error		0.14	0.36	0.32	0.28
M, 51–70 y	1,942	6.90	2.70	3.70	4.30
Standard error		0.12	0.19	0.16	0.15
M, 71+ y	1,255	5.73	2.40	3.20	3.60
Standard error		0.08	0.17	0.14	0.12
F, 9–13 y	1,216	5.32	4.05	4.39	4.58
Standard error		0.10	1.62	1.20	0.97
F, 14–18 y	949	5.04	2.00	2.70	3.20
Standard error		0.14	0.33	0.27	0.23
F, 19–30 y	1,901	5.30	2.63	3.27	3.63
Standard error		0.11	0.38	0.31	0.27
F, 31–50 y	2,939	5.33	2.88	3.48	3.83
Standard error		0.07	0.27	0.22	0.19
F, 51–70 y	2,065	4.82	2.24	2.86	3.22
Standard error		0.07	0.13	0.11	0.10
F, 71+ y	1,368	4.34	1.89	2.45	2.79
Standard error		0.08	0.18	0.15	0.14
Pregnant	346	6.50	4.17	4.70	4.96
Standard error		0.34	0.43	0.28	0.25
Lactating	99	8.01	5.63	6.30	6.67
Standard error		0.43	0.38	0.37	0.39
Pregnant/lactating	440	6.88	4.15	4.85	5.25
Standard error		0.26	0.22	0.23	0.24
All individuals	28,575	6.08	2.30	3.10	3.60
Standard error		0.05	0.08	0.07	0.07
All individuals (+P/L)	29,015	6.10	2.40	3.20	3.70
Standard error		0.05	0.08	0.07	0.07

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
1.20	1.50	1.90	2.40	2.90	4.20
1.80	2.40	3.30	4.50	5.40	6.70
2.90	3.80	5.00	6.20	7.20	9.40
4.46	5.05	5.69	6.32	6.71	7.49
0.50	0.09	0.45	0.93	1.25	1.89
5.75	6.56	7.46	8.37	8.97	10.22
0.28	0.18	0.27	0.49	0.68	1.13
6.50	7.80	9.30	10.80	11.70	13.60
0.43	0.26	0.31	0.62	0.86	1.39
7.30	8.50	9.80	11.10	11.90	13.50
0.16	0.17	0.18	0.21	0.23	0.29
6.50	7.70	9.10	10.60	11.60	13.80
0.21	0.16	0.19	0.35	0.49	0.83
5.30	6.60	8.10	9.90	11.20	14.10
0.14	0.13	0.14	0.24	0.33	0.59
4.50	5.50	6.70	8.10	9.10	11.30
0.10	0.08	0.11	0.20	0.29	0.52
4.91	5.30	5.70	6.07	6.30	6.76
0.55	0.11	0.51	1.03	1.35	2.01
3.90	4.90	6.00	7.10	7.90	9.40
0.17	0.15	0.23	0.37	0.49	0.84
4.30	5.18	6.16	7.10	7.72	9.12
0.19	0.11	0.18	0.34	0.48	0.88
4.46	5.23	6.08	6.93	7.50	8.70
0.14	0.08	0.11	0.21	0.30	0.52
3.88	4.69	5.62	6.57	7.20	8.52
0.08	0.07	0.08	0.13	0.17	0.29
3.42	4.22	5.13	6.05	6.64	7.86
0.11	0.08	0.13	0.20	0.25	0.44
5.48	6.34	7.37	8.28	8.81	9.92
0.37	0.40	0.56	0.54	0.47	0.43
7.30	8.00	8.71	9.36	9.75	10.50
0.42	0.45	0.48	0.50	0.52	0.58
5.96	6.80	7.72	8.60	9.15	10.24
0.25	0.27	0.29	0.30	0.31	0.34
4.50	5.80	7.30	8.90	10.10	12.70
0.06	0.05	0.06	0.09	0.14	0.24
4.60	5.80	7.30	8.90	10.10	12.60
0.06	0.05	0.06	0.10	0.15	0.26

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-11 Mean and Percentiles for Usual Daily Intake of Lysine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	1.24	0.40	0.60	0.70
Both sexes, 7–12 mo	827	2.15	0.60	0.80	1.00
Both sexes, 1–3 y	3,309	3.35	0.70	1.30	1.70
Both sexes, 4–8 y	3,448	4.23	2.72	3.10	3.32
Standard error		0.06	0.89	0.69	0.57
M, 9–13 y	1,219	5.55	3.01	3.64	4.00
Standard error		0.13	0.51	0.42	0.36
M, 14–18 y	909	6.91	3.40	4.20	4.70
Standard error		0.20	0.93	0.79	0.69
M, 19–30 y	1,902	7.66	4.20	5.00	5.50
Standard error		0.16	0.13	0.13	0.14
M, 31–50 y	2,533	6.97	3.30	4.20	4.70
Standard error		0.14	0.35	0.31	0.28
M, 51–70 y	1,942	6.00	2.30	3.10	3.60
Standard error		0.12	0.15	0.14	0.13
M, 71+ y	1,255	4.88	1.98	2.64	3.03
Standard error		0.09	0.20	0.18	0.16
F, 9–13 y	1,216	4.47	2.51	3.00	3.28
Standard error		0.09	0.07	0.07	0.07
F, 14–18 y	949	4.28	1.60	2.23	2.61
Standard error		0.12	0.29	0.25	0.21
F, 19–30 y	1,901	4.60	2.39	2.92	3.23
Standard error		0.12	0.43	0.35	0.31
F, 31–50 y	2,939	4.65	2.58	3.09	3.38
Standard error		0.07	0.34	0.28	0.24
F, 51–70 y	2,065	4.16	1.86	2.40	2.72
Standard error		0.06	0.14	0.14	0.13
F, 71+ y	1,368	3.71	1.59	2.09	2.39
Standard error		0.08	0.25	0.18	0.16
Pregnant	346	5.57	3.19	3.77	4.11
Standard error		0.22	0.25	0.34	0.34
Lactating	99	6.64	4.51	5.09	5.41
Standard error		0.32	0.24	0.27	0.29
Pregnant/lactating	440	5.85	3.41	4.03	4.38
Standard error		0.21	0.18	0.18	0.19
All individuals	28,575	5.26	1.90	2.60	3.10
Standard error		0.05	0.08	0.07	0.06
All individuals (+P/L)	29,015	5.27	2.00	2.70	3.10
Standard error		0.05	0.08	0.08	0.07

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.90	1.10	1.40	1.90	2.30	3.60
1.30	1.90	2.70	3.60	4.40	5.60
2.30	3.10	4.20	5.30	6.20	7.40
3.71	4.18	4.69	5.19	5.50	6.13
0.34	0.08	0.30	0.63	0.85	1.30
4.65	5.43	6.32	7.24	7.85	9.13
0.25	0.15	0.20	0.40	0.56	0.95
5.60	6.80	8.00	9.30	10.10	11.80
0.48	0.24	0.36	0.78	1.09	1.76
6.40	7.50	8.70	10.00	10.80	12.40
0.14	0.16	0.18	0.20	0.22	0.28
5.60	6.80	8.10	9.50	10.40	12.40
0.22	0.15	0.19	0.35	0.49	0.85
4.50	5.70	7.10	8.80	9.90	12.60
0.12	0.12	0.15	0.24	0.33	0.58
3.75	4.65	5.76	7.02	7.93	9.96
0.13	0.10	0.11	0.21	0.32	0.61
3.79	4.40	5.08	5.73	6.15	6.98
0.08	0.09	0.10	0.11	0.12	0.14
3.29	4.14	5.12	6.14	6.82	8.25
0.16	0.12	0.19	0.34	0.46	0.77
3.79	4.50	5.30	6.07	6.58	7.67
0.21	0.11	0.23	0.41	0.56	0.95
3.91	4.56	5.29	6.01	6.48	7.48
0.16	0.07	0.13	0.29	0.40	0.69
3.31	4.04	4.88	5.74	6.32	7.52
0.10	0.07	0.10	0.13	0.17	0.41
2.92	3.59	4.36	5.17	5.71	6.87
0.12	0.09	0.10	0.20	0.36	0.88
4.72	5.48	6.32	7.15	7.69	8.77
0.27	0.22	0.40	0.56	0.59	0.52
5.97	6.61	7.29	7.92	8.30	9.06
0.33	0.35	0.37	0.39	0.41	0.51
5.01	5.77	6.60	7.40	7.90	8.90
0.20	0.22	0.24	0.25	0.27	0.30
3.90	5.00	6.30	7.80	8.80	11.20
0.06	0.05	0.06	0.10	0.13	0.24
3.90	5.00	6.30	7.80	8.80	11.10
0.07	0.05	0.06	0.10	0.15	0.27

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-12 Mean and Percentiles for Usual Daily Intake of Methionine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.37	0.10	0.20	0.20
Both sexes, 7–12 mo	827	0.69	0.20	0.20	0.30
Both sexes, 1–3 y	3,309	1.13	0.30	0.40	0.60
Both sexes, 4–8 y	3,448	1.43	0.85	1.00	1.08
Standard error		0.03	0.21	0.16	0.14
M, 9–13 y	1,219	1.87	1.03	1.23	1.35
Standard error		0.05	0.14	0.12	0.11
M, 14–18 y	909	2.31	1.09	1.38	1.55
Standard error		0.07	0.27	0.23	0.21
M, 19–30 y	1,902	2.54	1.42	1.69	1.85
Standard error		0.05	0.04	0.05	0.05
M, 31–50 y	2,533	2.32	1.16	1.44	1.60
Standard error		0.04	0.15	0.13	0.12
M, 51–70 y	1,942	2.01	0.80	1.07	1.24
Standard error		0.04	0.06	0.05	0.04
M, 71+ y	1,255	1.66	0.70	0.92	1.06
Standard error		0.03	0.07	0.06	0.05
F, 9–13 y	1,216	1.51	1.18	1.27	1.32
Standard error		0.03	0.50	0.37	0.30
F, 14–18 y	949	1.44	0.53	0.75	0.88
Standard error		0.04	0.12	0.10	0.09
F, 19–30 y	1,901	1.55	0.78	0.96	1.07
Standard error		0.04	0.12	0.10	0.08
F, 31–50 y	2,939	1.56	0.88	1.05	1.15
Standard error		0.02	0.11	0.09	0.08
F, 51–70 y	2,065	1.40	0.63	0.81	0.92
Standard error		0.02	0.05	0.04	0.04
F, 71+ y	1,368	1.26	0.58	0.74	0.84
Standard error		0.03	0.07	0.06	0.05
Pregnant	346	1.89	1.10	1.30	1.41
Standard error		0.10	0.18	0.26	0.27
Lactating	99	2.23	1.54	1.73	1.83
Standard error		0.12	0.13	0.17	0.18
Pregnant/lactating	440	1.97	1.17	1.37	1.49
Standard error		0.07	0.06	0.06	0.07
All individuals	28,575	1.76	0.67	0.90	1.04
Standard error		0.02	0.03	0.03	0.03
All individuals (+P/L)	29,015	1.77	0.68	0.91	1.05
Standard error		0.02	0.03	0.03	0.03

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.30	0.30	0.40	0.60	0.70	1.20
0.40	0.60	0.90	1.20	1.40	1.90
0.80	1.10	1.40	1.80	2.00	2.50
1.23	1.41	1.61	1.80	1.93	2.18
0.09	0.05	0.09	0.16	0.22	0.34
1.57	1.83	2.14	2.44	2.64	3.04
0.08	0.05	0.07	0.12	0.16	0.30
1.86	2.25	2.70	3.15	3.43	4.02
0.15	0.08	0.11	0.24	0.33	0.53
2.14	2.50	2.90	3.30	3.55	4.07
0.05	0.05	0.06	0.07	0.07	0.09
1.90	2.26	2.68	3.12	3.41	4.02
0.09	0.05	0.07	0.15	0.20	0.35
1.54	1.92	2.38	2.89	3.27	4.12
0.04	0.04	0.05	0.08	0.10	0.18
1.29	1.59	1.94	2.34	2.63	3.25
0.04	0.03	0.04	0.07	0.11	0.19
1.40	1.50	1.61	1.70	1.76	1.88
0.18	0.04	0.15	0.31	0.41	0.61
1.11	1.39	1.72	2.07	2.30	2.80
0.06	0.04	0.07	0.13	0.18	0.30
1.26	1.52	1.80	2.08	2.26	2.65
0.06	0.04	0.06	0.11	0.15	0.26
1.32	1.54	1.77	2.01	2.17	2.49
0.05	0.02	0.04	0.09	0.12	0.21
1.12	1.37	1.65	1.94	2.13	2.53
0.03	0.02	0.03	0.04	0.06	0.11
1.01	1.23	1.47	1.72	1.89	2.26
0.04	0.03	0.03	0.07	0.10	0.17
1.61	1.86	2.13	2.40	2.58	2.93
0.22	0.12	0.19	0.28	0.28	0.18
2.01	2.22	2.43	2.63	2.76	3.00
0.16	0.12	0.14	0.17	0.19	0.20
1.69	1.94	2.22	2.48	2.65	2.98
0.07	0.07	0.08	0.09	0.09	0.10
1.31	1.68	2.12	2.59	2.90	3.58
0.02	0.02	0.02	0.03	0.05	0.08
1.32	1.68	2.12	2.59	2.90	3.57
0.02	0.02	0.02	0.04	0.05	0.09

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-13 Mean and Percentiles for Usual Daily Intake of Phenylalanine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.84	0.30	0.40	0.50
Both sexes, 7–12 mo	827	1.45	0.40	0.60	0.70
Both sexes, 1–3 y	3,309	2.25	0.50	1.00	1.20
Both sexes, 4–8 y	3,448	2.84	1.79	2.05	2.21
Standard error		0.04	0.54	0.42	0.34
M, 9–13 y	1,219	3.72	2.28	2.65	2.86
Standard error		0.10	0.34	0.27	0.24
M, 14–18 y	909	4.44	2.16	2.70	3.03
Standard error		0.12	0.45	0.38	0.33
M, 19–30 y	1,902	4.82	2.79	3.29	3.58
Standard error		0.10	0.11	0.12	0.11
M, 31–50 y	2,533	4.41	2.17	2.72	3.04
Standard error		0.07	0.18	0.15	0.14
M, 51–70 y	1,942	3.85	1.57	2.10	2.42
Standard error		0.07	0.11	0.09	0.08
M, 71+ y	1,255	3.22	1.43	1.84	2.09
Standard error		0.05	0.12	0.09	0.08
F, 9–13 y	1,216	2.97	1.79	2.09	2.26
Standard error		0.06	0.05	0.07	0.07
F, 14–18 y	949	2.83	1.18	1.58	1.81
Standard error		0.08	0.17	0.15	0.13
F, 19–30 y	1,901	2.98	1.52	1.87	2.07
Standard error		0.06	0.22	0.18	0.15
F, 31–50 y	2,939	2.97	1.64	1.97	2.17
Standard error		0.04	0.15	0.12	0.11
F, 51–70 y	2,065	2.69	1.26	1.60	1.81
Standard error		0.04	0.08	0.06	0.06
F, 71+ y	1,368	2.44	1.10	1.42	1.60
Standard error		0.04	0.13	0.11	0.10
Pregnant	346	3.63	2.20	2.56	2.77
Standard error		0.20	0.33	0.34	0.28
Lactating	99	4.44	3.16	3.53	3.73
Standard error		0.24	0.26	0.25	0.24
Pregnant/lactating	440	3.83	2.33	2.72	2.95
Standard error		0.15	0.12	0.13	0.13
All individuals	28,575	3.39	1.32	1.76	2.03
Standard error		0.03	0.05	0.04	0.04
All individuals (+P/L)	29,015	3.40	1.34	1.78	2.05
Standard error		0.03	0.05	0.04	0.04

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.60	0.80	1.00	1.30	1.50	2.20
0.90	1.30	1.80	2.40	2.80	3.70
1.60	2.10	2.80	3.40	3.90	5.30
2.48	2.81	3.17	3.52	3.74	4.18
0.20	0.06	0.19	0.39	0.52	0.78
3.23	3.67	4.16	4.66	4.98	5.67
0.16	0.10	0.16	0.30	0.39	0.63
3.61	4.34	5.16	5.97	6.49	7.53
0.23	0.13	0.20	0.39	0.52	0.83
4.11	4.75	5.45	6.15	6.59	7.48
0.09	0.11	0.13	0.13	0.13	0.16
3.61	4.30	5.10	5.93	6.49	7.68
0.10	0.07	0.10	0.18	0.25	0.41
2.99	3.70	4.53	5.45	6.12	7.62
0.07	0.07	0.08	0.13	0.17	0.30
2.53	3.09	3.76	4.51	5.03	6.18
0.06	0.04	0.07	0.12	0.18	0.34
2.57	2.94	3.34	3.72	3.97	4.45
0.07	0.06	0.06	0.07	0.08	0.09
2.24	2.75	3.34	3.95	4.35	5.20
0.10	0.08	0.12	0.19	0.26	0.43
2.44	2.91	3.45	3.96	4.29	5.03
0.11	0.06	0.12	0.21	0.28	0.49
2.51	2.92	3.38	3.84	4.14	4.77
0.08	0.04	0.06	0.12	0.16	0.28
2.17	2.62	3.13	3.66	4.01	4.74
0.05	0.04	0.04	0.06	0.09	0.20
1.95	2.38	2.86	3.34	3.65	4.28
0.07	0.04	0.06	0.13	0.17	0.28
3.13	3.58	4.07	4.56	4.86	5.48
0.20	0.30	0.39	0.38	0.34	0.25
4.06	4.43	4.81	5.15	5.35	5.74
0.24	0.25	0.29	0.33	0.35	0.36
3.34	3.80	4.29	4.76	5.05	5.61
0.15	0.17	0.17	0.17	0.17	0.17
2.55	3.24	4.07	4.95	5.54	6.79
0.03	0.03	0.03	0.05	0.07	0.11
2.57	3.25	4.07	4.94	5.52	6.75
0.03	0.03	0.03	0.06	0.08	0.13

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-14 Mean and Percentiles for Usual Daily Intake of Proline (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	1.34	0.40	0.60	0.80
Both sexes, 7–12 mo	827	2.39	0.70	0.90	1.10
Both sexes, 1–3 y	3,309	3.73	0.90	1.60	2.00
Both sexes, 4–8 y	3,448	4.66	2.93	3.37	3.62
Standard error		0.07	0.06	0.06	0.06
M, 9–13 y	1,219	6.00	3.49	4.12	4.48
Standard error		0.14	0.73	0.59	0.50
M, 14–18 y	909	7.00	3.40	4.30	4.80
Standard error		0.19	0.67	0.57	0.51
M, 19–30 y	1,902	7.31	4.87	5.50	5.85
Standard error		0.14	1.37	1.06	0.88
M, 31–50 y	2,533	6.54	3.30	4.10	4.50
Standard error		0.10	0.29	0.25	0.22
M, 51–70 y	1,942	5.65	2.30	3.10	3.60
Standard error		0.08	0.19	0.16	0.14
M, 71+ y	1,255	4.76	2.03	2.61	2.97
Standard error		0.08	0.10	0.08	0.07
F, 9–13 y	1,216	4.78	2.93	3.42	3.69
Standard error		0.09	0.08	0.09	0.09
F, 14–18 y	949	4.48	2.13	2.70	3.03
Standard error		0.13	0.42	0.35	0.31
F, 19–30 y	1,901	4.54	2.31	2.87	3.19
Standard error		0.07	0.34	0.27	0.23
F, 31–50 y	2,939	4.45	2.28	2.82	3.13
Standard error		0.06	0.18	0.15	0.13
F, 51–70 y	2,065	4.03	1.80	2.30	2.61
Standard error		0.06	0.10	0.10	0.10
F, 71+ y	1,368	3.69	1.67	2.14	2.42
Standard error		0.06	0.20	0.17	0.15
Pregnant	346	5.81	3.53	4.12	4.45
Standard error		0.33	0.25	0.27	0.29
Lactating	99	7.01	5.00	5.60	5.91
Standard error		0.50	0.36	0.37	0.42
Pregnant/lactating	440	6.10	3.72	4.35	4.70
Standard error		0.22	0.19	0.19	0.20
All individuals	28,575	5.19	2.00	2.70	3.10
Standard error		0.04	0.07	0.06	0.06
All individuals (+P/L)	29,015	5.21	2.00	2.70	3.10
Standard error		0.04	0.07	0.06	0.06

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.90	1.20	1.60	2.00	2.50	3.80
1.40	2.00	3.10	4.20	5.00	6.10
2.70	3.50	4.60	5.60	6.40	8.50
4.07	4.61	5.20	5.76	6.12	6.83
0.06	0.07	0.08	0.09	0.10	0.13
5.12	5.89	6.75	7.65	8.24	9.52
0.33	0.15	0.28	0.61	0.86	1.42
5.70	6.80	8.10	9.40	10.30	12.00
0.37	0.22	0.30	0.58	0.79	1.26
6.48	7.23	8.06	8.86	9.37	10.39
0.55	0.17	0.48	1.02	1.39	2.15
5.40	6.40	7.50	8.70	9.60	11.30
0.16	0.10	0.14	0.29	0.40	0.68
4.40	5.40	6.60	8.00	8.90	11.00
0.11	0.09	0.10	0.21	0.30	0.54
3.66	4.56	5.64	6.79	7.55	9.19
0.06	0.07	0.11	0.17	0.22	0.35
4.17	4.73	5.34	5.93	6.31	7.09
0.09	0.09	0.10	0.11	0.12	0.12
3.63	4.39	5.23	6.06	6.59	7.67
0.21	0.13	0.23	0.42	0.56	0.88
3.76	4.45	5.22	6.02	6.54	7.63
0.15	0.08	0.13	0.27	0.38	0.62
3.69	4.36	5.11	5.87	6.37	7.41
0.09	0.06	0.07	0.13	0.18	0.29
3.18	3.91	4.74	5.59	6.14	7.28
0.08	0.06	0.09	0.12	0.15	0.30
2.94	3.60	4.34	5.08	5.57	6.55
0.11	0.07	0.10	0.19	0.27	0.43
5.04	5.75	6.52	7.27	7.74	8.69
0.33	0.36	0.37	0.37	0.36	0.36
6.44	7.02	7.59	8.10	8.40	8.97
0.65	0.53	0.46	0.61	0.63	0.47
5.32	6.05	6.82	7.54	7.99	8.87
0.21	0.23	0.24	0.24	0.25	0.26
3.90	4.90	6.20	7.60	8.50	10.60
0.05	0.04	0.05	0.08	0.11	0.21
3.90	5.00	6.20	7.60	8.50	10.60
0.05	0.04	0.04	0.08	0.12	0.21

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-15 Mean and Percentiles for Usual Daily Intake of Serine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.93	0.30	0.50	0.50
Both sexes, 7–12 mo	827	1.57	0.50	0.70	0.80
Both sexes, 1–3 y	3,309	2.39	0.60	1.10	1.30
Both sexes, 4–8 y	3,448	2.98	1.77	2.08	2.26
Standard error		0.05	0.52	0.41	0.34
M, 9–13 y	1,219	3.88	2.31	2.71	2.94
Standard error		0.11	0.39	0.32	0.27
M, 14–18 y	909	4.58	2.17	2.74	3.08
Standard error		0.12	0.43	0.38	0.34
M, 19–30 y	1,902	4.91	2.88	3.40	3.68
Standard error		0.10	0.13	0.13	0.12
M, 31–50 y	2,533	4.53	2.20	2.77	3.11
Standard error		0.07	0.19	0.16	0.14
M, 51–70 y	1,942	3.96	1.64	2.18	2.51
Standard error		0.07	0.12	0.10	0.10
M, 71+ y	1,255	3.35	1.54	1.96	2.21
Standard error		0.05	0.11	0.10	0.09
F, 9–13 y	1,216	3.09	1.86	2.18	2.36
Standard error		0.05	0.05	0.06	0.06
F, 14–18 y	949	2.93	1.23	1.63	1.86
Standard error		0.08	0.17	0.14	0.12
F, 19–30 y	1,901	3.06	1.63	1.98	2.18
Standard error		0.06	0.25	0.20	0.17
F, 31–50 y	2,939	3.06	1.67	2.02	2.22
Standard error		0.04	0.15	0.13	0.11
F, 51–70 y	2,065	2.78	1.28	1.64	1.85
Standard error		0.04	0.08	0.08	0.09
F, 71+ y	1,368	2.53	1.14	1.46	1.66
Standard error		0.04	0.11	0.10	0.09
Pregnant	346	3.77	2.27	2.65	2.86
Standard error		0.18	0.15	0.15	0.14
Lactating	99	4.59	3.26	3.64	3.85
Standard error		0.26	0.24	0.25	0.26
Pregnant/lactating	440	3.97	2.40	2.81	3.05
Standard error		0.15	0.13	0.14	0.14
All individuals	28,575	3.51	1.38	1.84	2.12
Standard error		0.03	0.05	0.04	0.04
All individuals (+P/L)	29,015	3.52	1.40	1.85	2.14
Standard error		0.03	0.05	0.04	0.04

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.70	0.80	1.10	1.40	1.70	2.30
1.00	1.40	2.00	2.60	3.00	3.90
1.70	2.20	2.90	3.60	4.10	5.50
2.57	2.94	3.35	3.75	4.01	4.53
0.21	0.06	0.18	0.38	0.52	0.81
3.34	3.82	4.35	4.89	5.26	6.02
0.19	0.11	0.17	0.31	0.42	0.67
3.70	4.48	5.35	6.22	6.78	7.93
0.26	0.15	0.17	0.34	0.48	0.80
4.19	4.82	5.54	6.27	6.75	7.70
0.09	0.13	0.15	0.13	0.13	0.17
3.70	4.42	5.23	6.09	6.68	7.94
0.11	0.07	0.10	0.19	0.26	0.44
3.09	3.82	4.65	5.59	6.26	7.76
0.08	0.08	0.08	0.14	0.20	0.36
2.66	3.22	3.90	4.64	5.16	6.29
0.06	0.05	0.07	0.13	0.19	0.34
2.68	3.06	3.46	3.86	4.11	4.62
0.06	0.05	0.06	0.07	0.08	0.10
2.30	2.85	3.47	4.09	4.49	5.30
0.10	0.09	0.13	0.19	0.25	0.39
2.54	3.01	3.52	4.01	4.33	5.02
0.12	0.06	0.11	0.20	0.28	0.49
2.57	3.01	3.48	3.96	4.27	4.93
0.08	0.04	0.06	0.12	0.16	0.27
2.23	2.70	3.24	3.79	4.16	4.94
0.07	0.04	0.07	0.07	0.09	0.31
2.02	2.46	2.97	3.47	3.80	4.46
0.07	0.04	0.07	0.12	0.16	0.22
3.25	3.72	4.24	4.74	5.06	5.70
0.16	0.21	0.24	0.24	0.24	0.25
4.19	4.59	4.98	5.34	5.55	5.97
0.27	0.28	0.28	0.27	0.27	0.29
3.46	3.94	4.45	4.94	5.24	5.84
0.15	0.16	0.17	0.17	0.17	0.19
2.65	3.34	4.18	5.09	5.73	7.15
0.03	0.03	0.03	0.05	0.08	0.14
2.66	3.35	4.19	5.09	5.73	7.11
0.03	0.03	0.03	0.06	0.08	0.15

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-16 Mean and Percentiles for Usual Daily Intake of Threonine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.82	0.30	0.40	0.50
Both sexes, 7–12 mo	827	1.33	0.40	0.60	0.70
Both sexes, 1–3 y	3,309	1.97	0.50	0.80	1.10
Both sexes, 4–8 y	3,448	2.46	1.55	1.78	1.91
Standard error		0.03	0.35	0.27	0.23
M, 9–13 y	1,219	3.21	1.82	2.15	2.35
Standard error		0.08	0.24	0.20	0.17
M, 14–18 y	909	3.92	1.89	2.37	2.65
Standard error		0.11	0.52	0.44	0.38
M, 19–30 y	1,902	4.29	2.42	2.87	3.14
Standard error		0.09	0.08	0.09	0.10
M, 31–50 y	2,533	3.95	1.93	2.41	2.70
Standard error		0.08	0.19	0.16	0.14
M, 51–70 y	1,942	3.45	1.35	1.83	2.12
Standard error		0.06	0.09	0.08	0.07
M, 71+ y	1,255	2.86	1.22	1.60	1.82
Standard error		0.05	0.09	0.08	0.07
F, 9–13 y	1,216	2.57	1.49	1.77	1.92
Standard error		0.05	0.04	0.04	0.04
F, 14–18 y	949	2.45	0.93	1.29	1.50
Standard error		0.07	0.15	0.12	0.10
F, 19–30 y	1,901	2.61	1.33	1.64	1.81
Standard error		0.06	0.21	0.17	0.15
F, 31–50 y	2,939	2.64	1.45	1.75	1.91
Standard error		0.04	0.16	0.13	0.11
F, 51–70 y	2,065	2.40	1.12	1.42	1.60
Standard error		0.03	0.08	0.07	0.07
F, 71+ y	1,368	2.17	0.95	1.25	1.42
Standard error		0.04	0.10	0.08	0.08
Pregnant	346	3.22	1.93	2.28	2.48
Standard error		0.20	0.21	0.24	0.27
Lactating	99	3.88	2.72	3.04	3.22
Standard error		0.21	0.18	0.19	0.20
Pregnant/lactating	440	3.36	1.99	2.34	2.54
Standard error		0.13	0.11	0.11	0.12
All individuals	28,575	3.01	1.16	1.55	1.79
Standard error		0.03	0.04	0.04	0.04
All individuals (+P/L)	29,015	3.02	1.18	1.56	1.80
Standard error		0.03	0.05	0.04	0.04

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.60	0.70	0.90	1.20	1.50	2.10
0.90	1.20	1.60	2.20	2.60	3.50
1.40	1.80	2.40	3.00	3.50	4.50
2.15	2.43	2.74	3.05	3.24	3.62
0.14	0.04	0.12	0.26	0.35	0.54
2.71	3.15	3.65	4.15	4.47	5.12
0.12	0.07	0.12	0.22	0.31	0.58
3.17	3.82	4.56	5.30	5.78	6.76
0.27	0.13	0.20	0.44	0.60	0.97
3.62	4.21	4.87	5.53	5.95	6.81
0.10	0.09	0.10	0.11	0.12	0.16
3.21	3.85	4.57	5.30	5.81	6.90
0.11	0.10	0.11	0.19	0.26	0.43
2.64	3.29	4.08	4.98	5.62	7.07
0.07	0.07	0.08	0.13	0.17	0.29
2.23	2.74	3.36	4.06	4.56	5.67
0.06	0.05	0.06	0.11	0.16	0.29
2.20	2.54	2.91	3.27	3.49	3.95
0.05	0.05	0.06	0.07	0.08	0.09
1.89	2.37	2.93	3.51	3.90	4.74
0.08	0.07	0.11	0.18	0.25	0.43
2.13	2.55	3.02	3.47	3.76	4.41
0.11	0.06	0.10	0.19	0.26	0.48
2.22	2.59	3.01	3.43	3.70	4.29
0.08	0.04	0.06	0.13	0.18	0.31
1.93	2.33	2.79	3.27	3.58	4.24
0.05	0.04	0.05	0.07	0.09	0.19
1.72	2.10	2.54	2.99	3.30	3.94
0.06	0.04	0.05	0.10	0.14	0.27
2.80	3.17	3.58	4.01	4.30	4.92
0.32	0.28	0.25	0.27	0.27	0.27
3.52	3.87	4.23	4.57	4.77	5.17
0.21	0.22	0.23	0.23	0.24	0.27
2.90	3.32	3.78	4.22	4.49	5.04
0.12	0.13	0.14	0.14	0.15	0.16
2.24	2.85	3.60	4.41	4.99	6.27
0.03	0.03	0.03	0.05	0.08	0.13
2.26	2.87	3.61	4.41	4.98	6.23
0.03	0.03	0.03	0.05	0.08	0.14

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-17 Mean and Percentiles for Usual Daily Intake of Tryptophan (g), United States, NHANES III (1988–1994)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	793	0.25	0.10	0.10	0.10
Both sexes, 7–12 mo	827	0.41	0.10	0.20	0.20
Both sexes, 1–3 y	3,309	0.62	0.10	0.30	0.30
Both sexes, 4–8 y	3,448	0.77	0.47	0.54	0.58
Standard error		0.01	0.15	0.12	0.10
M, 9–13 y	1,219	1.00	0.55	0.66	0.72
Standard error		0.02	0.09	0.08	0.07
M, 14–18 y	909	1.20	0.56	0.71	0.80
Standard error		0.03	0.26	0.21	0.18
M, 19–30 y	1,902	1.28	0.74	0.88	0.96
Standard error		0.03	0.05	0.06	0.06
M, 31–50 y	2,533	1.18	0.61	0.76	0.84
Standard error		0.02	0.12	0.10	0.09
M, 51–70 y	1,942	1.04	0.41	0.56	0.64
Standard error		0.02	0.03	0.02	0.02
M, 71+ y	1,255	0.87	0.38	0.49	0.56
Standard error		0.01	0.03	0.03	0.03
F, 9–13 y	1,216	0.80	0.47	0.56	0.61
Standard error		0.01	0.01	0.02	0.02
F, 14–18 y	949	0.76	0.33	0.43	0.50
Standard error		0.02	0.05	0.04	0.04
F, 19–30 y	1,901	0.80	0.42	0.51	0.56
Standard error		0.02	0.06	0.06	0.05
F, 31–50 y	2,939	0.80	0.43	0.52	0.57
Standard error		0.01	0.05	0.04	0.03
F, 51–70 y	2,065	0.73	0.34	0.43	0.49
Standard error		0.01	0.02	0.02	0.02
F, 71+ y	1,368	0.67	0.31	0.40	0.45
Standard error		0.01	0.04	0.03	0.02
Pregnant	346	0.99	0.59	0.69	0.75
Standard error		0.04	0.07	0.11	0.11
Lactating	99	1.22	0.87	0.97	1.03
Standard error		0.07	0.07	0.07	0.07
Pregnant/lactating	440	1.05	0.63	0.74	0.80
Standard error		0.04	0.04	0.03	0.04
All individuals	28,575	0.91	0.36	0.48	0.55
Standard error		0.01	0.02	0.01	0.01
All individuals (+P/L)	29,015	0.91	0.37	0.48	0.56
Standard error		0.01	0.02	0.02	0.01

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.20	0.20	0.30	0.40	0.50	0.60
0.30	0.40	0.50	0.70	0.80	1.00
0.40	0.60	0.80	0.90	1.10	1.40
0.66	0.76	0.86	0.96	1.03	1.16
0.06	0.02	0.05	0.11	0.16	0.23
0.84	0.98	1.14	1.30	1.41	1.62
0.05	0.02	0.04	0.08	0.10	0.15
0.97	1.17	1.40	1.63	1.77	2.07
0.12	0.04	0.10	0.22	0.30	0.48
1.09	1.26	1.45	1.64	1.76	2.02
0.03	0.03	0.05	0.05	0.04	0.05
0.98	1.15	1.35	1.55	1.69	1.98
0.06	0.03	0.04	0.11	0.15	0.25
0.80	1.00	1.23	1.49	1.68	2.11
0.02	0.02	0.02	0.04	0.05	0.10
0.68	0.84	1.02	1.23	1.37	1.69
0.02	0.01	0.03	0.03	0.05	0.13
0.69	0.79	0.90	1.00	1.07	1.20
0.02	0.02	0.02	0.02	0.02	0.02
0.61	0.74	0.89	1.05	1.16	1.37
0.03	0.02	0.03	0.05	0.07	0.11
0.66	0.78	0.92	1.06	1.14	1.33
0.04	0.02	0.03	0.07	0.09	0.14
0.66	0.78	0.91	1.04	1.13	1.31
0.02	0.01	0.02	0.04	0.05	0.09
0.59	0.71	0.85	0.99	1.08	1.28
0.01	0.01	0.01	0.02	0.03	0.05
0.54	0.65	0.78	0.90	0.98	1.16
0.02	0.01	0.02	0.03	0.04	0.08
0.85	0.98	1.12	1.25	1.34	1.51
0.09	0.04	0.09	0.13	0.13	0.09
1.12	1.22	1.32	1.41	1.47	1.57
0.07	0.07	0.09	0.10	0.10	0.10
0.91	1.04	1.18	1.30	1.38	1.54
0.04	0.04	0.04	0.04	0.04	0.05
0.69	0.87	1.09	1.32	1.48	1.80
0.01	0.01	0.01	0.02	0.03	0.04
0.69	0.88	1.09	1.32	1.47	1.79
0.01	0.01	0.01	0.02	0.03	0.04

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-18 Mean and Percentiles for Usual Daily Intake of Tyrosine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	0.78	0.30	0.40	0.40
Both sexes, 7–12 mo	827	1.29	0.40	0.50	0.60
Both sexes, 1–3 y	3,309	1.90	0.40	0.80	1.00
Both sexes, 4–8 y	3,448	2.37	1.48	1.71	1.84
Standard error		0.03	0.41	0.32	0.26
M, 9–13 y	1,219	3.09	1.79	2.12	2.31
Standard error		0.08	0.26	0.21	0.18
M, 14–18 y	909	3.69	1.85	2.29	2.55
Standard error		0.10	0.39	0.33	0.29
M, 19–30 y	1,902	4.00	2.29	2.71	2.96
Standard error		0.08	0.07	0.07	0.07
M, 31–50 y	2,533	3.62	1.75	2.21	2.47
Standard error		0.06	0.16	0.14	0.12
M, 51–70 y	1,942	3.11	1.22	1.65	1.91
Standard error		0.05	0.07	0.07	0.06
M, 71+ y	1,255	2.59	1.11	1.45	1.65
Standard error		0.04	0.08	0.07	0.06
F, 9–13 y	1,216	2.47	1.47	1.73	1.87
Standard error		0.04	0.05	0.06	0.06
F, 14–18 y	949	2.33	0.99	1.30	1.49
Standard error		0.06	0.21	0.18	0.15
F, 19–30 y	1,901	2.43	1.23	1.52	1.69
Standard error		0.05	0.21	0.17	0.15
F, 31–50 y	2,939	2.41	1.30	1.58	1.73
Standard error		0.03	0.11	0.09	0.08
F, 51–70 y	2,065	2.17	0.98	1.26	1.42
Standard error		0.03	0.06	0.06	0.05
F, 71+ y	1,368	1.96	0.83	1.09	1.24
Standard error		0.04	0.09	0.08	0.07
Pregnant	346	2.97	1.88	2.18	2.33
Standard error		0.23	0.41	0.41	0.30
Lactating	99	3.63	2.56	2.87	3.03
Standard error		0.22	0.33	0.45	0.46
Pregnant/lactating	440	3.15	1.90	2.23	2.41
Standard error		0.12	0.10	0.11	0.11
All individuals	28,575	2.78	1.09	1.44	1.66
Standard error		0.02	0.04	0.04	0.03
All individuals (+P/L)	29,015	2.79	1.10	1.46	1.68
Standard error		0.02	0.04	0.04	0.04

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.60	0.70	0.90	1.10	1.40	2.10
0.80	1.10	1.60	2.10	2.60	3.20
1.40	1.80	2.30	3.00	3.30	4.30
2.07	2.35	2.65	2.94	3.13	3.50
0.16	0.04	0.14	0.30	0.40	0.61
2.64	3.04	3.48	3.94	4.24	4.87
0.13	0.09	0.10	0.18	0.25	0.41
3.03	3.62	4.28	4.93	5.35	6.21
0.21	0.12	0.16	0.32	0.44	0.72
3.40	3.94	4.54	5.13	5.51	6.28
0.07	0.08	0.09	0.10	0.11	0.13
2.94	3.52	4.18	4.88	5.36	6.38
0.09	0.07	0.09	0.16	0.23	0.39
2.38	2.97	3.68	4.49	5.06	6.33
0.06	0.05	0.06	0.10	0.14	0.26
2.01	2.48	3.04	3.66	4.10	5.07
0.05	0.04	0.05	0.09	0.13	0.23
2.13	2.44	2.77	3.09	3.30	3.72
0.05	0.05	0.06	0.07	0.07	0.06
1.83	2.27	2.75	3.24	3.55	4.17
0.11	0.07	0.12	0.21	0.28	0.43
1.99	2.37	2.81	3.24	3.52	4.14
0.10	0.05	0.10	0.19	0.26	0.46
2.02	2.37	2.76	3.15	3.40	3.94
0.06	0.03	0.05	0.09	0.13	0.21
1.73	2.11	2.55	2.99	3.28	3.87
0.04	0.03	0.04	0.06	0.08	0.13
1.53	1.90	2.32	2.75	3.02	3.58
0.05	0.04	0.05	0.10	0.13	0.21
2.57	2.89	3.30	3.74	4.03	4.60
0.17	0.42	0.45	0.31	0.23	0.25
3.31	3.63	3.95	4.24	4.42	4.75
0.38	0.24	0.27	0.36	0.38	0.33
2.74	3.12	3.54	3.94	4.18	4.67
0.12	0.13	0.13	0.13	0.14	0.15
2.09	2.66	3.34	4.06	4.55	5.59
0.03	0.02	0.03	0.04	0.06	0.10
2.10	2.67	3.34	4.06	4.54	5.55
0.03	0.02	0.03	0.05	0.07	0.11

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE D-19 Mean and Percentiles for Usual Daily Intake of Valine (g), United States, NHANES III (1988–1994)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	1.04	0.40	0.50	0.60
Both sexes, 7–12 mo	827	1.80	0.50	0.70	0.90
Both sexes, 1–3 y	3,309	2.70	0.60	1.10	1.50
Both sexes, 4–8 y	3,448	3.36	2.08	2.40	2.59
Standard error		0.05	0.60	0.47	0.39
M, 9–13 y	1,219	4.33	2.59	3.04	3.29
Standard error		0.09	0.40	0.33	0.28
M, 14–18 y	909	5.18	2.52	3.15	3.53
Standard error		0.14	0.54	0.46	0.41
M, 19–30 y	1,902	5.63	3.23	3.82	4.16
Standard error		0.11	0.09	0.10	0.10
M, 31–50 y	2,533	5.17	2.57	3.19	3.56
Standard error		0.10	0.25	0.22	0.19
M, 51–70 y	1,942	4.51	1.81	2.42	2.79
Standard error		0.08	0.12	0.10	0.10
M, 71+ y	1,255	3.76	1.59	2.09	2.39
Standard error		0.06	0.11	0.09	0.08
F, 9–13 y	1,216	3.48	2.06	2.42	2.63
Standard error		0.06	0.06	0.06	0.06
F, 14–18 y	949	3.31	1.33	1.80	2.08
Standard error		0.09	0.26	0.21	0.18
F, 19–30 y	1,901	3.47	1.78	2.19	2.42
Standard error		0.07	0.27	0.22	0.19
F, 31–50 y	2,939	3.48	1.91	2.30	2.52
Standard error		0.05	0.21	0.17	0.14
F, 51–70 y	2,065	3.16	1.45	1.86	2.10
Standard error		0.04	0.08	0.07	0.07
F, 71+ y	1,368	2.88	1.25	1.63	1.86
Standard error		0.05	0.16	0.14	0.12
Pregnant	346	4.25	2.75	3.09	3.24
Standard error		0.26	0.53	0.23	0.41
Lactating	99	5.19	3.66	4.10	4.33
Standard error		0.31	0.29	0.33	0.33
Pregnant/lactating	440	4.51	2.71	3.17	3.43
Standard error		0.17	0.14	0.15	0.15
All individuals	28,575	3.98	1.54	2.06	2.39
Standard error		0.03	0.05	0.05	0.05
All individuals (+P/L)	29,015	3.99	1.56	2.08	2.41
Standard error		0.03	0.06	0.05	0.05

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months of age and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating

25th	50th	75th	90th	95th	99th
0.80	0.90	1.20	1.50	1.90	2.90
1.10	1.60	2.20	3.00	3.60	4.40
1.90	2.50	3.30	4.10	4.70	6.30
2.92	3.32	3.75	4.17	4.43	4.96
0.23	0.06	0.20	0.43	0.58	0.89
3.73	4.26	4.85	5.45	5.84	6.65
0.19	0.10	0.18	0.33	0.45	0.74
4.21	5.07	6.02	6.98	7.60	8.85
0.30	0.17	0.23	0.45	0.62	1.02
4.78	5.54	6.37	7.20	7.73	8.79
0.10	0.12	0.13	0.15	0.15	0.19
4.23	5.05	5.96	6.90	7.55	8.95
0.14	0.15	0.14	0.23	0.32	0.53
3.47	4.32	5.32	6.45	7.27	9.14
0.09	0.08	0.09	0.15	0.20	0.39
2.93	3.60	4.41	5.32	5.97	7.41
0.07	0.06	0.07	0.13	0.18	0.33
3.00	3.44	3.91	4.37	4.66	5.24
0.06	0.07	0.07	0.08	0.09	0.10
2.59	3.21	3.92	4.66	5.15	6.18
0.13	0.09	0.14	0.27	0.38	0.67
2.85	3.40	4.01	4.60	4.98	5.82
0.13	0.07	0.13	0.24	0.33	0.59
2.93	3.42	3.97	4.51	4.87	5.63
0.10	0.05	0.08	0.17	0.23	0.40
2.53	3.08	3.70	4.34	4.77	5.67
0.05	0.05	0.05	0.08	0.11	0.17
2.28	2.80	3.40	4.00	4.39	5.17
0.09	0.05	0.08	0.16	0.23	0.36
3.57	4.14	4.83	5.45	5.80	6.53
0.58	0.36	0.80	0.67	0.41	0.32
4.73	5.18	5.64	6.05	6.31	6.79
0.33	0.33	0.35	0.37	0.37	0.37
3.90	4.46	5.06	5.64	6.00	6.72
0.16	0.18	0.19	0.19	0.20	0.22
2.99	3.78	4.75	5.80	6.55	8.19
0.04	0.03	0.04	0.06	0.09	0.15
3.00	3.80	4.77	5.80	6.54	8.15
0.04	0.03	0.04	0.06	0.09	0.17

status data or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics (NCHS), corrected data set (errata submitted to NCHS September 2001).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

E

Dietary Intake Data from the Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998

TABLE E-1 Mean and Percentiles for Usual Daily Intake of Energy (kcal), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	718	351	450	508
Standard error		10	20	15	14
Both sexes, 7–12 mo	530	999	538	657	725
Standard error		16	24	19	17
Both sexes, 1–3 y	3,949	1,404	730	905	999
Standard error		9	10	9	8
Both sexes, 4–8 y	3,935	1,789	1,047	1,243	1,345
Standard error		13	21	15	15
M, 9–13 y	595	2,265	1,289	1,550	1,694
Standard error		40	63	53	48
M, 14–18 y	474	2,840	1,344	1,676	1,877
Standard error		68	82	69	64
M, 19–30 y	920	2,818	1,223	1,607	1,834
Standard error		55	56	56	56
M, 31–50 y	1,806	2,554	1,180	1,512	1,695
Standard error		34	30	23	30
M, 51–70 y	1,680	2,162	962	1,257	1,430
Standard error		29	74	27	43
M, 71+ y	722	1,821	794	1,033	1,176
Standard error		28	64	36	29

25th	50th	75th	90th	95th	99th
597	687	810	966	1,083	1,352
10	13	12	19	29	61
843	976	1,128	1,300	1,422	1,685
15	15	20	30	40	66
1,162	1,372	1,612	1,849	2,007	2,350
8	9	11	13	16	27
1,534	1,759	2,012	2,272	2,435	2,792
12	12	17	21	32	41
1,940	2,226	2,545	2,885	3,118	3,619
42	41	47	63	79	123
2,256	2,748	3,324	3,923	4,322	5,159
57	70	106	132	155	270
2,236	2,718	3,284	3,921	4,374	5,378
56	56	67	96	126	216
2,032	2,476	2,984	3,500	3,859	4,703
30	32	47	69	89	154
1,738	2,109	2,525	2,959	3,250	3,856
55	29	66	51	66	259
1,440	1,773	2,150	2,527	2,771	3,268
28	31	49	55	68	155

continued

TABLE E-1 Continued

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
F, 9–13 y	606	1,910	1,103	1,298	1,412
Standard error		35	34	29	28
F, 14–18 y	449	1,901	1,016	1,238	1,365
Standard error		51	112	95	100
F, 19–30 y	808	1,791	896	1,115	1,242
Standard error		31	45	41	39
F, 31–50 y	1,690	1,694	809	1,040	1,171
Standard error		17	21	20	19
F, 51–70 y	1,605	1,536	755	952	1,065
Standard error		19	22	19	19
F, 71+ y	670	1,381	677	851	952
Standard error		22	49	25	29
Pregnant	81	1,986	1,173	1,401	1,525
Standard error		153	187	153	142
Lactating	44	2,138	1,126	1,346	1,479
Standard error		155	279	243	221
Pregnant/lactating	124	2,115	1,188	1,425	1,560
Standard error		65	112	102	96
All individuals	21,035	2,007	749	1,005	1,166
Standard error		14	8	7	8
All individuals (+P/L)	21,159	2,009	751	1,008	1,169
Standard error		14	7	7	8

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
1,619	1,877	2,164	2,452	2,637	3,015
27	32	45	63	77	109
1,594	1,872	2,177	2,473	2,661	3,034
92	55	64	72	77	193
1,473	1,757	2,073	2,384	2,582	2,979
34	30	43	56	63	89
1,396	1,659	1,953	2,262	2,471	2,910
18	17	20	25	30	48
1,266	1,507	1,772	2,040	2,218	2,587
17	18	22	31	37	49
1,134	1,356	1,602	1,842	1,994	2,298
34	23	36	33	40	118
1,736	1,978	2,227	2,458	2,599	2,869
138	155	190	230	258	312
1,733	2,066	2,463	2,887	3,174	3,796
188	170	206	306	396	632
1,799	2,088	2,402	2,706	2,897	3,274
84	69	67	90	114	176
1479	1,903	2,423	2,984	3,366	4,188
9	13	18	27	34	51
1,482	1,905	2,423	2,983	3,363	4,180
9	12	18	26	33	51

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-2 Mean and Percentiles for Usual Daily Intake of Carbohydrate (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	85	39	49	55
Standard error		1	4	2	1
Both sexes, 7–12 mo	530	134	72	86	94
Standard error		2	3	2	2
Both sexes, 1–3 y	3,949	191	93	117	131
Standard error		1	1	1	1
Both sexes, 4–8 y	3,935	244	139	167	181
Standard error		2	3	2	2
M, 9–13 y	595	306	164	198	218
Standard error		6	9	7	7
M, 14–18 y	474	379	168	214	242
Standard error		10	10	9	8
M, 19–30 y	920	345	140	189	216
Standard error		7	7	7	6
M, 31–50 y	1,806	308	126	169	195
Standard error		5	4	4	4
M, 51–70 y	1,680	262	99	139	162
Standard error		4	4	4	4
M, 71+ y	722	230	92	123	142
Standard error		4	5	4	4
F, 9–13 y	606	263	142	171	188
Standard error		6	4	4	4
F, 14–18 y	449	259	122	154	174
Standard error		7	11	10	10
F, 19–30 y	808	234	101	133	152
Standard error		4	7	7	8
F, 31–50 y	1,690	215	87	118	137
Standard error		2	3	3	3
F, 51–70 y	1,605	195	86	112	127
Standard error		2	3	2	2
F, 71+ y	670	182	78	103	118
Standard error		3	4	3	3
Pregnant	81	277	158	188	206
Standard error		12	25	20	18
Lactating	44	294	135	171	193
Standard error		27	54	47	42
Pregnant/lactating	124	285	143	177	197
Standard error		11	20	18	17
All individuals	21,035	256	89	123	145
Standard error		2	1	1	1
All individuals (+P/L)	21,159	256	89	123	145
Standard error		2	1	1	1

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
67	81	98	120	136	173
2	1	3	3	5	15
110	131	155	179	195	230
2	2	3	4	5	9
156	186	221	257	281	330
1	1	2	2	3	4
208	241	276	311	335	386
2	2	2	3	3	6
255	300	350	400	432	497
7	6	9	11	13	26
295	365	448	535	594	717
8	9	12	17	20	30
266	331	408	488	545	677
6	6	9	11	15	31
241	297	363	435	485	592
4	4	6	8	11	17
204	255	311	371	412	498
4	4	5	6	8	12
177	222	274	328	362	434
4	4	5	7	8	12
219	257	301	345	374	432
4	5	7	10	13	18
209	253	303	352	384	448
8	8	8	11	14	20
186	229	276	323	353	413
8	4	8	8	9	25
170	210	254	300	331	393
2	2	2	3	3	6
155	191	230	270	295	346
2	2	3	5	6	8
145	178	216	252	276	323
3	3	4	5	6	9
237	274	314	354	378	428
14	12	15	20	25	35
233	285	344	405	444	526
35	30	37	56	71	109
234	279	330	379	411	474
14	11	12	18	24	38
187	243	311	384	433	537
1	2	2	3	4	6
187	243	312	385	433	537
1	2	2	3	4	6

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-3 Mean and Percentiles for Usual Daily Percentage of Total Energy from Carbohydrate, United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	47.3	40.0	41.3	42.0
Standard error		0.4	0.3	0.3	0.3
Both sexes, 7–12 mo	530	54.2	41.2	44.6	46.5
Standard error		0.4	0.7	0.6	0.5
Both sexes, 1–3 y	3,949	54.8	41.9	45.7	47.7
Standard error		0.2	0.4	0.3	0.3
Both sexes, 4–8 y	3,935	55.0	44.5	47.6	49.3
Standard error		0.2	0.4	0.4	0.4
M, 9–13 y	595	54.1	45.8	48.2	49.5
Standard error		0.4	0.9	0.7	0.6
M, 14–18 y	474	53.7	43.3	46.3	47.9
Standard error		0.4	1.1	0.9	0.7
M, 19–30 y	920	49.8	36.9	40.8	42.9
Standard error		0.4	1.0	0.8	0.7
M, 31–50 y	1,805	49.0	34.4	38.8	41.1
Standard error		0.2	0.6	0.4	0.4
M, 51–70 y	1,680	49.0	31.9	37.1	39.8
Standard error		0.3	0.7	0.4	0.4
M, 71+ y	722	50.8	34.0	39.0	41.6
Standard error		0.4	0.7	0.6	0.5
F, 9–13 y	606	55.2	44.6	47.7	49.4
Standard error		0.4	0.6	0.5	0.4
F, 14–18 y	449	54.7	42.5	46.0	47.9
Standard error		0.6	1.1	0.9	0.8
F, 19–30 y	806	52.8	36.3	41.1	43.7
Standard error		0.4	1.1	0.8	0.7
F, 31–50 y	1,689	51.5	35.2	40.1	42.6
Standard error		0.3	0.7	0.5	0.5
F, 51–70 y	1,605	51.5	35.9	40.3	42.8
Standard error		0.3	0.7	0.6	0.5
F, 71+ y	669	53.1	37.5	42.0	44.5
Standard error		0.5	1.0	0.8	0.7
Pregnant	81	53.0	44.1	46.5	47.9
Standard error		1.3	3.8	2.9	2.5
Lactating	44	53.0	41.3	45.0	46.9
Standard error		3.2	8.9	6.0	4.7
Pregnant/lactating	124	53.5	44.4	47.1	48.5
Standard error		0.9	3.7	2.7	2.2
All individuals	21,030	51.8	36.0	40.6	43.0
Standard error		0.1	0.3	0.2	0.2
All individuals (+P/L)	21,154	51.8	36.0	40.6	43.1
Standard error		0.1	0.2	0.2	0.2

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day. The Iowa State University (ISU) method was used to estimate individual usual intakes of energy from carbohydrate and total energy. One g of carbohydrate was assumed to provide 4 kcal of energy. A modification of the ISU method was then used to estimate the distribution of the nutrient density (Goyeneche JJ, Carriquiry A, Fuller WA. 1997. Estimating bivariate usual intake distributions. *ASA Proceedings of the Biometrics Section*. Alexandria,

25th	50th	75th	90th	95th	99th
43.3	45.1	50.1	55.0	58.7	68.6
0.2	0.3	0.6	0.8	1.1	2.2
49.9	53.9	58.2	62.3	64.8	69.9
0.5	0.4	0.5	0.6	0.8	1.2
51.0	54.7	58.4	61.8	64.0	68.2
0.2	0.2	0.2	0.3	0.3	0.4
52.0	55.0	58.1	60.8	62.5	65.7
0.4	0.2	0.3	0.3	0.3	0.4
51.7	54.1	56.4	58.6	59.9	62.3
0.5	0.4	0.5	0.7	0.8	1.0
50.6	53.6	56.7	59.5	61.3	64.5
0.6	0.5	0.5	0.7	0.8	1.2
46.2	49.8	53.4	56.7	58.8	63.1
0.5	0.4	0.4	0.6	0.7	1.0
44.8	48.9	53.0	57.0	59.5	64.4
0.3	0.3	0.3	0.4	0.5	0.7
44.2	49.0	53.8	58.4	61.2	66.7
0.4	0.3	0.5	0.5	0.6	0.9
46.1	50.9	55.7	59.9	62.5	67.2
0.5	0.4	0.5	0.6	0.6	0.8
52.1	55.2	58.3	61.0	62.6	65.7
0.4	0.4	0.5	0.5	0.6	0.7
51.1	54.6	58.2	61.4	63.4	67.0
0.7	0.6	0.8	1.0	1.1	1.4
48.0	52.8	57.6	62.0	64.6	69.6
0.6	0.5	0.5	0.6	0.8	1.1
46.8	51.3	56.0	60.4	63.2	68.9
0.4	0.3	0.3	0.5	0.6	0.8
46.8	51.5	56.1	60.4	62.9	67.8
0.4	0.3	0.4	0.5	0.6	0.8
48.6	53.1	57.6	61.6	64.0	68.5
0.5	0.4	0.5	0.6	0.7	0.9
50.2	52.9	55.7	58.4	60.0	63.2
1.8	1.3	1.8	2.7	3.4	4.8
50.0	53.2	56.2	58.7	60.1	62.7
3.2	3.3	4.5	5.9	6.6	7.9
50.9	53.5	56.2	58.6	60.0	62.7
1.5	0.9	1.1	1.8	2.2	3.1
47.1	51.7	56.3	60.5	63.1	67.8
0.1	0.1	0.1	0.1	0.2	0.2
47.1	51.7	56.4	60.5	63.1	67.8
0.1	0.1	0.1	0.1	0.2	0.2

VA: American Statistical Association). Infants and children fed human milk and five individuals who had no food intake for the day were excluded from the analyses. One female was pregnant and lactating and was included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-4 Mean and Percentiles for Usual Daily Intake of Dietary Fiber (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	578	1.4	—[b]	—	—
Both sexes, 7–12 mo	530	5.7	0.9	1.9	2.5
Standard error		0.2	0.2	0.2	0.2
Both sexes, 1–3 y	3,949	9.5	3.5	4.8	5.6
Standard error		0.1	0.1	0.1	0.1
Both sexes, 4–8 y	3,935	12.2	6.0	7.4	8.3
Standard error		0.1	0.1	0.1	0.1
M, 9–13 y	595	15.2	6.9	8.7	9.9
Standard error		0.4	0.4	0.4	0.4
M, 14–18 y	474	17.7	7.6	9.8	11.1
Standard error		0.6	0.6	0.5	0.5
M, 19–30 y	920	18.5	5.9	8.5	10.1
Standard error		0.4	0.4	0.4	0.4
M, 31–50 y	1,806	18.9	6.7	9.3	10.9
Standard error		0.3	0.2	0.2	0.2
M, 51–70 y	1,680	18.5	5.5	8.2	9.9
Standard error		0.3	0.3	0.3	0.3
M, 71+ y	722	17.5	4.9	7.4	9.0
Standard error		0.4	0.4	0.4	0.4
F, 9–13 y	606	12.9	6.4	7.9	8.8
Standard error		0.2	0.4	0.3	0.3
F, 14–18 y	449	12.8	5.9	7.6	8.6
Standard error		0.5	0.6	0.6	0.6
F, 19–30 y	808	12.7	4.7	6.5	7.6
Standard error		0.3	0.3	0.3	0.3
F, 31–50 y	1,690	13.8	4.5	6.5	7.7
Standard error		0.2	0.3	0.2	0.3
F, 51–70 y	1,605	14.4	5.1	7.1	8.3
Standard error		0.2	0.2	0.2	0.2
F, 71+ y	670	14.0	4.3	6.3	7.6
Standard error		0.3	0.3	0.3	0.3
Pregnant	81	16.2	7.1	9.0	10.2
Standard error		1.0	1.3	1.2	1.2
Lactating	44	19.3	7.0	9.5	11.0
Standard error		1.4	1.9	1.9	1.9
Pregnant/lactating	124	17.7	6.7	9.0	10.4
Standard error		0.8	0.9	0.9	0.9
All individuals	21,035	15.1	3.6	5.7	7.1
Standard error		0.1	0.1	0.1	0.1
All individuals (+P/L)	21,159	15.2	3.6	5.7	7.1
Standard error		0.1	0.1	0.1	0.1

[a] M = male, F = female, P/L = pregnant and/or lactating.
[b] Value is less than 0.05.
NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
—	0.2	2.1	5.2	6.0	8.7
3.8	5.4	7.3	9.2	10.4	12.8
0.2	0.2	0.2	0.2	0.3	0.4
7.1	9.1	11.4	13.8	15.5	19.2
0.1	0.1	0.1	0.2	0.2	0.4
9.8	11.8	14.1	16.4	18.0	21.4
0.1	0.1	0.2	0.2	0.3	0.4
11.9	14.6	17.7	21.2	23.7	29.4
0.3	0.3	0.4	0.7	0.9	1.5
13.7	17.0	20.9	25.0	27.8	33.6
0.5	0.6	0.8	1.0	1.3	1.8
13.2	17.4	22.5	28.2	32.3	41.4
0.4	0.4	0.5	0.8	1.0	1.6
14.0	17.9	22.7	28.0	31.6	39.6
0.2	0.3	0.4	0.6	0.8	1.2
13.2	17.5	22.7	28.3	32.2	40.6
0.3	0.3	0.4	0.6	0.8	1.3
12.2	16.5	21.8	27.3	31.0	38.9
0.4	0.4	0.6	0.9	1.1	1.7
10.4	12.6	15.0	17.6	19.2	22.7
0.3	0.2	0.3	0.4	0.6	1.5
10.3	12.5	14.9	17.5	19.2	23.0
0.6	0.5	0.6	0.8	0.9	1.5
9.6	12.1	15.2	18.4	20.7	25.5
0.3	0.3	0.4	0.5	0.7	1.1
10.0	13.1	16.8	20.7	23.3	28.8
0.3	0.2	0.4	0.4	0.7	2.3
10.7	13.8	17.5	21.2	23.7	28.8
0.2	0.2	0.3	0.4	0.5	0.7
10.1	13.3	17.2	21.3	24.0	29.6
0.3	0.3	0.4	0.6	0.7	1.1
12.5	15.6	19.2	23.1	25.7	31.1
1.1	1.0	1.2	1.7	2.1	3.1
14.1	18.3	23.4	28.9	32.8	41.1
1.8	1.7	1.8	2.9	4.1	7.3
13.2	16.9	21.3	26.0	29.2	35.9
0.8	0.9	1.1	1.5	2.0	3.1
9.9	14.0	19.1	24.7	28.5	36.8
0.1	0.1	0.2	0.3	0.3	0.6
10.0	14.0	19.1	24.7	28.6	36.9
0.1	0.1	0.2	0.3	0.4	0.6

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-5 Mean and Percentiles for Usual Daily Intake of Total Fat (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	34.8	15.0	21.5	24.8
Standard error		0.6	1.1	1.1	1.0
Both sexes, 7–12 mo	530	39.5	17.4	23.8	27.2
Standard error		0.8	1.3	1.5	1.0
Both sexes, 1–3 y	3,949	51.0	23.3	30.1	33.8
Standard error		0.5	0.6	0.4	0.6
Both sexes, 4–8 y	3,935	65.4	35.0	42.0	46.0
Standard error		0.7	0.8	0.7	0.7
M, 9–13 y	595	84.0	47.0	56.0	62.0
Standard error		1.6	2.7	2.2	2.0
M, 14–18 y	474	105.6	45.0	59.0	67.0
Standard error		2.8	3.8	5.2	5.5
M, 19–30 y	920	103.7	42.0	56.0	65.0
Standard error		2.3	2.8	2.8	2.7
M, 31–50 y	1,806	97.4	37.0	51.0	59.0
Standard error		1.6	1.7	1.4	1.0
M, 51–70 y	1,680	82.6	29.0	40.0	48.0
Standard error		1.4	1.0	1.0	1.0
M, 71+ y	722	67.9	24.0	33.0	39.0
Standard error		1.5	1.2	1.2	1.1
F, 9–13 y	606	69.5	37.0	45.0	49.0
Standard error		1.2	1.8	1.6	1.4
F, 14–18 y	449	68.7	35.0	44.0	48.0
Standard error		2.1	4.1	3.7	3.4
F, 19–30 y	808	64.6	26.0	35.0	40.0
Standard error		1.4	1.7	1.7	1.7
F, 31–50 y	1,690	63.3	26.0	35.0	40.0
Standard error		0.9	1.0	0.9	0.9
F, 51–70 y	1,605	56.5	22.0	29.0	34.0
Standard error		1.0	1.0	1.0	1.0
F, 71+ y	670	49.4	20.0	27.0	31.0
Standard error		1.1	1.6	1.3	1.4
Pregnant	81	75.5	43.0	52.0	56.0
Standard error		5.2	6.0	5.2	4.9
Lactating	44	74.7	38.0	47.0	52.0
Standard error		5.3	9.4	7.9	7.0
Pregnant/lactating	124	76.7	41.0	50.0	55.0
Standard error		2.9	4.3	4.0	3.8
All individuals	21,035	74.7	24.0	34.0	40.0
Standard error		0.6	0.4	0.4	0.4
All individuals (+P/L)	21,159	74.7	24.0	34.0	40.0
Standard error		0.6	0.4	0.4	0.4

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
28.7	33.6	39.7	46.2	52.0	66.4
0.8	0.5	1.1	1.0	1.5	2.8
32.4	38.2	45.5	53.5	58.9	70.0
1.5	0.8	1.7	1.7	2.4	3.2
40.6	49.6	59.8	69.9	76.6	91.1
0.4	0.5	0.6	0.9	1.1	1.6
54.0	64.0	75.0	86.0	94.0	109.0
0.6	0.7	0.8	1.1	1.3	1.9
71.0	82.0	95.0	108.0	117.0	136.0
1.7	1.6	1.9	2.7	3.4	5.3
82.0	101.0	124.0	149.0	166.0	204.0
4.4	2.9	5.4	6.3	6.3	14.2
81.0	100.0	123.0	147.0	164.0	200.0
2.6	2.4	2.7	3.8	4.8	7.6
73.0	93.0	117.0	141.0	157.0	194.0
2.1	1.4	3.7	3.6	4.4	7.3
61.0	79.0	100.0	122.0	136.0	166.0
1.1	1.3	1.7	2.2	2.6	3.5
50.0	65.0	82.0	100.0	112.0	136.0
1.2	1.5	1.9	2.5	3.0	4.2
57.0	68.0	80.0	92.0	100.0	116.0
1.2	1.2	1.5	2.2	2.7	3.9
57.0	68.0	79.0	91.0	98.0	112.0
2.8	2.2	1.8	2.0	2.5	3.8
50.0	63.0	77.0	92.0	101.0	121.0
1.5	1.3	1.5	2.2	2.8	4.5
50.0	61.0	75.0	89.0	98.0	119.0
0.9	0.9	1.2	1.7	2.0	2.8
43.0	55.0	68.0	81.0	90.0	108.0
0.9	0.9	1.2	1.6	2.0	2.9
38.0	48.0	59.0	70.0	77.0	92.0
1.5	1.2	1.5	1.6	2.2	5.9
65.0	75.0	85.0	95.0	102.0	114.0
4.6	5.1	6.4	8.3	9.6	12.5
62.0	73.0	86.0	99.0	107.0	123.0
5.6	5.3	7.6	11.5	14.3	20.7
65.0	76.0	88.0	99.0	107.0	121.0
3.4	3.1	3.2	4.1	5.0	7.2
53.0	70.0	92.0	115.0	130.0	164.0
0.4	0.5	0.7	1.0	1.3	1.9
53.0	70.0	92.0	114.0	130.0	163.0
0.4	0.5	0.7	1.0	1.3	1.9

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-6 Mean and Percentiles for Usual Daily Percentage of Total Energy from Fat, United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	43.8	24.5	33.6	36.9
Standard error		0.3	2.1	1.6	0.8
Both sexes, 7–12 mo	530	35.5	21.1	26.0	28.4
Standard error		0.3	1.2	0.6	0.5
Both sexes, 1–3 y	3,949	32.2	21.8	25.0	26.6
Standard error		0.2	0.2	0.2	0.2
Both sexes, 4–8 y	3,935	32.4	24.2	26.6	27.9
Standard error		0.2	0.4	0.3	0.2
M, 9–13 y	595	33.1	26.6	28.5	29.5
Standard error		0.3	0.8	0.6	0.5
M, 14–18 y	474	33.0	23.5	26.4	27.9
Standard error		0.3	1.0	0.7	0.6
M, 19–30 y	920	32.6	23.2	26.1	27.5
Standard error		0.3	1.0	0.9	0.8
M, 31–50 y	1,805	33.6	21.3	25.1	27.1
Standard error		0.2	0.5	0.4	0.3
M, 51–70 y	1,680	33.7	19.3	23.6	25.9
Standard error		0.2	0.5	0.4	0.3
M, 71+ y	722	33.0	19.1	23.2	25.4
Standard error		0.4	0.8	0.6	0.5
F, 9–13 y	606	32.4	23.7	26.3	27.7
Standard error		0.3	0.8	0.6	0.5
F, 14–18 y	449	32.2	22.0	25.1	26.7
Standard error		0.5	1.1	0.9	0.8
F, 19–30 y	806	32.1	18.8	22.8	24.9
Standard error		0.4	0.9	0.7	0.7
F, 31–50 y	1,689	32.8	20.2	23.9	25.9
Standard error		0.2	0.5	0.4	0.4
F, 51–70 y	1,605	32.2	18.4	22.5	24.6
Standard error		0.3	0.7	0.6	0.5
F, 71+ y	669	31.7	18.2	22.1	24.2
Standard error		0.4	0.8	0.6	0.5
Pregnant	81	32.9	23.0	26.1	27.7
Standard error		0.9	2.1	1.5	1.3
Lactating	44	31.5	22.5	25.2	26.7
Standard error		1.3	3.4	2.5	2.1
Pregnant/lactating	124	32.4	23.0	25.9	27.4
Standard error		0.8	1.9	1.4	1.2
All individuals	21,030	32.8	19.8	23.8	25.9
Standard error		0.1	0.2	0.2	0.1
All individuals (+P/L)	21,154	32.8	19.8	23.8	25.9
Standard error		0.1	0.2	0.2	0.1

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day. The Iowa State University (ISU) method was used to estimate individual usual intakes of energy from fat and total energy. One g of fat was assumed to provide 9 kcal of energy. A modification of the ISU method was then used to estimate the distribution of the nutrient density (Goyeneche JJ, Carriquiry A, Fuller WA. 1997. Estimating bivariate usual intake distributions. *ASA Proceedings of the Biometrics Section*. Alexandria, VA: American Statistical Association). Infants and children fed human milk and five individuals who

25th	50th	75th	90th	95th	99th
41.2	45.5	47.3	48.7	49.4	50.2
1.1	0.5	0.2	0.3	0.3	0.7
32.2	35.9	39.2	42.0	43.6	46.6
0.4	0.4	0.4	0.4	0.5	0.6
29.3	32.2	35.1	37.7	39.3	42.3
0.2	0.2	0.2	0.2	0.2	0.3
30.0	32.4	34.7	36.8	38.1	40.4
0.2	0.2	0.2	0.2	0.3	0.4
31.2	33.1	35.0	36.6	37.6	39.5
0.4	0.3	0.3	0.5	0.5	0.7
30.4	33.1	35.7	38.0	39.3	41.8
0.4	0.4	0.5	0.6	0.8	1.0
29.9	32.6	35.3	37.5	38.9	41.4
0.7	0.3	0.5	0.6	0.6	0.8
30.3	33.7	37.0	39.9	41.8	45.2
0.2	0.2	0.2	0.3	0.3	0.4
29.6	33.7	37.7	41.3	43.4	47.3
0.2	0.2	0.3	0.4	0.4	0.5
29.0	33.0	36.9	40.4	42.5	46.3
0.4	0.4	0.4	0.5	0.6	0.8
30.0	32.5	34.9	37.1	38.4	40.8
0.4	0.3	0.3	0.3	0.4	0.5
29.4	32.3	35.1	37.6	39.1	41.9
0.6	0.5	0.6	0.7	0.8	1.0
28.4	32.1	35.9	39.3	41.5	45.6
0.6	0.4	0.8	0.9	0.8	1.3
29.2	32.8	36.4	39.6	41.6	45.2
0.3	0.2	0.3	0.3	0.4	0.5
28.2	32.2	36.3	39.9	42.1	46.2
0.4	0.3	0.3	0.4	0.5	0.7
27.7	31.6	35.6	39.3	41.4	45.6
0.5	0.4	0.5	0.6	0.7	0.9
30.2	33.0	35.7	37.9	39.3	41.7
1.0	1.0	1.1	1.4	1.6	1.9
29.1	31.6	34.1	36.3	37.5	39.8
1.5	1.3	1.7	2.3	2.7	3.5
29.9	32.5	35.0	37.2	38.5	40.9
0.9	0.8	0.9	1.1	1.3	1.6
29.2	32.9	36.4	39.7	41.6	45.4
0.1	0.1	0.1	0.1	0.2	0.2
29.2	32.9	36.4	39.7	41.6	45.4
0.1	0.1	0.1	0.1	0.2	0.2

had no food intake for the day were excluded from the analyses. One female was pregnant and lactating and was included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-7 Mean and Percentiles for Usual Daily Intake of Saturated Fatty Acids (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	13.9	5.4	8.1	9.5
Standard error		0.3	0.4	0.4	0.4
Both sexes, 7–12 mo	530	15.9	6.2	8.9	10.4
Standard error		0.4	0.6	0.5	0.5
Both sexes, 1–3 y	3,949	20.2	8.7	11.4	13.0
Standard error		0.2	0.2	0.2	0.2
Both sexes, 4–8 y	3,935	24.3	12.4	15.2	16.8
Standard error		0.3	0.3	0.3	0.3
M, 9–13 y	595	30.3	17.5	20.8	22.6
Standard error		0.6	0.9	0.7	0.6
M, 14–18 y	474	37.4	14.8	19.8	22.8
Standard error		1.2	1.3	1.2	1.1
M, 19–30 y	920	35.7	13.6	18.7	21.7
Standard error		0.8	1.0	1.0	1.0
M, 31–50 y	1,806	33.1	11.4	16.0	18.7
Standard error		0.6	0.4	0.4	0.3
M, 51–70 y	1,680	27.0	8.3	12.1	14.5
Standard error		0.5	0.3	0.3	0.3
M, 71+ y	722	22.6	7.0	10.0	12.0
Standard error		0.6	0.4	0.4	0.4
F, 9–13 y	606	25.4	12.8	15.7	17.5
Standard error		0.5	0.7	0.6	0.5
F, 14–18 y	449	23.8	10.9	14.1	16.0
Standard error		0.9	1.4	1.5	1.7
F, 19–30 y	808	21.8	7.7	10.7	12.5
Standard error		0.5	0.6	0.5	0.5
F, 31–50 y	1,690	21.1	7.8	10.8	12.6
Standard error		0.4	0.3	0.4	0.5
F, 51–70 y	1,605	18.2	6.3	8.7	10.3
Standard error		0.3	0.4	0.4	0.4
F, 71+ y	670	16.1	5.8	8.0	9.4
Standard error		0.4	0.4	0.4	0.4
Pregnant	81	27.6	14.0	17.4	19.4
Standard error		1.4	2.2	1.9	1.7
Lactating	44	26.5	11.5	15.1	17.2
Standard error		2.1	4.3	3.4	2.8
Pregnant/lactating	124	27.5	13.3	16.8	18.8
Standard error		1.0	1.6	1.3	1.2
All individuals	21,035	25.6	7.7	11.2	13.4
Standard error		0.2	0.1	0.1	0.1
All individuals (+P/L)	21,159	25.6	7.8	11.2	13.5
Standard error		0.2	0.1	0.1	0.1

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
11.2	13.3	16.0	18.9	21.5	27.9
0.3	0.3	0.3	0.5	0.6	1.2
12.6	15.2	18.7	22.5	25.0	29.9
0.4	0.4	0.5	0.7	0.9	1.3
15.9	19.6	23.9	28.2	31.1	37.2
0.2	0.2	0.3	0.4	0.4	0.6
19.9	23.7	28.1	32.6	35.5	41.8
0.3	0.3	0.3	0.4	0.5	0.8
25.8	29.7	34.1	38.5	41.5	47.6
0.6	0.6	0.7	0.9	1.1	1.5
28.4	35.6	44.4	54.2	61.2	76.9
1.1	1.2	1.6	2.4	3.2	5.1
27.3	34.2	42.5	51.4	57.6	71.1
0.9	0.9	1.0	1.5	1.9	3.2
24.0	31.4	40.3	49.4	55.8	70.8
0.4	0.6	0.8	1.4	1.9	3.4
19.2	25.6	33.3	41.5	47.0	58.8
0.3	0.4	0.6	0.9	1.1	1.7
15.9	21.3	27.8	34.8	39.5	49.7
0.4	0.5	0.8	1.2	1.5	2.3
20.7	24.7	29.4	34.1	37.1	43.5
0.5	0.5	0.6	0.9	1.1	1.6
19.3	23.2	27.6	32.2	35.4	42.1
1.6	1.0	0.8	0.8	1.1	3.5
16.1	20.9	26.4	32.1	35.9	43.8
0.5	0.5	0.7	0.9	1.2	1.7
16.0	20.3	25.4	30.7	34.4	42.2
0.5	0.4	0.6	0.7	0.7	1.6
13.3	17.3	22.1	27.1	30.5	37.5
0.3	0.3	0.4	0.6	0.7	1.1
12.0	15.4	19.5	23.7	26.4	32.3
0.4	0.4	0.4	0.6	0.7	1.1
22.9	27.1	31.8	36.3	39.2	44.8
1.3	1.3	1.8	2.8	3.5	5.1
21.1	25.9	31.3	36.6	40.0	46.8
1.9	1.9	3.5	5.6	7.1	10.1
22.5	27.0	31.9	36.8	39.8	45.9
1.0	1.0	1.5	2.2	2.7	3.9
17.9	24.0	31.6	39.9	45.5	57.7
0.1	0.2	0.3	0.4	0.5	0.8
17.9	24.0	31.6	39.8	45.5	57.6
0.1	0.2	0.3	0.4	0.5	0.8

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-8 Mean and Percentiles for Usual Daily Intake of Monounsaturated Fatty Acids (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	12.1	3.7	5.9	7.3
Standard error		0.3	0.3	0.3	0.4
Both sexes, 7–12 mo	530	13.8	5.1	7.3	8.6
Standard error		0.3	0.4	0.3	0.3
Both sexes, 1–3 y	3,949	18.8	8.2	10.7	12.1
Standard error		0.2	0.2	0.2	0.2
Both sexes, 4–8 y	3,935	24.9	12.7	15.6	17.3
Standard error		0.3	0.3	0.3	0.3
M, 9–13 y	595	32.5	17.5	21.3	23.4
Standard error		0.6	1.2	1.0	0.9
M, 14–18 y	474	41.5	17.9	23.2	26.3
Standard error		1.1	1.3	1.3	1.2
M, 19–30 y	920	40.2	15.8	21.5	24.9
Standard error		0.9	1.2	1.1	1.1
M, 31–50 y	1,806	37.6	14.0	19.3	22.5
Standard error		0.6	0.6	0.5	0.4
M, 51–70 y	1,680	31.8	10.7	15.1	17.9
Standard error		0.5	0.4	0.4	0.4
M, 71+ y	722	26.1	8.7	12.4	14.7
Standard error		0.6	0.5	0.5	0.5
F, 9–13 y	606	26.8	13.9	16.9	18.7
Standard error		0.5	0.8	0.7	0.6
F, 14–18 y	449	26.6	13.5	16.7	18.6
Standard error		0.8	1.7	1.5	1.4
F, 19–30 y	808	24.8	9.5	12.9	15.0
Standard error		0.5	0.7	0.6	0.6
F, 31–50 y	1,690	24.0	9.2	12.7	14.7
Standard error		0.4	0.4	0.4	0.3
F, 51–70 y	1,605	21.3	7.6	10.6	12.5
Standard error		0.4	0.4	0.4	0.4
F, 71+ y	670	18.9	7.3	9.9	11.4
Standard error		0.5	0.5	0.5	0.5
Pregnant	81	27.2	17.4	20.0	21.5
Standard error		1.8	2.3	1.8	1.6
Lactating	44	27.0	16.3	19.0	20.6
Standard error		1.9	4.3	3.5	3.0
Pregnant/lactating	124	27.8	16.0	19.0	20.8
Standard error		1.0	1.7	1.5	1.4
All individuals	21,035	28.7	8.4	12.3	14.9
Standard error		0.2	0.1	0.2	0.2
All individuals (+P/L)	21,159	28.6	8.5	12.4	14.9
Standard error		0.2	0.1	0.2	0.2

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human

25th	50th	75th	90th	95th	99th
9.6	11.7	14.2	17.4	19.8	25.1
0.4	0.4	0.3	0.7	0.6	0.9
10.8	13.4	16.3	19.6	21.9	26.9
0.3	0.3	0.4	0.6	0.8	1.2
14.7	18.2	22.2	26.2	28.8	34.6
0.1	0.2	0.2	0.4	0.5	0.7
20.5	24.3	28.8	33.3	36.2	42.5
0.2	0.3	0.3	0.4	0.5	0.8
27.2	31.8	37.1	42.6	46.3	54.2
0.7	0.6	0.8	1.2	1.6	2.5
32.4	40.2	49.2	58.5	64.7	77.5
1.2	1.1	1.3	1.7	2.2	3.4
31.1	38.7	47.7	57.4	64.0	78.4
1.0	1.0	1.1	1.6	2.0	3.2
28.4	36.0	45.0	54.7	61.3	75.6
0.6	0.6	1.1	1.3	1.6	2.5
23.3	30.4	38.7	47.4	53.1	65.1
0.5	0.5	0.7	0.9	1.0	1.4
19.1	25.0	31.8	38.8	43.5	53.2
0.5	0.6	0.7	1.0	1.2	1.7
22.0	26.2	30.9	35.7	38.9	45.4
0.5	0.5	0.7	1.0	1.3	1.9
22.0	26.2	30.8	35.3	38.1	43.9
1.2	0.9	0.7	0.9	1.2	1.8
18.9	24.0	29.7	35.5	39.3	47.1
0.5	0.5	0.6	0.8	1.0	1.4
18.5	23.2	28.6	34.4	38.2	46.5
0.3	0.4	0.5	0.7	0.8	1.1
16.0	20.5	25.8	31.3	34.9	42.3
0.3	0.4	0.5	0.6	0.8	1.2
14.3	18.2	22.6	27.2	30.2	36.5
0.5	0.5	0.5	0.6	0.8	1.2
24.1	27.1	30.2	33.1	34.8	38.3
1.5	1.8	2.5	3.3	3.8	5.0
23.3	26.6	30.2	33.7	36.0	40.4
2.3	1.9	2.8	4.2	5.3	7.6
23.8	27.5	31.4	35.2	37.5	42.2
1.2	1.1	1.3	1.7	2.1	3.1
19.9	26.9	35.4	44.7	51.1	64.8
0.2	0.2	0.3	0.4	0.5	0.7
19.9	26.9	35.4	44.7	51.0	64.6
0.2	0.2	0.3	0.4	0.5	0.7

milk were excluded from all analyses. One female was pregnant and lactating and was included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-9 Mean and Percentiles for Usual Daily Intake of Linoleic acid (*n*-6 18:2) (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	6.7	3.5	4.4	4.8
Standard error		0.1	0.2	0.1	0.1
Both sexes, 7–12 mo	530	6.9	2.8	3.8	4.4
Standard error		0.2	0.1	0.2	0.2
Both sexes, 1–3 y	3,949	7.3	2.6	3.6	4.2
Standard error		0.1	—[b]	0.1	0.1
Both sexes, 4–8 y	3,935	10.1	4.4	5.7	6.4
Standard error		0.1	0.1	0.1	0.1
M, 9–13 y	595	13.4	5.0	6.6	7.6
Standard error		0.4	0.2	0.2	0.3
M, 14–18 y	474	16.6	6.4	8.5	9.8
Standard error		0.5	0.3	0.3	0.4
M, 19–30 y	920	17.6	6.0	8.4	9.9
Standard error		0.5	0.2	0.3	0.3
M, 31–50 y	1,806	17.0	6.2	8.4	9.8
Standard error		0.3	0.1	0.2	0.2
M, 51–70 y	1,680	15.3	5.4	7.4	8.7
Standard error		0.3	0.2	0.2	0.2
M, 71+ y	722	12.2	4.3	5.9	6.9
Standard error		0.4	0.2	0.2	0.2
F, 9–13 y	606	11.0	4.4	5.8	6.6
Standard error		0.3	0.2	0.2	0.2
F, 14–18 y	449	11.7	4.7	6.2	7.1
Standard error		0.5	0.3	0.3	0.4
F, 19–30 y	808	11.8	4.5	6.0	6.9
Standard error		0.3	0.1	0.2	0.2
F, 31–50 y	1,690	11.7	4.6	6.2	7.1
Standard error		0.2	0.2	0.2	0.2
F, 51–70 y	1,605	11.0	4.2	5.6	6.5
Standard error		0.2	0.1	0.1	0.1
F, 71+ y	670	9.3	3.6	4.8	5.5
Standard error		0.3	0.2	0.2	0.2
Pregnant	81	13.9	5.7	7.5	8.6
Standard error		1.1	0.7	0.8	0.8
Lactating	44	13.5	5.7	7.3	8.2
Standard error		1.5	0.7	0.8	0.9
Pregnant/lactating	124	13.7	5.7	7.4	8.5
Standard error		0.9	0.6	0.7	0.7
All individuals	21,035	13.0	3.9	5.6	6.7
Standard error		0.1	0.1	0.1	0.1
All individuals (+P/L)	21,159	13.0	3.9	5.6	6.7
Standard error		0.1	0.1	0.1	0.1

[a] M = male, F = female, P/L = pregnant and/or lactating.
[b] Value is less than 0.05.
NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
5.6	6.5	7.6	8.8	9.7	11.8
0.1	0.1	0.1	0.2	0.3	0.7
5.5	6.7	8.1	9.5	10.5	12.7
0.2	0.2	0.2	0.3	0.3	0.7
5.3	6.9	8.7	10.8	12.3	15.4
0.1	0.1	0.1	0.1	0.2	0.3
7.8	9.7	11.9	14.3	15.9	19.5
0.1	0.1	0.2	0.2	0.3	0.4
9.7	12.5	16.2	20.2	23.0	29.3
0.3	0.4	0.5	0.8	1.1	2.0
12.4	15.8	20.0	24.5	27.5	34.0
0.4	0.5	0.7	0.9	1.1	1.5
12.8	16.7	21.4	26.4	29.7	36.8
0.4	0.5	0.6	0.7	0.8	1.2
12.5	16.1	20.5	25.2	28.4	35.2
0.2	0.3	0.4	0.6	0.7	1.3
11.2	14.5	18.6	22.9	25.8	31.9
0.2	0.3	0.3	0.4	0.4	0.6
8.9	11.6	14.9	18.3	20.7	25.7
0.3	0.4	0.5	0.6	0.7	0.8
8.3	10.5	13.2	16.0	18.0	22.1
0.2	0.3	0.4	0.5	0.6	0.9
8.9	11.2	14.0	16.8	18.7	22.8
0.4	0.5	0.6	0.7	0.8	1.0
8.7	11.2	14.3	17.5	19.7	24.5
0.2	0.3	0.4	0.5	0.7	1.4
8.8	11.1	13.9	16.9	18.9	23.3
0.2	0.3	0.3	0.4	0.5	0.8
8.2	10.5	13.2	16.1	18.1	22.2
0.2	0.2	0.3	0.4	0.4	0.6
7.0	8.9	11.2	13.7	15.4	19.1
0.2	0.3	0.3	0.4	0.5	0.7
10.7	13.4	16.5	19.8	22.0	26.5
0.9	1.1	1.3	1.6	1.9	2.5
10.1	12.7	16.0	19.6	22.1	27.9
1.1	1.4	1.8	2.5	3.1	4.9
10.5	13.1	16.2	19.5	21.7	26.2
0.8	0.9	1.1	1.3	1.6	2.1
8.9	12.0	16.0	20.6	23.9	31.3
0.1	0.1	0.2	0.2	0.3	0.4
8.9	12.0	16.0	20.6	23.9	31.3
0.1	0.1	0.2	0.2	0.3	0.4

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-10 Mean and Percentiles for Usual Daily Intake of Total *n*-3 Fatty Acids (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	0.72	0.38	0.46	0.51
Standard error		0.02	0.01	0.01	0.01
Both sexes, 7–12 mo	530	0.78	0.40	0.48	0.53
Standard error		0.02	0.01	0.01	0.01
Both sexes, 1–3 y	3,949	0.81	0.37	0.47	0.53
Standard error		0.01	0.01	0.01	0.01
Both sexes, 4–8 y	3,935	1.03	0.48	0.61	0.68
Standard error		0.01	0.01	0.01	0.01
M, 9–13 y	595	1.32	0.56	0.71	0.81
Standard error		0.04	0.02	0.02	0.03
M, 14–18 y	474	1.74	0.72	0.92	1.05
Standard error		0.05	0.03	0.03	0.03
M, 19–30 y	920	1.77	0.70	0.93	1.07
Standard error		0.05	0.03	0.03	0.03
M, 31–50 y	1,806	1.86	0.73	0.97	1.11
Standard error		0.04	0.03	0.02	0.02
M, 51–70 y	1,680	1.71	0.67	0.89	1.02
Standard error		0.04	0.02	0.03	0.03
M, 71+ y	722	1.41	0.54	0.71	0.82
Standard error		0.05	0.02	0.02	0.02
F, 9–13 y	606	1.08	0.48	0.60	0.68
Standard error		0.02	0.02	0.02	0.02
F, 14–18 y	449	1.22	0.52	0.68	0.78
Standard error		0.05	0.03	0.03	0.04
F, 19–30 y	808	1.26	0.51	0.66	0.76
Standard error		0.04	0.02	0.02	0.03
F, 31–50 y	1,690	1.28	0.54	0.70	0.80
Standard error		0.03	0.02	0.02	0.02
F, 51–70 y	1,605	1.25	0.52	0.67	0.77
Standard error		0.03	0.01	0.02	0.02
F, 71+ y	670	1.07	0.45	0.58	0.66
Standard error		0.03	0.02	0.02	0.02
Pregnant	81	1.49	0.67	0.85	0.95
Standard error		0.11	0.06	0.07	0.08
Lactating	44	1.50	0.66	0.81	0.91
Standard error		0.29	0.08	0.10	0.12
Pregnant/lactating	124	1.47	0.65	0.82	0.92
Standard error		0.12	0.05	0.06	0.07
All individuals	21,035	1.40	0.46	0.63	0.75
Standard error		0.01	0.01	0.01	0.01
All individuals (+P/L)	21,159	1.40	0.46	0.64	0.75
Standard error		0.01	0.01	0.01	0.01

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: *n*-3 Fatty acids represent the daily intake of 18:3 (*n*-3 and *n*-6) + *n*-3 20:5 + *n*-3 22:5 + *n*-3 22:6 fatty acids per individual; estimates therefore may overestimate intake of total *n*-3 fatty acids. Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children

25th	50th	75th	90th	95th	99th
0.58	0.69	0.82	0.98	1.11	1.43
0.01	0.01	0.02	0.04	0.06	0.12
0.62	0.74	0.89	1.06	1.18	1.49
0.01	0.02	0.03	0.04	0.05	0.08
0.63	0.78	0.94	1.13	1.25	1.53
0.01	0.01	0.01	0.02	0.02	0.03
0.81	0.99	1.20	1.43	1.58	1.92
0.01	0.01	0.02	0.02	0.03	0.04
0.99	1.25	1.56	1.91	2.15	2.67
0.03	0.03	0.05	0.07	0.09	0.16
1.31	1.65	2.08	2.54	2.86	3.56
0.04	0.05	0.06	0.08	0.10	0.14
1.33	1.69	2.12	2.57	2.87	3.51
0.04	0.05	0.06	0.07	0.08	0.12
1.39	1.77	2.24	2.74	3.08	3.84
0.04	0.04	0.06	0.08	0.10	0.14
1.28	1.63	2.05	2.51	2.83	3.54
0.04	0.04	0.04	0.05	0.07	0.15
1.04	1.33	1.69	2.09	2.37	2.97
0.03	0.04	0.06	0.08	0.10	0.15
0.83	1.03	1.28	1.55	1.74	2.14
0.02	0.02	0.03	0.04	0.05	0.07
0.95	1.17	1.43	1.72	1.92	2.37
0.04	0.05	0.06	0.07	0.08	0.11
0.95	1.20	1.51	1.85	2.10	2.65
0.03	0.03	0.04	0.07	0.10	0.22
0.98	1.22	1.52	1.85	2.08	2.57
0.02	0.04	0.04	0.04	0.05	0.08
0.95	1.19	1.49	1.82	2.04	2.53
0.02	0.02	0.03	0.04	0.05	0.07
0.81	1.02	1.27	1.55	1.74	2.16
0.02	0.03	0.03	0.04	0.05	0.07
1.16	1.43	1.76	2.09	2.32	2.79
0.09	0.11	0.14	0.17	0.20	0.27
1.10	1.39	1.78	2.24	2.58	3.39
0.16	0.24	0.36	0.54	0.68	1.07
1.13	1.40	1.74	2.11	2.37	2.93
0.08	0.11	0.15	0.21	0.25	0.36
0.97	1.30	1.71	2.18	2.51	3.25
0.01	0.01	0.02	0.02	0.03	0.05
0.98	1.30	1.71	2.18	2.51	3.25
0.01	0.01	0.02	0.02	0.03	0.05

fed human milk were excluded from all analyses. One female was pregnant and lactating and was included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-11 Mean and Percentiles for Usual Daily Intake of Linolenic Acid (g), United States, CSFII (1994–1996, 1998)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 0–6 mo	596	0.72	0.38	0.46	0.50
Standard error		0.02	0.01	0.01	0.01
Both sexes, 7–12 mo	530	0.77	0.39	0.48	0.53
Standard error		0.02	0.01	0.01	0.01
Both sexes, 1–3 y	3,949	0.77	0.35	0.45	0.50
Standard error		0.01	0.01	0.01	0.01
Both sexes, 4–8 y	3,935	0.97	0.46	0.58	0.65
Standard error		0.01	0.01	0.01	0.01
M, 9–13 y	595	1.26	0.53	0.69	0.78
Standard error		0.04	0.02	0.03	0.04
M, 14–18 y	474	1.65	0.65	0.85	0.98
Standard error		0.05	0.03	0.03	0.03
M, 19–30 y	920	1.66	0.62	0.84	0.98
Standard error		0.05	0.03	0.03	0.03
M, 31–50 y	1,806	1.73	0.65	0.87	1.01
Standard error		0.04	0.03	0.02	0.02
M, 51–70 y	1,680	1.55	0.58	0.77	0.90
Standard error		0.03	0.02	0.02	0.03
M, 71+ y	722	1.26	0.48	0.63	0.73
Standard error		0.04	0.02	0.02	0.02
F, 9–13 y	606	1.03	0.46	0.58	0.65
Standard error		0.02	0.02	0.02	0.02
F, 14–18 y	449	1.13	0.47	0.61	0.70
Standard error		0.05	0.03	0.05	0.06
F, 19–30 y	808	1.18	0.46	0.60	0.70
Standard error		0.03	0.02	0.02	0.02
F, 31–50 y	1,690	1.19	0.48	0.63	0.72
Standard error		0.02	0.02	0.02	0.02
F, 51–70 y	1,605	1.13	0.46	0.60	0.68
Standard error		0.02	0.01	0.01	0.01
F, 71+ y	670	0.97	0.40	0.51	0.59
Standard error		0.03	0.01	0.02	0.02
Pregnant	81	1.42	0.62	0.79	0.89
Standard error		0.10	0.06	0.07	0.07
Lactating	44	1.42	0.61	0.75	0.84
Standard error		0.27	0.06	0.08	0.10
Pregnant/lactating	124	1.40	0.60	0.76	0.86
Standard error		0.12	0.05	0.06	0.06
All individuals	21,035	1.30	0.43	0.59	0.69
Standard error		0.01	0.01	0.01	0.01
All individuals (+P/L)	21,159	1.30	0.43	0.59	0.69
Standard error		0.01	0.01	0.01	0.01

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Linolenic acid includes both *n*-3 and *n*-6 forms. Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One

25th	50th	75th	90th	95th	99th
0.58	0.69	0.82	0.98	1.11	1.43
0.01	0.01	0.02	0.04	0.06	0.12
0.61	0.73	0.88	1.05	1.17	1.47
0.01	0.02	0.02	0.04	0.05	0.08
0.60	0.74	0.90	1.08	1.20	1.46
0.01	0.01	0.01	0.02	0.02	0.03
0.78	0.94	1.13	1.34	1.48	1.79
0.01	0.01	0.02	0.02	0.02	0.04
0.96	1.19	1.48	1.81	2.05	2.61
0.04	0.04	0.04	0.07	0.09	0.20
1.22	1.56	1.98	2.44	2.76	3.47
0.04	0.05	0.06	0.08	0.10	0.15
1.24	1.59	2.01	2.44	2.74	3.36
0.04	0.04	0.06	0.07	0.08	0.11
1.27	1.63	2.08	2.57	2.90	3.64
0.04	0.03	0.06	0.08	0.10	0.16
1.14	1.47	1.87	2.30	2.59	3.23
0.03	0.03	0.04	0.05	0.05	0.10
0.93	1.19	1.52	1.88	2.13	2.67
0.03	0.04	0.05	0.07	0.08	0.11
0.79	0.99	1.22	1.47	1.64	2.01
0.02	0.02	0.03	0.04	0.04	0.07
0.87	1.09	1.35	1.63	1.81	2.20
0.06	0.05	0.05	0.07	0.08	0.16
0.87	1.11	1.41	1.75	1.98	2.52
0.02	0.03	0.04	0.06	0.09	0.19
0.90	1.13	1.41	1.72	1.94	2.41
0.02	0.02	0.03	0.04	0.05	0.07
0.85	1.08	1.36	1.66	1.86	2.31
0.02	0.02	0.03	0.04	0.04	0.06
0.73	0.91	1.15	1.41	1.60	2.03
0.02	0.03	0.04	0.04	0.08	0.24
1.09	1.36	1.68	2.02	2.24	2.72
0.08	0.10	0.12	0.14	0.17	0.22
1.03	1.31	1.69	2.14	2.48	3.28
0.14	0.22	0.35	0.54	0.70	1.12
1.06	1.33	1.67	2.03	2.29	2.86
0.08	0.10	0.15	0.20	0.25	0.37
0.90	1.20	1.59	2.02	2.32	3.00
0.01	0.01	0.02	0.02	0.03	0.04
0.91	1.21	1.59	2.02	2.32	3.00
0.01	0.01	0.02	0.02	0.03	0.04

female was pregnant and lactating and was included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-12 Mean and Percentiles for Average Daily Intake of *n*-3 Eicosapentaenoic Acid (20:5) Fatty Acids (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	578	—[b]	—	—	—
Both sexes, 7–12 mo	487	0.002	—	—	—
Both sexes, 1–3 y	3,777	0.008	—	—	—
Both sexes, 4–8 y	3,769	0.012	—	—	—
M, 9–13 y	569	0.016	—	—	—
M, 14–18 y	446	0.018	—	—	—
M, 19–30 y	854	0.030	—	—	—
M, 31–50 y	1,684	0.038	—	—	—
M, 51–70 y	1,606	0.046	—	—	—
M, 71+ y	674	0.049	—	—	—
F, 9–13 y	580	0.012	—	—	—
F, 14–18 y	436	0.016	—	—	—
F, 19–30 y	760	0.024	—	—	—
F, 31–50 y	1,614	0.027	—	—	—
F, 51–70 y	1,539	0.035	—	—	—
F, 71+ y	623	0.029	—	—	—
Pregnant	71	0.017	—	—	—
Lactating	42	0.026	—	—	—
Pregnant/lactating	112	0.020	—	—	—
All individuals	19,996	0.028	—	—	—
All individuals (+P/L)	20,108	0.028	—	—	—

[a] M = male, F = female, P/L = pregnant and/or lactating.
[b] Value is less than 0.0005.
NOTE: Estimates represent the unadjusted distribution of the 2-day average intake reported per individual. Estimates were calculated using SAS PROC UNIVARIATE. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was included in both the Pregnant and Lactating catego-

25th	50th	75th	90th	95th	99th
—	—	—	—	—	0.003
—	—	0.002	0.004	0.007	0.038
—	0.002	0.006	0.018	0.035	0.118
—	0.002	0.007	0.023	0.051	0.208
—	0.002	0.009	0.039	0.075	0.231
—	0.003	0.010	0.032	0.093	0.270
0.001	0.007	0.019	0.058	0.135	0.469
0.001	0.007	0.022	0.112	0.206	0.442
0.002	0.007	0.033	0.122	0.219	0.550
0.001	0.005	0.022	0.166	0.310	0.662
—	0.002	0.007	0.030	0.061	0.220
—	0.004	0.009	0.029	0.066	0.365
—	0.004	0.012	0.046	0.128	0.314
0.001	0.005	0.015	0.068	0.136	0.367
0.001	0.005	0.018	0.088	0.172	0.461
0.001	0.004	0.014	0.071	0.163	0.374
—	0.004	0.016	0.031	0.086	0.133
0.001	0.006	0.017	0.088	0.147	0.367
0.001	0.005	0.017	0.053	0.133	0.319
0.001	0.004	0.014	0.066	0.141	0.392
0.001	0.004	0.014	0.066	0.141	0.392

ries. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of 2-day average intake distributions are not reliable.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-13 Mean and Percentiles for Usual Daily Intake of *n*-3 Docosapentaenoic Acid (22:5) (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	578	—[b]	—	—	—
Both sexes, 7–12 mo	487	0.001	—	—	—
Both sexes, 1–3 y	3,777	0.005	—	—	—
Both sexes, 4–8 y	3,769	0.007	—	—	—
M, 9–13 y	569	0.009	—	—	—
M, 14–18 y	446	0.012	—	—	—
M, 19–30 y	854	0.016	—	—	—
M, 31–50 y	1,684	0.018	—	—	—
M, 51–70 y	1,606	0.019	—	—	—
M, 71+ y	674	0.015	—	—	—
F, 9–13 y	580	0.007	—	—	—
F, 14–18 y	436	0.009	—	—	—
F, 19–30 y	760	0.011	—	—	—
F, 31–50 y	1,614	0.013	—	—	—
F, 51–70 y	1,539	0.013	—	—	—
F, 71+ y	623	0.011	—	—	—
Pregnant	71	0.007	—	—	—
Lactating	42	0.012	—	—	—
Pregnant/lactating	112	0.009	—	—	—
All individuals	19,996	0.013	—	—	—
All individuals (+P/L)	20,108	0.013	—	—	—

[a] M = male, F = female, P/L = pregnant and/or lactating.
[b] Value is less than 0.0005.
NOTE: Estimates represent the unadjusted distribution of the 2-day average intake reported per individual. Estimates were calculated using SAS PROC UNIVARIATE. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was included in both the Pregnant and Lactating catego-

25th	50th	75th	90th	95th	99th
—	—	—	—	0.001	0.004
—	—	0.001	0.005	0.007	0.014
—	0.001	0.006	0.012	0.019	0.041
—	0.002	0.007	0.017	0.027	0.065
—	0.003	0.011	0.025	0.040	0.074
—	0.005	0.015	0.033	0.052	0.098
—	0.007	0.021	0.040	0.050	0.120
—	0.009	0.022	0.044	0.067	0.188
—	0.008	0.022	0.048	0.087	0.174
—	0.005	0.016	0.042	0.070	0.130
—	0.003	0.009	0.018	0.025	0.055
—	0.005	0.013	0.020	0.032	0.065
—	0.005	0.012	0.026	0.039	0.111
—	0.006	0.015	0.029	0.047	0.107
—	0.006	0.015	0.030	0.051	0.134
—	0.005	0.013	0.029	0.043	0.093
—	0.003	0.010	0.024	0.029	0.042
—	0.009	0.016	0.029	0.040	0.093
—	0.004	0.013	0.025	0.034	0.062
—	0.005	0.015	0.032	0.050	0.118
—	0.005	0.015	0.031	0.050	0.118

ries. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of 2-day average intake distributions are not reliable.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-14 Mean and Percentiles for Usual Daily Intake of *n*-3 Docosahexaneoic Acid (22:6) (g), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	—[b]	—	—	—
Standard error		0.001	—	—	—
Both sexes, 7–12 mo	530	0.030	—	0.001	0.001
Standard error		0.008	—	—	—
Both sexes, 1–3 y	3,949	0.032	0.003	0.005	0.007
Standard error		0.001	—	—	—
Both sexes, 4–8 y	3,935	0.050	0.003	0.007	0.010
Standard error		0.005	—	0.001	0.001
M, 9–13 y	595	0.063	0.003	0.007	0.011
Standard error		0.010	—	0.001	0.001
M, 14–18 y	474	0.072	0.009	0.016	0.022
Standard error		0.012	0.001	0.002	0.003
M, 19–30 y	920	0.079	0.013	0.021	0.028
Standard error		0.006	0.001	0.002	0.002
M, 31–50 y	1,806	0.094	0.017	0.028	0.035
Standard error		0.006	0.001	0.002	0.002
M, 51–70 y	1,680	0.111	0.019	0.031	0.040
Standard error		0.007	0.002	0.002	0.003
M, 71+ y	722	0.128	0.012	0.022	0.030
Standard error		0.019	0.001	0.002	0.003
F, 9–13 y	606	0.055	0.002	0.005	0.008
Standard error		0.009	—	0.001	0.001
F, 14–18 y	449	0.062	0.008	0.014	0.019
Standard error		0.009	0.001	0.002	0.003
F, 19–30 y	808	0.067	0.008	0.014	0.019
Standard error		0.006	0.001	0.001	0.002
F, 31–50 y	1,690	0.071	0.011	0.019	0.024
Standard error		0.009	0.001	0.001	0.002
F, 51–70 y	1,605	0.089	0.011	0.020	0.026
Standard error		0.006	0.001	0.001	0.002
F, 71+ y	670	0.077	0.010	0.018	0.024
Standard error		0.010	0.001	0.002	0.002
Pregnant	81	0.051	0.009	0.015	0.019
Standard error		0.014	0.002	0.004	0.005
Lactating	44	0.053	0.010	0.016	0.021
Standard error		0.019	0.003	0.005	0.006
Pregnant/lactating	124	0.052	0.009	0.015	0.019
Standard error		0.012	0.002	0.003	0.004
All individuals	21,035	0.057	0.007	0.013	0.017
Standard error		0.019	0.001	0.003	0.004
All individuals (+P/L)	21,159	0.057	0.007	0.013	0.017
Standard error		0.018	0.001	0.003	0.004

[a] M = male, F = female, P/L = pregnant and/or lactating.
[b] Value is less than 0.0005.
NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
—	—	—	0.001	0.001	0.003
—	—	—	0.001	0.002	0.007
0.003	0.008	0.024	0.065	0.119	0.370
—	0.001	0.005	0.016	0.032	0.118
0.013	0.023	0.041	0.066	0.088	0.148
0.001	0.001	0.002	0.003	0.004	0.008
0.018	0.035	0.063	0.107	0.144	0.251
0.001	0.003	0.006	0.011	0.015	0.028
0.021	0.041	0.079	0.138	0.191	0.344
0.003	0.006	0.012	0.023	0.033	0.065
0.034	0.057	0.092	0.141	0.180	0.284
0.005	0.009	0.016	0.026	0.034	0.058
0.042	0.066	0.101	0.146	0.181	0.269
0.003	0.005	0.008	0.012	0.015	0.023
0.052	0.079	0.120	0.171	0.211	0.311
0.003	0.004	0.007	0.011	0.014	0.023
0.060	0.093	0.142	0.205	0.255	0.380
0.004	0.006	0.009	0.014	0.019	0.031
0.050	0.089	0.159	0.266	0.363	0.651
0.006	0.011	0.023	0.043	0.063	0.127
0.017	0.034	0.068	0.123	0.174	0.325
0.003	0.005	0.011	0.020	0.028	0.054
0.030	0.049	0.080	0.121	0.155	0.242
0.004	0.007	0.012	0.018	0.024	0.040
0.031	0.052	0.086	0.132	0.170	0.271
0.003	0.005	0.008	0.014	0.019	0.032
0.037	0.058	0.090	0.133	0.167	0.253
0.003	0.006	0.011	0.019	0.025	0.042
0.042	0.069	0.113	0.173	0.222	0.350
0.002	0.004	0.008	0.014	0.019	0.035
0.037	0.061	0.098	0.149	0.190	0.297
0.004	0.007	0.012	0.020	0.027	0.045
0.028	0.043	0.066	0.094	0.115	0.167
0.007	0.011	0.018	0.028	0.036	0.055
0.030	0.046	0.068	0.095	0.116	0.168
0.009	0.015	0.024	0.036	0.046	0.071
0.029	0.044	0.066	0.094	0.115	0.168
0.006	0.009	0.015	0.023	0.029	0.045
0.028	0.046	0.074	0.111	0.139	0.209
0.007	0.014	0.024	0.039	0.052	0.083
0.028	0.046	0.074	0.111	0.139	0.209
0.007	0.013	0.024	0.039	0.051	0.082

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-15 Mean and Percentiles for Usual Daily Intake of Cholesterol (mg), United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	13	—[b]	—	1
Standard error		1	—	—	—
Both sexes, 7–12 mo	530	74	3	7	12
Standard error		5	1	1	1
Both sexes, 1–3 y	3,949	189	64	89	104
Standard error		2	2	2	2
Both sexes, 4–8 y	3,935	206	81	106	122
Standard error		3	2	2	2
M, 9–13 y	595	259	135	163	179
Standard error		13	12	11	11
M, 14–18 y	474	319	135	174	198
Standard error		11	14	13	12
M, 19–30 y	920	345	120	166	193
Standard error		12	12	11	12
M, 31–50 y	1,806	345	118	165	193
Standard error		5	6	5	5
M, 51–70 y	1,680	317	107	150	176
Standard error		9	7	7	7
M, 71+ y	722	267	83	119	142
Standard error		7	5	5	5
F, 9–13 y	606	205	89	114	129
Standard error		7	6	6	7
F, 14–18 y	449	222	99	127	143
Standard error		10	16	15	14
F, 19–30 y	808	210	76	104	121
Standard error		6	8	8	7
F, 31–50 y	1,690	219	78	107	125
Standard error		4	4	4	4
F, 51–70 y	1,605	208	71	99	116
Standard error		5	4	4	4
F, 71+ y	670	189	64	89	105
Standard error		5	5	5	5
Pregnant	81	280	129	164	185
Standard error		22	22	21	20
Lactating	44	246	169	187	198
Standard error		27	56	45	39
Pregnant/lactating	124	271	121	154	174
Standard error		17	17	16	16
All individuals	21,035	256	52	85	108
Standard error		2	1	1	1
All individuals (+P/L)	21,159	257	53	86	109
Standard error		2	1	1	1

[a] M = male, F = female, P/L = pregnant and/or lactating.
[b] Value is less than 0.5.
NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
3	7	17	32	45	79
—	—	1	3	5	11
24	47	98	174	227	348
2	3	8	13	17	26
134	175	229	292	336	430
2	2	3	5	6	9
152	194	246	304	344	431
2	2	4	7	9	15
210	250	299	350	385	460
14	16	15	15	19	32
245	306	379	455	507	616
11	11	14	21	27	41
246	323	420	527	601	766
12	12	20	25	30	51
248	324	419	525	598	753
5	5	7	11	15	24
226	295	386	486	554	697
8	9	11	14	17	25
186	248	329	417	476	598
6	7	10	14	18	27
158	195	241	292	329	410
7	7	9	12	14	22
174	214	260	310	343	416
13	11	10	13	17	29
154	199	253	313	355	448
6	6	6	10	13	22
160	206	265	330	374	471
3	4	5	8	10	16
149	195	253	318	362	455
4	5	7	9	11	16
136	178	229	286	326	412
5	6	7	9	12	18
224	273	328	383	418	489
19	21	27	38	47	68
218	243	270	297	315	352
29	26	39	62	79	117
213	262	320	379	418	499
16	16	20	28	34	49
157	230	327	439	519	698
2	2	3	5	6	10
158	230	327	438	518	696
2	2	3	5	6	9

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-16 Mean and Percentiles for Usual Daily Intake of Protein (g), United States, CSFII (1994–1996, 1998)

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 0–6 mo	596	15.9	7.4	9.6	10.9
Standard error		0.3	0.5	0.4	0.5
Both sexes, 7–12 mo	530	28.3	11.1	14.4	16.5
Standard error		0.8	0.7	0.6	0.6
Both sexes, 1–3 y	3,949	50.9	24.4	31.3	34.9
Standard error		0.4	0.5	0.4	0.5
Both sexes, 4–8 y	3,935	62.5	33.8	40.8	44.7
Standard error		0.6	0.6	0.6	0.6
M, 9–13 y	595	79.1	46.0	54.0	59.0
Standard error		1.5	2.2	2.0	1.8
M, 14–18 y	474	99.0	51.0	62.0	69.0
Standard error		2.3	4.0	3.6	3.3
M, 19–30 y	920	104.0	49.0	62.0	70.0
Standard error		2.0	2.7	2.5	2.5
M, 31–50 y	1,806	99.4	49.0	61.0	67.0
Standard error		1.1	1.6	0.9	1.2
M, 51–70 y	1,680	86.8	41.0	53.0	59.0
Standard error		1.5	1.6	1.8	1.5
M, 71+ y	722	72.5	32.0	42.0	48.0
Standard error		1.2	3.0	1.7	1.8
F, 9–13 y	606	65.3	37.1	44.4	48.5
Standard error		1.2	1.6	1.5	1.4
F, 14–18 y	449	66.5	36.4	44.4	48.8
Standard error		2.0	3.9	3.5	3.7
F, 19–30 y	808	63.3	33.0	40.0	44.0
Standard error		1.4	1.9	1.6	1.7
F, 31–50 y	1,690	64.9	32.0	41.0	46.0
Standard error		0.7	0.8	0.8	0.8
F, 51–70 y	1,605	61.7	32.4	40.0	44.3
Standard error		0.8	1.2	1.1	1.0
F, 71+ y	670	56.4	26.8	34.0	38.2
Standard error		0.9	1.5	1.3	1.2
Pregnant	81	78.2	45.0	54.0	60.0
Standard error		2.6	9.2	7.0	5.6
Lactating	44	79.7	48.2	55.8	60.3
Standard error		4.7	6.4	5.5	5.2
Pregnant/lactating	124	79.7	43.0	53.0	58.0
Standard error		2.5	3.5	3.1	3.0
All individuals	21,035	75.2	26.0	36.0	42.0
Standard error		0.4	0.3	0.3	0.3
All individuals (+P/L)	21,159	75.3	26.0	36.0	42.0
Standard error		0.4	0.3	0.3	0.3

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day and were adjusted using the Iowa State University method. Mean, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Infants and children fed human milk were excluded from all analyses. One female was pregnant and lactating and was

25th	50th	75th	90th	95th	99th
12.9	15.1	18.1	21.9	24.7	31.2
0.3	0.5	0.3	0.5	0.6	1.3
20.6	26.5	34.0	42.5	48.5	62.0
0.6	0.7	1.0	1.6	2.1	3.5
41.3	49.8	59.1	68.4	74.7	88.4
0.4	0.4	0.4	0.8	0.8	1.3
52.1	61.2	71.5	81.9	88.7	103.5
0.6	0.6	0.7	0.9	1.1	1.7
68.0	78.0	89.0	101.0	108.0	125.0
1.6	1.5	1.7	2.2	2.6	4.0
81.0	97.0	114.0	132.0	144.0	168.0
2.7	2.3	3.0	4.6	5.9	9.1
83.0	101.0	121.0	142.0	157.0	190.0
2.1	2.2	2.5	3.4	4.6	8.9
80.0	97.0	115.0	135.0	147.0	174.0
1.0	1.0	1.4	2.6	2.9	4.3
71.0	85.0	100.0	117.0	128.0	152.0
1.4	2.0	1.8	2.3	2.7	3.8
58.0	71.0	85.0	99.0	108.0	125.0
1.8	1.3	2.4	2.2	2.4	7.0
55.6	64.0	73.6	83.6	90.5	105.4
1.2	1.2	1.5	2.3	2.9	4.4
56.5	65.4	75.3	85.3	92.1	106.1
3.3	2.0	1.6	2.3	3.5	8.9
52.0	62.0	73.0	84.0	91.0	107.0
1.7	1.3	1.8	2.4	2.8	4.1
54.0	64.0	75.0	86.0	93.0	109.0
0.8	0.7	0.7	1.1	1.4	2.2
51.8	60.8	70.6	80.4	86.8	99.9
0.9	0.8	0.9	1.2	1.4	2.0
45.8	55.2	65.7	76.0	82.6	95.7
1.1	1.0	1.0	1.2	1.4	1.9
68.0	78.0	88.0	97.0	103.0	113.0
3.6	2.7	4.3	6.9	8.5	11.9
68.4	78.4	89.6	100.8	108.1	122.9
4.9	5.0	5.6	6.9	8.1	11.5
68.0	79.0	91.0	102.0	109.0	122.0
2.7	2.6	3.0	4.0	5.0	7.2
54.0	71.0	92.0	114.0	129.0	160.0
0.3	0.3	0.5	0.8	1.1	1.8
55.0	71.0	92.0	114.0	129.0	160.0
0.3	0.3	0.5	0.8	1.1	1.7

included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-17 Mean and Percentiles for Usual Daily Percentage of Total Energy from Protein, United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	596	8.9	7.3	7.7	7.8
Standard error		0.1	0.2	0.2	0.1
Both sexes, 7–12 mo	530	11.1	6.6	7.6	8.2
Standard error		0.2	0.1	0.1	0.1
Both sexes, 1–3 y	3,949	14.6	10.1	11.4	12.0
Standard error		0.1	0.1	0.1	0.1
Both sexes, 4–8 y	3,935	14.1	10.4	11.4	11.9
Standard error		0.1	0.1	0.1	0.1
M, 9–13 y	595	14.2	10.9	11.8	12.3
Standard error		0.2	0.3	0.3	0.2
M, 14–18 y	474	14.3	11.4	12.3	12.7
Standard error		0.2	0.7	0.6	0.5
M, 19–30 y	920	15.2	10.3	11.6	12.3
Standard error		0.2	0.3	0.2	0.2
M, 31–50 y	1,805	16.0	11.1	12.3	13.0
Standard error		0.1	0.2	0.1	0.1
M, 51–70 y	1,680	16.5	11.2	12.5	13.3
Standard error		0.2	0.2	0.3	0.2
M, 71+ y	722	16.4	11.1	12.5	13.2
Standard error		0.2	0.4	0.3	0.3
F, 9–13 y	606	13.9	10.2	11.2	11.7
Standard error		0.2	0.3	0.2	0.2
F, 14–18 y	449	14.3	10.2	11.3	11.9
Standard error		0.3	0.5	0.4	0.4
F, 19–30 y	806	14.6	9.0	10.5	11.3
Standard error		0.3	0.4	0.3	0.3
F, 31–50 y	1,689	15.8	10.3	11.8	12.5
Standard error		0.1	0.3	0.2	0.2
F, 51–70 y	1,605	16.6	11.3	12.7	13.5
Standard error		0.1	0.2	0.2	0.2
F, 71+ y	669	16.7	11.4	12.7	13.5
Standard error		0.2	0.3	0.3	0.2
Pregnant	81	15.6	10.8	12.1	12.8
Standard error		0.6	0.6	0.6	0.6
Lactating	44	15.5	12.2	13.1	13.6
Standard error		0.7	0.9	0.8	0.8
Pregnant/lactating	124	15.6	13.8	14.3	14.6
Standard error		0.4	2.2	1.6	1.3
All individuals	21,030	15.4	9.6	11.0	11.8
Standard error		0.1	0.1	0.1	0.1
All individuals (+P/L)	21,154	15.4	9.6	11.0	11.9
Standard error		0.1	0.1	0.1	0.1

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Estimates are based on respondents' intakes on the first surveyed day. The Iowa State University (ISU) method was used to estimate individual usual intakes of energy from protein and total energy. One g of protein was assumed to provide 4 kcal of energy. A modification of the ISU method was then used to estimate the distribution of the nutrient density (Goyeneche JJ, Carriquiry A, Fuller WA. 1997. Estimating bivariate usual intake distributions. *ASA Proceedings of the Biometrics Section.* Alexandria, VA: American Statistical Association). Infants and children fed human milk and five individuals

25th	50th	75th	90th	95th	99th
8.2	8.8	9.5	10.3	10.9	11.9
0.1	0.1	0.1	0.2	0.3	0.5
9.1	10.4	12.6	15.0	16.4	19.2
0.1	0.2	0.3	0.4	0.5	0.6
13.2	14.5	16.0	17.3	18.1	19.8
0.1	0.1	0.1	0.1	0.1	0.2
12.9	14.0	15.2	16.3	17.0	18.4
0.1	0.1	0.1	0.1	0.2	0.2
13.1	14.1	15.2	16.2	16.9	18.1
0.2	0.2	0.2	0.3	0.3	0.5
13.4	14.3	15.1	16.0	16.5	17.6
0.3	0.2	0.3	0.5	0.6	0.9
13.6	15.1	16.7	18.3	19.4	21.5
0.2	0.2	0.3	0.3	0.4	0.6
14.3	15.8	17.5	19.1	20.1	22.2
0.1	0.1	0.2	0.2	0.2	0.3
14.6	16.3	18.1	19.9	21.0	23.3
0.2	0.2	0.2	0.3	0.4	0.4
14.6	16.2	18.0	19.8	20.9	23.1
0.2	0.2	0.2	0.3	0.4	0.7
12.7	13.8	15.0	16.2	16.9	18.3
0.2	0.2	0.2	0.2	0.2	0.3
12.9	14.2	15.5	16.8	17.5	19.0
0.3	0.3	0.3	0.3	0.4	0.5
12.7	14.4	16.2	18.0	19.2	21.6
0.3	0.3	0.4	0.4	0.5	0.6
13.9	15.6	17.4	19.2	20.4	22.7
0.2	0.1	0.2	0.2	0.2	0.5
14.8	16.4	18.2	20.0	21.1	23.6
0.1	0.1	0.2	0.2	0.3	0.5
14.8	16.5	18.3	20.1	21.3	23.7
0.2	0.2	0.2	0.3	0.4	0.6
14.1	15.5	17.0	18.5	19.4	21.2
0.6	0.7	0.7	0.8	0.8	1.0
14.4	15.5	16.6	17.6	18.3	19.6
0.7	0.6	0.7	0.7	0.9	1.2
15.0	15.6	16.1	16.6	16.9	17.5
0.8	0.4	0.8	1.4	1.8	2.6
13.3	15.1	17.1	19.1	20.4	22.9
0.1	0.1	0.1	0.1	0.1	0.2
13.3	15.1	17.1	19.1	20.4	22.9
0.1	0.1	0.1	0.1	0.1	0.2

who had no food intake for the day were excluded from the analyses. One female was pregnant and lactating and was included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE E-18 Mean and Percentiles for Usual Daily Percentage of Total Energy from Alcohol, United States, CSFII (1994–1996, 1998)

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	578	—[b]	—	—	—
Both sexes, 7–12 mo	487	—	—	—	—
Both sexes, 1–3 y	3,777	—	—	—	—
Both sexes, 4–8 y	3,769	—	—	—	—
M, 9–13 y	569	—	—	—	—
M, 14–18 y	446	0.2	—	—	—
M, 19–30 y	854	3.1	—	—	—
M, 31–50 y	1,683	2.4	—	—	—
M, 51–70 y	1,606	2.1	—	—	—
M, 71+ y	674	1.6	—	—	—
F, 9–13 y	580	—	—	—	—
F, 14–18 y	436	0.1	—	—	—
F, 19–30 y	758	1.5	—	—	—
F, 31–50 y	1,613	1.3	—	—	—
F, 51–70 y	1,539	1.3	—	—	—
F, 71+ y	622	0.5	—	—	—
Pregnant	71	—	—	—	—
Lactating	42	0.2	—	—	—
Pregnant/lactating	112	0.1	—	—	—
All individuals	19,991	1.3	—	—	—
All individuals (+P/L)	20,103	1.3	—	—	—

[a] M = male, F = female, P/L = pregnant and/or lactating.
[b] Value is less than 0.05
NOTE: Estimates represent the unadjusted distribution of the 2-day average percentage of kcal from alcohol calculated per individual. One g of alcohol was assumed to provide 7 kcal of energy. Estimates were calculated using SAS PROC UNIVARIATE. Infants and children fed human milk and five individuals who had no food intake for the day were excluded from the analyses. One female was pregnant and lactating and was included

25th	50th	75th	90th	95th	99th
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	—	—	0.1
—	—	—	—	—	0.1
—	—	—	—	—	0.1
—	—	—	—	—	4.3
—	—	3.4	11.0	17.0	31.2
—	—	2.5	8.5	12.8	23.3
—	—	1.9	7.5	11.4	22.3
—	—	—	5.1	12.5	20.8
—	—	—	—	—	0.1
—	—	—	—	0.1	2.6
—	—	—	5.8	9.9	20.1
—	—	—	5.1	9.5	18.3
—	—	—	5.1	9.4	18.2
—	—	—	0.1	4.2	11.7
—	—	—	—	0.2	0.7
—	—	—	—	—	4.8
—	—	—	—	0.2	4.8
—	—	—	4.6	9.3	19.8
—	—	—	4.5	9.2	19.7

in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

F

Canadian Dietary Intake Data, 1990–1997

TABLE F-1 Mean and Percentiles for Dietary Energy Intake (kcal), Canada (1990–1997)

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	1,362	2,980.2	1,992	2,120	2,436
Standard error		45.2	75	33	25
M, 31–50 y	2,371	2,637.1	1,545	1,797	2,149
Standard error		33.5	81	44	24
M, 51–70 y	2,416	2,224.0	1,418	1,546	1,794
Standard error		35.8	81	30	31
M, 71–74 y	478	2,025.8	1,213	1,360	1,672
Standard error		55.6	99	57	69
F, 19–30 y	1,456	1,890.4	1,189	1,327	1,521
Standard error		27.8	57	19	17
F, 31–50 y	2,687	1,752.2	1,124	1,217	1,421
Standard error		24.0	42	14	14
F, 51–70 y	2,481	1,543.2	932	1,077	1,268
Standard error		28.2	51	27	19
F, 71–74 y	474	1,531.3	920	1,030	1,188
Standard error		70.8	64	39	35
Total	13,725	2,168.6	1,173	1,304	1,575
Standard error		16.0	30	11	12

[a] M = male, F = female.

NOTE: Estimates were adjusted for intraindividual variability using the modified NAS method of Karpinski K, Nargundkar M. 1992. *Nova Scotia Nutrition Survey Methodology Report.* Technical document #451311-001, Bureau of Biostatistics and Computer Appli-

50th	75th	90th	95th
2,810	3,194	3,679	4,050
22	26	65	185
2,548	2,947	3,322	3,537
23	36	38	154
2,165	2,530	2,949	3,167
34	42	56	130
1,994	2,311	2,730	2,976
34	46	111	84
1,773	2,054	2,350	2,552
19	19	37	85
1,658	1,930	2,206	2,395
15	18	28	91
1,498	1,753	1,988	2,176
20	26	38	78
1,438	1,638	1,994	2,252
30	45	118	266
1,998	2,554	3,072	3,353
15	20	24	110

cations, Food Directorate, Health Canada; and National Center for Health Statistics. 1994. *Consensus Workshop on Dietary Assessment: Nutrition Monitoring and Tracking the Year 2000 Objectives.* Maryland: U.S. Department of Health and Human Services. Variability for the percentiles has been estimated using SUDAAN v8.0, Taylor linearization method.

TABLE F-2 Mean and Percentiles for Dietary Carbohydrate Intake (Percent of Energy), Canada (1990–1997)

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	1,362	47.7	37.9	40.2	43.8
Standard error		0.4	0.9	0.5	0.3
M, 31–50 y	2,371	47.0	37.0	39.5	43.2
Standard error		0.4	1.2	0.5	0.2
M, 51–70 y	2,416	47.2	36.7	39.5	43.3
Standard error		0.4	1.3	0.6	0.4
M, 71–74 y	478	49.2	36.5	38.9	43.9
Standard error		0.8	1.7	1.0	1.0
F, 19–30 y	1,456	49.6	40.5	42.6	45.7
Standard error		0.4	0.8	0.3	0.3
F, 31–50 y	2,687	48.3	38.9	40.8	45.2
Standard error		0.4	0.8	0.4	0.3
F, 51–70 y	2,481	51.6	41.3	44.1	47.2
Standard error		0.4	1.2	0.6	0.5
F, 71–74 y	474	52.1	42.9	46.0	49.8
Standard error		0.8	1.7	1.2	0.8
Total	13,725	48.5	38.4	40.8	44.5
Standard error		0.2	0.6	0.2	0.2

[a] M = male, F = female.

NOTE: Estimates were adjusted for intraindividual variability using the modified NAS method of Karpinski K, Nargundkar M. 1992. *Nova Scotia Nutrition Survey Methodology Report*. Technical document #451311-001, Bureau of Biostatistics and Computer Appli-

50th	75th	90th	95th
47.4	51.4	55.2	57.0
0.3	0.3	0.4	0.8
46.9	50.8	54.7	56.7
0.3	0.4	0.4	0.8
47.4	51.3	55.3	57.9
0.4	0.3	0.4	0.8
49.2	54.2	59.2	61.4
0.8	0.7	1.1	1.0
49.4	53.2	56.2	58.2
0.3	0.2	0.4	0.6
48.9	52.5	56.4	58.4
0.2	0.3	0.4	0.6
51.3	54.9	57.9	60.0
0.3	0.3	0.4	0.8
52.7	55.0	57.7	60.4
0.4	0.5	0.6	1.4
48.6	52.6	56.1	58.2
0.1	0.1	0.2	0.5

cations, Food Directorate, Health Canada; and National Center for Health Statistics. 1994. *Consensus Workshop on Dietary Assessment: Nutrition Monitoring and Tracking the Year 2000 Objectives.* Maryland: U.S. Department of Health and Human Services. Variability for the percentiles has been estimated using SUDAAN v8.0, Taylor linearization method.

TABLE F-3 Mean and Percentiles for Dietary Fat Intake (Percent of Energy), Canada (1990–1997)

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	1,362	33.7	26.8	28.8	31.7
Standard error		0.3	1.0	0.4	0.2
M, 31–50 y	2,371	33.8	25.9	27.6	31.0
Standard error		0.3	0.8	0.3	0.3
M, 51–70 y	2,416	33.2	23.6	25.9	29.7
Standard error		0.5	0.9	0.4	0.3
M, 71–74 y	478	32.7	22.8	24.4	27.9
Standard error		0.7	1.1	0.8	0.8
F, 19–30 y	1,456	33.0	24.5	26.8	29.6
Standard error		0.3	0.8	0.4	0.2
F, 31–50 y	2,687	33.4	24.8	26.8	29.8
Standard error		0.3	0.7	0.4	0.2
F, 51–70 y	2,481	30.8	22.9	24.9	27.8
Standard error		0.4	0.9	0.4	0.3
F, 71–74 y	474	30.5	21.8	24.8	27.1
Standard error		0.7	1.2	0.7	0.4
Total	13,725	33.1	24.6	26.7	29.8
Standard error		0.1	0.5	0.2	0.1

[a] M = male, F = female.

NOTE: Estimates were adjusted for intraindividual variability using the modified NAS method of Karpinski K, Nargundkar M. 1992. *Nova Scotia Nutrition Survey Methodology Report*. Technical document #451311-001, Bureau of Biostatistics and Computer Appli-

50th	75th	90th	95th
34.2	36.5	38.2	39.5
0.2	0.2	0.2	0.5
33.9	36.8	39.6	41.5
0.2	0.2	0.3	0.6
33.4	36.6	40.1	42.0
0.2	0.4	0.4	1.1
32.4	36.8	41.5	43.1
0.5	0.6	0.6	1.0
33.1	36.4	39.1	40.7
0.2	0.2	0.3	0.6
33.1	36.	39.4	41.5
0.2	0.2	0.3	0.6
31.2	34.8	37.5	39.3
0.4	0.2	0.4	1.0
30.5	33.6	37.0	39.7
0.5	0.6	1.2	1.2
33.3	36.3	39.2	41.0
0.1	0.1	0.1	0.5

cations, Food Directorate, Health Canada; and National Center for Health Statistics. 1994. *Consensus Workshop on Dietary Assessment: Nutrition Monitoring and Tracking the Year 2000 Objectives.* Maryland: U.S. Department of Health and Human Services. Variability for the percentiles has been estimated using SUDAAN v8.0, Taylor linearization method.

TABLE F-4 Mean and Percentages for Dietary Saturated Fat Intake (Percent of Energy), Canada (1990–1997)

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	1,362	12.4	8.6	9.5	10.7
Standard error		0.2	0.4	0.1	0.1
M, 31–50 y	2,371	12.2	8.0	9.0	10.5
Standard error		0.2	0.3	0.2	0.1
M, 51–70 y	2,416	12.0	6.7	7.9	9.6
Standard error		0.2	0.5	0.2	0.2
M, 71–74 y	478	11.6	6.3	7.3	9.3
Standard error		0.4	0.5	0.5	0.3
F, 19–30 y	1,456	12.1	7.8	8.8	10.2
Standard error		0.2	0.3	0.2	0.1
F, 31–50 y	2,687	12.0	7.5	8.3	9.9
Standard error		0.2	0.3	0.1	0.1
F, 51–70 y	2,481	10.9	6.5	7.4	8.9
Standard error		0.2	0.3	0.2	0.1
F, 71–74 y	474	10.7	6.2	6.7	8.5
Standard error		0.4	0.3	0.3	0.3
Total	13,725	12.0	7.4	8.4	10.0
Standard error		0.1	0.2	0.1	0.1

[a]M = male, F = female.

NOTE: Estimates were adjusted for intraindividual variability using the modified NAS method of Karpinski K, Nargundkar M. 1992. *Nova Scotia Nutrition Survey Methodology Report*. Technical document #451311-001, Bureau of Biostatistics and Computer Appli-

50th	75th	90th	95th
12.2	13.6	15.0	15.8
0.1	0.1	0.1	0.3
12.0	13.6	15.0	16.0
0.1	0.1	0.2	0.3
11.8	13.7	15.8	16.7
0.2	0.2	0.3	0.6
11.2	13.2	14.6	17.2
0.4	0.3	0.7	
11.8	13.4	15.0	16.1
0.1	0.1	0.2	0.3
11.5	13.2	14.8	16.1
0.1	0.1	0.2	0.4
10.8	12.5	14.1	15.3
0.1	0.2	0.2	0.6
10.2	12.4	14.5	15.5
0.3	0.5	0.5	0.6
11.7	13.4	15.0	16.1
0.0	0.0	0.1	0.3

cations, Food Directorate, Health Canada; and National Center for Health Statistics. 1994. *Consensus Workshop on Dietary Assessment: Nutrition Monitoring and Tracking the Year 2000 Objectives*. Maryland: U.S. Department of Health and Human Services. Variability for the percentiles has been estimated using SUDAAN v8.0, Taylor linearization method.

TABLE F-5 Mean and Percentiles for Dietary Protein Intake (Percent of Energy), Canada (1990–1997)

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	1,362	15.9	12.8	13.4	14.4
Standard error		0.2	0.4	0.1	0.1
M, 31–50 y	2,371	16.3	12.9	13.6	14.6
Standard error		0.2	0.4	0.1	0.1
M, 51–70 y	2,416	16.7	12.8	13.5	14.4
Standard error		0.2	0.4	0.1	0.1
M, 71–74 y	478	17.1	12.2	13.3	14.1
Standard error		0.5	0.8	0.3	0.2
F, 19–30 y	1,456	16.0	12.6	13.2	14.4
Standard error		0.2	0.4	0.1	0.1
F, 31–50 y	2,687	16.7	12.6	13.4	14.7
Standard error		0.2	0.3	0.1	0.1
F, 51–70 y	2,481	16.6	12.7	13.6	14.8
Standard error		0.2	0.4	0.2	0.1
F, 71–74 y	474	16.9	13.1	13.6	14.7
Standard error		0.4	0.4	0.2	0.2
Total	13,725	16.4	12.8	13.5	14.5
Standard error		0.1	0.2	0.1	0.0

[a] M = male, F = female.

NOTE: Estimates were adjusted for intraindividual variability using the modified NAS method of Karpinski K, Nargundkar M. 1992. *Nova Scotia Nutrition Survey Methodology Report*. Technical document #451311-001, Bureau of Biostatistics and Computer Appli-

50th	75th	90th	95th
15.3	16.3	17.3	18.4
0.1	0.1	0.2	0.5
15.8	17.0	18.2	19.2
0.1	0.1	0.1	0.5
16.0	17.5	18.9	20.1
0.1	0.2	0.2	0.7
15.8	17.6	20.6	22.2
0.3	0.3	0.7	1.1
15.5	16.4	17.5	18.2
0.1	0.1	0.1	0.5
15.8	17.2	18.6	19.7
0.1	0.1	0.2	0.4
15.9	17.4	18.8	19.6
0.1	0.2	0.2	0.4
16.0	17.4	19.1	20.3
0.2	0.2	0.4	0.5
15.7	17.0	18.4	19.4
0.0	0.0	0.1	0.3

cations, Food Directorate, Health Canada; and National Center for Health Statistics. 1994. *Consensus Workshop on Dietary Assessment: Nutrition Monitoring and Tracking the Year 2000 Objectives.* Maryland: U.S. Department of Health and Human Services. Variability for the percentiles has been estimated using SUDAAN v8.0, Taylor linearization method.

G

Special Analyses for Dietary Fats

TABLE G-1 Minimum Saturated Fat Intake Using Nonvegetarian Menus[a]

	Saturated Fat (%)	
Total Fat (%)	*n*-3 (α-linolenic acid) = 0.6% and *n*-6 (linoleic acid) = 5%	*n*-3 (α-linolenic acid) = 1.2% and *n*-6 (linoleic acid) = 10%
20	2.8	2.7
25	3.6	3.2
30	4.3	3.9
35	5.0	4.5

[a] Ten nonvegetarian menus were created using Nutritionist Five, Version 2.3 (First Databank, San Bruno, CA). In general, brand products were not used because data for linoleic and α-linolenic acids were not available for these products. Since canola and soybean oils are the primary sources of α-linolenic acid in the U.S. diet (Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, Hargrove RL, Zhao G, Etherton TD. 2000. Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr* 71:179S–188S), these oils were used when possible. When attempting to keep saturated fat as low as possible and linoleic and α-linolenic acid at defined levels, rich sources of monounsaturated fats were incorporated.

TABLE G-2 Minimum Saturated Fat Intake Using Vegetarian Menus[a]

	Saturated Fat (%)	
Total Fat (%)	*n*-3 (α-linolenic acid) = 0.6% and *n*-6 (linoleic acid) = 5%	*n*-3 (α-linolenic acid) = 1.2% and *n*-6 (linoleic acid) = 10%
20	2.8	2.7
20	2.7	2.6
25	3.6	3.2
30	4.3	3.9
35	4.9	4.5

[a] Ten nonvegetarian menus were created using Nutritionist Five, Version 2.3 (First Databank, San Bruno, CA). In general, brand products were not used because data for linoleic and α-linolenic acids were not available for these products. Since canola and soybean oils are the primary sources of α-linolenic acid in the U.S. diet (Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, Hargrove RL, Zhao G, Etherton TD. 2000. Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr* 71:179S–188S), these oils were used when possible. When attempting to keep saturated fat as low as possible and linoleic and α-linolenic acid at defined levels, rich sources of monounsaturated fats were incorporated.

H

Body Composition Data Based on the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

TABLE H-1 Body Measurement Summary Statistics, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

Measure	Sex[a]	n[b]	Mean[c]	Standard Error[c]
Percent body fat[e]	M	7,324	21.9	0.1
	F	7,724	32.4	0.2
Body mass index (kg/m^2)	M	7,918	26.5	0.1
	F	8,522	26.4	0.1
Weight (kg)	M	7,918	82.0	0.3
	F	8,524	69.2	0.3
Height (cm)	M	7,921	175.6	0.1
	F	8,540	161.8	0.1
Waist circumference (cm)	M	7,559	95.1	0.2
	F	8,105	88.6	0.3
Triceps skinfold (mm)[f]	M	7,532	13.1	0.1
	F	7,870	23.5	0.2

[a] M = male, F = female. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[b] n = Number of individuals with valid measurements; total sample size was 7,936 men and 8,553 women (nonpregnant/nonlactating).
[c] Means and standard errors were calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
[d] Standard deviation = standard error multiplied by the square root of the sample size (n).
[e] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Standard Deviation[d]	Minimum	Maximum
11.6	0.4	49.4
17.8	0.6	58.6
7.8	13.8	70.2
11.7	11.7	79.6
29.4	38.4	241.8
31.1	31.2	213.5
9.9	139.4	206.5
9.9	126.9	183.1
18.6	58.9	174.1
30.2	57.5	170.4
9.7	2.6	46.8
15.2	1.9	48.5

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$
Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

f Skinfold thickness exceeding 48.5 mm was too large for the caliper; measurements were not recorded for these individuals and they were excluded from analyses involving triceps skinfold.

DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-2 Body Measurement Summary Statistics, Men and Women 19 Years of Age and Older with Body Mass Index (BMI) ≥ 18.5 and < 25 kg/m^2, NHANES III (1988–1994)

Measure	Sex[a]	n[b]	Mean[c]	Standard Error[c]
Percent body fat[e]	M	2,828	17.6	0.1
	F	2,899	26.7	0.2
BMI (kg/m^2)	M	3,055	22.7	0.1
	F	3,170	22.0	< 0.05
Weight (kg)	M	3,055	69.7	0.3
	F	3,170	57.9	0.1
Height (cm)	M	3,055	175.3	0.2
	F	3,170	162.3	0.1
Waist circumference (cm)	M	2,907	84.7	0.2
	F	3,024	78.0	0.2
Triceps skinfold (mm)	M	2,937	9.7	0.1
	F	3,039	18.2	0.1

[a] M = male, F = female. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[b] n = Number of individuals with valid measurements; total sample size was 3,055 men and 3,170 women (nonpregnant/nonlactating).
[c] Means and standard errors were calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
[d] Standard deviation = standard error multiplied by the square root of the sample size (n).

Standard Deviation[d]	Minimum	Maximum
7.8	0.4	31.7
8.9	6.8	37.8
3.2	18.5	24.9
2.2	18.5	24.9
13.9	40.7	103.5
6.9	32.5	79.1
10.9	142.7	206.5
7.7	126.9	183.1
8.9	62.8	106.0
13.4	59.4	114.3
5.6	2.8	28.9
7.2	1.9	40.0

[e] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$
Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for four individuals; these individuals were excluded from analyses involving percent body fat.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-3 Regression Analysis of Body Measurements: Percent Body Fat[a] Versus Body Mass Index (BMI), Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,324)	Intercept	–4.3422	0.6765
	BMI (kg/m^2)	0.9921	0.0261
	R square value	0.5549	
F (7,724)	Intercept	1.4303	0.6787
	BMI (kg/m^2)	1.1735	0.0256
	R square value	0.7745	

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$

Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

Test for H_0: Parameter = 0	Probability > |T|
–6.4190	0.0000
38.0077	0.0000
2.1073	0.0399
45.8088	0.0000

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-4 Regression Analysis of Body Measurements: Percent Body Fat[a] Versus Body Mass Index (BMI) and Waist Circumference, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,142)	Intercept	–11.8819	0.5909
	BMI (kg/m^2)	0.3632	0.0442
	Waist circumference (cm)	0.2547	0.0134
	R square value	0.6082	
F (7,498)	Intercept	–3.5296	0.6029
	BMI (kg/m^2)	0.8294	0.0334
	Waist circumference (cm)	0.1588	0.0085
	R square value	0.7910	
		F Value	Numerator Degrees of Freedom
M	Overall fit	1,669.3326	2
F	Overall fit	1,812.6733	2

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$

Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

Test for H_0: Parameter = 0	Probability > |T|
–20.1097	0.0000
8.2191	0.0000
18.9496	0.0000
–5.8545	0.0000
24.8456	0.0000
18.6091	0.0000

Denominator Degrees of Freedom	Probability > F
51	0.0000
51	0.0000

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-5 Regression Analysis of Body Measurements: Percent Body Fat Versus Body Mass Index (BMI) and Triceps Skinfold,[a] Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,091)	Intercept	–2.5154	0.5854
	BMI (kg/m^2)	0.7997	0.0261
	Triceps skinfold (mm)	0.2499	0.0162
	R square value	0.5796	
F (7,266)	Intercept	1.1686	0.4238
	BMI (kg/m^2)	0.9386	0.0214
	Triceps skinfold (mm)	0.2765	0.0102
	R square value	0.8167	
		F Value	Numerator Degrees of Freedom
M	Overall fit	1,384.0891	2
F	Overall fit	4,851.3613	2

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$
Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat. Skinfold thickness exceeding 48.5

Test for H_0: Parameter = 0	Probability > |T|
–4.2966	0.0001
30.5997	0.0000
15.4193	0.0000
2.7573	0.0080
43.9202	0.0000
26.9924	0.0000

Denominator Degrees of Freedom	Probability > F
51	0.0000
51	0.0000

mm was too large for the caliper; measurements were not recorded for these individuals. These individuals were excluded from analyses involving triceps skinfold.

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.

[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.

DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-6 Regression Analysis of Body Measurements: Percent Body Fat[a] Versus Height, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,324)	Intercept	21.6690	2.6860
	Height (cm)	0.0016	0.0155
	R square value	0	
F (7,724)	Intercept	42.4383	2.5259
	Height (cm)	–0.0620	0.0156
	R square value	0.0026	

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$

Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

Test for H_0: Parameter = 0	Probability > |T|
8.0674	0.0000
0.1013	0.9197
16.8016	0.0000
–3.9684	0.0002

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-7 Regression Analysis of Body Measurements: Percent Body Fat[a] Versus Body Weight, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,324)	Intercept	1.4555	0.5302
	Body weight (kg)	0.2500	0.0065
	R square value	0.4363	
F (7,724)	Intercept	3.9622	0.5224
	Body weight (kg)	0.4114	0.0076
	R square value	0.6961	

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$
Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

Test for H_0: Parameter = 0	Probability > |T|
2.7450	0.0083
38.3096	0.0000
7.5851	0.0000
54.3469	0.0000

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-8 Regression Analysis of Body Measurements: Percent Body Fat Versus Triceps Skinfold,[a] Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,091)	Intercept	13.4488	0.2295
	Triceps skinfold (mm)	0.6394	0.0121
	R square value	0.4099	
F (7,266)	Intercept	13.6974	0.2295
	Triceps skinfold (mm)	0.7821	0.0076
	R square value	0.6522	

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

$$\text{Men:} \quad FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$$
$$\text{Women:} \quad FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat. Skinfold thickness exceeding 48.5

Test for H_0: Parameter = 0	Probability > |T|
58.5945	0.0000
53.0528	0.0000
59.6845	0.0000
102.6052	0.0000

mm was too large for the caliper; measurements were not recorded for these individuals. These individuals were excluded from analyses involving triceps skinfold.

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.

[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.

DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-9 Regression Analysis of Body Measurements: Percent Body Fat[a] Versus Waist Circumference, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,142)	Intercept	–13.3247	0.6059
	Waist circumference (cm)	0.3712	0.0062
	R square value	0.5949	
F (7,498)	Intercept	–8.6807	0.5524
	Waist circumference (cm)	0.4645	0.0060
	R square value	0.7133	

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$

Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

Test for H_0: Parameter = 0	Probability > |T|
–21.9934	0.0000
59.6373	0.0000
–15.7148	0.0000
77.4189	0.0000

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-10 Regression Analysis of Body Measurements: Percent Body Fat[a] Versus Waist Circumference Squared, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,142)	Intercept	5.1113	0.3783
	Waist circumference squared (cm^2)	0.0018	0.0000
	R square value	0.5739	
F (7,498)	Intercept	13.1167	0.3910
	Waist circumference squared (cm^2)	0.0024	0.0000
	R square value	0.6753	

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

Men: $FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$

Women: $FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

Test for H_0: Parameter = 0	Probability > |T|
13.5125	0.0000
46.6337	0.0000
33.5446	0.0000
52.9711	0.0000

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-11 Regression Analysis of Body Measurements: Percent Body Fat[a] Versus Body Mass Index (BMI) and Waist Circumference Squared, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,142)	Intercept	–0.0181	0.7131
	BMI (kg/m^2)	0.4438	0.0427
	Waist circumference squared (cm^2)	0.0011	0.0001
	R square value	0.5923	
F (7,498)	Intercept	2.7339	0.6573
	BMI (kg/m^2)	0.9833	0.0289
	Waist circumference squared (cm^2)	0.0005	0.0000
	R square value	0.7790	
		F Value	Numerator Degrees of Freedom
M	Overall fit	1,091.7233	2
F	Overall fit	1,069.7605	2

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

$$\text{Men:} \quad FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$$
$$\text{Women:} \quad FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

	Test for H_0: Parameter = 0	Probability > |T|
	–0.0254	0.9798
	10.3803	0.0000
	16.5537	0.0000
	4.1596	0.0001
	34.0405	0.0000
	10.3676	0.0000

	Denominator Degrees of Freedom	Probability > F
	51	0.0000
	51	0.0000

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-12 Regression Analysis of Body Measurements: Body Mass Index Versus Percent Body Fat,[a] Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,324)	Intercept	14.2220	0.3354
	Percent body fat	0.5594	0.0162
	R square value	0.5549	
F (7,724)	Intercept	5.0073	0.3761
	Percent body fat	0.6600	0.0120
	R square value	0.7745	

[a] Percent body fat = 100 × (W – FFM)/W; FFM for each survey respondent was derived using the following equations:

$$\text{Men:} \quad FFM = -10.68 + 0.65\ H^2/R + 0.26\ W + 0.02\ R$$
$$\text{Women:} \quad FFM = -9.53 + 0.69\ H^2/R + 0.17\ W + 0.02\ R$$

where FFM = fat free mass (kg), H = height (cm), R = resistance (ohms), W = weight (kg). The estimate of FFM exceeded W for eight individuals; these individuals were excluded from analyses involving percent body fat.

TABLE H-13 Regression Analysis of Body Measurements: Body Mass Index Versus Triceps Skinfold,[a] Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[c]	
Sex (n)[b]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,530)	Intercept	19.9043	0.1401
	Triceps skinfold (mm)	0.4924	0.0103
	R square value	0.4770	
F (7,858)	Intercept	13.3202	0.1626
	Triceps skinfold (mm)	0.5412	0.0082
	R square value	0.6269	

[a] Skinfold thickness exceeding 48.5 mm was too large for the caliper; measurements were not recorded for these individuals. These individuals were excluded from analyses involving triceps skinfold.
[b] M = male, F = female, n = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and

Test for H_0: Parameter = 0	Probability > |T|
42.4069	0.0000
34.6035	0.0000
13.3153	0.0000
55.2223	0.0000

[b] M = male, F = female, *n* = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

Test for H_0: Parameter = 0	Probability > |T|
142.1172	0.0000
47.9364	0.0000
81.9403	0.0000
65.6884	0.0000

lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.
[c] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

TABLE H-14 Regression Analysis of Body Measurements: Body Mass Index Versus Waist Circumference, Men and Women 19 Years of Age and Older, NHANES III (1988–1994)

		Results[b]	
Sex (n)[a]	Parameter	Parameter Estimate	Standard Error of Estimate
M (7,558)	Intercept	–4.2050	0.3413
	Waist circumference (cm)	0.3230	0.0037
	R square value	0.8142	
F (8,096)	Intercept	–6.2774	0.3461
	Waist circumference (cm)	0.3692	0.0042
	R square value	0.8014	

[a] M = male, F = female, n = number of individuals with valid measurements. Pregnant and/or lactating women and women who had "blank but applicable" pregnancy and lactating status or who responded "I don't know" to questions on pregnancy and lactating status were excluded from all analyses.

Test for H_0: Parameter = 0	Probability > |T|
–12.3199	0.0000
87.2406	0.0000
–18.1401	0.0000
88.0352	0.0000

[b] Regression calculated with National Center for Health Statistics (NCHS) sampling weights and WesVar Complex Samples Version 3.0.
DATA SOURCE: U.S. Department of Health and Human Services, NCHS.

I

Doubly Labeled Water Data Used to Predict Energy Expenditure

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TABLE I-1 Infants and Very Young Children (0 Through 2 Years of Age) Within the 3rd to 97th Percentile for Body Mass Index (BMI)

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
1	F	0.22	0.59	5.0	14.1	280
1	M	0.22	0.60	5.8	15.9	304
1	M	0.22	0.60	6.3	17.6	369
1	F	0.22	0.59	5.8	16.5	288
1	F	0.22	0.60	5.8	16.4	320
1	F	0.23	0.64	7.2	17.8	392
1	M	0.23	0.61	7.0	18.7	375
1	F	0.23	0.59	5.7	16.5	306
1	F	0.23	0.59	5.0	14.5	263
1	F	0.23	0.58	6.0	17.5	329
1	F	0.23	0.62	6.4	16.9	381
1	M	0.24	0.60	6.0	17.0	NR
1	F	0.24	0.62	6.1	15.6	363
1	F	0.24	0.62	6.9	18.0	405
1	F	0.24	0.60	5.3	14.8	317
1	M	0.24	0.58	5.5	16.3	286
1	F	0.24	0.62	6.0	15.7	371
1	F	0.24	0.58	5.5	16.7	359
1	F	0.24	0.62	6.5	16.8	330
1	F	0.24	0.63	6.2	16.0	319
1	M	0.24	0.62	6.5	16.8	356
1	M	0.24	0.59	5.5	15.8	346
1	F	0.25	0.60	6.0	16.6	326
1	M	0.25	0.65	5.2	14.2	332
1	M	0.25	0.61	6.4	17.2	389
1	M	0.25	0.61	7.2	19.2	NR
1	M	0.25	0.63	6.3	15.8	334
1	M	0.25	0.62	6.0	15.6	404
1	F	0.25	0.60	6.7	18.5	336
1	M	0.25	0.60	5.2	14.4	354
1	M	0.25	0.65	7.5	17.6	435
1	F	0.25	0.60	5.3	15.0	304
1	M	0.25	0.60	5.6	15.7	362
1	F	0.26	0.60	5.5	15.5	305
1	F	0.26	0.60	6.1	17.1	338
1	F	0.26	0.59	6.0	17.4	361
1	F	0.26	0.62	5.8	15.3	358
1	F	0.26	0.64	7.4	18.0	NR
1	F	0.26	0.62	6.6	17.6	346
1	M	0.26	0.62	6.3	16.2	321
1	F	0.26	0.60	6.1	16.6	349
1	M	0.26	0.62	6.9	17.9	366
1	F	0.26	0.60	6.4	18.0	NR
1	M	0.26	0.60	6.4	18.0	328

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
258	391	78.7	56.4	52.1
316	451	77.5	52.3	54.3
345	305	48.3	58.6	54.7
305	370	64.2	50.1	52.9
310	436	74.6	54.7	53.0
389	446	61.8	54.3	54.0
388	381	54.3	53.3	55.2
301	335	58.8	53.7	52.9
262	330	65.5	52.2	52.1
317	351	58.8	55.1	53.1
343	385	60.0	59.4	53.5
328	326	54.3	NA	54.5
323	389	64.1	59.8	53.2
369	563	82.0	59.0	53.8
277	400	75.6	60.0	52.4
299	326	58.9	51.8	54.0
320	565	93.8	61.6	53.2
291	340	61.6	64.9	52.7
349	622	95.6	50.6	53.6
332	322	51.7	51.2	53.3
357	396	61.0	54.8	54.8
298	394	71.5	62.9	54.0
320	321	53.3	54.1	53.2
277	434	84.1	64.3	53.6
353	406	63.0	60.3	54.8
401	516	71.2	NA	55.3
347	433	68.3	52.8	54.7
324	445	74.8	67.9	54.4
358	359	53.8	50.3	53.7
276	388	75.4	68.8	53.6
413	517	69.4	58.3	55.4
280	446	83.6	57.0	52.5
303	370	66.0	64.6	54.1
289	302	55.0	55.5	52.7
324	436	71.7	55.5	53.2
322	354	58.6	59.7	53.2
308	412	70.8	61.6	53.0
400	623	84.3	NA	54.1
356	355	53.4	52.2	53.6
344	346	55.0	51.1	54.7
322	390	64.3	57.7	53.2
382	658	95.0	52.8	55.1
340	407	64.0	NA	53.4
353	330	51.2	51.0	54.8

continued

TABLE I-1 Continued

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
1	F	0.27	0.60	6.0	16.6	390
1	F	0.27	0.62	5.7	14.8	328
1	F	0.27	0.62	6.6	17.2	331
1	F	0.27	0.60	5.5	15.1	356
1	M	0.27	0.61	5.7	15.3	NR
1	F	0.27	0.60	5.9	16.6	351
1	F	0.27	0.65	7.1	16.9	339
1	M	0.27	0.62	6.6	17.3	401
1	F	0.27	0.61	5.6	15.0	372
1	F	0.27	0.60	5.8	16.1	385
1	F	0.28	0.62	6.5	16.8	402
1	F	0.28	0.61	6.2	16.7	405
1	M	0.28	0.59	5.4	15.9	367
1	F	0.28	0.63	6.6	17.0	379
1	M	0.28	0.63	7.1	18.0	426
1	M	0.28	0.65	7.0	16.8	401
2	F	0.44	0.67	6.9	15.6	390
2	F	0.45	0.68	8.0	17.6	446
2	M	0.46	0.68	7.2	15.6	420
2	F	0.47	0.63	6.4	15.9	380
2	F	0.47	0.68	7.5	16.3	372
2	F	0.47	0.69	8.1	17.0	463
2	F	0.47	0.64	7.3	17.9	462
2	F	0.48	0.66	7.0	16.4	424
2	F	0.48	0.66	7.6	17.6	460
2	F	0.48	0.67	8.1	18.2	407
2	M	0.48	0.67	8.9	19.8	456
2	M	0.48	0.64	6.8	16.7	359
2	F	0.48	0.65	7.6	17.8	420
2	F	0.48	0.64	7.2	17.4	394
2	M	0.48	0.66	7.4	16.8	459
2	M	0.48	0.70	8.1	16.4	548
2	M	0.48	0.72	8.9	17.2	502
2	F	0.48	0.66	7.2	16.3	473
2	F	0.49	0.66	7.7	17.8	386
2	M	0.49	0.68	7.2	15.4	411
2	F	0.49	0.69	8.4	17.4	503
2	F	0.49	0.67	8.1	17.9	426
2	M	0.49	0.66	7.9	18.3	448
2	F	0.49	0.65	7.1	16.5	446
2	M	0.49	0.69	8.1	17.3	502
2	F	0.50	0.67	8.4	18.8	438
2	F	0.50	0.64	6.9	16.8	416
2	M	0.50	0.67	7.5	16.5	465
2	F	0.50	0.66	7.8	18.2	411

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
316	524	87.9	65.4	53.1
300	415	73.2	58.0	52.8
353	389	59.0	50.3	53.6
288	506	92.6	65.2	52.6
310	510	89.1	NA	54.2
314	392	66.3	59.3	53.1
384	542	76.2	47.6	54.0
363	579	87.7	60.8	54.9
298	422	74.8	66.1	52.8
305	391	67.8	66.7	52.9
348	444	68.4	62.0	53.5
332	562	90.4	65.2	53.3
293	410	75.4	67.5	53.9
356	387	58.4	57.1	53.6
395	640	89.6	59.7	55.3
386	391	55.9	57.3	55.2
370	498	72.4	56.6	53.8
437	654	81.5	55.5	54.4
396	433	60.3	58.5	55.3
342	476	74.5	59.5	53.5
405	488	65.4	49.8	54.2
443	501	61.6	56.9	54.5
394	479	65.7	63.4	54.1
379	529	75.2	60.2	53.9
410	611	80.8	60.9	54.2
441	760	93.9	50.3	54.5
497	429	48.4	51.5	56.1
376	452	66.1	52.6	55.1
410	575	76.0	55.4	54.2
388	489	68.0	54.9	54.0
407	599	81.4	62.3	55.4
452	718	88.6	67.6	55.8
500	661	74.2	56.3	56.1
389	716	99.5	65.7	54.0
418	414	53.7	50.1	54.3
396	550	76.7	57.3	55.3
456	607	72.7	60.3	54.6
441	482	59.5	52.6	54.5
437	656	83.4	57.0	55.6
380	494	70.0	63.2	53.9
452	778	96.0	62.0	55.8
457	576	68.8	52.3	54.6
370	419	60.9	60.4	53.8
416	478	63.9	62.0	55.5
426	740	94.4	52.4	54.4

continued

TABLE I-1 Continued

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
2	F	0.50	0.67	7.1	16.0	500
2	M	0.50	0.69	9.3	19.7	553
2	F	0.50	0.66	7.4	17.0	501
2	M	0.50	0.68	8.3	18.2	474
2	F	0.50	0.64	7.2	17.5	423
2	F	0.50	0.68	7.0	15.3	417
2	F	0.51	0.65	8.3	19.6	452
2	F	0.51	0.71	9.1	18.1	519
2	M	0.51	0.68	7.9	17.2	487
2	F	0.51	0.68	8.0	17.4	444
2	M	0.51	0.67	9.1	20.2	494
2	F	0.51	0.68	7.5	16.1	405
2	F	0.51	0.67	6.9	15.5	426
2	M	0.52	0.64	6.5	15.6	413
2	M	0.52	0.69	7.8	16.4	445
2	F	0.52	0.67	7.8	17.3	477
2	M	0.52	0.67	8.4	18.6	538
2	M	0.52	0.69	8.0	16.8	532
2	F	0.53	0.67	7.4	16.6	425
2	M	0.53	0.66	7.3	16.8	431
2	F	0.53	0.67	6.6	14.9	394
2	M	0.53	0.69	8.4	17.5	529
2	F	0.53	0.68	7.6	16.4	487
2	F	0.54	0.69	8.4	17.9	485
2	F	0.54	0.70	8.8	17.8	522
2	M	0.55	0.69	8.4	17.8	445
2	F	0.56	0.69	8.7	18.2	475
3	M	0.73	0.71	8.2	16.3	555
3	F	0.73	0.70	8.2	16.7	496
3	M	0.73	0.69	7.3	15.6	498
3	F	0.73	0.71	8.2	16.2	514
3	M	0.73	0.73	10.6	19.9	621
3	F	0.74	0.73	9.5	17.8	497
3	F	0.74	0.69	7.2	15.2	473
3	F	0.74	0.74	9.3	16.9	592
3	F	0.74	0.72	8.3	16.0	NR
3	F	0.74	0.71	8.0	15.7	511
3	M	0.74	0.75	10.0	17.7	566
3	F	0.74	0.73	8.9	17.0	478
3	F	0.74	0.70	9.2	18.5	554
3	F	0.74	0.74	10.3	19.1	569
3	F	0.74	0.68	7.9	17.0	485
3	M	0.74	0.74	9.2	17.0	561
3	M	0.74	0.72	8.0	15.4	NR
3	F	0.74	0.69	8.2	17.5	434

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
384	635	89.2	70.2	54.0
524	592	63.5	59.4	56.3
398	689	93.5	68.1	54.1
465	566	68.0	56.9	55.9
391	578	80.0	58.5	54.0
380	448	63.6	59.2	53.9
454	577	69.4	54.4	54.6
499	657	72.3	57.2	54.9
440	464	58.7	61.6	55.7
435	603	75.4	55.5	54.4
511	555	61.0	54.3	56.2
404	448	60.0	54.4	54.2
373	486	70.2	61.4	53.8
354	598	92.5	63.9	54.8
437	541	68.9	56.7	55.6
424	750	96.0	61.1	54.3
472	657	77.9	63.8	55.9
448	736	91.6	66.2	55.7
399	436	59.0	57.6	54.1
404	598	82.0	59.1	55.4
355	443	66.8	59.4	53.6
470	734	87.3	62.9	55.9
412	748	98.4	64.0	54.2
458	625	74.5	57.8	54.6
484	662	74.9	59.1	54.8
467	739	88.4	53.3	55.9
478	725	83.1	54.4	54.8
459	732	89.0	67.4	55.8
446	554	67.7	60.7	54.5
406	654	89.1	67.9	55.4
446	686	83.8	62.8	54.5
601	803	75.7	58.5	56.6
524	523	55.0	52.2	55.0
389	593	82.3	65.7	54.0
513	699	74.9	63.4	55.0
454	764	91.8	NA	54.6
434	543	68.1	64.0	54.4
564	964	96.5	56.6	56.5
490	727	81.4	53.6	54.8
504	804	87.6	60.3	54.9
572	786	76.0	55.1	55.3
429	560	71.0	61.4	54.4
517	850	92.4	61.0	56.2
444	618	77.5	NA	55.7
448	712	86.6	52.8	54.5

continued

TABLE I-1 Continued

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
3	M	0.74	0.70	10.0	20.2	503
3	F	0.74	0.70	8.0	16.4	526
3	F	0.74	0.73	9.3	17.6	510
3	F	0.74	0.71	9.4	18.7	609
3	F	0.75	0.69	8.9	18.5	563
3	M	0.75	0.68	7.4	16.3	470
3	M	0.75	0.70	8.1	16.6	490
3	M	0.75	0.73	8.8	16.7	594
3	M	0.75	0.73	9.0	17.2	596
3	F	0.75	0.70	7.5	15.3	428
3	F	0.75	0.70	8.6	17.5	500
2	M	0.75	0.71	8.6	17.0	497
3	F	0.75	0.75	9.8	17.4	551
3	F	0.76	0.71	8.6	17.0	526
3	F	0.76	0.68	8.2	17.7	435
3	F	0.76	0.70	8.2	16.9	537
3	M	0.76	0.73	9.6	17.9	433
3	M	0.76	0.71	8.5	16.8	547
3	F	0.76	0.69	8.0	16.7	NR
3	F	0.76	0.72	9.1	17.5	NR
3	M	0.76	0.73	9.1	17.4	594
3	M	0.76	0.71	9.9	19.6	NR
3	F	0.76	0.70	9.4	19.1	557
3	M	0.76	0.75	8.5	15.4	547
3	F	0.77	0.71	7.4	15.0	459
3	F	0.77	0.70	8.1	16.4	481
3	F	0.77	0.70	8.8	17.9	447
3	F	0.77	0.73	8.6	16.4	610
3	F	0.77	0.69	8.3	17.4	492
3	F	0.77	0.73	8.8	16.3	508
3	M	0.77	0.72	9.0	17.6	566
3	M	0.78	0.71	8.0	15.7	541
3	F	0.78	0.70	8.4	17.0	479
3	M	0.79	0.73	9.5	17.7	592
3	F	0.79	0.71	9.0	17.8	507
3	M	0.82	0.74	9.2	17.0	628
3	F	0.92	0.75	9.2	16.5	NR
4	M	0.97	0.72	8.8	17.1	NR
4	M	0.98	0.75	9.0	15.8	609
4	F	0.98	0.75	9.8	17.4	624
4	F	0.98	0.72	10.3	20.2	NR
4	M	0.98	0.75	8.8	15.9	564
4	F	0.99	0.80	10.6	16.7	641
4	M	0.99	0.77	9.9	16.7	594
4	M	0.99	0.77	11.7	20.0	615
4	F	0.99	0.77	10.0	17.2	617

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
557	879	89.1	51.0	56.4
437	585	72.9	65.6	54.4
512	788	84.8	54.8	55.0
520	751	79.5	64.5	55.0
486	725	81.8	63.5	54.8
412	758	102.0	63.2	55.4
454	747	91.8	60.2	55.8
496	711	80.4	67.2	56.1
508	492	54.4	65.9	56.2
407	609	81.1	57.1	54.2
469	649	75.7	58.4	54.7
478	620	72.6	58.1	56.0
540	698	71.3	56.3	55.1
472	620	71.9	61.1	54.7
449	576	69.9	52.7	54.6
450	539	65.4	65.1	54.6
538	610	63.8	45.3	56.3
475	670	78.9	64.4	55.9
435	786	98.3	NA	54.4
500	662	72.7	NA	54.9
513	764	83.6	65.0	56.2
559	840	84.8	NA	56.4
516	923	98.4	59.3	55.0
478	727	85.1	64.1	56.0
402	558	75.1	61.7	54.1
440	574	71.2	59.6	54.5
480	605	69.0	51.0	54.8
473	780	90.2	70.6	54.7
455	627	75.2	59.0	54.6
480	509	58.1	58.0	54.8
506	802	88.9	62.7	56.2
447	654	81.5	67.4	55.7
458	744	88.7	57.0	54.6
533	754	79.6	62.5	56.3
491	656	73.3	56.7	54.8
519	674	73.1	68.1	56.2
508	582	63.0	NA	55.0
491	751	85.6	NA	56.0
503	812	90.6	67.9	56.1
550	754	77.1	63.8	55.1
572	778	75.2	NA	55.3
494	539	61.1	64.0	56.1
585	852	80.6	60.6	55.4
556	705	71.6	60.2	56.4
666	911	77.8	52.5	56.9
555	839	83.5	61.3	55.2

continued

TABLE I-1 Continued

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
4	F	0.99	0.78	9.5	15.6	556
4	F	0.99	0.79	10.3	16.6	649
4	F	0.99	0.74	9.9	18.0	639
4	F	0.99	0.71	8.9	17.4	638
4	M	0.99	0.74	10.8	19.8	649
4	F	0.99	0.75	9.1	16.2	588
4	M	0.99	0.77	10.2	17.2	592
4	F	0.99	0.76	10.5	18.4	510
4	F	1.00	0.74	9.9	18.3	579
4	M	1.00	0.74	8.8	16.1	605
4	M	1.00	0.81	10.6	16.3	571
4	F	1.00	0.74	8.9	16.1	NR
4	M	1.00	0.75	9.4	16.8	593
4	F	1.00	0.71	8.8	17.4	456
4	F	1.00	0.75	8.9	15.8	NR
4	M	1.00	0.76	9.6	16.5	641
4	F	1.01	0.75	8.2	14.5	553
4	M	1.01	0.75	10.2	18.0	581
4	F	1.01	0.74	8.9	16.1	611
4	M	1.01	0.78	10.0	16.3	530
4	F	1.01	0.77	9.8	16.6	604
4	F	1.01	0.77	10.6	18.1	589
4	M	1.01	0.75	9.8	17.3	660
4	F	1.01	0.75	8.9	15.9	NR
4	M	1.01	0.75	8.8	15.8	NR
4	F	1.01	0.72	8.9	17.1	530
4	M	1.02	0.76	10.3	17.8	646
4	F	1.02	0.73	9.1	17.3	641
4	M	1.02	0.77	9.9	16.8	640
4	M	1.02	0.75	11.1	19.4	750
4	F	1.02	0.76	10.0	17.4	609
4	F	1.02	0.76	9.5	16.4	593
4	F	1.03	0.74	9.2	16.9	612
4	F	1.03	0.76	10.9	18.8	580
4	F	1.03	0.79	9.8	15.8	689
4	F	1.04	0.78	9.6	15.9	541
4	M	1.04	0.73	8.4	15.9	612
4	F	1.04	0.79	10.8	17.2	NR
4	F	1.04	0.78	9.7	16.1	599
3	M	1.06	0.75	9.9	17.6	660
4	F	1.07	0.75	8.6	15.4	543
4	F	1.16	0.78	10.1	16.6	573
5	M	1.44	0.84	11.0	15.7	731
5	F	1.45	0.85	12.4	17.2	859
5	M	1.45	0.84	11.2	15.9	568

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
521	647	68.3	58.7	55.0
571	747	72.3	62.8	55.3
546	866	87.4	64.5	55.2
485	738	83.4	72.1	54.8
615	1,053	97.0	59.8	56.7
501	711	78.0	64.5	54.9
578	852	83.4	58.0	56.5
582	961	91.4	48.5	55.4
544	885	89.7	58.6	55.2
495	674	76.4	68.6	56.1
601	1,068	100.6	53.8	56.7
487	599	67.5	NA	54.8
528	586	62.6	63.3	56.3
479	555	63.4	52.1	54.8
486	676	76.2	NA	54.8
543	804	83.6	66.6	56.4
447	589	71.9	67.6	54.5
577	802	78.7	56.9	56.5
487	844	95.0	68.8	54.8
564	624	62.4	53.1	56.5
540	698	71.2	61.6	55.2
587	544	51.3	55.6	55.4
554	828	84.2	67.2	56.4
489	878	98.4	NA	54.8
493	751	85.5	NA	56.1
486	789	89.0	59.7	54.8
584	747	72.4	62.6	56.6
500	836	91.9	70.4	54.9
558	681	69.0	64.8	56.4
628	935	84.6	67.8	56.8
553	593	59.1	60.8	55.2
522	612	64.5	62.6	55.0
509	909	98.2	66.1	55.0
602	922	84.9	53.4	55.5
543	894	90.8	69.9	55.2
528	597	62.3	56.4	55.1
470	783	93.0	72.8	55.9
600	730	67.4	NA	55.4
534	891	92.0	61.8	55.1
559	789	79.7	66.6	56.4
469	750	87.5	63.3	54.7
558	875	86.6	56.7	55.2
627	926	83.8	66.1	56.8
692	899	72.5	69.3	55.8
638	1,054	93.8	50.6	56.8

continued

TABLE I-1 Continued

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
5	M	1.47	0.81	10.1	15.6	694
5	F	1.47	0.83	11.0	16.2	690
5	M	1.47	0.82	11.5	17.0	722
5	F	1.47	0.82	11.7	17.5	717
5	M	1.48	0.80	9.8	15.3	697
5	F	1.48	0.78	9.3	15.3	582
5	M	1.49	0.87	12.5	16.7	733
5	M	1.49	0.80	11.6	18.3	806
5	M	1.49	0.82	11.2	16.6	650
5	M	1.49	0.81	12.3	19.0	718
4	F	1.49	0.80	9.4	14.6	588
5	M	1.49	0.83	11.2	16.2	705
5	F	1.49	0.81	9.9	15.0	560
5	F	1.49	0.77	9.9	16.7	550
5	M	1.50	0.85	11.8	16.4	662
5	M	1.50	0.82	10.2	15.3	720
5	F	1.50	0.78	9.5	15.6	592
5	M	1.50	0.83	11.8	17.1	NR
5	F	1.50	0.83	11.1	16.1	696
5	F	1.50	0.85	12.7	17.7	NR
5	F	1.50	0.85	11.2	15.6	NR
5	F	1.50	0.78	10.1	16.5	NR
5	F	1.50	0.81	8.9	13.5	531
5	F	1.50	0.80	9.8	15.4	585
5	F	1.50	0.85	11.9	16.6	708
5	F	1.50	0.85	11.6	16.0	695
5	F	1.51	0.83	12.0	17.4	677
5	F	1.51	0.81	11.0	16.6	588
5	M	1.51	0.83	10.4	15.1	588
5	F	1.51	0.80	10.0	15.8	648
5	F	1.51	0.80	10.0	15.5	554
5	M	1.51	0.79	9.3	14.9	643
5	F	1.51	0.83	11.0	16.0	634
5	F	1.51	0.83	10.8	15.8	679
5	F	1.51	0.82	12.9	19.2	636
5	F	1.51	0.79	11.3	18.2	612
5	F	1.52	0.80	11.5	17.8	NR
5	M	1.52	0.81	10.4	15.8	654
5	F	1.52	0.81	9.8	15.0	620
5	F	1.53	0.79	9.7	15.5	NR
5	F	1.54	0.82	10.2	15.2	694
5	F	1.54	0.84	11.1	15.8	618
5	F	1.54	0.80	10.0	15.6	669
5	M	1.54	0.88	11.6	14.9	743
5	F	1.54	0.86	11.9	16.2	628

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
570	935	92.8	68.8	56.5
611	858	77.9	62.7	55.5
654	867	75.4	62.7	56.9
653	790	67.4	61.2	55.7
555	779	79.1	70.8	56.4
512	626	67.2	62.5	55.0
713	978	78.3	58.7	57.1
663	852	73.2	69.2	56.9
636	1,097	98.0	58.0	56.8
704	991	80.3	58.2	57.0
519	854	90.6	62.3	55.0
639	1,031	91.6	62.6	56.8
544	565	57.3	56.8	55.2
544	595	60.3	55.8	55.2
672	934	79.2	56.1	56.9
580	930	90.7	70.2	56.6
521	605	64.0	62.6	55.0
672	1,024	86.8	NA	56.9
617	899	80.8	62.6	55.5
710	933	73.5	NA	55.9
619	743	66.6	NA	55.5
558	890	88.1	NA	55.2
486	654	73.7	59.8	54.8
541	842	85.8	59.7	55.2
661	683	57.5	59.7	55.7
645	729	62.9	60.0	55.6
666	1,162	97.2	56.7	55.7
612	1,076	97.6	53.4	55.5
588	731	70.4	56.6	56.6
554	619	61.7	64.5	55.2
554	969	96.6	55.2	55.2
524	831	89.1	68.9	56.3
608	808	73.7	57.8	55.5
598	739	68.6	63.0	55.4
723	1,194	92.4	49.2	55.9
630	860	75.8	54.0	55.6
637	1,108	96.7	NA	55.6
586	822	79.5	63.2	56.6
540	598	61.1	63.4	55.1
536	866	89.0	NA	55.1
565	971	95.0	67.9	55.3
618	858	77.1	55.5	55.5
550	907	91.1	67.2	55.2
660	759	65.4	64.0	56.9
661	1,109	93.5	52.9	55.7

continued

TABLE I-1 Continued

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
5	M	1.54	0.81	10.7	16.2	751
5	F	1.56	0.84	11.5	16.3	638
5	F	1.56	0.84	12.6	17.9	692
5	F	1.59	0.85	12.3	17.1	592
5	F	1.59	0.84	11.5	16.3	NR
5	F	1.61	0.82	10.2	15.1	681
5	M	1.62	0.82	10.5	15.5	700
6	F	1.93	0.92	14.1	16.6	829
6	F	1.97	0.86	11.4	15.4	700
6	F	1.98	0.89	11.7	14.9	747
6	F	1.98	0.86	12.6	17.2	NR
6	F	1.98	0.88	12.2	15.6	766
6	M	1.98	0.90	11.9	14.8	753
6	M	1.98	0.87	11.6	15.3	674
6	F	1.99	0.83	10.8	15.7	690
6	F	1.99	0.90	13.1	16.0	745
6	M	1.99	0.88	13.0	16.8	NR
6	F	1.99	0.88	11.3	14.8	681
6	F	1.99	0.92	13.2	15.8	844
6	F	2.00	0.83	9.9	14.5	539
6	F	2.00	0.86	12.7	17.0	788
6	M	2.00	0.90	12.6	15.6	740
6	M	2.00	0.84	10.5	14.9	621
6	M	2.00	0.86	12.1	16.2	691
6	F	2.00	0.88	11.6	15.0	627
6	M	2.00	0.89	11.8	15.0	NR
6	M	2.00	0.88	12.8	16.3	814
6	M	2.00	0.85	11.3	15.7	NR
6	M	2.00	0.86	10.8	14.7	585
6	F	2.01	0.87	12.2	16.0	684
6	M	2.01	0.90	12.9	16.1	NR
6	F	2.01	0.87	11.2	14.6	684
6	F	2.01	0.89	12.0	15.1	566
6	M	2.01	0.87	11.2	14.8	702
6	M	2.01	0.88	12.5	16.1	591
6	F	2.01	0.90	13.0	16.2	NR
6	F	2.01	0.92	12.6	14.9	667
6	F	2.01	0.85	11.4	16.0	688
6	F	2.01	0.86	12.5	17.0	600
6	F	2.01	0.92	12.9	15.2	628
6	F	2.01	0.85	12.6	17.6	NR
6	F	2.01	0.88	12.4	16.0	NR
6	F	2.02	0.93	14.2	16.5	679
6	F	2.02	0.87	11.8	15.5	798
6	F	2.03	0.89	13.0	16.3	806

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
609	942	87.7	69.9	56.7
641	730	63.3	55.4	55.6
701	858	68.4	55.2	55.8
684	968	79.0	48.3	55.8
641	719	62.4	NA	55.6
565	867	84.7	66.5	55.3
592	942	90.0	66.9	56.6
791	1,189	84.4	58.8	56.1
634	1,003	88.0	61.4	55.6
652	813	69.4	63.8	55.7
706	1,022	80.8	NA	55.9
677	854	70.3	63.0	55.8
677	1,188	100.0	63.4	57.0
659	904	78.1	58.2	56.9
602	1,075	99.1	63.6	55.4
730	782	59.9	57.1	55.9
741	1,250	96.4	NA	57.2
628	871	77.1	60.2	55.6
740	1,085	82.1	63.8	56.0
547	840	84.8	54.4	55.2
708	855	67.5	62.2	55.9
721	922	73.1	58.7	57.1
594	811	77.2	59.2	56.6
690	1,059	87.5	57.1	57.0
648	1,036	89.0	53.9	55.6
673	920	77.9	NA	56.9
729	1,078	84.5	63.8	57.1
642	757	67.0	NA	56.8
612	935	86.6	54.2	56.7
680	921	75.5	56.1	55.8
737	881	68.4	NA	57.2
621	786	70.4	61.1	55.5
670	1,119	93.1	47.1	55.7
639	977	86.9	62.4	56.8
712	856	68.6	47.4	57.1
729	1,127	86.5	NA	55.9
702	1,201	95.5	53.1	55.8
633	723	63.5	60.4	55.6
699	1,193	95.3	47.9	55.8
720	844	65.6	48.8	55.9
702	755	60.1	NA	55.8
692	1,023	82.5	NA	55.8
797	1,099	77.4	47.8	56.1
655	1,172	99.7	67.8	55.7
727	1,029	79.2	62.0	55.9

continued

TABLE I-1 Continued

RR	Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
6	F	2.03	0.82	11.2	16.5	635
6	M	2.04	0.88	11.4	14.8	798
6	F	2.04	0.85	11.5	15.8	725
6	F	2.05	0.84	10.7	15.2	646
6	F	2.11	0.90	12.5	15.5	572

NOTE: RR = number of repeated doubly labeled water measurements on the same subject, BEEo = basal energy expenditure (BEE) as observed in the study, BEEp = BEE as predicted using Schofield equations (Schofield WN. 1985. Predicting basal metabolic

BEEp (kcal/d)	TEE (kcal/d)	TEE/kg	BMRo/kg	BMRp/kg
621	921	82.4	56.8	55.5
648	908	79.7	70.0	56.8
638	845	73.7	63.2	55.6
592	978	91.6	60.5	55.4
696	837	67.2	45.8	55.8

rate, new standards and review of previous work. *Human Nutr Clin Nutr* 39C:5–41), TEE= total energy expenditure, F = female, M = male, NR = not reported, NA = not applicable.

TABLE I-2 Normal Weight Children, 3 Through 18 Years of Age with Body Mass Index (BMI) ≥ 85th Percentile

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
M	3.0	1.13	20.3	15.9	1,080	1,132
M	4.0	1.07	18.4	16.1	960	1,010
M	4.0	1.13	20.0	15.7	970	1,083
M	4.0	1.11	19.5	15.8	965	1,060
M	4.0	1.07	18.6	16.3	NR	1,008
M	4.2	1.03	16.9	15.9	NR	944
M	4.2	1.11	19.1	15.4	NR	1,044
M	4.2	1.02	17.1	16.5	NR	939
M	4.3	1.06	17.6	15.6	NR	974
M	4.4	1.06	16.6	14.8	NR	948
M	4.5	1.07	19.1	16.6	NR	1,001
M	4.6	1.04	16.0	14.7	NR	920
M	4.7	1.04	16.2	15.0	NR	916
M	4.8	1.02	16.3	15.6	NR	898
M	5.0	1.12	17.6	14.0	840	987
M	5.0	1.13	18.9	14.8	940	1,019
M	5.0	1.05	16.1	14.6	810	908
M	5.0	1.12	19.8	15.8	845	1,029
M	5.0	1.21	20.3	13.9	1,030	1,103
M	5.0	1.09	19.1	16.1	980	994
M	5.0	1.07	16.7	14.6	850	934
M	5.0	1.17	22.4	16.4	1,135	1,115
M	5.0	1.03	15.4	14.5	810	880
M	5.0	1.14	21.1	16.2	1,050	1,068
M	5.0	1.07	15.9	13.9	790	919
M	5.0	1.18	21.6	15.5	1,030	1,106
M	5.0	1.12	19.5	15.6	935	1,023
M	5.0	1.16	21.6	16.0	1,150	1,092
M	5.0	1.19	21.8	15.4	1,155	1,117
M	5.0	1.10	17.6	14.6	925	973
M	5.0	1.11	18.0	14.6	940	987
M	5.0	1.16	19.8	14.7	965	1,058
M	5.0	1.10	17.8	14.7	1,010	976
M	5.0	1.20	21.8	15.1	975	1,124
M	5.0	1.10	19.5	16.1	1,025	1,009
M	5.0	1.16	20.9	15.5	1,045	1,079
M	5.0	1.11	17.2	14.0	960	972
M	5.0	1.09	18.5	15.6	1,010	983
M	5.0	1.08	16.8	14.4	885	943
M	5.0	1.06	17.6	15.7	880	944
M	5.0	1.19	23.1	16.3	1,055	1,142
M	5.0	1.14	18.2	14.0	960	1,013
M	5.0	1.10	19.2	15.9	970	1,003
M	5.0	1.14	19.4	14.9	1,035	1,036
M	5.0	1.19	20.4	14.4	975	1,090

TEE	PALo	PALp	PALCAT
1,684	1.56	1.49	LA
1,334	1.39	1.32	S
1,483	1.53	1.37	LA
1,506	1.56	1.42	LA
1,565	NR	1.55	LA
1,150	NR	1.22	S
1,523	NR	1.46	LA
1,341	NR	1.43	LA
1,341	NR	1.38	S
1,154	NR	1.22	S
1,370	NR	1.37	S
1,107	NR	1.20	S
1,212	NR	1.32	S
1,525	NR	1.70	A
1,052	1.25	1.07	S
1,098	1.17	1.08	S
1,013	1.25	1.12	S
1,164	1.38	1.13	S
1,258	1.22	1.14	S
1,142	1.17	1.15	S
1,084	1.28	1.16	S
1,304	1.15	1.17	S
1,041	1.29	1.18	S
1,265	1.20	1.18	S
1,090	1.38	1.19	S
1,328	1.29	1.20	S
1,230	1.32	1.20	S
1,330	1.16	1.22	S
1,370	1.19	1.23	S
1,196	1.29	1.23	S
1,236	1.31	1.25	S
1,329	1.38	1.26	S
1,231	1.22	1.26	S
1,421	1.46	1.26	LA
1,277	1.25	1.27	S
1,368	1.31	1.27	S
1,238	1.29	1.27	S
1,257	1.24	1.28	S
1,210	1.37	1.28	S
1,223	1.39	1.30	S
1,496	1.42	1.31	LA
1,332	1.39	1.32	S
1,324	1.37	1.32	S
1,371	1.32	1.32	S
1,454	1.49	1.33	LA

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
M	5.0	1.08	17.3	14.8	975	953
M	5.0	1.07	18.6	16.2	1,035	970
M	5.0	1.14	20.0	15.4	1,055	1,047
M	5.0	1.20	21.8	15.1	1,055	1,124
M	5.0	1.10	19.0	15.7	1,020	1,000
M	5.0	1.21	22.3	15.2	1,120	1,141
M	5.0	1.13	18.9	14.8	1,120	1,019
M	5.0	1.09	17.3	14.6	846	960
M	5.0	1.12	19.3	15.4	1,055	1,020
M	5.0	1.13	19.0	14.9	1,055	1,021
M	5.0	1.19	21.4	15.1	1,295	1,110
M	5.0	1.19	22.4	15.8	1,085	1,129
M	5.0	1.09	19.0	16.0	995	992
M	5.0	1.13	18.5	14.5	1,010	1,011
M	5.0	1.13	19.6	15.4	1,050	1,032
M	5.0	1.10	19.4	16.0	1,005	1,007
M	5.0	1.10	18.7	15.5	955	994
M	5.0	1.14	21.0	16.2	1,120	1,066
M	5.0	1.02	16.1	15.5	NR	887
M	5.0	1.12	18.3	14.6	1,010	1,000
M	5.0	1.20	23.0	16.0	1,080	1,148
M	5.0	1.11	18.8	15.3	955	1,003
M	5.0	1.15	20.6	15.6	1,068	1,066
M	5.0	1.12	17.5	14.0	1,080	985
M	5.0	1.18	21.3	15.3	980	1,101
M	5.0	1.10	18.5	15.0	989	997
M	5.0	1.06	18.0	16.0	1,005	952
M	5.0	1.11	17.1	13.9	1,070	970
M	5.0	1.09	18.5	15.6	905	983
M	5.0	1.12	19.6	15.6	1,005	1,025
M	5.0	1.13	20.0	15.7	1,140	1,040
M	5.0	1.10	17.4	14.4	NR	967
M	5.0	1.07	16.2	14.1	NR	923
M	5.1	1.05	16.5	15.0	NR	909
M	5.1	1.09	19.1	16.1	NR	989
M	5.2	1.17	19.0	13.9	NR	1,042
M	5.3	1.09	17.8	15.0	NR	956
M	5.5	1.12	18.4	14.8	NR	978
M	5.5	1.11	19.8	16.0	NR	1,002
M	5.5	1.13	19.0	14.8	NR	1,000
M	5.6	1.20	21.8	15.1	NR	1,100
M	5.6	1.17	22.6	16.6	NR	1,088
M	5.6	1.11	19.3	15.7	NR	985
M	5.8	1.13	20.0	15.6	NR	1,004
M	6.0	1.21	24.2	16.5	1,145	1,134

TEE	PALo	PALp	PALCAT
1,282	1.32	1.35	S
1,310	1.27	1.35	S
1,419	1.34	1.36	S
1,525	1.45	1.36	LA
1,363	1.34	1.36	S
1,559	1.39	1.37	S
1,399	1.25	1.37	S
1,318	1.56	1.37	LA
1,401	1.33	1.37	S
1,406	1.33	1.38	S
1,533	1.18	1.38	S
1,580	1.46	1.40	LA
1,389	1.40	1.40	S
1,419	1.40	1.40	LA
1,451	1.38	1.41	S
1,418	1.41	1.41	LA
1,404	1.47	1.41	LA
1,533	1.37	1.44	S
1,276	NR	1.44	LA
1,444	1.43	1.44	LA
1,662	1.54	1.45	LA
1,458	1.53	1.45	LA
1,553	1.45	1.46	LA
1,480	1.37	1.50	S
1,658	1.69	1.51	A
1,508	1.52	1.51	LA
1,441	1.43	1.51	LA
1,484	1.39	1.53	S
1,508	1.67	1.53	A
1,608	1.60	1.57	A
1,889	1.66	1.82	A
1,437	NR	1.49	LA
1,058	NR	1.15	S
1,347	NR	1.48	LA
1,362	NR	1.38	S
1,278	NR	1.23	S
1,421	NR	1.49	LA
1,521	NR	1.55	LA
1,392	NR	1.39	S
1,599	NR	1.60	LA
2,129	NR	1.94	VA
1,435	NR	1.32	S
1,253	NR	1.27	S
1,244	NR	1.24	S
1,328	1.16	1.17	S

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
M	6.0	1.14	18.8	14.5	965	981
M	6.0	1.13	19.6	15.4	1,020	989
M	6.0	1.17	22.4	16.4	1,045	1,071
M	6.0	1.22	24.0	16.1	1,160	1,138
M	6.0	1.10	20.0	16.5	1,000	975
M	6.0	1.19	21.5	15.2	1,040	1,068
M	6.0	1.14	20.1	15.5	945	1,006
M	6.0	1.25	25.0	16.0	1,205	1,178
M	6.0	1.16	21.2	15.8	1,135	1,041
M	6.0	1.21	22.4	15.3	965	1,100
M	6.0	1.15	21.5	16.3	1,058	1,040
M	6.0	1.16	19.8	14.7	1,140	1,014
M	6.0	1.13	20.0	15.7	NR	995
M	6.1	1.17	23.1	16.9	NR	1,079
M	6.2	1.22	23.6	15.9	NR	1,120
M	6.3	1.26	24.2	15.3	NR	1,158
M	6.5	1.20	23.4	16.3	NR	1,087
M	6.6	1.12	18.1	14.4	NR	928
M	6.9	1.22	20.6	13.9	NR	1,029
M	6.9	1.20	21.3	14.8	NR	1,032
M	7.0	1.26	24.6	15.5	1,120	1,134
M	7.0	1.10	17.0	14.0	NR	874
M	7.0	1.26	22.0	13.9	1,010	1,084
M	7.0	1.20	24.6	17.0	NR	1,092
M	7.0	1.25	24.5	15.7	1,120	1,125
M	7.0	1.23	24.2	16.0	1,250	1,105
M	7.2	1.23	26.0	17.2	NR	1,131
M	7.2	1.20	21.5	15.0	NR	1,023
M	7.3	1.29	26.1	15.6	NR	1,174
M	7.8	1.27	24.8	15.4	NR	1,111
M	7.8	1.21	24.2	16.5	NR	1,056
M	8.0	1.22	25.1	16.9	1,057	1,072
M	8.0	1.21	23.7	16.2	910	1,038
M	8.0	1.32	27.2	15.6	1,035	1,184
M	8.0	1.26	27.0	17.0	1,180	1,137
M	8.0	1.27	22.4	13.9	NR	1,055
M	8.3	1.35	31.4	17.3	NR	1,274
M	8.3	1.36	31.9	17.2	NR	1,289
M	8.5	1.32	29.1	16.8	NR	1,195
M	9.0	1.31	31.0	18.1	1,025	1,206
M	9.1	1.30	26.8	15.9	NR	1,114
M	9.1	1.26	26.5	16.7	NR	1,080
M	9.1	1.43	32.8	16.0	NR	1,322
M	9.6	1.34	28.6	16.0	NR	1,152
M	9.6	1.37	28.8	15.4	NR	1,179

TEE	PALo	PALp	PALCAT
1,200	1.24	1.22	S
1,258	1.23	1.27	S
1,381	1.32	1.29	S
1,574	1.36	1.38	S
1,361	1.36	1.40	S
1,508	1.45	1.41	LA
1,447	1.53	1.44	LA
1,725	1.43	1.46	LA
1,592	1.40	1.53	LA
1,696	1.76	1.54	A
1,628	1.54	1.57	LA
1,621	1.42	1.60	LA
1,692	NR	1.70	A
1,385	NR	1.28	S
1,536	NR	1.37	S
1,584	NR	1.37	S
1,880	NR	1.73	A
1,082	NR	1.17	S
1,509	NR	1.47	LA
1,370	NR	1.33	S
1,586	1.42	1.40	LA
1,277	NR	1.46	LA
1,606	1.59	1.48	LA
1,780	NR	1.63	A
1,847	1.65	1.64	A
1,873	1.50	1.69	LA
1,331	NR	1.18	S
1,697	NR	1.66	A
1,731	NR	1.48	LA
1,555	NR	1.40	LA
1,730	NR	1.64	A
1,603	1.52	1.50	LA
1,610	1.77	1.55	A
1,974	1.91	1.67	VA
1,937	1.64	1.70	A
1,937	NR	1.84	A
1,460	NR	1.15	S
2,338	NR	1.81	A
1,523	NR	1.27	S
1,671	1.63	1.39	A
1,533	NR	1.38	S
1,692	NR	1.57	LA
2,177	NR	1.65	A
1,178	NR	1.02	S
1,524	NR	1.29	S

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
M	9.6	1.39	30.6	15.8	NR	1,230
M	9.7	1.33	31.3	17.8	NR	1,192
M	9.9	1.43	37.3	18.2	NR	1,374
M	10.0	1.46	35.4	16.6	1,185	1,354
M	10.0	1.40	32.2	16.4	1,120	1,250
M	10.0	1.51	35.2	15.4	1,374	1,386
M	10.0	1.41	33.8	17.0	NR	1,289
M	10.0	1.49	37.7	17.1	NR	1,416
M	10.0	1.50	41.5	18.4	1,330	1,500
M	10.0	1.46	40.9	19.2	1,540	1,460
M	10.0	1.43	34.4	16.8	1,265	1,314
M	10.0	1.39	32.2	16.7	1,276	1,243
M	10.4	1.25	25.0	16.0	NR	988
M	11.0	1.36	30.4	16.4	NR	1,144
M	11.0	1.37	35.2	18.8	1,105	1,243
M	11.0	1.48	34.5	15.8	1,305	1,308
M	12.0	1.60	50.0	19.5	NR	1,647
M	12.5	1.59	44.5	17.6	1,480	1,513
M	13.0	1.56	43.4	17.8	1,310	1,449
M	13.0	1.56	44.0	18.0	1,490	1,464
M	13.3	1.65	54.1	19.8	2,042	1,706
M	13.8	1.56	44.1	18.1	1,537	1,428
M	14.0	1.74	67.1	22.2	1,925	1,989
M	14.1	1.59	52.6	20.8	1,681	1,599
M	14.1	1.54	45.8	19.3	1,610	1,433
M	14.5	1.71	64.2	21.9	1,946	1,892
M	14.5	1.67	50.0	17.9	1,712	1,589
M	15.0	1.76	52.1	16.7	1,682	1,676
M	15.6	1.89	70.6	19.8	1,935	2,094
M	18.0	1.72	57.7	19.5	1,663	1,620
M	18.0	1.72	59.0	19.9	1,437	1,646
M	18.8	1.64	69.2	25.6	1,654	1,752
F	3.8	1.18	23.2	16.5	NR	1,044
F	4.0	1.04	16.7	15.4	905	901
F	4.0	1.10	18.0	14.9	965	948
F	4.0	1.13	19.2	15.0	890	977
F	4.0	1.06	15.4	13.7	893	903
F	4.0	1.04	16.9	15.6	875	902
F	4.0	0.98	15.0	15.7	NR	848
F	4.1	1.07	16.7	14.6	NR	916
F	4.4	1.06	16.0	14.2	NR	901
F	4.5	1.01	16.0	15.6	NR	869
F	4.6	1.04	17.9	16.6	NR	900
F	4.6	1.04	16.6	15.4	NR	888
F	4.6	1.03	15.2	14.3	NR	871

TEE	PALo	PALp	PALCAT
1,859	NR	1.51	LA
1,462	NR	1.23	S
2,725	NR	1.98	VA
1,763	1.49	1.30	LA
1,781	1.59	1.42	LA
1,975	1.44	1.42	LA
1,844	NR	1.43	LA
2,125	NR	1.50	LA
2,318	1.74	1.55	A
2,474	1.61	1.69	A
2,265	1.79	1.72	A
2,302	1.80	1.85	A
1,891	NR	1.92	VA
1,602	NR	1.40	LA
1,834	1.66	1.48	A
1,945	1.49	1.49	LA
2,460	NR	1.49	LA
2,576	1.74	1.70	A
2,404	1.84	1.66	A
2,511	1.69	1.72	A
3,644	1.78	2.14	A
2,675	1.74	1.87	A
3,370	1.75	1.69	A
2,578	1.53	1.61	LA
2,814	1.75	1.96	A
3,257	1.67	1.72	A
3,172	1.85	2.00	A
2,979	1.77	1.78	A
4,130	2.13	1.97	VA
2,145	1.29	1.32	S
2,969	2.07	1.80	VA
3,749	2.27	2.14	VA
1,390	NR	1.33	S
1,164	1.29	1.29	S
1,252	1.30	1.32	S
1,357	1.52	1.39	LA
1,357	1.52	1.50	LA
1,534	1.75	1.70	A
1,059	NR	1.25	S
935	NR	1.02	S
1,130	NR	1.25	S
1,278	NR	1.47	LA
1,116	NR	1.24	S
924	NR	1.04	S
1,176	NR	1.35	S

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	4.6	1.06	18.2	16.1	NR	916
F	4.8	1.03	16.2	15.3	NR	876
F	4.9	1.07	17.5	15.3	NR	910
F	5.0	1.15	19.9	15.0	885	977
F	5.0	1.14	20.9	16.1	920	979
F	5.0	1.02	16.0	15.4	820	865
F	5.0	1.13	18.2	14.2	940	951
F	5.0	1.17	18.8	13.7	930	981
F	5.0	1.11	19.1	15.5	840	946
F	5.0	1.03	14.6	13.8	845	860
F	5.0	1.12	20.3	16.2	880	961
F	5.0	1.17	22.7	16.6	1,030	1,012
F	5.0	1.10	18.9	15.6	810	938
F	5.0	1.13	17.9	14.0	975	949
F	5.0	1.17	19.1	14.0	910	983
F	5.0	1.12	18.5	14.8	960	947
F	5.0	1.02	17.4	16.7	810	876
F	5.0	1.14	21.6	16.6	885	984
F	5.0	1.19	21.9	15.5	1,050	1,018
F	5.0	1.08	18.3	15.7	850	921
F	5.0	1.08	19.0	16.3	935	926
F	5.0	1.09	17.7	14.9	895	922
F	5.0	1.16	20.4	15.2	1,000	987
F	5.0	1.05	17.8	16.1	900	898
F	5.0	1.08	17.9	15.4	910	917
F	5.0	1.19	20.4	14.4	970	1,006
F	5.0	1.10	17.9	14.8	900	930
F	5.0	1.12	20.1	16.0	1,040	960
F	5.0	1.13	19.7	15.4	890	963
F	5.0	1.13	19.6	15.4	1,015	962
F	5.0	1.11	18.9	15.3	890	944
F	5.0	1.09	19.0	16.0	960	932
F	5.0	1.12	20.5	16.3	990	963
F	5.0	1.11	18.8	15.3	800	943
F	5.0	1.07	16.1	14.1	810	897
F	5.0	1.08	16.7	14.3	965	908
F	5.0	1.18	20.9	15.0	1,015	1,004
F	5.0	1.07	16.1	14.1	935	897
F	5.0	1.12	20.1	16.0	880	960
F	5.0	1.08	17.6	15.1	985	915
F	5.0	1.10	17.3	14.3	845	925
F	5.0	1.09	19.3	16.2	849	935
F	5.0	1.08	15.9	13.6	880	902
F	5.0	1.10	19.9	16.4	870	946
F	5.0	1.07	17.9	15.6	990	911
F	5.0	1.19	20.8	14.7	985	1,009

TEE	PALo	PALp	PALCAT
1,637	NR	1.79	A
1,355	NR	1.55	LA
1,028	NR	1.13	S
1,014	1.15	1.04	S
1,110	1.21	1.13	S
982	1.20	1.14	S
1,098	1.17	1.15	S
1,148	1.23	1.17	S
1,120	1.33	1.18	S
1,031	1.22	1.20	S
1,158	1.32	1.20	S
1,233	1.20	1.22	S
1,146	1.41	1.22	LA
1,161	1.19	1.22	S
1,204	1.32	1.22	S
1,161	1.21	1.23	S
1,079	1.33	1.23	S
1,215	1.37	1.23	S
1,267	1.20	1.24	S
1,146	1.35	1.24	S
1,178	1.26	1.27	S
1,175	1.31	1.27	S
1,272	1.27	1.29	S
1,166	1.30	1.30	S
1,194	1.31	1.30	S
1,311	1.35	1.30	S
1,212	1.35	1.30	S
1,251	1.20	1.30	S
1,255	1.41	1.30	LA
1,255	1.24	1.30	S
1,241	1.39	1.31	S
1,231	1.28	1.32	S
1,272	1.28	1.32	S
1,248	1.56	1.32	LA
1,192	1.47	1.33	LA
1,208	1.25	1.33	S
1,344	1.32	1.34	S
1,203	1.29	1.34	S
1,288	1.46	1.34	LA
1,239	1.26	1.35	S
1,257	1.49	1.36	LA
1,270	1.50	1.36	LA
1,239	1.41	1.37	LA
1,315	1.51	1.39	LA
1,271	1.28	1.40	S
1,416	1.44	1.40	LA

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	5.0	1.12	18.2	14.5	985	945
F	5.0	1.13	20.6	16.1	922	970
F	5.0	1.15	21.6	16.3	980	990
F	5.0	1.09	18.2	15.3	795	926
F	5.0	1.15	18.5	14.0	835	966
F	5.0	1.04	17.0	15.7	950	885
F	5.0	1.19	23.5	16.6	1,055	1,030
F	5.0	1.15	21.4	16.2	940	989
F	5.0	1.14	19.8	15.2	795	970
F	5.0	1.14	21.2	16.3	1,070	981
F	5.0	1.21	23.3	15.9	1,000	1,041
F	5.0	1.12	17.9	14.3	965	942
F	5.0	1.15	19.5	14.7	1,005	974
F	5.0	1.03	16.0	15.1	890	871
F	5.0	1.21	22.2	15.2	945	1,033
F	5.0	1.11	20.1	16.3	970	954
F	5.0	1.14	20.5	15.8	970	975
F	5.0	1.12	18.7	14.9	860	949
F	5.0	1.17	19.1	14.0	975	983
F	5.0	1.17	21.8	15.9	974	1,004
F	5.0	1.11	19.9	16.2	990	952
F	5.0	1.11	19.7	16.0	990	950
F	5.0	1.06	18.2	16.2	840	907
F	5.0	1.10	18.2	15.0	935	932
F	5.2	1.10	18.5	15.3	NR	931
F	5.2	1.10	19.1	15.8	NR	935
F	5.3	1.09	19.7	16.6	NR	933
F	5.6	1.09	17.2	14.4	NR	908
F	5.6	1.13	19.4	15.2	NR	950
F	5.6	1.17	21.6	15.8	NR	993
F	5.7	1.22	20.9	14.0	NR	1,016
F	5.8	1.19	22.6	15.9	NR	1,010
F	6.0	1.10	18.9	15.6	980	920
F	6.0	1.13	19.9	15.6	925	947
F	6.0	1.13	18.6	14.6	780	937
F	6.0	1.01	13.7	13.4	875	823
F	6.0	1.17	19.3	14.1	980	967
F	6.0	1.09	19.1	16.1	870	916
F	6.0	1.22	23.6	15.9	1,152	1,032
F	6.0	1.19	23.2	16.4	1,130	1,010
F	6.0	1.18	20.2	14.5	NR	981
F	6.0	1.16	21.0	15.6	NR	974
F	6.0	1.27	26.9	16.7	NR	1,090
F	6.1	1.13	18.7	14.6	NR	935
F	6.1	1.09	18.0	15.2	NR	904
F	6.2	1.16	21.8	16.3	NR	975

TEE	PALo	PALp	PALCAT
1,330	1.35	1.41	S
1,368	1.48	1.41	LA
1,411	1.44	1.42	LA
1,329	1.67	1.44	A
1,406	1.68	1.46	A
1,299	1.37	1.47	S
1,519	1.44	1.47	LA
1,458	1.55	1.47	LA
1,431	1.80	1.48	A
1,451	1.36	1.48	S
1,541	1.54	1.48	LA
1,395	1.45	1.48	LA
1,442	1.43	1.48	LA
1,299	1.46	1.49	LA
1,550	1.64	1.50	A
1,438	1.48	1.51	LA
1,480	1.53	1.52	LA
1,443	1.68	1.52	A
1,510	1.55	1.54	LA
1,556	1.60	1.55	LA
1,478	1.49	1.55	LA
1,485	1.50	1.56	LA
1,466	1.75	1.62	A
1,526	1.63	1.64	A
1,326	NR	1.42	LA
1,488	NR	1.59	LA
1,851	NR	1.98	VA
1,573	NR	1.73	A
1,205	NR	1.27	S
1,327	NR	1.34	S
1,239	NR	1.22	S
1,463	NR	1.45	LA
1,153	1.18	1.25	S
1,205	1.30	1.27	S
1,265	1.62	1.35	A
1,129	1.29	1.37	S
1,404	1.43	1.45	LA
1,353	1.56	1.48	LA
1,548	1.34	1.50	S
1,623	1.44	1.61	LA
1,589	NR	1.62	A
1,588	NR	1.63	A
1,798	NR	1.65	A
1,116	NR	1.19	S
1,494	NR	1.65	A
1,427	NR	1.46	LA

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	6.2	1.15	21.6	16.3	NR	969
F	6.2	1.16	21.7	16.1	NR	976
F	6.3	1.14	18.8	14.5	NR	939
F	6.4	1.11	18.0	14.7	NR	911
F	6.5	1.20	20.6	14.3	NR	990
F	6.6	1.21	24.4	16.8	NR	1,019
F	6.6	1.20	20.3	14.1	NR	983
F	6.6	1.23	23.7	15.8	NR	1,025
F	6.6	1.29	26.8	16.0	NR	1,092
F	6.7	1.21	21.8	15.0	NR	996
F	6.8	1.18	20.4	14.6	NR	968
F	6.8	1.25	23.2	15.0	NR	1,031
F	6.8	1.17	21.4	15.7	NR	966
F	7.0	1.26	21.7	13.7	1,075	1,025
F	7.0	1.24	24.0	15.6	1,085	1,030
F	7.0	1.31	24.5	14.3	1,160	1,078
F	7.0	1.30	28.5	16.9	1,115	1,103
F	7.0	1.19	22.2	15.7	1,015	985
F	7.1	1.19	24.0	17.0	NR	998
F	7.1	1.29	27.6	16.6	NR	1,087
F	7.2	1.25	25.6	16.4	NR	1,046
F	7.3	1.34	29.8	16.6	NR	1,134
F	7.3	1.24	24.6	16.1	NR	1,026
F	7.3	1.26	23.2	14.7	NR	1,028
F	7.5	1.18	22.2	16.1	NR	967
F	7.5	1.23	22.8	15.0	NR	1,005
F	7.5	1.20	24.2	16.8	1,123	997
F	7.6	1.31	29.8	17.5	NR	1,107
F	7.6	1.27	26.4	16.3	NR	1,057
F	7.7	1.26	25.8	16.2	1,217	1,045
F	7.7	1.34	31.2	17.4	NR	1,137
F	7.8	1.30	29.2	17.2	1,200	1,096
F	7.9	1.21	22.8	15.7	932	984
F	7.9	1.20	22.6	15.6	NR	979
F	8.0	1.26	26.2	16.6	969	1,040
F	8.0	1.32	29.8	17.2	1,066	1,107
F	8.0	1.29	24.0	14.4	NR	1,045
F	8.0	1.21	22.1	15.2	1,024	977
F	8.0	1.26	25.0	15.8	1,035	1,033
F	8.0	1.33	30.2	17.0	NR	1,119
F	8.0	1.29	24.7	14.8	1,078	1,050
F	8.0	1.28	27.4	16.6	994	1,067
F	8.1	1.25	27.9	17.9	847	1,047
F	8.1	1.17	21.5	15.6	1,058	950
F	8.1	1.30	27.2	16.2	1,037	1,072
F	8.1	1.28	27.4	16.6	1,113	1,066

TEE	PALo	PALp	PALCAT
1,912	NR	1.97	VA
1,302	NR	1.33	S
1,498	NR	1.60	LA
1,016	NR	1.12	S
1,224	NR	1.24	S
1,663	NR	1.63	A
1,207	NR	1.23	S
1,594	NR	1.55	LA
1,704	NR	1.56	LA
1,369	NR	1.37	S
1,062	NR	1.10	S
1,285	NR	1.25	S
1,504	NR	1.56	LA
1,424	1.32	1.39	S
1,441	1.33	1.40	S
1,590	1.37	1.47	S
1,852	1.66	1.68	A
1,688	1.66	1.71	A
1,308	NR	1.31	S
1,597	NR	1.47	LA
1,359	NR	1.30	S
1,769	NR	1.56	LA
1,518	NR	1.48	LA
1,701	NR	1.65	A
1,536	NR	1.59	LA
1,744	NR	1.73	A
1,623	1.44	1.63	LA
1,725	NR	1.56	LA
1,666	NR	1.58	LA
2,192	1.80	2.10	A
1,308	NR	1.15	S
1,593	1.33	1.45	S
1,549	1.66	1.57	A
1,279	NR	1.31	S
1,263	1.30	1.21	S
1,764	1.65	1.59	A
1,555	NR	1.49	LA
1,610	1.57	1.65	LA
1,450	1.40	1.40	LA
1,618	NR	1.45	LA
1,562	1.45	1.49	LA
1,655	1.67	1.55	A
1,754	2.07	1.68	VA
1,500	1.42	1.58	LA
1,370	1.32	1.28	S
1,632	1.47	1.53	LA

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	8.1	1.31	28.6	16.7	1,122	1,091
F	8.1	1.30	28.0	16.6	NR	1,081
F	8.1	1.29	24.4	14.6	966	1,047
F	8.1	1.27	22.2	13.8	913	1,013
F	8.1	1.25	26.8	17.1	1,040	1,040
F	8.1	1.28	28.0	17.2	1,096	1,064
F	8.2	1.25	22.1	14.2	1,164	1,000
F	8.2	1.35	29.4	16.1	1,146	1,121
F	8.2	1.35	28.3	15.6	1,136	1,110
F	8.2	1.27	24.8	15.4	NR	1,034
F	8.2	1.33	30.9	17.4	1,153	1,122
F	8.3	1.30	28.3	16.7	1,110	1,082
F	8.3	1.25	24.1	15.5	1,194	1,014
F	8.3	1.30	26.1	15.4	1,137	1,062
F	8.3	1.21	22.2	15.1	NR	974
F	8.3	1.37	29.4	15.6	NR	1,133
F	8.3	1.37	30.3	16.3	NR	1,135
F	8.3	1.32	29.0	16.6	NR	1,097
F	8.3	1.36	29.2	15.9	NR	1,122
F	8.3	1.31	24.5	14.4	NR	1,052
F	8.3	1.34	24.4	13.6	971	1,072
F	8.3	1.35	27.5	15.0	1,178	1,106
F	8.3	1.31	27.0	15.7	938	1,075
F	8.3	1.31	25.9	15.1	988	1,065
F	8.3	1.24	23.6	15.3	974	1,004
F	8.4	1.34	25.7	14.4	NR	1,081
F	8.4	1.22	21.0	14.1	955	970
F	8.4	1.21	24.6	16.8	904	992
F	8.4	1.28	26.0	15.9	1,155	1,045
F	8.4	1.26	25.4	16.0	1,048	1,029
F	8.4	1.26	27.4	17.3	1,116	1,043
F	8.4	1.24	24.4	15.9	1,024	1,008
F	8.4	1.34	28.5	15.9	NR	1,102
F	8.4	1.25	26.4	17.0	NR	1,027
F	8.5	1.30	24.5	14.5	NR	1,046
F	8.5	1.26	25.0	15.7	1,091	1,027
F	8.5	1.33	27.8	15.7	1,037	1,090
F	8.5	1.31	26.4	15.3	1,010	1,069
F	8.6	1.29	25.9	15.6	1,069	1,049
F	8.6	1.35	29.8	16.4	989	1,116
F	8.6	1.31	31.4	18.2	1,207	1,107
F	8.6	1.30	24.8	14.8	1,150	1,044
F	8.6	1.40	30.2	15.5	1,170	1,150
F	8.6	1.26	26.8	17.0	NR	1,033
F	8.6	1.25	27.4	17.6	NR	1,034
F	8.6	1.35	27.2	15.0	NR	1,093

TEE	PALo	PALp	PALCAT
1,445	1.29	1.33	S
1,671	NR	1.55	LA
1,384	1.43	1.32	LA
1,626	1.78	1.61	A
1,785	1.72	1.72	A
1,709	1.56	1.61	LA
1,642	1.41	1.64	LA
1,856	1.62	1.66	A
1,434	1.26	1.29	S
2,425	NR	2.35	VA
2,385	2.07	2.13	VA
1,919	1.73	1.77	A
1,627	1.36	1.61	S
1,812	1.59	1.71	LA
1,235	NR	1.27	S
1,538	NR	1.36	S
1,554	NR	1.37	S
1,506	NR	1.37	S
1,599	NR	1.42	LA
1,727	NR	1.64	A
1,637	1.68	1.53	A
1,854	1.57	1.68	LA
1,324	1.41	1.23	LA
1,520	1.54	1.43	LA
1,294	1.33	1.29	S
1,453	NR	1.34	S
1,588	1.66	1.64	A
1,379	1.53	1.39	LA
2,081	1.80	1.99	A
1,806	1.72	1.75	A
2,225	1.99	2.13	VA
1,535	1.50	1.52	LA
1,824	NR	1.66	A
2,045	NR	1.99	VA
1,465	NR	1.40	LA
1,920	1.76	1.87	A
1,475	1.42	1.35	LA
2,160	2.14	2.02	VA
1,527	1.43	1.45	LA
1,771	1.79	1.59	A
2,119	1.76	1.91	A
2,181	1.90	2.09	A
1,798	1.54	1.56	LA
1,516	NR	1.47	LA
1,577	NR	1.52	LA
1,872	NR	1.71	A

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	8.6	1.38	30.4	16.0	982	1,138
F	8.7	1.31	31.1	18.2	1,096	1,099
F	8.7	1.30	28.9	17.0	1,118	1,080
F	8.7	1.37	34.1	18.1	NR	1,163
F	8.7	1.28	25.4	15.5	1,041	1,037
F	8.7	1.24	21.8	14.2	953	983
F	8.7	1.30	25.1	14.8	1,114	1,049
F	8.7	1.28	27.4	16.8	1,142	1,050
F	8.8	1.28	24.0	14.8	1,044	1,021
F	8.8	1.35	33.0	18.0	1,294	1,140
F	8.8	1.35	32.8	18.1	1,204	1,135
F	8.8	1.36	26.3	14.3	1,320	1,091
F	8.8	1.28	27.8	17.0	993	1,052
F	8.8	1.25	21.9	14.1	NR	985
F	8.8	1.30	24.1	14.4	961	1,033
F	8.8	1.28	29.5	18.0	964	1,066
F	8.9	1.33	28.5	16.1	907	1,089
F	8.9	1.33	28.6	16.1	1,079	1,091
F	8.9	1.33	29.4	16.5	NR	1,097
F	8.9	1.32	28.9	16.5	1,086	1,088
F	8.9	1.35	28.6	15.7	NR	1,102
F	8.9	1.37	29.1	15.6	NR	1,115
F	8.9	1.26	28.2	17.8	NR	1,043
F	8.9	1.35	29.0	15.8	1,202	1,107
F	8.9	1.29	23.9	14.3	980	1,029
F	8.9	1.32	27.0	15.5	1,164	1,071
F	9.0	1.30	26.0	15.4	983	1,049
F	9.0	1.34	28.7	15.9	1,122	1,097
F	9.0	1.40	32.7	16.7	1,283	1,166
F	9.0	1.34	29.4	16.2	1,038	1,104
F	9.0	1.36	29.6	16.0	NR	1,115
F	9.0	1.44	39.0	19.0	NR	1,232
F	9.0	1.31	31.5	18.4	1,160	1,098
F	9.0	1.43	38.6	18.8	1,205	1,230
F	9.0	1.28	30.0	18.3	1,208	1,066
F	9.0	1.26	23.7	14.8	956	1,006
F	9.0	1.33	29.9	17.0	1,093	1,095
F	9.1	1.24	26.0	16.9	1,103	1,009
F	9.1	1.29	28.6	17.2	NR	1,061
F	9.1	1.27	26.2	16.4	NR	1,026
F	9.1	1.42	36.5	18.1	NR	1,205
F	9.1	1.25	26.0	16.7	NR	1,016
F	9.1	1.30	25.2	15.0	NR	1,039
F	9.1	1.34	27.9	15.5	1,112	1,088
F	9.2	1.34	25.9	14.4	1,167	1,070
F	9.2	1.27	25.4	15.7	1,122	1,023

TEE	PALo	PALp	PALCAT
1,887	1.92	1.66	VA
1,992	1.82	1.81	A
1,684	1.51	1.56	LA
1,901	NR	1.63	A
1,518	1.46	1.46	LA
1,689	1.77	1.72	A
1,733	1.56	1.65	LA
1,900	1.66	1.81	A
1,580	1.51	1.55	LA
2,237	1.73	1.96	A
1,996	1.66	1.76	A
1,820	1.38	1.67	S
1,351	1.36	1.28	S
1,153	NR	1.17	S
1,718	1.79	1.66	A
1,321	1.37	1.24	S
1,530	1.69	1.40	A
2,201	2.04	2.02	VA
1,369	NR	1.25	S
2,184	2.01	2.01	VA
1,277	NR	1.16	S
1,468	NR	1.32	S
1,404	NR	1.35	S
1,644	1.37	1.49	S
1,812	1.85	1.76	A
1,906	1.64	1.78	A
1,425	1.45	1.36	LA
1,850	1.65	1.69	A
1,795	1.40	1.54	S
1,625	1.5	1.47	LA
1,815	NR	1.63	A
2,103	NR	1.71	A
2,116	1.82	1.93	A
1,301	1.08	1.06	S
1,756	1.45	1.65	LA
1,750	1.83	1.74	A
1,560	1.43	1.42	LA
1,455	1.32	1.44	S
1,394	NR	1.31	S
1,365	NR	1.33	S
1,818	NR	1.51	LA
1,671	NR	1.64	A
1,718	NR	1.65	A
1,534	1.38	1.41	S
1,573	1.35	1.47	S
1,764	1.57	1.72	LA

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	9.2	1.33	31.7	17.9	NR	1,109
F	9.2	1.45	33.9	16.2	NR	1,198
F	9.2	1.29	25.1	15.0	1,087	1,032
F	9.3	1.33	29.6	16.9	NR	1,087
F	9.3	1.35	28.6	15.7	NR	1,095
F	9.4	1.27	22.4	14.0	NR	991
F	9.4	1.22	23.1	15.5	881	970
F	9.5	1.38	34.1	18.0	NR	1,152
F	9.7	1.36	28.8	15.7	NR	1,092
F	9.7	1.44	34.3	16.5	NR	1,189
F	9.8	1.25	22.2	14.2	1,193	973
F	9.8	1.36	31.4	17.0	1,116	1,113
F	9.8	1.45	37.8	18.1	NR	1,218
F	9.8	1.31	27.5	16.2	NR	1,049
F	9.9	1.40	32.7	16.7	NR	1,148
F	10.0	1.43	34.4	16.8	1,025	1,179
F	10.0	1.48	37.4	17.1	1,190	1,233
F	10.0	1.37	33.2	17.7	NR	1,132
F	10.0	1.36	35.9	19.4	1,010	1,147
F	10.0	1.44	34.1	16.4	1,120	1,182
F	10.0	1.42	35.7	17.7	1,255	1,183
F	10.0	1.40	37.9	19.3	1,460	1,187
F	10.0	1.45	32.4	15.4	1,213	1,175
F	10.0	1.41	38.1	19.2	1,230	1,195
F	10.2	1.42	30.8	15.3	NR	1,140
F	10.2	1.36	32.1	17.3	1,038	1,114
F	10.3	1.40	34.0	17.2	1,183	1,155
F	10.3	1.45	36.7	17.5	NR	1,204
F	10.3	1.38	30.7	16.2	NR	1,109
F	10.4	1.35	32.2	17.7	NR	1,103
F	10.5	1.52	38.2	16.4	1,254	1,258
F	10.6	1.45	40.0	19.0	1,228	1,225
F	10.6	1.45	34.5	16.3	1,272	1,183
F	10.8	1.45	40.8	19.4	1,577	1,227
F	10.9	1.50	37.2	16.5	1,237	1,230
F	10.9	1.41	29.4	14.8	1,203	1,110
F	11.0	1.37	32.1	17.1	NR	1,105
F	11.0	1.45	37.5	17.8	NR	1,199
F	11.2	1.53	35.2	15.1	1,175	1,225
F	11.4	1.56	42.6	17.6	1,277	1,296
F	11.5	1.59	47.6	18.9	1,284	1,356
F	11.5	1.53	47.7	20.4	1,355	1,320
F	11.6	1.41	36.7	18.4	1,186	1,158
F	11.7	1.52	41.6	17.9	1,168	1,265
F	11.7	1.40	35.8	18.4	1,109	1,138
F	11.8	1.56	46.0	18.8	1,228	1,322

TEE	PALo	PALp	PALCAT
1,495	NR	1.35	S
2,498	NR	2.08	VA
1,750	1.61	1.69	A
1,372	NR	1.26	S
1,395	NR	1.27	S
1,392	NR	1.40	LA
1,374	1.56	1.42	LA
1,570	NR	1.36	S
1,527	NR	1.40	S
1,971	NR	1.66	A
1,303	1.09	1.34	S
1,580	1.42	1.42	LA
1,405	NR	1.15	S
1,484	NR	1.41	LA
1,669	NR	1.45	LA
1,449	1.41	1.23	LA
1,792	1.51	1.45	LA
1,674	NR	1.48	LA
1,707	1.69	1.49	A
1,920	1.71	1.62	A
2,001	1.59	1.69	LA
2,150	1.47	1.81	LA
2,170	1.79	1.85	A
2,265	1.84	1.90	A
1,336	NR	1.17	S
1,809	1.74	1.62	A
1,555	1.32	1.35	S
1,594	NR	1.32	S
1,705	NR	1.54	LA
1,532	NR	1.39	S
2,395	1.91	1.90	VA
2,698	2.20	2.20	VA
2,117	1.66	1.79	A
1,966	1.25	1.60	S
1,757	1.42	1.43	LA
2,480	2.06	2.23	VA
1,290	NR	1.1	S
1,830	NR	1.53	LA
1,795	1.53	1.47	LA
1,982	1.55	1.53	LA
1,599	1.25	1.18	S
2,647	1.95	2.00	VA
2,110	1.78	1.82	A
2,098	1.80	1.66	A
1,437	1.30	1.26	S
1,610	1.31	1.22	S

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	11.8	1.46	41.0	19.1	1,281	1,220
F	11.9	1.48	37.1	16.9	1,163	1,200
F	12.0	1.55	41.1	17.0	1,225	1,274
F	12.0	1.59	48.0	19.0	1,246	1,351
F	12.0	1.55	35.9	15.0	1,223	1,229
F	12.0	1.42	35.0	17.3	1,175	1,143
F	12.1	1.37	34.6	18.4	1,194	1,106
F	12.2	1.56	45.7	18.9	1,045	1,307
F	12.3	1.60	53.4	21.0	1,605	1,393
F	12.4	1.48	38.2	17.6	1,237	1,195
F	12.4	1.60	46.2	18.0	1,385	1,335
F	12.5	1.62	42.6	16.2	1,145	1,317
F	12.5	1.51	45.8	20.0	1,400	1,277
F	12.5	1.56	44.8	18.3	1,238	1,299
F	12.6	1.61	49.0	19.0	1,482	1,360
F	12.7	1.47	40.7	18.9	1,210	1,203
F	12.8	1.49	37.6	16.9	1,194	1,191
F	12.9	1.50	39.8	17.6	1,206	1,217
F	12.9	1.56	39.7	16.2	1,216	1,253
F	13.0	1.67	57.5	20.6	1,568	1,458
F	13.1	1.63	48.2	18.1	1,362	1,358
F	13.2	1.62	40.7	15.4	1,151	1,293
F	13.4	1.50	37.1	16.4	1,231	1,188
F	13.4	1.65	52.3	19.1	1,529	1,400
F	13.6	1.57	48.0	19.6	1,298	1,308
F	13.8	1.70	56.8	19.7	1,403	1,455
F	14.0	1.57	52.9	21.4	1,364	1,343
F	14.0	1.64	44.4	16.6	1,367	1,315
F	14.1	1.62	58.6	22.4	NR	1,416
F	14.2	1.55	51.5	21.5	NR	1,314
F	14.2	1.62	45.2	17.1	1,181	1,311
F	14.3	1.60	48.6	19.0	1,437	1,321
F	14.4	1.65	51.9	19.2	1,764	1,375
F	14.5	1.61	51.0	19.7	NR	1,343
F	14.5	1.53	41.5	17.7	1,269	1,218
F	14.6	1.70	64.2	22.2	1,491	1,502
F	14.6	1.75	63.2	20.6	1,759	1,525
F	14.6	1.62	49.7	18.9	1,174	1,337
F	14.7	1.71	57.9	19.9	1,391	1,454
F	14.7	1.67	57.8	20.7	1,290	1,430
F	14.8	1.58	44.6	17.8	1,004	1,271
F	14.8	1.58	56.4	22.7	1,317	1,359
F	14.8	1.63	48.7	18.4	1,383	1,329
F	14.9	1.54	45.9	19.5	1,101	1,248
F	15.0	1.68	55.4	19.6	1,463	1,413
F	15.1	1.58	48.9	19.6	1,267	1,295

TEE	PALo	PALp	PALCAT
2,442	1.91	2.00	VA
2,030	1.74	1.69	A
1,589	1.30	1.25	S
2,020	1.62	1.49	A
2,307	1.89	1.88	A
1,658	1.41	1.45	LA
1,988	1.66	1.80	A
1,845	1.77	1.41	A
2,913	1.81	2.09	A
2,222	1.80	1.86	A
2,202	1.59	1.65	LA
1,496	1.31	1.14	S
2,855	2.04	2.24	VA
2,460	1.99	1.89	VA
1,864	1.26	1.37	S
2,106	1.74	1.75	A
2,038	1.71	1.71	A
1,968	1.63	1.62	A
2,213	1.82	1.77	A
2,645	1.69	1.81	A
2,691	1.98	1.98	VA
2,350	2.04	1.82	VA
2,056	1.67	1.73	A
2,472	1.62	1.77	A
2,122	1.63	1.62	A
2,950	2.10	2.03	VA
3,241	2.38	2.41	VA
2,386	1.75	1.81	A
2,310	NR	1.63	A
2,095	NR	1.59	LA
1,741	1.47	1.33	LA
2,430	1.69	1.84	A
2,365	1.34	1.72	S
2,149	NR	1.60	A
1,913	1.51	1.57	LA
2,791	1.87	1.86	A
2,196	1.25	1.44	S
1,750	1.49	1.31	LA
2,424	1.74	1.67	A
3,021	2.34	2.11	VA
1,853	1.85	1.46	A
2,408	1.83	1.77	A
2,268	1.64	1.71	A
1,680	1.53	1.35	LA
2,139	1.46	1.51	LA
2,503	1.98	1.93	VA

continued

TABLE I-2 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)	BEEp (kcal/d)
F	15.2	1.53	52.1	22.3	1,307	1,290
F	15.2	1.50	46.0	20.4	1,176	1,222
F	15.3	1.66	57.6	21.0	1,340	1,410
F	15.3	1.70	61.8	21.5	NR	1,467
F	15.4	1.55	54.6	22.8	1,049	1,318
F	15.4	1.62	52.7	20.1	1,352	1,346
F	15.5	1.66	51.6	18.8	1,317	1,358
F	15.5	1.64	51.1	19.0	1,243	1,344
F	15.6	1.57	57.2	23.1	1,279	1,351
F	15.6	1.70	61.9	21.5	1,338	1,465
F	15.6	1.68	60.9	21.6	1,482	1,444
F	15.7	1.68	62.7	22.1	1,358	1,460
F	15.8	1.62	55.3	21.0	1,338	1,363
F	15.8	1.59	46.5	18.5	1,129	1,268
F	16.0	1.61	48.5	18.7	1,362	1,298
F	16.2	1.58	56.1	22.6	1,522	1,334
F	16.2	1.63	55.7	21.0	1,246	1,362
F	16.4	1.54	51.5	21.6	1,286	1,272
F	18.0	1.70	67.3	23.3	1,432	1,466
F	18.0	1.72	58.9	19.9	1,494	1,413
F	18.0	1.62	58.5	22.3	1,472	1,346
F	18.0	1.77	58.1	18.5	1,484	1,437
F	18.0	1.62	60.3	23.0	1,353	1,361

NOTE: BEEo = basal energy expenditure (BEE) as observed in the study, BEEp as predicted based on the following equations:

Girls: BEEp (kcal/d) = 189 – 17.6 × Age (y) + 625 × Height (m) + 7.9 × Weight (kg)
Boys: BEEp (kcal/d) = 68 – 43.3 × Age (y) + 712 × Height (m) + 19.2 × Weight (kg).

TEE	PALo	PALp	PALCAT
2,645	2.02	2.05	VA
2,550	2.17	2.09	VA
2,989	2.23	2.12	VA
3,598	NR	2.45	VA
1,452	1.38	1.10	S
2,759	2.04	2.05	VA
2,383	1.81	1.75	A
2,010	1.62	1.50	A
2,256	1.76	1.67	A
2,791	2.09	1.91	VA
2,391	1.61	1.66	A
2,243	1.65	1.54	A
1,875	1.40	1.38	LA
1,718	1.52	1.35	LA
1,837	1.35	1.42	S
2,610	1.71	1.96	A
2,508	2.01	1.84	VA
1,309	1.02	1.03	S
2,349	1.64	1.60	A
2,345	1.57	1.66	LA
2,304	1.56	1.71	LA
2,713	1.83	1.89	A
2,634	1.95	1.94	VA

TEE = total energy expenditure, PALo = physical activity level (PAL) as observed in the study, PALp = TEE/BEE, PALCAT = PAL category (S = sedentary, LA = low active, A = active, VA = very active), M = male, F = female, NR = not reported, NA = not applicable.

TABLE I-3 Normal Weight Adults with Body Mass Index (BMI) from 18.5 up to 25 kg/m^2

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
M	20.0	1.77	67.6	21.6	1,399
M	20.0	1.79	75.4	23.5	1,656
M	20.0	1.82	74.0	22.3	1,948
M	21.0	1.83	66.9	20.0	1,721
M	21.0	1.83	71.1	21.2	1,852
M	21.0	1.78	75.8	23.9	1,722
M	21.0	1.83	75.1	22.4	1,840
M	22.0	1.83	70.2	21.0	1,888
M	22.0	1.92	77.8	21.1	1,898
M	22.0	1.82	67.9	20.5	1,900
M	22.0	1.75	67.0	21.9	1,574
M	23.0	1.70	68.2	23.6	1,783
M	23.0	1.77	67.0	21.4	1,709
M	23.0	1.76	68.8	22.2	1,498
M	23.0	1.91	86.1	23.6	1,881
M	23.0	1.81	73.2	22.3	1,809
M	23.7	1.79	67.0	20.9	1,706
M	23.7	1.79	77.8	24.3	1,895
M	23.7	1.79	66.0	20.6	1,800
M	24.0	1.80	72.7	22.4	1,520
M	24.0	1.72	66.0	22.3	1,802
M	24.0	1.74	75.0	24.8	1,880
M	25.0	1.61	57.2	22.1	1,593
M	25.0	1.72	72.8	24.6	1,718
M	25.0	1.81	72.3	22.1	1,893
M	25.0	1.75	63.5	20.7	1,613
M	25.0	1.78	70.3	22.2	1,582
M	25.0	1.72	57.9	19.6	1,577
M	26.0	1.78	65.8	20.7	1,745
M	26.0	1.76	70.6	22.8	1,829
M	26.0	1.85	75.4	22.0	1,769
M	27.0	1.76	65.2	21.0	1,580
M	27.0	1.84	71.5	21.1	1,685
M	27.0	1.85	68.2	19.9	1,802
M	28.0	1.75	64.8	21.2	1,557
M	28.0	1.82	78.5	23.7	1,924
M	28.0	1.81	75.7	23.1	2,072
M	28.0	1.84	84.3	24.9	2,060
M	29.0	1.81	68.2	20.8	1,840
M	29.0	1.83	74.4	22.2	2,055
M	29.0	1.78	77.3	24.4	1,831
M	29.0	1.88	73.5	20.8	1,946
M	29.0	1.83	67.0	20.0	1,652
M	29.0	1.90	80.2	22.2	1,809
M	29.0	1.78	68.0	21.5	1,845

TEE	PALo	PALCAT
2,148	1.54	LA
3,119	1.88	A
3,697	1.90	A
3,076	1.79	A
3,415	1.84	A
3,247	1.89	A
3,743	2.03	VA
3,120	1.65	A
3,346	1.76	A
3,353	1.76	A
2,848	1.81	A
2,176	1.22	S
2,820	1.65	A
2,613	1.74	A
3,442	1.83	A
3,693	2.04	VA
2,936	1.72	A
3,317	1.75	A
3,580	1.99	VA
2,318	1.53	LA
3,585	1.99	VA
3,857	2.05	VA
2,390	1.50	LA
2,964	1.72	A
3,298	1.74	A
2,868	1.78	A
3,157	2.00	VA
3,434	2.18	VA
2,559	1.47	LA
3,731	2.04	VA
3,783	2.14	VA
2,263	1.43	LA
2,923	1.73	A
3,623	2.01	VA
2,177	1.40	S
2,770	1.44	LA
3,382	1.63	A
3,681	1.79	A
2,801	1.52	LA
3,138	1.53	LA
2,842	1.55	LA
3,114	1.60	A
2,660	1.61	A
3,191	1.76	A
3,310	1.79	A

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
M	30.0	1.80	77.1	23.8	1,869
M	30.0	1.72	60.1	20.3	1,518
M	30.0	1.83	71.3	21.3	1,864
M	31.0	1.82	79.8	24.1	1,977
M	31.0	1.84	75.4	22.3	1,530
M	31.0	1.73	59.6	19.9	1,460
M	31.0	1.97	88.5	22.8	1,711
M	31.0	1.89	76.6	21.4	1,589
M	32.0	1.78	73.0	23.0	1,740
M	32.0	1.79	77.1	24.1	1,816
M	33.0	1.73	64.0	21.4	1,671
M	33.0	1.81	66.2	20.2	1,752
M	33.0	1.79	69.4	21.7	1,554
M	33.0	1.71	64.5	22.1	1,509
M	33.0	1.76	73.3	23.7	1,597
M	33.0	1.86	83.9	24.3	1,522
M	33.0	1.72	68.5	23.2	1,625
M	33.0	1.77	67.9	21.7	1,684
M	34.0	1.88	75.6	21.4	1,864
M	34.0	1.86	73.8	21.3	2,075
M	34.0	1.78	71.6	22.6	1,570
M	34.0	1.81	73.7	22.5	1,893
M	34.0	1.69	67.2	23.5	1,673
M	35.0	1.73	64.5	21.5	1,561
M	35.0	1.77	75.4	24.1	1,654
M	35.0	1.80	72.0	22.2	1,721
M	36.0	1.82	81.7	24.8	1,960
M	36.0	1.81	76.8	23.4	1,794
M	37.0	1.69	70.3	24.6	1,577
M	37.0	1.78	73.0	23.0	1,585
M	37.0	1.73	69.9	23.4	1,635
M	38.0	1.83	81.0	24.2	1,716
M	38.0	1.65	58.0	21.3	1,752
M	38.0	1.81	75.0	22.9	1,594
M	38.0	1.73	66.5	22.2	1,479
M	38.0	1.73	72.1	24.1	1,769
M	39.0	1.70	62.3	21.6	1,410
M	39.0	1.69	66.8	23.4	1,558
M	39.0	1.85	74.2	21.7	1,697
M	39.0	1.75	59.4	19.4	1,554
M	39.0	1.79	73.6	23.0	1,647
M	40.0	1.76	69.7	22.5	1,601
M	40.0	1.85	76.6	22.4	2,034
M	40.0	1.86	71.0	20.5	1,522
M	40.0	1.82	71.1	21.5	1,706
M	40.0	1.82	73.8	22.3	1,589

TEE	PALo	PALCAT
2,866	1.53	LA
2,347	1.55	LA
3,181	1.71	A
3,040	1.54	LA
2,433	1.59	LA
2,574	1.76	A
3,121	1.82	A
3,035	1.91	VA
2,933	1.69	A
4,206	2.32	VA
2,390	1.43	LA
2,569	1.47	LA
2,510	1.62	A
2,536	1.68	A
2,725	1.71	A
2,813	1.85	A
3,291	2.02	VA
3,805	2.26	VA
2,820	1.51	LA
3,657	1.76	A
2,842	1.81	A
3,542	1.87	A
3,250	1.94	VA
2,426	1.55	LA
2,684	1.62	A
3,728	2.17	VA
3,112	1.59	LA
3,499	1.95	VA
2,486	1.58	LA
3,162	2.00	VA
3,310	2.02	VA
2,770	1.61	A
2,868	1.64	A
2,813	1.76	A
2,796	1.89	A
3,609	2.04	VA
2,366	1.68	A
2,741	1.76	A
3,155	1.86	A
2,940	1.89	A
3,143	1.91	VA
2,605	1.63	A
3,370	1.66	A
2,567	1.69	A
2,985	1.75	A
2,796	1.76	A

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
M	40.0	1.77	75.2	24.0	1,436
M	40.0	1.77	78.3	25.0	1,582
M	40.0	1.77	63.4	20.2	1,288
M	40.0	1.84	71.5	21.1	1,604
M	40.0	1.73	66.3	22.2	1,565
M	40.0	1.77	74.9	23.9	1,613
M	41.0	1.79	62.4	19.5	1,669
M	41.0	1.77	77.0	24.6	1,666
M	42.0	1.72	59.1	20.0	1,464
M	43.0	1.65	57.2	21.0	1,439
M	43.0	1.73	70.5	23.6	1,797
M	46.0	1.85	78.1	22.8	2,464
M	47.0	1.76	74.4	24.0	1,587
M	48.0	1.77	70.3	22.4	1,697
M	48.0	1.77	77.4	24.7	2,194
M	48.0	1.75	74.9	24.5	1,843
M	54.0	1.76	65.4	21.1	1,400
M	56.0	1.86	81.2	23.5	1,440
M	56.0	1.66	56.6	20.5	1,360
M	57.0	1.81	78.2	23.9	1,840
M	59.0	1.64	59.8	22.2	1,496
M	59.0	1.84	80.3	23.7	1,945
M	59.0	1.86	84.4	24.4	1,600
M	59.0	1.81	78.6	24.0	1,640
M	60.0	1.80	69.0	21.3	1,530
M	63.0	1.68	63.5	22.5	1,354
M	63.0	1.69	69.1	24.2	1,370
M	64.0	1.66	68.4	24.8	1,810
M	65.0	1.83	78.1	23.3	1,650
M	65.0	1.83	81.0	24.2	1,820
M	66.0	1.68	65.9	23.4	1,210
M	67.0	1.75	66.9	21.8	1,426
M	67.0	1.67	66.3	23.8	1,440
M	68.0	1.80	61.0	18.8	1,354
M	68.0	1.74	59.2	19.6	1,210
M	69.0	1.61	63.7	24.6	1,417
M	69.0	1.64	65.1	24.2	1,310
M	69.0	1.75	73.2	23.9	1,915
M	70.0	1.76	74.5	24.0	1,611
M	70.0	1.74	70.1	23.2	1,420
M	71.0	1.85	74.5	21.8	1,560
M	71.0	1.83	79.6	23.8	2,060
M	71.0	1.78	77.5	24.4	1,413
M	72.0	1.66	64.8	23.5	1,380
M	72.0	1.74	70.6	23.3	1,640
M	72.0	1.74	56.4	18.6	1,300

TEE	PALo	PALCAT
2,643	1.84	A
2,964	1.87	A
2,459	1.91	VA
3,384	2.11	VA
3,346	2.14	VA
3,501	2.17	VA
2,988	1.79	A
3,317	1.99	VA
3,456	2.36	VA
2,653	1.84	A
3,630	2.02	VA
3,473	1.41	LA
2,452	1.55	LA
2,851	1.68	A
3,767	1.72	A
3,313	1.80	A
2,118	1.51	LA
2,189	1.52	LA
3,061	2.25	VA
2,320	1.26	S
2,065	1.38	S
2,892	1.49	LA
2,517	1.57	LA
2,941	1.79	A
2,470	1.61	A
2,338	1.73	A
2,686	1.96	VA
2,398	1.32	S
2,833	1.72	A
3,274	1.80	A
1,950	1.61	A
2,176	1.53	LA
2,526	1.75	A
2,002	1.48	LA
2,076	1.72	A
1,972	1.39	S
1,822	1.39	S
3,027	1.58	LA
2,751	1.71	A
2,846	2.00	VA
2,124	1.36	S
3,353	1.63	A
2,756	1.95	VA
1,699	1.23	S
2,583	1.58	LA
2,656	2.04	VA

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
M	73.0	1.87	80.5	23.0	1,930
M	73.0	1.82	79.0	23.8	1,563
M	74.0	1.72	63.0	21.3	1,463
M	74.0	1.74	72.1	23.8	1,430
M	74.0	1.76	74.8	24.1	1,592
M	74.0	1.84	74.9	22.1	1,580
M	74.0	1.75	73.3	23.9	1,506
M	74.0	1.65	66.7	24.5	1,365
M	75.0	1.69	69.1	24.2	1,351
M	75.0	1.71	63.8	21.8	1,446
M	76.0	1.74	74.3	24.5	1,692
M	76.0	1.74	65.7	21.7	1,260
M	76.0	1.73	63.6	21.2	1,500
M	77.0	1.77	77.3	24.7	1,417
M	77.0	1.70	59.9	20.7	1,527
M	77.0	1.60	59.9	23.4	1,279
M	77.0	1.80	76.9	23.7	1,501
M	77.0	1.71	69.3	23.7	1,133
M	78.0	1.75	61.6	20.1	1,420
M	79.0	1.72	66.9	22.6	1,522
M	79.0	1.73	63.6	21.2	1,530
M	79.0	1.81	76.8	23.4	1,549
M	80.0	1.66	64.4	23.4	1,472
M	81.0	1.73	66.0	22.1	1,456
M	84.0	1.73	65.0	21.7	1,427
M	87.0	1.73	73.1	24.4	1,472
M	90.0	1.75	75.9	24.8	1,420
M	91.0	1.65	66.0	24.2	1,260
M	94.0	1.70	65.0	22.5	1,587
M	95.0	1.73	69.0	23.1	1,685
M	95.0	1.70	53.6	18.5	1,298
M	96.0	1.72	64.0	21.6	1,243
F	20.0	1.75	72.5	23.7	1,623
F	20.0	1.75	61.8	20.2	1,484
F	20.0	1.65	65.1	23.9	1,520
F	21.0	1.61	63.4	24.5	1,491
F	21.0	1.58	52.7	21.1	1,215
F	21.0	1.67	55.6	19.9	1,243
F	21.0	1.66	60.1	21.8	1,259
F	22.0	1.70	55.9	19.3	1,326
F	23.0	1.64	56.2	20.9	1,395
F	23.0	1.56	47.1	19.3	1,338
F	23.0	1.63	52.0	19.6	1,219
F	23.0	1.73	68.7	23.0	1,632
F	23.0	1.64	56.4	21.0	1,334
F	23.0	1.68	64.1	22.7	1,396

TEE	PALo	PALCAT
2,471	1.28	S
2,137	1.37	S
1,816	1.24	S
1,906	1.33	S
2,557	1.61	A
2,638	1.67	A
2,732	1.81	A
2,498	1.83	A
2,245	1.66	A
2,498	1.73	A
2,242	1.32	S
2,132	1.69	A
2,629	1.75	A
2,036	1.44	LA
2,302	1.51	LA
1,993	1.56	LA
2,438	1.62	A
2,376	2.10	VA
2,035	1.43	LA
2,232	1.47	LA
2,422	1.58	LA
3,114	2.01	VA
1,991	1.35	S
1,795	1.23	S
1,460	1.02	S
1,556	1.06	S
1,925	1.36	S
2,072	1.65	A
1,831	1.15	S
2,170	1.29	S
1,761	1.36	S
1,850	1.49	LA
2,732	1.68	A
2,677	1.80	A
2,799	1.84	A
2,452	1.64	A
2,205	1.81	A
2,653	2.13	VA
2,523	2.00	VA
2,550	1.92	VA
1,845	1.32	S
2,132	1.59	LA
2,032	1.67	A
2,949	1.81	A
2,653	1.99	VA
2,835	2.03	VA

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	23.0	1.77	62.1	19.8	1,193
F	23.0	1.68	61.0	21.6	1,461
F	23.0	1.67	58.5	21.0	1,039
F	23.0	1.71	59.2	20.2	1,333
F	23.7	1.79	61.8	19.3	1,482
F	23.7	1.79	62.1	19.4	1,191
F	24.0	1.70	68.2	23.6	1,469
F	24.0	1.79	71.4	22.3	1,526
F	24.0	1.63	62.9	23.7	1,458
F	24.0	1.73	57.8	19.3	1,482
F	24.2	1.61	58.8	22.6	1,211
F	25.0	1.69	63.4	22.2	1,775
F	25.0	1.75	72.1	23.5	1,618
F	25.0	1.66	65.5	23.8	1,508
F	25.0	1.65	64.2	23.6	1,591
F	25.0	1.60	53.3	20.8	1,112
F	25.2	1.74	68.3	22.4	1,404
F	25.3	1.51	42.6	18.6	1,253
F	26.0	1.62	54.1	20.6	1,323
F	26.0	1.58	53.4	21.4	1,322
F	26.0	1.71	55.3	18.9	1,434
F	26.2	1.61	55.6	21.6	1,102
F	26.4	1.64	54.2	20.2	1,293
F	26.5	1.69	58.0	20.2	1,373
F	26.5	1.61	50.8	19.7	1,125
F	26.7	1.54	50.9	21.4	1,172
F	26.8	1.63	51.0	19.1	1,184
F	27.0	1.64	58.2	21.6	1,306
F	27.0	1.71	65.7	22.5	1,499
F	27.0	1.76	59.9	19.3	1,482
F	27.0	1.70	65.0	22.5	1,494
F	27.0	1.68	52.3	18.5	1,484
F	27.0	1.65	58.1	21.3	1,424
F	27.0	1.68	56.7	20.1	1,386
F	27.0	1.66	56.0	20.3	1,386
F	27.0	1.78	68.1	21.5	1,363
F	27.3	1.66	56.8	20.5	1,339
F	27.3	1.66	51.4	18.6	1,210
F	27.4	1.55	51.0	21.3	1,145
F	27.4	1.68	58.1	20.5	1,260
F	27.5	1.60	63.3	24.6	1,347
F	27.6	1.69	59.3	20.9	1,409
F	27.6	1.69	55.7	19.4	1,392
F	27.6	1.64	51.9	19.3	1,231
F	27.9	1.59	61.2	24.2	1,229
F	28.0	1.77	68.2	21.8	1,721

TEE	PALo	PALCAT
2,605	2.18	VA
3,248	2.22	VA
2,314	2.23	VA
2,659	1.99	VA
2,792	1.88	A
2,530	2.12	VA
2,176	1.48	LA
2,522	1.65	A
2,510	1.72	A
2,746	1.85	A
2,218	1.83	A
2,154	1.21	S
2,617	1.62	A
2,572	1.71	A
2,738	1.72	A
2,111	1.90	A
2,493	1.78	A
2,711	2.16	VA
1,552	1.17	S
1,800	1.36	S
3,529	2.46	VA
1,844	1.67	A
2,077	1.61	A
2,431	1.77	A
2,484	2.21	VA
2,059	1.76	A
2,319	1.96	VA
2,255	1.73	A
2,196	1.47	LA
2,199	1.48	LA
2,373	1.59	LA
2,567	1.73	A
2,498	1.75	A
2,534	1.83	A
2,844	2.05	VA
2,856	2.10	VA
2,526	1.89	A
2,140	1.77	A
1,811	1.58	LA
2,130	1.69	A
2,409	1.79	A
3,443	2.44	VA
2,006	1.44	LA
2,021	1.64	A
1,913	1.56	LA
2,531	1.47	LA

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	28.0	1.67	59.3	21.3	1,114
F	28.0	1.67	66.7	23.9	1,530
F	28.0	1.65	62.2	22.8	1,414
F	28.0	1.65	62.1	22.9	1,361
F	28.4	1.67	65.4	23.4	1,357
F	29.0	1.77	66.4	21.2	1,482
F	29.0	1.64	66.8	24.8	1,430
F	29.0	1.75	76.2	24.9	1,466
F	29.0	1.60	57.7	22.6	1,380
F	29.0	1.50	51.0	22.7	1,121
F	29.0	1.63	65.5	24.7	1,600
F	29.0	1.68	60.3	21.4	1,469
F	29.0	1.61	48.0	18.5	1,166
F	29.1	1.57	56.8	23.1	1,214
F	29.4	1.63	51.3	19.2	1,110
F	29.7	1.65	53.0	19.4	1,189
F	30.0	1.64	52.9	19.6	1,293
F	30.0	1.59	53.6	21.2	1,410
F	30.0	1.64	60.4	22.4	1,484
F	30.0	1.78	64.7	20.4	1,306
F	30.6	1.58	51.9	20.7	1,235
F	31.0	1.66	68.0	24.5	1,426
F	31.0	1.80	69.5	21.5	1,497
F	31.0	1.70	59.8	20.7	1,402
F	31.0	1.75	69.6	22.7	1,446
F	31.0	1.55	59.1	24.6	1,040
F	31.0	1.66	61.8	22.4	1,012
F	31.1	1.59	53.0	21.0	1,383
F	31.4	1.60	52.9	20.6	1,107
F	31.5	1.61	51.2	19.7	1,300
F	31.6	1.56	46.9	19.2	1,018
F	31.8	1.67	64.1	23.0	1,433
F	32.0	1.81	70.4	21.5	1,577
F	32.0	1.57	52.6	21.3	1,195
F	32.0	1.56	53.6	22.0	1,355
F	32.0	1.71	62.1	21.2	1,501
F	32.2	1.63	61.1	22.9	1,493
F	32.6	1.65	65.3	24.0	1,545
F	32.7	1.60	52.4	20.4	1,374
F	32.7	1.64	56.1	20.9	1,330
F	33.0	1.57	49.5	20.1	1,477
F	33.0	1.65	53.3	19.6	1,135
F	33.1	1.76	62.2	20.0	1,368
F	33.5	1.65	63.5	23.4	1,302
F	33.5	1.61	48.7	18.8	1,294
F	33.6	1.65	53.8	19.8	1,205

TEE	PALo	PALCAT
1,809	1.62	A
2,490	1.63	A
2,468	1.75	A
2,406	1.77	A
3,241	2.39	VA
2,365	1.60	LA
2,091	1.46	LA
2,161	1.47	LA
2,081	1.51	LA
1,695	1.51	LA
2,822	1.76	A
2,867	1.95	VA
2,630	2.26	VA
2,377	1.96	VA
2,119	1.91	VA
2,798	2.35	VA
1,882	1.46	LA
2,455	1.74	A
2,885	1.94	VA
3,156	2.42	VA
2,453	1.99	VA
2,375	1.67	A
2,284	1.53	LA
2,154	1.54	LA
2,673	1.85	A
2,055	1.98	VA
2,431	2.40	VA
2,286	1.65	A
2,197	1.98	VA
2,110	1.62	A
2,082	2.05	VA
3,381	2.36	VA
2,390	1.52	LA
1,888	1.58	LA
2,247	1.66	A
2,703	1.80	A
2,184	1.46	LA
2,422	1.57	LA
2,536	1.85	A
2,270	1.71	A
2,685	1.82	A
2,277	2.01	VA
2,684	1.96	VA
2,756	2.12	VA
2,452	1.90	A
2,346	1.95	VA

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	33.6	1.59	49.4	19.5	1,313
F	34.0	1.60	61.3	23.9	1,298
F	34.0	1.67	69.0	24.6	1,274
F	34.2	1.72	61.5	20.8	1,452
F	34.3	1.64	63.9	23.7	1,444
F	34.5	1.68	53.4	18.8	1,412
F	34.6	1.62	62.5	23.8	1,232
F	35.0	1.60	62.2	24.3	1,362
F	35.0	1.66	55.4	20.1	1,398
F	35.7	1.58	55.5	22.2	1,290
F	35.8	1.72	56.3	19.1	1,263
F	35.9	1.67	63.8	22.8	1,208
F	35.9	1.66	58.1	21.2	1,393
F	36.0	1.65	62.8	23.1	1,309
F	36.0	1.66	58.7	21.3	1,202
F	36.1	1.57	54.0	21.8	1,267
F	36.2	1.66	59.2	21.4	1,290
F	36.7	1.66	61.8	22.5	1,212
F	37.5	1.71	65.2	22.4	1,501
F	37.6	1.67	55.2	19.7	1,272
F	37.6	1.66	60.3	21.9	1,153
F	37.9	1.61	53.5	20.7	1,343
F	38.0	1.73	68.5	22.9	1,458
F	38.0	1.61	54.2	20.9	1,291
F	38.8	1.67	60.4	21.6	1,491
F	39.0	1.62	60.2	22.9	1,346
F	39.0	1.73	57.5	19.2	1,434
F	39.2	1.61	50.8	19.5	1,181
F	39.6	1.66	62.5	22.7	1,348
F	41.0	1.61	48.7	18.8	1,341
F	41.0	1.65	64.4	23.7	1,482
F	41.0	1.68	65.8	23.3	1,386
F	41.0	1.58	59.5	23.8	1,345
F	42.0	1.64	60.1	22.3	1,496
F	43.0	1.54	52.6	22.2	1,044
F	43.0	1.59	62.3	24.6	1,181
F	45.0	1.61	52.7	20.3	1,123
F	51.0	1.63	50.6	19.0	1,197
F	55.0	1.67	63.8	22.9	1,212
F	55.0	1.62	51.8	19.7	1,226
F	55.0	1.66	63.1	22.7	1,377
F	55.0	1.58	57.9	23.2	1,089
F	56.0	1.66	58.9	21.4	1,440
F	56.0	1.67	61.8	22.2	1,138
F	56.0	1.61	57.6	22.2	1,364
F	56.0	1.60	57.7	22.5	1,139

TEE	PALo	PALCAT
2,403	1.83	A
2,347	1.81	A
2,053	1.61	A
2,534	1.75	A
2,182	1.51	LA
2,155	1.53	LA
2,518	2.04	VA
1,876	1.38	S
2,916	2.09	VA
2,236	1.73	A
2,650	2.10	VA
2,276	1.88	A
2,726	1.96	VA
1,987	1.52	LA
2,357	1.96	VA
2,354	1.86	A
2,039	1.58	LA
3,004	2.48	VA
2,020	1.35	S
2,596	2.04	VA
2,473	2.14	VA
2,476	1.84	A
2,414	1.66	A
2,223	1.72	A
2,908	1.95	VA
2,453	1.82	A
2,218	1.55	LA
2,678	2.27	VA
2,548	1.89	A
1,989	1.48	LA
2,366	1.60	LA
2,318	1.67	A
3,037	2.26	VA
2,909	1.94	VA
1,991	1.91	VA
2,765	2.34	VA
2,151	1.91	VA
2,141	1.79	A
1,912	1.58	LA
2,193	1.79	A
2,604	1.89	A
2,173	1.99	VA
2,316	1.61	A
1,936	1.70	A
2,657	1.95	VA
2,240	1.97	VA

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	56.0	1.76	69.7	22.5	1,404
F	57.0	1.55	55.6	23.1	1,244
F	57.0	1.64	61.7	22.8	1,182
F	57.0	1.60	53.5	20.9	1,060
F	57.0	1.64	64.0	23.8	1,330
F	57.0	1.76	57.8	18.6	1,291
F	58.0	1.62	59.9	22.8	1,228
F	58.0	1.68	65.7	23.3	1,140
F	59.0	1.71	64.9	22.1	1,268
F	60.0	1.60	61.9	24.2	1,642
F	60.0	1.62	57.1	21.7	1,238
F	60.0	1.64	62.3	23.2	1,601
F	60.0	1.64	61.3	22.8	1,048
F	60.0	1.56	56.0	23.0	1,051
F	60.0	1.60	57.8	22.5	1,123
F	60.0	1.64	57.0	21.2	1,122
F	60.0	1.67	64.6	23.2	1,204
F	61.0	1.57	52.5	21.3	1,319
F	61.0	1.60	51.6	20.3	1,102
F	61.0	1.58	52.3	21.0	1,113
F	61.0	1.64	61.8	23.0	1,269
F	61.0	1.71	66.1	22.7	1,178
F	62.0	1.64	64.4	23.9	1,269
F	62.0	1.59	63.1	25.0	1,336
F	62.0	1.64	55.3	20.5	1,151
F	62.0	1.65	61.1	22.4	1,130
F	62.0	1.60	49.2	19.2	1,109
F	63.0	1.68	53.6	19.0	1,220
F	63.0	1.64	64.0	23.8	1,280
F	63.0	1.63	56.4	21.2	1,500
F	63.0	1.60	53.9	21.1	1,030
F	63.0	1.70	57.6	20.0	1,194
F	63.0	1.65	60.7	22.3	1,100
F	63.0	1.58	59.3	23.6	1,210
F	64.0	1.69	67.6	23.7	1,120
F	64.0	1.50	56.0	24.7	1,139
F	64.0	1.66	63.5	23.1	1,008
F	64.0	1.51	57.0	25.0	1,181
F	64.0	1.72	56.6	19.1	1,104
F	64.0	1.65	54.3	19.9	1,234
F	64.0	1.52	50.0	21.6	989
F	65.0	1.65	65.5	24.1	1,339
F	65.0	1.69	69.1	24.2	1,454
F	65.0	1.56	56.5	23.2	1,117
F	65.0	1.64	59.9	22.3	1,278
F	65.0	1.64	54.1	20.2	1,132

TEE	PALo	PALCAT
3,067	2.18	VA
1,738	1.40	S
1,721	1.46	LA
1,784	1.68	A
2,264	1.70	A
2,318	1.80	A
1,814	1.48	LA
1,796	1.58	LA
2,597	2.05	VA
1,932	1.18	S
1,593	1.29	S
2,622	1.64	A
1,854	1.77	A
2,070	1.97	VA
2,239	1.99	VA
2,287	2.04	VA
2,469	2.05	VA
2,166	1.64	A
1,883	1.71	A
2,015	1.81	A
2,426	1.91	VA
2,340	1.99	VA
2,189	1.73	A
2,328	1.74	A
2,208	1.92	VA
2,275	2.01	VA
2,543	2.29	VA
1,575	1.29	S
1,876	1.47	LA
2,280	1.52	LA
1,671	1.62	A
2,044	1.71	A
1,910	1.74	A
2,376	1.96	VA
1,407	1.26	S
1,624	1.43	LA
1,684	1.67	A
2,223	1.88	A
2,137	1.93	VA
2,677	2.17	VA
2,199	2.22	VA
1,352	1.01	S
1,889	1.30	S
1,772	1.59	LA
2,118	1.66	A
2,577	2.28	VA

continued

TABLE I-3 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	66.0	1.68	60.8	21.5	1,696
F	66.0	1.68	69.4	24.6	1,482
F	67.0	1.58	57.0	22.8	1,159
F	67.0	1.56	54.8	22.5	1,154
F	67.0	1.67	66.0	23.7	1,267
F	68.0	1.63	65.7	24.7	1,280
F	68.0	1.65	52.0	19.1	1,100
F	68.0	1.68	66.6	23.6	1,362
F	68.0	1.69	65.4	22.9	1,230
F	68.0	1.56	47.5	19.5	1,090
F	69.0	1.56	55.4	22.8	1,070
F	70.0	1.63	61.3	23.1	1,152
F	70.0	1.72	61.0	20.6	1,226
F	70.0	1.66	52.3	19.0	1,037
F	70.0	1.64	61.2	22.8	1,512
F	70.0	1.58	56.8	22.8	1,260
F	71.0	1.78	79.1	25.0	1,420
F	71.0	1.65	57.4	21.1	1,189
F	71.0	1.62	54.8	20.9	1,236
F	72.0	1.58	52.7	21.1	1,120
F	72.0	1.63	56.2	21.2	1,140
F	72.0	1.65	66.4	24.4	1,180
F	73.0	1.62	57.8	22.0	1,498
F	74.0	1.68	62.7	22.2	1,123
F	76.0	1.57	46.2	18.7	1,109
F	83.0	1.54	53.0	22.3	1,200
F	86.0	1.59	53.0	21.0	1,123
F	87.0	1.52	48.0	20.8	1,049
F	88.0	1.55	49.5	20.6	1,188
F	89.0	1.50	51.0	22.7	1,135
F	89.0	1.53	56.8	24.3	1,162
F	91.0	1.52	45.5	19.7	1,097
F	92.0	1.49	45.0	20.3	1,004
F	93.0	1.73	61.0	20.4	1,386
F	95.0	1.52	46.7	20.2	1,336
F	95.0	1.56	56.7	23.3	1,152
F	96.0	1.61	55.7	21.5	1,363
F	96.0	1.50	56.0	24.9	1,130
F	96.0	1.56	53.0	21.8	1,016
F	96.0	1.52	50.3	21.8	1,032

NOTE: BEEo = basal energy expenditure (BEE) as observed in the study, TEE = total energy expenditure, PALo = physical activity level (PAL) as observed in the study,

TEE	PALo	PALCAT
1,941	1.14	S
2,359	1.59	LA
1,627	1.40	LA
1,859	1.61	A
2,710	2.14	VA
1,678	1.31	S
1,513	1.37	S
1,955	1.44	LA
1,919	1.56	LA
1,925	1.77	A
1,686	1.58	LA
1,369	1.19	S
1,795	1.46	LA
1,601	1.54	LA
2,353	1.56	LA
2,282	1.81	A
1,684	1.19	S
1,665	1.40	S
2,070	1.68	A
1,659	1.48	LA
1,854	1.63	A
1,937	1.64	A
1,776	1.19	S
2,089	1.86	A
2,298	2.07	VA
1,525	1.27	S
1,269	1.13	S
1,274	1.21	S
1,599	1.35	S
1,231	1.08	S
1,393	1.20	S
1,424	1.30	S
1,061	1.06	S
1,491	1.08	S
1,434	1.07	S
1,537	1.33	S
1,448	1.06	S
1,233	1.09	S
1,150	1.13	S
1,429	1.38	S

PALCAT = PAL category (S = sedentary, LA = low active, A = active, VA = very active), M = male, F = female.

TABLE I-4 Pregnant Women with Prepregnancy Body Mass Index (BMI) from 18.5 up to 25 kg/m^2

Gestation (wk)	Age (y)	Height (m)	Weight (kg)	BMI
36	26	1.59	65.9	*26.1*
36	27	1.68	70.6	*25.0*
6	28.8	1.64	62.2	*23.1*
12	28.8	1.64	63.3	*23.5*
18	28.8	1.64	65.4	*24.3*
24	28.8	1.64	68.7	*25.5*
30	28.8	1.64	71.7	*26.7*
36	28.8	1.64	73.6	*27.4*
30	29	1.65	70.2	*25.8*
16–18	29	1.65	63.7	*23.4*
36	29	1.73	64.8	*21.7*
36	29	1.66	72.7	*26.4*
8–10	29.1	NR	NR	NR
24–26	29.1	NR	NR	NR
34–36	29.1	NR	NR	NR
36	30	1.66	64.2	*23.3*
36	30	1.57	56.6	*23.0*
36	31	1.63	57.4	*21.6*
36	32	1.55	67.6	*28.2*
36	34	1.60	68.2	*26.6*
36	38	1.73	91.3	*30.5*
36	40	1.65	71.9	*26.4*

NOTE: BEEo = basal energy expenditure (BEE) as observed in the study, TEE = total energy expenditure, PALo = Physical activity level (PAL) as observed in the study, PALCAT = PAL category (S = sedentary, LA = low active, A = active, VA = very active),

BEEo (kcal/d)	TEE (kcal/d)	PALo	PALCAT
1,730	2,389	*1.38*	S
1,869	2,730	*1.46*	LA
1,504	2,323	1.54	LA
1,488	2,427	1.64	A
1,493	2,457	1.65	A
1,580	2,623	1.66	A
1,650	2,676	1.62	A
1,804	2,689	1.50	LA
1,649	2,988	1.82	A
1,434	2,294	1.65	A
1,757	2,182	*1.24*	S
1,745	2,916	1.66	A
1,305	2,048	*1.57*	LA
1,544	2,411	*1.56*	LA
1,691	2,729	*1.61*	A
1,934	2,497	*1.29*	S
1,539	2,653	*1.72*	A
1,750	2,636	*1.51*	LA
1,671	2,326	*1.39*	S
1,773	2,457	*1.39*	S
1,833	2,661	*1.45*	LA
1,532	2,168	*1.42*	LA

NR = not reported. Values in *italics* are calculated; BEEo values in **bold** were reported as resting metabolic rate in the study.

TABLE I-5 Lactating Women with Prepregnancy Body Mass Index (BMI) from 18.5 up to 25 kg/m^2

Month of Lactation	Age (y)	Height (m)	Weight (kg)	BMI
1	26	1.59	54.2	*21.4*
2	26	1.59	53.2	*21.1*
3	26	1.59	52.7	*20.8*
1	27	1.68	60.4	*21.4*
2	27	1.68	59.9	*21.2*
3	27	1.68	60.7	*21.5*
2	28	1.67	64.4	*23.1*
6	28	1.67	63.0	*22.6*
1	29	1.73	55.8	*18.6*
2	29	1.73	56.3	*18.8*
3	29	1.73	56.7	*18.9*
1–1.5	29.1	NR	NR	NR
1	30	1.66	55.9	*20.3*
1	30	1.57	50.6	*20.5*
2	30	1.66	56.2	*20.4*
2	30	1.57	50.0	*20.3*
3	30	1.66	55.2	*20.0*
3	30	1.57	49.7	*20.2*
3	30.4	1.63	62.8	23.5
1	31	1.63	48.7	*18.3*
2	31	1.63	49.3	*18.6*
3	31	1.63	49.1	*18.5*
3–6.5	31.3	1.68	64.8	*23.0*
1	32	1.55	56.7	*23.6*
2	32	1.55	57.0	*23.7*
3	32	1.55	56.4	*23.5*
1	34	1.60	60.2	*23.5*
2	34	1.60	59.8	*23.4*
3	34	1.60	59.2	*23.1*
1	38	1.73	83.4	*27.9*
2	38	1.73	83.2	*27.8*
3	38	1.73	83.0	*27.7*
1	40	1.65	62.9	*23.1*
2	40	1.65	63.8	*23.4*
3	40	1.65	63.6	*23.4*

NOTE: BEEo = basal energy expenditure (BEE) as observed in the study, TEE = total energy expenditure, PALo = physical activity level (PAL) as observed in the study, PALCAT = PAL category (S = sedentary, LA = low active, A = active, VA = very active),

BEEo (kcal/d)	TEE (kcal/d)	PALo	Milk Energy Output (kcal/d)
1,255	1,612	*1.28*	531
1,238	1,871	*1.51*	548
1,262	1,729	*1.37*	539
1,362	1,948	*1.43*	523
1,358	2,013	*1.48*	339
1,386	2,127	*1.53*	425
1,410	2,533	1.82	NR
1,434	2,581	1.79	NR
1,396	2,124	*1.52*	490
1,343	2,190	*1.63*	526
1,262	2,131	*1.69*	605
1,329	2,147	*1.62*	NR
1,565	2,380	*1.52*	567
1,358	1,883	*1.39*	480
1,573	2,339	*1.49*	511
1,319	2,176	*1.65*	490
1,372	2,406	*1.75*	379
1,281	2,334	*1.82*	477
1,331	2,414	1.79	483
1,370	2,520	*1.84*	531
1,379	2,516	*1.82*	617
1,346	2,636	*1.96*	467
1,377	2,414	*1.75*	538
1,575	1,800	*1.14*	665
1,248	2,100	*1.68*	699
1,303	1,876	*1.44*	693
1,432	2,124	*1.48*	540
1,503	2,065	*1.37*	400
1,355	1,700	*1.25*	428
1,497	3,105	*2.07*	290
1,527	2,525	*1.65*	NR
1,471	2,579	*1.75*	552
1,262	1,609	*1.28*	750
1,484	1,925	*1.30*	655
1,417	1,871	*1.32*	735

NR = not reported. Values in *italics* are calculated. BEEo values in **bold** were reported as resting metabolic rate (RMR) in the study.

TABLE I-6 Overweight/Obese Children, 3 Through 18 Years of Age, with Body Mass Index (BMI) > 85th Percentile

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
M	4.0	1.07	21.7	18.9	NR
M	4.0	1.02	18.1	17.4	NR
M	4.1	1.17	23.2	20.2	NR
M	4.3	1.21	29.7	20.3	NR
M	4.6	1.07	20.3	17.7	NR
M	4.8	1.07	20.8	18.3	NR
M	5.0	1.18	29.8	21.4	1,220
M	5.0	1.18	30.7	22.0	1,010
M	5.0	1.15	22.4	16.9	1,085
M	5.0	1.09	25.1	21.1	1,020
M	5.0	1.15	22.3	16.9	1,060
M	5.0	1.11	22.1	17.9	1,030
M	5.0	1.19	26.5	18.7	1,235
M	5.0	1.18	28.9	20.8	1,200
M	5.0	1.20	31.0	21.5	1,235
M	5.0	1.18	28.5	20.5	1,205
M	5.0	1.11	21.7	17.6	980
M	5.0	1.19	36.1	25.5	1,385
M	5.0	1.08	19.9	17.1	1,015
M	5.0	1.13	23.9	18.7	1,300
M	5.0	1.21	35.3	24.1	1,325
M	5.0	1.12	25.4	20.2	1,135
M	5.0	1.19	32.1	22.7	1,310
M	5.0	1.20	24.9	17.3	1,150
M	5.0	1.17	27.3	19.9	1,185
M	5.0	1.16	35.5	26.4	1,210
M	5.0	1.23	28.6	18.9	1,320
M	5.0	1.23	32.3	21.4	1,200
M	5.0	1.17	23.8	17.4	1,115
M	5.0	1.17	23.4	17.1	1,145
M	5.0	1.15	26.5	20.0	1,185
M	5.0	1.16	23.6	17.5	1,045
M	5.0	1.18	23.7	17.0	1,170
M	5.0	1.15	22.7	17.2	1,195
M	5.0	1.12	24.4	19.5	1,235
M	5.0	1.18	32.1	23.1	1,465
M	5.0	1.21	26.5	18.1	1,105
M	5.0	1.11	23.9	19.4	1,085
M	5.0	1.15	24.0	18.1	1,215
M	5.0	1.12	22.5	17.9	1,035
M	5.0	1.19	26.0	18.4	1,250
M	5.0	1.19	26.3	18.6	1,191
M	5.0	1.11	20.9	17.0	1,125
M	5.0	1.22	37.9	25.5	1,470

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,100	1,342	1.22	NR	S
1,015	1,017	1.00	NR	S
1,117	1,632	1.46	NR	LA
1,279	1,905	1.49	NR	LA
1,053	1,478	1.40	NR	LA
1,053	1,572	1.49	NR	LA
1,244	1,418	1.14	1.16	S
1,259	1,481	1.18	1.47	LA
1,108	1,336	1.21	1.23	S
1,128	1,388	1.23	1.36	S
1,107	1,389	1.26	1.31	S
1,086	1,370	1.26	1.33	S
1,193	1,529	1.28	1.24	S
1,229	1,577	1.28	1.31	S
1,273	1,633	1.28	1.32	S
1,223	1,571	1.28	1.30	S
1,080	1,401	1.30	1.43	LA
1,354	1,758	1.30	1.27	S
1,037	1,359	1.31	1.34	S
1,125	1,477	1.31	1.14	S
1,349	1,795	1.33	1.35	S
1,146	1,529	1.33	1.35	S
1,287	1,725	1.34	1.32	S
1,171	1,588	1.36	1.38	S
1,198	1,627	1.36	1.37	S
1,331	1,818	1.37	1.50	LA
1,246	1,721	1.38	1.30	S
1,307	1,807	1.38	1.51	LA
1,140	1,576	1.38	1.41	LA
1,133	1,581	1.40	1.38	S
1,177	1,659	1.41	1.40	LA
1,132	1,600	1.41	1.53	LA
1,142	1,621	1.42	1.39	S
1,113	1,581	1.42	1.32	S
1,129	1,621	1.44	1.31	S
1,283	1,842	1.44	1.26	S
1,202	1,729	1.44	1.56	LA
1,117	1,608	1.44	1.48	LA
1,135	1,635	1.44	1.35	S
1,097	1,585	1.44	1.53	LA
1,185	1,718	1.45	1.37	S
1,190	1,751	1.47	1.47	LA
1,066	1,581	1.48	1.41	LA
1,396	2,071	1.48	1.41	LA

continued

TABLE I-6 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
M	5.0	1.17	23.9	17.5	1,150
M	5.0	1.20	30.5	21.2	1,245
M	5.0	1.06	18.9	16.8	1,040
M	5.0	1.17	26.0	19.0	1,085
M	5.0	1.21	28.7	19.6	1,225
M	5.0	1.20	27.0	18.8	1,135
M	5.0	1.17	25.8	18.8	1,175
M	5.0	1.22	39.6	26.6	1,380
M	5.0	1.21	29.4	20.1	1,345
M	5.0	1.15	30.8	23.3	1,240
M	5.1	1.16	23.1	17.1	NR
M	5.1	1.21	24.5	16.8	NR
M	5.2	1.18	24.7	17.6	NR
M	5.3	1.18	25.2	17.9	NR
M	5.6	1.13	21.8	17.2	NR
M	5.6	1.07	20.0	17.5	NR
M	5.6	1.15	25.0	18.9	NR
M	5.7	1.13	27.2	21.2	NR
M	5.7	1.24	26.4	17.1	NR
M	6.0	1.20	33.6	23.3	1,125
M	6.0	1.15	25.0	18.9	965
M	6.0	1.22	29.2	19.6	1,215
M	6.0	1.28	30.5	18.6	1,250
M	6.0	1.19	37.1	26.2	1,285
M	6.0	1.21	28.5	19.5	1,300
M	6.0	1.13	22.9	17.9	995
M	6.0	1.23	29.7	19.6	1,080
M	6.0	1.24	27.6	18.0	1,280
M	6.5	1.27	36.7	22.8	NR
M	6.5	1.20	29.0	19.9	NR
M	7.0	1.24	27.1	17.6	NR
M	7.0	1.30	35.6	21.2	NR
M	7.0	1.34	31.4	17.5	1,194
M	7.0	1.26	38.9	24.5	1,430
M	7.2	1.23	30.0	19.8	NR
M	7.3	1.19	25.6	18.1	NR
M	7.3	1.32	34.3	19.8	NR
M	7.4	1.34	31.2	17.4	NR
M	7.4	1.33	45.1	25.5	NR
M	7.7	1.24	35.7	23.2	NR
M	7.7	1.28	29.3	17.7	NR
M	7.9	1.32	33.0	18.9	NR
M	7.9	1.35	36.0	19.8	NR
M	8.0	1.38	35.9	18.9	1,170
M	8.0	1.36	33.5	18.1	1,165
M	8.2	1.53	68.4	29.2	NR

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,142	1,718	1.50	1.49	LA
1,265	1,926	1.52	1.55	LA
1,012	1,554	1.54	1.49	LA
1,177	1,810	1.54	1.67	A
1,239	1,911	1.54	1.56	LA
1,206	1,866	1.55	1.64	A
1,173	1,831	1.56	1.56	LA
1,425	2,229	1.56	1.62	A
1,250	1,964	1.57	1.46	LA
1,248	2,049	1.64	1.65	A
1,120	1,558	1.39	NR	S
1,165	1,658	1.42	NR	LA
1,155	2,741	2.37	NR	VA
1,159	1,284	1.11	NR	S
1,069	1,462	1.37	NR	S
1,015	1,122	1.11	NR	S
1,132	1,442	1.27	NR	S
1,157	1,168	1.01	NR	S
1,188	1,780	1.50	NR	LA
1,283	1,642	1.28	1.46	LA
1,118	1,496	1.34	1.55	LA
1,218	1,705	1.40	1.40	LA
1,264	1,776	1.40	1.42	LA
1,337	2,018	1.51	1.57	LA
1,202	1,848	1.54	1.42	LA
1,075	1,688	1.57	1.70	A
1,230	1,943	1.58	1.80	A
1,199	1,957	1.63	1.53	LA
1,347	1,609	1.19	NR	S
1,190	1,960	1.65	NR	A
1,159	2,156	1.86	NR	A
1,322	1,687	1.28	NR	S
1,271	1,996	1.57	1.67	A
1,363	2,186	1.60	1.53	LA
1,195	1,676	1.40	NR	LA
1,101	1,448	1.32	NR	S
1,299	1,836	1.41	NR	LA
1,254	1,707	1.36	NR	S
1,482	2,515	1.70	NR	A
1,278	1,386	1.08	NR	S
1,190	1,915	1.61	NR	A
1,258	1,484	1.18	NR	S
1,322	2,975	2.25	NR	VA
1,330	2,110	1.59	1.80	A
1,281	2,109	1.65	1.81	A
1,928	2,657	1.38	NR	S

continued

TABLE I-6 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
M	8.4	1.42	53.4	26.5	NR
M	9.0	1.40	39.0	19.9	NR
M	9.0	1.38	45.5	24.0	NR
M	9.0	1.40	41.9	21.4	1,465
M	9.1	1.48	48.3	22.2	NR
M	9.3	1.40	40.0	20.4	NR
M	9.3	1.41	54.6	27.5	NR
M	9.5	1.38	41.9	22.0	NR
M	9.7	1.46	47.8	22.6	NR
M	9.8	1.51	56.9	25.0	NR
M	9.9	1.44	41.8	20.0	NR
M	10.0	1.49	78.0	35.1	2,155
M	10.0	1.51	66.5	29.2	1,610
M	10.0	1.46	59.6	28.0	1,705
M	10.0	1.52	55.2	23.9	1,510
M	10.0	1.44	42.4	20.4	1,330
M	10.0	1.52	66.7	28.9	1,815
M	10.0	1.47	68.7	31.8	1,805
M	10.0	1.44	59.1	28.5	1,650
M	10.0	1.49	56.3	25.4	1,775
M	10.0	1.45	52.9	25.2	1,565
M	10.0	1.44	57.8	27.9	1,515
M	10.0	1.45	80.2	38.1	1,930
M	10.0	1.56	69.3	28.5	1,960
M	10.0	1.46	53.8	25.2	1,450
M	10.0	1.44	42.8	20.6	1,405
M	10.0	1.37	41.4	22.1	1,320
M	10.0	1.49	56.6	25.5	1,770
M	10.0	1.47	51.9	24.0	1,570
M	10.0	1.42	48.6	24.1	1,695
M	10.0	1.52	63.4	27.4	1,795
M	10.0	1.44	40.8	19.7	1,435
M	10.2	1.36	66.1	35.7	NR
M	10.5	1.42	48.0	24.0	NR
M	11.0	1.62	54.3	20.7	1,520
M	11.0	1.56	63.9	26.2	NR
M	13.9	1.69	66.5	23.3	1,865
F	4.0	1.10	23.0	19.0	945
F	4.0	1.08	20.7	17.7	1,020
F	4.0	1.09	20.0	16.8	NR
F	4.2	1.09	25.4	21.5	NR
F	4.2	1.03	18.5	17.4	NR
F	4.4	1.03	18.0	17.0	NR
F	4.5	0.99	16.7	16.9	NR
F	4.5	1.12	22.3	17.8	NR
F	4.6	1.05	20.5	18.7	NR

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,625	2,648	1.63	NR	A
1,356	1,808	1.33	NR	S
1,455	2,091	1.44	NR	LA
1,405	2,306	1.64	1.57	LA
1,540	2,724	1.77	NR	A
1,363	1,841	1.35	NR	S
1,611	3,341	2.07	NR	VA
1,379	2,276	1.65	NR	A
1,503	2,461	1.64	NR	A
1,674	2,406	1.44	NR	LA
1,392	2,063	1.48	NR	LA
2,012	2,602	1.29	1.21	S
1,828	2,458	1.34	1.53	LA
1,692	2,427	1.43	1.42	LA
1,643	2,381	1.45	1.58	LA
1,396	2,036	1.46	1.53	LA
1,836	2,678	1.46	1.48	LA
1,848	2,720	1.47	1.51	LA
1,675	2,466	1.47	1.49	LA
1,649	2,432	1.47	1.37	S
1,576	2,342	1.49	1.50	LA
1,653	2,475	1.50	1.63	A
2,032	3,096	1.52	1.60	A
1,896	2,979	1.57	1.52	LA
1,595	2,508	1.57	1.73	A
1,403	2,223	1.58	1.58	LA
1,350	2,141	1.59	1.62	A
1,654	2,653	1.60	1.50	LA
1,567	2,515	1.60	1.60	A
1,491	2,453	1.64	1.45	LA
1,780	2,985	1.68	1.66	A
1,369	2,414	1.76	1.68	A
1,751	2,132	1.22	NR	S
1,462	1,878	1.28	NR	S
1,637	2,294	1.40	1.51	LA
1,773	2,652	1.50	NR	LA
1,772	2,964	1.67	1.59	LA
1,076	1,377	1.28	1.46	LA
1,040	1,345	1.29	1.32	S
1,034	1,152	1.11	NR	S
1,096	1,420	1.30	NR	S
992	1,404	1.42	NR	LA
978	1,156	1.18	NR	S
947	1,066	1.13	NR	S
1,059	1,516	1.43	NR	LA
1,009	1,261	1.25	NR	S

continued

TABLE I-6 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	4.7	1.17	25.2	18.4	NR
F	4.7	1.10	20.9	17.3	NR
F	4.8	1.09	22.5	18.9	NR
F	5.0	1.19	27.8	19.6	1,110
F	5.0	1.21	28.0	19.1	1,185
F	5.0	1.13	24.7	19.3	1,010
F	5.0	1.13	26.6	20.8	980
F	5.0	1.08	20.3	17.4	970
F	5.0	1.09	23.7	19.9	980
F	5.0	1.16	25.4	18.9	930
F	5.0	1.12	23.8	19.0	1,035
F	5.0	1.14	22.0	16.9	830
F	5.0	1.19	31.0	21.9	1,205
F	5.0	1.15	22.5	17.0	1,010
F	5.0	1.23	39.7	26.2	1,355
F	5.0	1.10	24.5	20.2	980
F	5.0	1.19	30.6	21.6	1,150
F	5.0	1.1	21.8	17.7	975
F	5.0	1.26	28.1	17.7	1,025
F	5.0	1.21	29.5	20.1	1,180
F	5.0	1.23	30.1	19.9	1,105
F	5.0	1.21	42.9	29.3	1,490
F	5.0	1.17	27.3	19.9	1,135
F	5.0	1.21	27.2	18.6	980
F	5.0	1.25	30.3	19.4	1,315
F	5.0	1.13	22.6	17.7	895
F	5.0	1.18	24.2	17.4	1,040
F	5.0	1.24	38.5	25.0	1,160
F	5.0	1.22	29.2	19.6	1,200
F	5.0	1.20	25.5	17.7	1,150
F	5.0	1.13	21.4	16.8	1,030
F	5.0	1.15	27.3	20.6	1,105
F	5.0	1.17	25.5	18.6	1,045
F	5.0	1.14	24.7	19.0	1,045
F	5.0	1.12	21.2	16.9	905
F	5.0	1.13	22.9	17.9	1,095
F	5.0	1.13	21.7	17.0	935
F	5.0	1.23	34.7	22.9	1,344
F	5.0	1.16	31.5	23.4	1,185
F	5.0	1.23	28.4	18.8	1,085
F	5.0	1.21	31.4	21.4	1,240
F	5.0	1.18	26.3	18.9	1,120
F	5.0	1.16	38.4	28.5	1,450
F	5.0	1.10	21.0	17.4	1,027
F	5.0	1.17	25.0	18.3	1,165

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,108	1,395	1.26	NR	S
1,030	1,321	1.28	NR	S
1,044	1,506	1.44	NR	LA
1,139	1,304	1.14	1.17	S
1,149	1,341	1.17	1.13	S
1,080	1,268	1.17	1.26	S
1,104	1,323	1.20	1.35	S
1,008	1,258	1.25	1.30	S
1,054	1,317	1.25	1.34	S
1,099	1,379	1.25	1.48	LA
1,066	1,343	1.26	1.30	S
1,050	1,326	1.26	1.60	LA
1,179	1,538	1.30	1.28	S
1,060	1,388	1.31	1.37	S
1,301	1,712	1.32	1.26	S
1,067	1,407	1.32	1.44	LA
1,174	1,555	1.32	1.35	S
1,037	1,376	1.33	1.41	LA
1,167	1,554	1.33	1.52	LA
1,167	1,563	1.34	1.32	S
1,182	1,591	1.35	1.44	LA
1,334	1,798	1.35	1.21	S
1,126	1,528	1.36	1.35	S
1,139	1,547	1.36	1.58	LA
1,191	1,627	1.37	1.24	S
1,054	1,441	1.37	1.61	A
1,091	1,500	1.37	1.44	LA
1,289	1,783	1.38	1.54	LA
1,167	1,624	1.39	1.35	S
1,114	1,551	1.39	1.35	S
1,039	1,452	1.40	1.41	LA
1,119	1,565	1.40	1.42	LA
1,104	1,546	1.40	1.48	LA
1,084	1,522	1.40	1.46	LA
1,033	1,455	1.41	1.61	A
1,058	1,495	1.41	1.37	S
1,043	1,483	1.42	1.59	LA
1,239	1,763	1.42	1.31	S
1,175	1,683	1.43	1.42	LA
1,161	1,686	1.45	1.55	LA
1,191	1,752	1.47	1.41	LA
1,117	1,652	1.48	1.48	LA
1,260	1,893	1.50	1.31	S
1,024	1,571	1.53	1.53	LA
1,098	1,699	1.55	1.46	LA

continued

TABLE I-6 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	5.0	1.22	34.5	23.2	1,146
F	5.0	1.19	26.4	18.6	1,250
F	5.1	1.08	21.3	18.3	NR
F	5.1	1.22	31.9	21.4	NR
F	5.2	1.00	19.0	18.3	NR
F	5.4	1.14	23.8	18.4	NR
F	5.4	1.14	22.0	16.8	NR
F	5.8	1.15	22.6	17.1	NR
F	5.8	1.14	22.0	16.9	NR
F	5.8	1.14	22.1	17.0	NR
F	5.8	1.14	23.0	17.7	NR
F	6.0	1.20	30.4	21.1	1,235
F	6.0	1.23	32.3	21.4	1,185
F	6.0	1.12	21.4	17.1	1,010
F	6.0	1.27	32.2	20.0	1,205
F	6.2	1.20	29.0	20.1	NR
F	6.3	1.18	23.9	17.1	NR
F	6.4	1.31	45.4	26.5	NR
F	6.5	1.19	27.7	19.5	NR
F	6.6	1.24	44.9	29.4	NR
F	6.7	1.34	44.1	24.7	NR
F	6.8	1.29	34.0	20.4	NR
F	6.9	1.25	39.7	25.4	NR
F	7.0	1.28	30.9	18.8	NR
F	7.0	1.25	28.0	18.0	NR
F	7.0	1.18	24.8	17.8	1,030
F	7.0	1.24	28.4	18.5	1,030
F	7.0	1.32	31.1	17.8	1,160
F	7.0	1.25	32.6	20.9	NR
F	7.1	1.22	32.9	21.9	NR
F	7.1	1.17	27.1	19.8	NR
F	7.2	1.19	33.0	23.3	NR
F	7.3	1.22	26.5	17.9	NR
F	7.4	1.33	32.0	18.0	1,109
F	7.5	1.21	27.9	19.1	NR
F	7.6	1.35	39.1	21.5	NR
F	7.6	1.34	44.2	24.8	NR
F	7.7	1.37	55.6	29.5	NR
F	7.8	1.13	50.0	39.2	NR
F	7.8	1.22	26.6	17.8	1,028
F	7.9	1.28	28.9	17.8	NR
F	7.9	1.35	34.7	19.0	1,177
F	8.0	1.36	52.0	28.3	NR
F	8.0	1.26	29.7	18.8	NR
F	8.3	1.34	37.5	21.0	1,239

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,233	1,915	1.55	1.67	A
1,122	1,976	1.76	1.58	LA
1,017	1,210	1.19	NR	S
1,198	1,583	1.32	NR	S
966	1,104	1.14	NR	S
1,059	1,523	1.44	NR	LA
1,039	1,642	1.58	NR	LA
1,039	1,721	1.66	NR	A
1,029	1,468	1.43	NR	LA
1,030	1,348	1.31	NR	S
1,040	1,148	1.10	NR	S
1,148	1,419	1.24	1.15	S
1,182	1,540	1.30	1.30	S
1,009	1,507	1.49	1.49	LA
1,195	1,905	1.59	1.58	LA
1,126	1,795	1.59	NR	LA
1,052	1,376	1.31	NR	S
1,361	1,987	1.46	NR	LA
1,097	1,417	1.29	NR	S
1,324	1,913	1.44	NR	LA
1,346	2,516	1.87	NR	A
1,202	1,931	1.61	NR	A
1,257	1,568	1.25	NR	S
1,155	1,323	1.15	NR	S
1,108	1,612	1.45	NR	LA
1,045	1,621	1.55	1.57	LA
1,111	1,764	1.59	1.71	A
1,172	2,065	1.76	1.78	A
1,166	2,299	1.97	NR	VA
1,159	1,211	1.05	NR	S
1,067	1,399	1.31	NR	S
1,144	1,760	1.54	NR	LA
1,071	1,648	1.54	NR	LA
1,176	2,071	1.76	1.87	A
1,081	1,465	1.36	NR	S
1,267	1,660	1.31	NR	S
1,323	2,246	1.70	NR	A
1,475	1,980	1.34	NR	S
1,319	1,863	1.41	NR	LA
1,059	2,158	2.04	2.10	VA
1,105	1,569	1.42	NR	LA
1,203	2,003	1.67	1.70	A
1,416	2,472	1.75	NR	A
1,103	1,619	1.47	NR	LA
1,223	2,222	1.82	1.79	A

continued

TABLE I-6 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	8.3	1.32	32.5	18.8	NR
F	8.3	1.37	35.3	18.8	1,225
F	8.4	1.30	32.0	19.0	1,121
F	8.4	1.38	37.8	20.0	NR
F	8.4	1.38	35.6	18.5	NR
F	8.4	1.50	66.0	29.3	NR
F	8.4	1.31	41.5	24.2	NR
F	8.5	1.33	32.5	18.3	NR
F	8.6	1.36	35.5	19.2	1,254
F	8.6	1.25	30.1	19.2	NR
F	8.6	1.30	31.7	18.6	NR
F	8.7	1.32	40.9	23.5	NR
F	8.7	1.32	43.0	24.5	NR
F	8.7	1.33	35.5	20.0	NR
F	8.7	1.38	43.8	23.0	NR
F	8.7	1.30	31.1	18.5	1,123
F	8.8	1.39	54.1	28.0	NR
F	8.8	1.55	58.0	24.1	NR
F	8.8	1.28	34.2	21.2	NR
F	8.8	1.34	35.4	19.6	1,034
F	8.8	1.43	41.1	20.2	1,193
F	8.9	1.37	35.9	19.2	1,415
F	8.9	1.26	29.4	18.4	1,180
F	9.0	1.30	34.9	20.6	1,308
F	9.0	1.53	60.8	26.0	1,485
F	9.1	1.38	50.6	26.4	NR
F	9.1	1.42	38.7	19.2	1,111
F	9.5	1.53	65.5	28.1	NR
F	9.5	1.40	44.3	22.6	NR
F	9.6	1.43	45.9	22.4	NR
F	9.6	1.41	44.6	22.4	NR
F	9.6	1.44	51.3	24.9	NR
F	9.7	1.48	42.2	19.2	1,508
F	9.9	1.47	62.6	29.0	NR
F	9.9	1.43	46.8	22.9	NR
F	10.0	1.54	69.8	29.4	1,695
F	10.0	1.50	70.4	31.3	1,678
F	10.0	1.47	65.9	30.5	1,625
F	10.0	1.37	38.6	20.6	1,240
F	10.0	1.54	73.0	30.8	1,540
F	10.0	1.44	45.8	22.1	1,530
F	10.0	1.40	54.1	27.6	1,385
F	10.0	1.51	64.8	28.4	1,605
F	10.0	1.51	60.3	26.4	1,535
F	10.0	1.47	46.3	21.4	1,400

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,152	1,734	1.50	NR	LA
1,207	1,682	1.39	1.37	S
1,139	2,415	2.12	2.15	VA
1,236	1,683	1.36	NR	S
1,212	1,687	1.39	NR	S
1,630	2,699	1.66	NR	A
1,260	2,286	1.81	NR	A
1,153	1,921	1.67	NR	A
1,198	1,381	1.15	1.10	S
1,092	1,432	1.31	NR	S
1,131	1,585	1.40	NR	LA
1,248	1,481	1.19	NR	S
1,276	1,949	1.53	NR	LA
1,184	2,625	2.22	NR	VA
1,304	2,211	1.70	NR	A
1,117	1,503	1.35	1.34	S
1,433	2,049	1.43	NR	LA
1,537	2,209	1.44	NR	LA
1,144	1,766	1.54	NR	LA
1,185	2,066	1.74	2.00	VA
1,284	2,313	1.80	1.94	VA
1,196	2,304	1.93	1.63	A
1,079	2,347	2.17	1.99	VA
1,160	2,344	2.02	1.79	A
1,559	2,131	1.37	1.44	LA
1,380	2,342	1.70	NR	A
1,244	1,990	1.60	1.79	A
1,603	2,300	1.43	NR	LA
1,296	2,198	1.70	NR	A
1,323	2,126	1.61	NR	A
1,300	2,224	1.71	NR	A
1,392	2,397	1.72	NR	A
1,293	2,291	1.77	1.52	LA
1,536	2,294	1.49	NR	LA
1,327	2,246	1.69	NR	A
1,648	2,353	1.43	1.39	S
1,641	2,439	1.49	1.45	LA
1,575	2,380	1.51	1.46	LA
1,202	1,817	1.51	1.47	LA
1,687	2,565	1.52	1.67	A
1,315	2,011	1.53	1.31	S
1,404	2,192	1.56	1.58	LA
1,575	2,467	1.57	1.54	LA
1,519	2,397	1.58	1.56	LA
1,332	2,109	1.58	1.51	LA

continued

TABLE I-6 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	10.0	1.38	41.5	21.8	1,260
F	10.0	1.57	76.0	30.8	1,920
F	10.0	1.39	45.7	23.7	1,360
F	10.0	1.56	60.7	24.9	1,875
F	10.0	1.45	55.0	26.2	1,580
F	10.0	1.41	42.9	21.6	1,340
F	10.0	1.44	64.2	31.0	1,625
F	10.0	1.47	56.9	26.3	1,535
F	10.1	1.46	43.5	20.3	NR
F	10.2	1.38	40.6	21.3	1,298
F	10.3	1.48	44.1	20.2	NR
F	10.4	1.55	52.1	21.6	1,478
F	10.5	1.48	45.5	20.6	1,261
F	10.6	1.63	57.7	21.7	1,448
F	10.6	1.45	47.9	22.8	1,294
F	10.9	1.41	46.9	23.6	1,214
F	11.0	1.64	78.2	29.1	1,717
F	11.0	1.57	80.2	32.5	1,815
F	11.1	1.43	46.0	22.5	1,292
F	11.5	1.50	72.4	32.2	1,783
F	11.8	1.54	59.3	25.0	1,541
F	11.9	1.65	59.6	21.9	1,071
F	11.9	1.60	56.5	21.9	1,554
F	11.9	1.68	59.1	21.0	1,486
F	12.0	1.59	56.7	22.4	1,386
F	12.0	1.56	53.2	22.0	1,534
F	12.0	1.48	48.2	22.0	NR
F	12.1	1.64	72.8	27.1	NR
F	12.4	1.57	55.7	22.5	1,265
F	12.4	1.62	64.3	24.4	1,593
F	12.5	1.48	64.1	29.2	1,271
F	12.5	1.62	65.2	24.8	1,488
F	12.6	1.54	60.1	25.2	1,404
F	12.6	1.55	56.9	23.7	1,400
F	12.9	1.49	55.0	24.7	1,460
F	14.2	1.65	91.0	33.3	1,438
F	14.5	1.66	66.3	24.1	1,577
F	14.7	1.59	64.7	25.5	1,458
F	14.7	1.60	75.5	29.5	1,698
F	14.8	1.62	61.7	23.5	1,423
F	14.9	1.67	76.0	27.3	1,528
F	14.9	1.61	65.0	25.2	1,548
F	15.0	1.59	82.8	32.8	1,555
F	15.0	1.75	83.1	27.1	1,522
F	15.3	1.62	65.2	25.0	1,538

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,241	1,988	1.60	1.58	LA
1,735	2,801	1.61	1.46	LA
1,297	2,100	1.62	1.54	LA
1,542	2,530	1.64	1.35	S
1,433	2,371	1.65	1.50	LA
1,269	2,123	1.67	1.58	LA
1,544	2,627	1.70	1.62	A
1,463	2,723	1.86	1.77	A
1,293	1,916	1.48	NR	LA
1,224	1,599	1.31	1.23	S
1,299	3,025	2.33	NR	VA
1,423	1,993	1.40	1.35	S
1,314	2,809	2.14	2.23	VA
1,511	2,569	1.70	1.77	A
1,327	2,946	2.22	2.28	VA
1,295	2,630	2.03	2.17	VA
1,761	2,990	1.70	1.74	A
1,760	2,655	1.51	1.46	LA
1,285	2,601	2.02	2.01	VA
1,625	2,913	1.79	1.63	A
1,469	2,820	1.92	1.83	A
1,509	2,635	1.75	2.46	VA
1,454	2,482	1.71	1.60	LA
1,511	1,719	1.14	1.16	S
1,450	2,655	1.83	1.92	VA
1,395	1,650	1.18	1.08	S
1,305	1,687	1.29	NR	S
1,662	2,592	1.56	NR	LA
1,420	2,015	1.42	1.59	LA
1,544	2,499	1.62	1.57	LA
1,490	1,630	1.09	1.28	S
1,551	2,661	1.72	1.79	A
1,460	2,485	1.70	1.77	A
1,422	2,784	1.96	1.99	VA
1,370	1,886	1.38	1.29	S
1,836	3,414	1.86	2.37	VA
1,525	3,581	2.35	2.27	VA
1,477	1,798	1.22	1.23	S
1,613	2,868	1.78	1.69	A
1,447	2,443	1.69	1.72	A
1,638	3,095	1.89	2.03	VA
1,480	1,965	1.33	1.27	S
1,693	2,584	1.53	1.66	A
1,751	2,986	1.71	1.96	VA
1,474	3,119	2.12	2.03	VA

continued

TABLE I-6 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI	BEEo (kcal/d)
F	15.6	1.51	68.1	29.9	1,543
F	16.0	1.75	87.7	28.5	1,725
F	16.3	1.65	73.4	27.0	1,625

NOTE: BEEo = basal energy expenditure (BEE) as observed in the study, BEEp = BEE as predicted based on the following equations:

Girls: BEEp (kcal/d) = 515.8 – 26.8 × Age (y) + 347 × Height (m) + 12.4 × Weight (kg)
Boys: BEEp (kcal/d) = 419.9 – 33.5 × Age (y) + 418.9 × Height (m) + 16.7 × Weight (kg).

BEEp (kcal/d)	TEE	PALp	PALo	PALCAT
1,467	1,934	1.32	1.25	S
1,783	3,367	1.89	1.95	VA
1,562	3,215	2.06	1.98	VA

TEE = total energy expenditure, PALo = physical activity level (PAL) as observed in the study, PALp = TEE/BEEp, PALCAT = PAL category (S = sedentary, LA = low active, A = active, VA = very active), M = male, F = female, NR = not reported.

TABLE I-7 Overweight/Obese Adults with Body Mass Index (BMI) ≥ 25 kg/m^2

Sex	Age (y)	Height (m)	Weight (kg)	BMI
M	20.0	1.79	81.4	25.4
M	23.7	1.79	87.7	27.4
M	26.0	1.90	94.1	26.1
M	27.0	1.75	77.6	25.3
M	29.0	1.82	83.0	25.1
M	29.0	1.72	76.5	25.9
M	29.0	1.87	97.0	27.7
M	30.0	1.79	81.7	25.5
M	30.0	1.87	215.7	61.7
M	30.0	1.85	101.4	29.6
M	30.0	1.83	87.7	26.2
M	32.0	1.84	88.7	26.2
M	32.0	1.74	78.2	25.8
M	32.0	1.83	88.3	26.4
M	32.0	1.82	89.0	26.9
M	32.0	1.88	125.1	35.4
M	33.0	1.81	88.6	27.0
M	33.0	1.71	90.6	31.0
M	34.0	1.81	82.7	25.3
M	34.0	1.83	92.7	27.7
M	34.0	1.66	98.2	35.6
M	35.0	1.78	160.4	50.6
M	35.0	1.90	95.1	26.3
M	35.0	1.73	77.2	25.8
M	35.0	1.92	131.6	35.7
M	35.0	1.82	99.0	29.9
M	35.0	1.82	101.9	30.8
M	36.0	1.87	120.2	34.4
M	36.0	1.75	89.0	29.1
M	36.0	1.80	86.6	26.7
M	36.0	1.89	122.3	34.2
M	37.0	1.73	105.6	35.3
M	37.0	1.75	103.9	33.9
M	37.0	1.78	97.0	30.6
M	37.0	1.81	94.7	28.9
M	37.0	1.80	100.2	30.9
M	37.0	1.81	106.2	32.4
M	38.0	1.80	140.0	43.2
M	38.0	1.83	99.9	29.8
M	38.0	1.87	127.8	36.5
M	39.0	1.78	80.2	25.3
M	39.0	1.76	78.1	25.2
M	39.0	1.79	84.4	26.3
M	39.0	1.82	85.0	25.7

BEEo (kcal/d)	TEE	PALo	PALCAT
1,720	3,311	1.92	VA
1,764	3,938	2.23	VA
2,127	3,456	1.62	A
1,649	2,897	1.76	A
1,649	2,968	1.80	A
1,785	3,396	1.90	VA
2,314	4,704	2.03	VA
1,783	2,652	1.49	LA
3,035	4,661	1.54	LA
2,075	3,619	1.74	A
1,766	3,991	2.26	VA
1,960	2,646	1.35	S
1,816	2,749	1.51	LA
1,816	3,014	1.66	A
1,931	3,248	1.68	A
2,271	3,848	1.69	A
1,745	3,210	1.84	A
1,735	3,767	2.17	VA
1,826	3,021	1.65	A
2,137	3,647	1.71	A
2,149	4,056	1.89	A
2,916	3,585	1.23	S
2,223	3,458	1.56	LA
2,137	3,872	1.81	A
2,294	5,129	2.24	VA
1,965	4,558	2.32	VA
1,843	4,534	2.46	VA
2,419	3,850	1.59	LA
1,943	3,384	1.74	A
1,742	3,131	1.80	A
2,096	3,850	1.84	A
1,974	3,109	1.58	LA
1,769	3,322	1.88	A
1,931	3,719	1.93	VA
1,984	4,135	2.08	VA
1,754	3,743	2.13	VA
2,094	4,534	2.17	VA
2,820	3,776	1.34	S
2,067	4,149	2.01	VA
2,557	5,139	2.01	VA
1,649	2,438	1.48	LA
1,795	2,925	1.63	A
1,824	3,604	1.98	VA
1,864	3,920	2.10	VA

continued

TABLE I-7 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI
M	40.0	1.73	77.0	25.7
M	40.0	1.71	74.6	25.5
M	40.0	1.75	77.1	25.2
M	40.0	1.86	139.5	40.3
M	40.0	1.64	73.9	27.5
M	40.0	1.83	92.2	27.5
M	40.0	1.74	94.8	31.3
M	40.0	1.74	81.1	26.8
M	41.0	1.76	89.0	28.7
M	41.0	1.74	79.7	26.3
M	41.0	1.72	77.0	26.0
M	41.0	1.71	86.4	29.5
M	41.0	1.81	86.5	26.4
M	41.0	1.77	85.8	27.4
M	42.0	1.76	115.6	37.3
M	42.0	1.77	111.3	35.5
M	42.0	1.67	72.7	26.1
M	42.0	1.81	82.5	25.2
M	43.0	1.77	109.4	34.9
M	44.0	1.81	102.4	31.3
M	44.0	1.83	113.2	33.8
M	44.0	1.85	104.5	30.5
M	45.0	1.82	89.1	26.9
M	46.0	1.68	111.8	39.6
M	46.0	1.79	96.6	30.1
M	46.0	1.69	84.5	29.6
M	47.0	1.70	114.9	39.8
M	47.0	1.71	88.5	30.3
M	48.0	1.90	107.5	29.8
M	48.0	1.73	80.9	27.0
M	49.0	1.78	142.1	44.8
M	49.0	1.77	111.7	35.7
M	50.0	1.81	110.0	33.6
M	50.0	1.81	113.8	34.7
M	50.0	1.82	100.3	30.3
M	52.0	1.80	92.3	28.5
M	53.0	1.79	80.8	25.2
M	53.0	1.80	114.6	35.4
M	53.0	1.62	80.5	30.7
M	54.0	1.85	139.7	40.8
M	55.0	1.83	111.6	33.3
M	56.0	1.82	91.4	27.6
M	57.0	1.83	109.0	32.5
M	57.0	1.73	94.5	31.6
M	57.0	1.82	96.0	29.0
M	57.0	1.78	97.9	30.9

BEEo (kcal/d)	TEE	PALo	PALCAT
1,721	2,701	1.57	LA
1,539	2,741	1.78	A
1,685	3,059	1.82	A
2,000	3,774	1.89	A
1,463	2,856	1.95	VA
1,814	3,549	1.96	VA
1,718	3,437	2.00	VA
1,807	4,044	2.24	VA
1,936	3,131	1.62	A
1,587	2,899	1.83	A
1,750	3,356	1.92	VA
1,816	3,635	2.00	VA
1,752	3,568	2.04	VA
1,802	3,870	2.15	VA
2,225	3,351	1.51	LA
2,127	3,291	1.55	LA
1,611	2,514	1.56	LA
1,678	2,930	1.75	A
1,907	3,413	1.79	A
2,180	4,460	2.05	VA
2,041	4,352	2.13	VA
2,079	4,804	2.31	VA
2,144	3,026	1.41	LA
2,474	4,520	1.83	A
1,804	3,322	1.84	A
1,702	3,425	2.01	VA
1,900	3,891	2.05	VA
1,585	3,351	2.11	VA
2,146	2,868	1.34	S
1,625	3,310	2.04	VA
2,345	4,610	1.97	VA
2,151	4,491	2.09	VA
1,977	3,248	1.64	A
1,960	3,317	1.69	A
1,871	4,500	2.40	VA
1,950	2,910	1.49	LA
1,580	2,820	1.79	A
2,050	4,303	2.10	VA
1,656	3,681	2.22	VA
2,275	4,496	1.98	VA
2,020	3,384	1.68	A
1,673	3,408	2.04	VA
1,864	2,868	1.54	LA
1,620	2,610	1.61	A
1,660	2,714	1.63	A
1,862	4,054	2.18	VA

continued

TABLE I-7 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI
M	57.0	1.76	99.4	32.1
M	59.0	1.76	86.6	28.0
M	60.0	1.60	75.3	29.4
M	60.0	1.77	78.5	25.1
M	61.0	1.73	78.5	26.2
M	61.0	1.78	119.8	37.8
M	61.0	1.76	89.0	28.7
M	62.0	1.77	87.4	27.9
M	62.0	1.66	74.8	27.1
M	63.0	1.69	83.5	29.2
M	63.0	1.80	94.2	29.1
M	63.0	1.72	98.2	33.2
M	64.0	1.72	78.8	26.6
M	64.0	1.70	80.3	27.8
M	65.0	1.76	83.0	26.8
M	65.0	1.80	109.7	33.9
M	65.0	1.62	74.2	28.3
M	65.0	1.63	70.1	26.4
M	66.0	1.64	88.6	32.9
M	66.0	1.64	108.3	40.3
M	67.0	1.69	72.4	25.3
M	67.0	1.78	105.2	33.2
M	67.0	1.67	89.5	32.1
M	68.0	1.78	88.9	28.1
M	68.0	1.70	78.1	27.0
M	68.0	1.76	88.1	28.4
M	68.0	1.72	74.2	25.1
M	68.0	1.70	90.0	31.1
M	69.0	1.85	102.6	30.0
M	69.0	1.84	98.2	29.0
M	69.0	1.91	101.2	27.7
M	69.0	1.69	76.4	26.8
M	70.0	1.80	92.9	28.7
M	70.0	1.79	83.0	25.9
M	70.0	1.70	80.1	27.7
M	70.0	1.69	86.7	30.3
M	70.0	1.72	95.4	32.2
M	70.0	1.76	87.6	28.3
M	70.0	1.63	76.7	28.8
M	70.0	1.80	82.8	25.5
M	70.0	1.76	85.8	27.7
M	70.0	1.77	80.0	25.5
M	70.0	1.83	97.6	29.1
M	71.0	1.68	77.7	27.5
M	71.0	1.80	94.8	29.2
M	71.0	1.78	86.6	27.3

BEEo (kcal/d)	TEE	PALo	PALCAT
1,843	4,238	2.30	VA
1,849	3,360	1.82	A
1,570	2,796	1.78	A
1,541	3,517	2.28	VA
1,540	2,337	1.52	LA
2,055	3,456	1.68	A
1,618	2,725	1.68	A
1,520	2,782	1.83	A
1,410	3,258	2.31	VA
1,699	2,763	1.63	A
1,550	2,793	1.80	A
1,915	3,464	1.81	A
1,590	2,566	1.61	A
1,506	3,172	2.11	VA
1,640	1,898	1.16	S
2,100	3,049	1.45	LA
1,575	3,023	1.92	VA
1,467	2,868	1.95	VA
1,770	2,077	1.17	S
1,757	2,816	1.60	A
1,503	2,588	1.72	A
1,910	3,546	1.86	A
1,620	3,109	1.92	VA
1,891	2,694	1.42	LA
1,540	2,231	1.45	LA
1,663	2,622	1.58	LA
1,640	2,848	1.74	A
1,520	2,671	1.76	A
1,820	2,416	1.33	S
1,950	2,862	1.47	LA
1,977	3,305	1.67	A
1,483	3,293	2.22	VA
1,901	2,387	1.26	S
1,781	2,510	1.41	LA
1,879	2,658	1.41	LA
1,740	2,479	1.42	LA
1,510	2,176	1.44	LA
1,901	2,845	1.50	LA
1,441	2,294	1.59	LA
1,852	3,011	1.63	A
1,430	2,349	1.64	A
1,690	2,875	1.70	A
1,599	3,090	1.93	VA
1,680	2,139	1.27	S
1,647	2,335	1.42	LA
1,946	3,231	1.66	A

continued

TABLE I-7 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI
M	72.0	1.86	120.3	34.8
M	72.0	1.75	98.4	32.1
M	72.0	1.72	81.9	27.7
M	72.0	1.79	88.9	27.7
M	72.0	1.88	93.2	26.4
M	72.0	1.79	85.0	26.5
M	73.0	1.72	90.9	30.7
M	73.0	1.70	77.4	26.8
M	73.0	1.77	78.9	25.2
M	74.0	1.69	87.3	30.5
M	74.0	1.76	80.8	26.1
M	75.0	1.67	70.3	25.2
M	75.0	1.72	86.8	29.3
M	76.0	1.67	78.8	28.3
M	76.0	1.66	71.7	26.0
M	76.0	1.68	72.8	25.8
M	77.0	1.65	75.5	27.7
M	77.0	1.78	83.3	26.3
M	77.0	1.66	72.3	26.2
M	78.0	1.70	79.8	27.6
M	80.0	1.75	89.7	29.3
M	80.0	1.72	77.2	26.1
M	81.0	1.71	83.0	28.4
M	85.0	1.62	70.2	26.7
M	86.0	1.70	79.0	27.3
M	86.0	1.63	73.0	27.5
M	89.0	1.65	74.5	27.4
M	90.0	1.70	85.0	29.4
M	93.0	1.65	70.0	25.7
F	20.0	1.67	71.2	25.5
F	20.0	1.70	130.4	45.1
F	22.0	1.72	84.4	28.5
F	24.0	1.70	75.3	26.1
F	24.0	1.70	113.2	39.2
F	24.0	1.76	95.7	30.9
F	24.0	1.73	137.7	46.0
F	24.0	1.55	68.6	28.6
F	24.0	1.65	71.6	26.3
F	24.7	1.57	85.0	34.6
F	25.0	1.69	85.2	29.8
F	25.4	1.69	81.0	28.4
F	26.0	1.63	69.0	26.0
F	26.0	1.72	77.9	26.3
F	26.0	1.71	77.2	26.4
F	26.4	1.59	63.3	25.1
F	27.0	1.72	80.3	27.1

BEEo (kcal/d)	TEE	PALo	PALCAT
1,710	2,284	1.34	S
1,800	2,785	1.55	LA
1,728	3,019	1.75	A
1,738	3,121	1.80	A
1,940	3,546	1.83	A
1,699	3,837	2.26	VA
2,588	3,004	1.16	S
1,570	1,979	1.26	S
1,356	2,640	1.95	VA
1,546	2,538	1.64	A
1,350	2,937	2.18	VA
1,551	2,008	1.29	S
1,922	3,114	1.62	A
2,046	2,314	1.13	S
1,704	2,531	1.49	LA
1,300	2,002	1.54	LA
1,611	2,242	1.39	S
1,948	2,732	1.40	LA
1,298	2,032	1.57	LA
1,858	2,157	1.16	S
1,824	2,923	1.60	A
1,540	2,661	1.73	A
1,512	2,219	1.47	LA
1,400	2,055	1.47	LA
1,618	1,962	1.21	S
1,518	2,153	1.42	LA
1,499	2,084	1.39	S
1,575	1,895	1.20	S
1,324	1,831	1.38	S
1,508	2,584	1.71	A
1,864	3,298	1.77	A
1,601	2,904	1.81	A
1,709	2,327	1.36	S
1,977	3,002	1.52	LA
1,785	3,083	1.73	A
1,993	3,458	1.74	A
1,243	2,438	1.96	VA
1,346	2,962	2.20	VA
1,485	2,940	1.98	VA
1,530	2,653	1.73	A
1,673	2,851	1.70	A
1,385	2,135	1.54	LA
1,546	2,658	1.72	A
1,637	3,019	1.84	A
1,292	2,569	1.99	VA
1,728	2,588	1.50	LA

continued

TABLE I-7 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI
F	27.0	1.64	85.4	31.8
F	27.0	1.63	68.5	25.8
F	27.0	1.64	75.3	28.0
F	27.0	1.73	93.5	31.3
F	27.1	1.73	86.5	28.9
F	27.5	1.57	64.3	26.0
F	27.7	1.56	67.5	27.9
F	27.8	1.70	100.2	34.5
F	28.2	1.61	80.6	31.1
F	28.7	1.74	76.5	25.3
F	29.0	1.64	86.1	32.0
F	29.0	1.59	64.9	25.7
F	29.0	1.62	86.6	33.0
F	29.1	1.74	82.0	27.2
F	29.5	1.57	79.4	32.4
F	30.0	1.74	86.3	28.4
F	30.1	1.58	71.8	28.6
F	30.2	1.60	76.9	30.1
F	30.9	1.55	63.1	26.2
F	30.9	1.68	82.5	29.3
F	31.0	1.55	62.9	26.2
F	31.0	1.68	94.5	33.5
F	31.0	1.60	74.8	29.2
F	31.2	1.70	73.1	25.2
F	31.3	1.66	86.4	31.5
F	31.8	1.70	102.2	35.4
F	32.0	1.60	74.9	29.3
F	32.0	1.60	73.8	28.8
F	32.0	1.64	70.3	26.1
F	32.0	1.63	116.9	44.0
F	32.0	1.67	74.1	26.6
F	32.6	1.65	102.5	37.8
F	33.0	1.61	74.2	28.6
F	33.0	1.65	83.6	30.7
F	33.0	1.73	78.2	26.2
F	33.5	1.65	72.8	26.8
F	34.0	1.69	79.6	27.9
F	34.0	1.66	79.8	29.0
F	34.0	1.69	75.7	26.5
F	34.0	1.70	77.5	26.8
F	35.0	1.67	120.1	43.1
F	35.0	1.68	97.5	34.5
F	35.0	1.65	90.3	33.2
F	35.1	1.68	97.8	34.6
F	35.2	1.62	74.8	28.4
F	35.3	1.63	72.8	27.4

BEEo (kcal/d)	TEE	PALo	PALCAT
1,685	2,703	1.60	A
1,300	2,165	1.67	A
1,288	2,739	2.13	VA
1,857	2,754	1.48	LA
1,465	2,569	1.75	A
1,261	2,326	1.84	A
1,271	1,613	1.27	S
1,379	3,080	2.23	VA
1,474	2,749	1.87	A
1,297	2,497	1.92	VA
1,601	2,526	1.58	LA
1,396	2,412	1.73	A
1,721	3,609	2.10	VA
1,501	2,882	1.92	VA
1,315	2,452	1.86	A
1,574	3,009	1.91	VA
1,402	2,811	2.00	VA
1,390	2,699	1.94	VA
1,386	2,298	1.66	A
1,525	1,694	1.11	S
1,410	2,065	1.46	LA
1,721	3,035	1.76	A
1,360	2,952	2.17	VA
1,653	3,072	1.86	A
1,569	2,967	1.89	A
1,843	3,230	1.75	A
1,599	2,365	1.48	LA
1,615	2,576	1.60	LA
1,350	2,306	1.71	A
1,900	3,384	1.78	A
1,692	3,411	2.02	VA
1,731	3,317	1.92	VA
1,348	2,490	1.85	A
1,793	3,317	1.85	A
1,444	2,996	2.08	VA
1,546	2,628	1.70	A
1,582	2,684	1.70	A
1,556	3,033	1.95	VA
1,427	2,865	2.01	VA
1,352	2,894	2.14	VA
2,302	3,031	1.32	S
1,759	2,911	1.65	A
1,635	2,964	1.81	A
1,446	2,675	1.85	A
1,558	2,980	1.91	VA
1,548	2,793	1.80	A

continued

TABLE I-7 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI
F	35.8	1.69	72.0	25.3
F	36.0	1.71	96.6	33.0
F	37.0	1.69	84.0	29.4
F	37.0	1.62	86.6	33.0
F	37.0	1.62	94.8	36.1
F	37.0	1.70	77.6	26.9
F	38.0	1.70	113.9	39.4
F	38.0	1.64	90.4	33.6
F	39.0	1.59	79.7	31.5
F	39.0	1.65	94.0	34.5
F	39.3	1.60	76.4	29.9
F	40.0	1.67	80.3	28.8
F	40.0	1.63	140.6	52.9
F	41.0	1.72	98.6	33.3
F	41.0	1.80	103.5	31.9
F	42.0	1.72	163.5	55.3
F	42.0	1.63	70.1	26.4
F	43.0	1.60	85.6	33.4
F	44.0	1.67	80.8	29.0
F	44.0	1.80	105.5	32.6
F	44.0	1.70	84.0	29.1
F	45.0	1.70	89.9	31.1
F	47.0	1.54	72.6	30.6
F	48.0	1.76	97.3	31.4
F	49.0	1.63	83.9	31.6
F	52.0	1.68	71.4	25.3
F	53.0	1.70	84.4	29.2
F	53.0	1.65	73.9	27.1
F	54.0	1.57	101.6	41.2
F	54.0	1.64	93.8	34.9
F	54.0	1.63	135.2	50.9
F	55.0	1.67	111.6	40.0
F	55.0	1.59	76.0	30.1
F	55.0	1.54	62.0	26.0
F	55.0	1.72	88.5	29.9
F	55.0	1.69	81.4	28.5
F	56.0	1.71	92.5	31.6
F	56.0	1.66	73.3	26.6
F	56.0	1.64	68.9	25.4
F	56.0	1.62	114.0	43.4
F	56.0	1.57	76.8	31.1
F	56.0	1.68	88.0	31.0
F	56.0	1.57	68.2	27.6
F	56.0	1.68	71.2	25.2
F	56.0	1.71	73.8	25.2
F	57.0	1.50	56.5	25.1

BEEo (kcal/d)	TEE	PALo	PALCAT
1,454	2,635	1.81	A
1,702	2,674	1.57	LA
1,630	2,507	1.54	LA
1,611	2,734	1.70	A
1,642	3,121	1.90	VA
1,267	2,746	2.17	VA
1,697	2,813	1.66	A
1,683	3,172	1.88	A
1,730	2,357	1.36	S
1,900	2,887	1.52	LA
1,291	2,607	2.02	VA
1,494	2,514	1.68	A
1,764	3,112	1.76	A
1,867	2,947	1.58	LA
1,745	3,466	1.99	VA
2,576	4,391	1.70	A
1,315	2,701	2.05	VA
1,793	3,578	2.00	VA
1,508	2,550	1.69	A
1,879	3,466	1.84	A
1,484	3,105	2.09	VA
1,745	2,486	1.42	LA
1,362	2,495	1.83	A
1,659	2,978	1.80	A
1,554	2,665	1.72	A
1,221	1,979	1.62	A
1,319	2,125	1.61	A
1,276	2,311	1.81	A
1,480	2,160	1.46	LA
1,480	2,599	1.76	A
1,695	3,028	1.79	A
1,520	2,039	1.34	S
1,200	2,007	1.67	A
1,416	2,432	1.72	A
1,522	2,689	1.77	A
1,507	3,255	2.16	VA
1,650	2,307	1.40	S
1,424	2,002	1.41	LA
1,475	2,479	1.68	A
1,510	2,555	1.69	A
1,414	2,421	1.71	A
1,439	2,489	1.73	A
1,307	2,419	1.85	A
1,353	2,565	1.90	A
1,180	2,706	2.29	VA
1,207	1,471	1.22	S

continued

TABLE I-7 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI
F	57.0	1.58	72.0	28.8
F	57.0	1.68	74.5	26.5
F	57.0	1.58	74.1	29.7
F	57.0	1.63	68.5	25.8
F	58.0	1.71	86.8	29.7
F	58.0	1.58	75.7	30.3
F	59.0	1.70	106.8	37.0
F	59.0	1.50	94.0	41.8
F	60.0	1.54	63.8	26.9
F	60.0	1.66	99.1	36.0
F	60.0	1.79	83.5	26.1
F	60.0	1.70	73.2	25.3
F	60.0	1.72	93.3	31.5
F	60.0	1.55	60.1	25.0
F	61.0	1.69	86.5	30.3
F	61.0	1.48	99.4	45.4
F	61.0	1.67	97.4	34.9
F	61.0	1.62	69.0	26.3
F	62.0	1.56	75.8	31.1
F	62.0	1.60	103.4	40.4
F	62.0	1.62	81.6	31.1
F	62.0	1.64	73.4	27.3
F	62.0	1.62	70.3	26.6
F	63.0	1.50	74.4	33.1
F	63.0	1.62	73.0	27.8
F	63.0	1.66	87.7	31.8
F	63.0	1.64	80.6	30.0
F	63.0	1.62	112.0	42.7
F	64.0	1.57	83.2	33.8
F	64.0	1.59	69.3	27.4
F	64.0	1.64	69.2	25.7
F	64.0	1.59	79.2	31.3
F	64.0	1.71	74.4	25.4
F	64.0	1.50	60.4	26.7
F	64.0	1.64	78.3	29.1
F	64.0	1.61	72.0	27.8
F	65.0	1.68	120.6	42.7
F	65.0	1.63	80.1	30.1
F	65.0	1.57	73.5	29.8
F	65.0	1.56	74.8	30.7
F	65.0	1.52	61.1	26.4
F	65.0	1.55	63.8	26.5
F	65.0	1.52	62.1	26.7
F	66.0	1.66	73.5	26.7
F	66.0	1.57	62.8	25.5
F	67.0	1.60	74.7	29.2

BEEo (kcal/d)	TEE	PALo	PALCAT
1,390	1,698	1.22	S
1,266	2,106	1.66	A
1,209	2,221	1.84	A
1,138	2,315	2.03	VA
1,860	2,314	1.24	S
1,348	2,143	1.59	LA
1,540	2,536	1.65	A
1,520	2,751	1.81	A
1,123	1,276	1.14	S
1,670	2,198	1.32	S
1,351	2,108	1.56	LA
1,382	2,243	1.62	A
1,526	2,717	1.78	A
1,080	1,958	1.81	A
1,640	2,114	1.29	S
1,370	1,904	1.39	S
1,500	2,166	1.44	LA
1,090	1,716	1.57	LA
1,510	1,619	1.07	S
1,440	2,034	1.41	LA
1,370	2,399	1.75	A
1,135	2,057	1.81	A
1,305	2,537	1.94	VA
1,550	1,794	1.16	S
1,270	1,766	1.39	S
1,594	2,290	1.44	LA
1,439	2,218	1.54	LA
1,610	2,510	1.56	LA
1,740	2,106	1.21	S
1,252	1,644	1.31	S
1,301	1,934	1.49	LA
1,370	2,058	1.50	LA
1,360	2,224	1.64	A
1,089	1,830	1.68	A
1,341	2,302	1.72	A
1,296	2,354	1.82	A
1,840	2,066	1.12	S
1,339	1,634	1.22	S
1,210	1,667	1.38	S
1,235	1,791	1.45	LA
1,132	1,716	1.52	LA
1,304	2,036	1.56	LA
1,194	1,976	1.66	A
1,367	2,079	1.52	LA
1,245	1,991	1.60	LA
1,397	2,190	1.57	LA

continued

TABLE I-7 Continued

Sex	Age (y)	Height (m)	Weight (kg)	BMI
F	67.0	1.62	80.5	30.7
F	67.0	1.55	65.7	27.3
F	68.0	1.65	81.8	30.0
F	68.0	1.61	66.6	25.7
F	68.0	1.63	79.0	29.7
F	69.0	1.64	79.5	29.6
F	69.0	1.64	81.4	30.3
F	69.0	1.58	71.0	28.4
F	70.0	1.66	76.2	27.7
F	70.0	1.46	53.4	25.1
F	70.0	1.67	79.2	28.4
F	70.0	1.58	74.8	30.0
F	71.0	1.55	66.5	27.7
F	71.0	1.65	85.5	31.4
F	72.0	1.55	73.6	30.6
F	73.0	1.50	58.8	26.1
F	73.0	1.63	68.5	25.8
F	74.0	1.60	64.4	25.2
F	75.0	1.57	63.4	25.7
F	76.0	1.60	68.0	26.6
F	76.0	1.64	67.8	25.2
F	76.0	1.57	76.5	31.0
F	77.0	1.62	68.1	25.9
F	78.0	1.59	66.4	26.3
F	78.0	1.49	65.4	29.4
F	79.0	1.56	78.6	32.3
F	79.0	1.46	60.8	28.5
F	80.0	1.62	68.7	26.2
F	81.0	1.53	62.1	26.5
F	84.0	1.43	52.5	25.7
F	86.0	1.58	66.0	26.4
F	88.0	1.54	63.5	26.8
F	89.0	1.55	64.2	26.7
F	91.0	1.76	79.6	25.8
F	93.0	1.61	70.0	27.0
F	94.0	1.63	74.0	27.9
F	95.0	1.50	72.3	32.1
F	95.0	1.52	63.0	27.3
F	95.0	1.67	80.0	28.7
F	96.0	1.72	85.0	28.7

NOTE: BEEo = basal energy expenditure (BEE) as observed in the study, TEE = total energy expenditure, PALo = physical activity level (PAL) as observed in the study, PALCAT = PAL category (S = sedentary, LA = low active, A = active, VA = very active), M = male, F = female.

BEEo (kcal/d)	TEE	PALo	PALCAT
1,522	2,412	1.58	LA
1,319	2,141	1.62	A
1,426	2,224	1.56	LA
1,145	2,237	1.95	VA
1,253	2,543	2.03	VA
1,845	2,138	1.16	S
1,270	1,610	1.27	S
1,465	2,282	1.56	LA
1,300	1,838	1.41	LA
1,051	1,756	1.67	A
1,250	2,295	1.84	A
1,331	3,091	2.32	VA
1,274	1,403	1.10	S
1,410	2,217	1.57	LA
1,230	1,966	1.60	LA
1,221	1,547	1.27	S
1,250	1,699	1.36	S
1,195	1,918	1.60	A
1,230	2,105	1.71	A
1,331	1,709	1.28	S
1,180	1,557	1.32	S
1,170	1,889	1.61	A
1,362	2,285	1.68	A
1,235	1,537	1.24	S
1,181	1,556	1.32	S
1,120	1,554	1.39	S
1,120	1,579	1.41	LA
1,140	2,403	2.11	VA
1,440	1,846	1.28	S
910	1,017	1.12	S
1,434	1,929	1.34	S
1,152	1,809	1.57	LA
1,319	1,484	1.12	S
1,432	2,180	1.52	LA
1,350	1,463	1.08	S
1,439	2,055	1.43	LA
1,403	1,477	1.05	S
1,269	1,946	1.53	LA
1,083	1,671	1.54	LA
1,348	1,568	1.16	S

TABLE I-8 Coefficients and Standard Errors (SE) for the Prediction of Total Energy Expenditure (TEE) in Normal-Weight Children 3 Through 18 Years of Age with Body Mass Index ≥ 3rd and < 85th Percentile

	Males		Females	
TEE Fits	Coefficient	SE (asym)	Coefficient	SE (asym)
A:Constant	88.5	110.8	135.3	82.8
B:Age coefficient	–61.9	7.0	–30.8	5.4
C2	1.13	0.01	1.16	0.02
C3	1.26	0.02	1.31	0.03
C4	1.42	0.03	1.56	0.04
D:Weight coefficient	26.7	1.75	10.0	1.16
E:Height coefficient	903	124.8	934	91.1
Number	167		358	
SE fit	82.8		96.7	
R squared	0.98		0.95	

TABLE I-9 Coefficients and Standard Errors (SE) for the Prediction of Total Energy Expenditure (TEE) in Normal-Weight Men and Women 19 Years of Age and Older with Body Mass Index ≥ 18.5 and < 25 kg/m^2

	Males		Females	
TEE Fits	Coefficient	SE (asym)	Coefficient	SE (asym)
A:Constant	661.8	722.7	354.1	451.0
B:Age coefficient	–9.53	1.24	–6.91	0.91
C2	1.11	0.06	1.12	0.05
C3	1.25	0.10	1.27	0.08
C4	1.48	0.17	1.45	0.12
D:Weight coefficient	15.91	3.50	9.36	2.53
E:Height coefficient	539.6	439.2	726	298
Number	169		238	
SE fit	284.5		231.6	
R squared	0.75		0.74	

TABLE I-10 Coefficients and Standard Errors (SE) for the Prediction of Total Energy Expenditure (TEE) in Overweight/Obese Men and Women 19 Years of Age and Older with Body Mass Index ≥ 25 kg/m^2

	Males		Females	
TEE Fits	Coefficient	SE (asym)	Coefficient	SE (asym)
A:Constant	1,085.6	666.7	447.6	433.8
B:Age coefficient	–10.08	1.68	–7.95	1.03
C2	1.12	0.06	1.16	0.05
C3	1.29	0.10	1.27	0.07
C4	1.59	0.19	1.44	0.11
D:Weight coefficient	13.7	1.30	11.4	0.98
E:Height coefficient	416	324	619	249
Number	165		195	
SE fit	296.6		228.2	
R squared	0.84		0.83	

TABLE I-11 Coefficients and Standard Errors (SE) for the Prediction of Total Energy Expenditure (TEE) in Normal and Overweight/Obese Men and Women 19 Years of Age and Older with Body Mass Index ≥ 18.5 kg/m^2

	Males		Females	
TEE Fits	Coefficient	SE (asym)	Coefficient	SE (asym)
A:Constant	864.1	445.3	386.5	297.5
B:Age coefficient	–9.72	0.96	–7.31	0.66
C2	1.12	0.04	1.14	0.03
C3	1.27	0.07	1.27	0.05
C4	1.54	0.11	1.45	0.08
D:Weight coefficient	14.2	0.92	10.9	0.65
E:Height coefficient	503.0	220.8	660.7	166.4
Number	334		433	
SE fit	288.0		229.1	
R squared	0.82		0.79	

TABLE I-12 Coefficients and Standard Errors (SE) for the Prediction of Total Energy Expenditure (TEE) in Overweight/Obese Boys and Girls 3 Through 18 Years of Age with Body Mass Index ≥ 85th Percentile

	Males		Females	
TEE Fits	Coefficient	SE (asym)	Coefficient	SE (asym)
A:Constant	59.9	173.9	464.0	115.3
B:Age coefficient	–84.9	12.1	–43.4	7.42
C2	1.12	0.02	1.18	0.02
C3	1.21	0.03	1.35	0.04
C4	1.52	0.06	1.63	0.07
D:Weight coefficient	21.6	1.27	15.0	0.92
E:Height coefficient	1,153	194.6	679.8	120.0
Number	127		192	
SE fit	99.0		107.1	
R squared	0.96		0.96	

TABLE I-13 Coefficients and Standard Errors (SE) for the Prediction of Total Energy Expenditure (TEE) in Normal and Overweight/Obese Children 3 Through 18 Years of Age with Body Mass Index ≥ 3rd Percentile

	Males		Females	
TEE Fits	Coefficient	SE (asym)	Coefficient	SE (asym)
A:Constant	–114.1	98.2	389.2	62.9
B:Age coefficient	–50.9	5.61	–41.2	3.64
C2	1.12	0.01	1.18	0.01
C3	1.24	0.02	1.35	0.02
C4	1.45	0.03	1.60	0.04
D:Weight coefficient	19.5	0.74	15.0	0.44
E:Height coefficient	1,161.4	111.8	701.6	67.3
Number	127		192	
Number	294		549	
SE fit	95.2		100.7	
R squared	0.97		0.96	

J

Association of Added Sugars Intake and Intake of Other Nutrients

TABLE J-1 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Children 4 Through 8 Years of Age

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	244	608	827	711
Calcium, mg	977	1,042	985	908
Standard error	31	23	15	16
Comparison	abcde[c]	abc	abc	ade
Percent > AI (800 mg/d)	69	95	85	78
Magnesium, mg	241	257	237	222
Standard error	6.3	5.2	5.2	3.4
Comparison	abcde	abc	abcde	acde
Percent < EAR (110 mg/d)	0	0	0	0
Vitamin A, RAE	684	722	715	778
Standard error	32	19	13	26
Comparison	abcdef	abcde	abcde	abcd
Percent < EAR (275 μg/d)	0.4	0	0.9	0.1
Vitamin E, mg α-tocopherol[d]	4.6	5.9	5.3	5.5
Standard error	0.2	0.2	0.1	0.1
Comparison	aefg	bcd	bcde	bcde
Percent < EAR (6 mg/d)	76	53	68	65
Iron, mg	12.7	14.4	13.4	12.8
Standard error	0.4	0.3	0.2	0.2
Comparison	acdef	bc	abcde	acde
Percent < EAR (4.1 mg/d)	0	0	0	0
Zinc, mg	9.1	10.3	9.0	8.8
Standard error	0.2	0.2	0.2	0.2
Comparison	acde	b	acde	acde
Percent < EAR (4 mg/d)	0	0	0	0

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
504	297	130	127
899	771	703	NA[b]
22	32	43	NA
ade	fg	fg	
77	41	25	NA
219	197	188	NA
3.7	5.8	9.7	NA
acdeg	fg	efg	
0	0	0	NA
668	568	504	NA
19	38	40	NA
abcef	aefg	fg	
7.1	0.7	3.6	NA
5.2	4.7	4.0	NA
0.1	0.1	0.3	NA
acdef	aefg	afg	
77	95	99	NA
12.6	11.6	10.0	NA
0.2	0.3	0.6	NA
acdef	aefg	fg	
0	0	0	NA
8.7	7.9	6.8	NA
0.2	0.2	0.4	NA
acde	fg	fg	
0	0	0.4	NA

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-2 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Boys 9 Through 13 Years of Age

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	81	171	278	236
Calcium, mg	1,301	1,177	1,155	1,045
Standard error	43	48	37	32
Comparison	abc[b]	abcde	abcde	bcdeg
Percent > AI (1,300 mg/d)	50	27	23	15
Magnesium, mg	301	297	305	264
Standard error	9.9	5.1	8.7	6.3
Comparison	abceh	abceh	abceh	deh
Percent < EAR (200 mg/d)	8.0	0	0.2	15.4
Vitamin A, RAE	808	757	764	730
Standard error	49	39	38	35
Comparison	abcdefgh	abcdefgh	abcdefgh	abcdefgh
Percent < EAR (445 μg/d)	9.6	3.1	3.2	14.6
Vitamin E, mg α-tocopherol[c]	5.9	6.8	7.7	6.7
Standard error	0.4	0.3	0.3	0.2
Comparison	abdefgh	abcdefg	bcdeg	abcdefg
Percent < EAR (9 mg/d)	81	94	64	96
Iron, mg	16.1	17.0	17.3	15.7
Standard error	0.7	0.6	0.5	0.4
Comparison	abcdegh	abcdegh	abcdegh	abcdegh
Percent < EAR (5.9 mg/d)	0.2	0	0	0
Zinc, mg	12.5	12.6	12.6	11.1
Standard error	0.4	0.6	0.4	0.3
Comparison	abcde	abcde	abce	abdef
Percent < EAR (7 mg/d)	2.1	0.03	1.4	0

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
195	127	64	67
1,138	826	951	769
29	28	43	57
bcde	fgh	dfgh	fgh
22	6.9	8.7	0
281	226	219	247
7.2	6.4	10.2	16.7
abcdeh	fgh	fgh	abcdefgh
11.1	24.1	31	3.9
813	611	710	659
44	44	54	53
abcdegh	abcdfgh	abcdefgh	abcdefgh
8.3	16.3	4.6	4.0
7.3	5.9	5.9	4.8
0.4	0.4	0.5	0.3
abcdefg	abdefgh	abcdefgh	afgh
80	95	99	99.7
15.9	12.7	13.6	14.2
0.5	0.4	1.2	0.9
abcdegh	fgh	abcdefgh	abcdefgh
0	0.7	0	0
12.5	9.8	8.0	
0.4	0.3	0.4	
abcde	df	g	
0	12.9	24	

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-3 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Boys 14 Through 18 Years of Age

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	54	112	153	191
Calcium, mg	1,236	1,162	1,213	1,195
Standard error	100	71	53	45
Comparison	abcdef[c]	abcdef	abcdef	abcdef
Percent > AI (1,300 mg/d)	43	41	42	42
Magnesium, mg	328	365	323	314
Standard error	16	15	13	10.3
Comparison	abcdefg	abcdeg	abcdefg	abcdefg
Percent < EAR (340 mg/d)	66	31	58	60
Vitamin A, RAE	676	706	737	903
Standard error	50	49	41	53
Comparison	abcefg	abcdefg	abcdefg	bcde
Percent < EAR (630 μg/d)	39	42	34	4.5
Vitamin E, mg α-tocopherol[d]	7.2	10.2	7.5	13.2
Standard error	0.4	0.7	0.3	1.7
Comparison	acefg	bde	acefg	bde
Percent < EAR (12 mg/d)	99	100	86	45
Iron, mg	16.6	18.9	19.0	23.4
Standard error	0.8	0.9	0.7	1.4
Comparison	abdefg	abcdefg	abcdef	bcdef
Percent < EAR (7.7 mg/d)	0	0.3	0	0
Zinc, mg	14.2	15.4	15.0	18.9
Standard error	0.7	0.8	0.6	1.4
Comparison	abcdef	abcdef	abcd	abcdef
Percent < EAR (8.5 mg/d)	1.5	0.4	0.7	2.7

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
165	101	66	66
1,167	955	747	NA[b]
42	70	49	NA
abcdef	abcdefg	fg	
29	17	4.2	NA
326	286	335	NA
10.5	18.3	49	NA
abcdefg	acdefg	abcdefg	
55	75	51	NA
770	615	546	NA
52	45	48	NA
abcdef	abcefg	abcfg	
33	52	70	NA
8.5	7.1	7.0	NA
0.3	0.4	0.4	NA
abcdef	acefg	acfg	
93	91	99	NA
19.7	17.5	15.6	NA
0.7	2.0	0.8	NA
abcdef	abcdefg	abfg	
0	0.2	0.3	NA
15.1	12.3	12.9	NA
0.6	1.8	0.9	NA
abdef	abdef	abcefg	
2.5	17.2	6.1	NA

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-4 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Men 19 Through 50 Years of Age

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	656	814	915	810
Calcium, mg	909	1,040	1,115	964
Standard error	19	21	22	19
Comparison	adefg[b]	bcd	bc	abdef
Percent > AI (1,000 mg/d)	40	54	68	46
Magnesium, mg (19–30 y)	384	436	373	370
Standard error	10	11	7	8
Comparison	acd	b	acd	acd
Percent < EAR (330 mg/d)	2.7	8.5	33	17
Magnesium, mg (31–50 y)	370	401	400	339
Standard error	7	7	8	7
Comparison	abc	abc	abc	defg
Percent < EAR (350 mg/d)	42	29	11	57
Vitamin A, RAE	737	694	953	764
Standard error	31	19	27	22
Comparison	abdef	abdef	c	abdef
Percent < EAR (625 μg/d)	32	44	23	30
Vitamin E, mg α-tocopherol[c]	7.8	10.3	9.5	9.8
Standard error	0.2	0.2	0.2	0.2
Comparison	aefg	bcd	bce	bcd
Percent < EAR (12 mg/d)	86	80	85.2	91
Iron, mg	16.9	19.5	20	18.7
Standard error	0.3	0.4	0.3	0.3
Comparison	aef	bcd	bcd	bcd
Percent < EAR (6 mg/d)	0.2	0	0	0

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
565	312	190	173
917	912	798	624
21	30	37	27
adefg	adefg	aefg	h
36	15	31	2.7
304	287	265	217
7	12	12	9
efg	efg	efgh	gh
63	72	76	91
321	321	308	236
7	9	14	17
defg	defg	defg	h
62	68	71	82
725	682	409	360
26	40	26	27
abdef	abdef	gh	gh
35	43	73	85
8.5	7.5	7.2	5.2
0.2	0.2	0.3	0.4
ae	afg	afg	h
92	98	100	99
17.1	16.0	14.1	11.5
0.3	0.5	0.5	0.6
aef	aefg	fg	h
0	<0.05	2.6	3.1

continued

TABLE J-4 Continued

Nutrient[a]	Percent of Energy from Added Sugars			
	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
Zinc, mg	15	16.3	16.2	14.9
Standard error	0.3	0.3	0.3	0.3
Comparison	abcd	abc	abc	ad
Percent < EAR (9.4 mg/d)	5.9	0	0	4.2

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
13.6	12.6	11.2	9.1
0.3	0.3	0.4	0.4
ef	efg	fg	h
07	0	26	48

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.
DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-5 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Men 51 Years of Age and Older

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	707	736	694	476
Calcium, mg	768	835	821	790
Standard error	19	18	18	19
Comparison	abcdef[b]	abcde	abcde	abcdef
Percent > AI (1,200 mg/d)	18	15	13	13
Magnesium, mg	336	339	327	303
Standard error	6	5	5	6
Comparison	abce	abc	abcde	cde
Percent < EAR (350 mg/d)	54	54.2	61	65
Vitamin A, RAE	698	811	879	842
Standard error	24	23	28	28
Comparison	aefg	bcdefg	bcdef	bcdefg
Percent < EAR (625 μg/d)	43	29	20	28
Vitamin E, mg α-tocopherol[c]	7.2	7.2	8.5	7.6
Standard error	0.2	0.2	0.2	0.2
Comparison	abdef	abdef	cde	abcdef
Percent < EAR (12 mg/d)	90	85	95	97
Iron, mg	15.1	16.9	17.1	17.8
Standard error	0.3	0.3	0.4	0.5
Comparison	aefg	bcdef	bcdef	bcdf
Percent < EAR (6 mg/d)	1.8	0	0	0
Zinc, mg	12.3	12.3	12.9	11.7
Standard error	0.3	0.3	0.3	0.3
Comparison	abcdefg	abcdefg	abcdfg	abcdefg
Percent < EAR (9.4 mg/d)	24	17	11	25

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
282	151	87	64
773	672	585	600
29	38	37	45
abcdef	abdefgh	fgh	fgh
14	11	4.4	0
306	246	240	237
9	9	11	17
acde	fgh	fgh	fgh
65	82	93	97
748	693	624	424
37	53	69	60
abcdefg	abcdefg	abdefgh	gh
37	35	50	81
7.9	6.5	5.6	4.0
0.3	0.4	0.4	0.3
abcdef	abdefg	fg	h
82	90	96	100
15.5	15.2	13.3	10.8
0.5	0.7	0.8	0.7
abcefg	abcdefg	aefgh	gh
0.3	0.6	0.5	0
11.1	12.7	18.9	8.3
0.4	0.7	3.0	0.6
abdefg	abcdefg	abcdefg	h
27	0.7	14.5	58

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-6 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Girls 9 Through 13 Years of Age

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	75	167	247	259
Calcium, mg	884	1,063	944	883
Standard error	183	35	28	27
Comparisons	abcdefgh[b]	abc	abcd	acde
Percent > AI (1,300 mg/d)	16	15	4.2	7.9
Magnesium, mg	255	280	235	230
Standard error	9	7	6	7
Comparison	abcdg	ab	acdg	acdeg
Percent < EAR (200 mg/d)	16	0	17	30
Vitamin A, RAE	650	729	741	741
Standard error	207	57	34	34
Comparison	abcdefgh	abcdeg	abcdeg	abcdeg
Percent < EAR (420 μg/d)	16	6.4	3.5	2.7
Vitamin E, mg α-tocopherol[c]	5.4	5.9	5.8	6.2
Standard error	0.3	0.3	0.2	0.3
Comparison	abcdefg	abcdeg	abcdeg	abcdeg
Percent < EAR (9 mg/d)	97	80	97	89
Iron, mg	15.7	15.8	13.5	13.2
Standard error	6.1	0.6	0.5	0.5
Comparison	abcdefgh	abg	acdeg	acdeg
Percent < EAR (5.7 mg/d)	1.9	0	0	0.2
Zinc, mg	10.7	10.5	9.3	9.8
Standard error	0.4	0.3	0.3	0.4
Comparison	abcdg	abcdg	abcdeg	abcdeg
Percent < EAR (7 mg/d)	12	5.7	17	14

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
210	124	70	64
785	614	720	479
29	24	23	26
adeg	af	aeg	ah
1.5	0.2	2.4	0
208	180	221	133
6	4	11	8
deg	f	acdeg	h
44	73	35	90
606	413	553	406
32	26	57	69
abcdegh	afgh	abcdefgh	aefgh
18	51	19	52
5.5	4.6	5.7	3.3
0.3	0.2	0.3	0.3
abcdefg	aefg	abcdefg	h
95	99	87	97
12.3	10.5	12.8	8.2
0.5	0.3	0.8	0.5
acdeg	afg	abcdefg	ah
0.2	0	0.2	10.5
8.4	7.3	10.6	5.1
0.3	0.3	1.0	0.4
cdefg	efg	abcdefg	h
23	43	4.5	77

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-7 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Girls 14 Through 18 Years of Age

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	57	122	147	196
Calcium, mg	689	929	938	807
Standard error	72	60	38	29
Comparison	abcdefg[b]	abcd	abcd	abcde
Percent > AI (1,300 mg/d)	4.5	28	11	0.7
Magnesium, mg	350	264	261	221
Standard error	57	11	9	6
Comparison	abcdef	abce	abce	ade
Percent < EAR (300 mg/d)	34	65	77	85
Vitamin A, RAE	407	613	688	642
Standard error	42	41	38	41
Comparison	aefg	bcdg	bcd	bcdg
Percent < EAR (485 μ/d)	76	31	22	18
Vitamin E, mg α-tocopherol[c]	6.0	8.5	6.5	9.8
Standard error	0.6	0.5	0.3	1.0
Comparison	acefg	bd	acdefg	bcde
Percent < EAR (12 mg/d)	99	100	100	69
Iron, mg	12.7	12.5	14.2	13.9
Standard error	0.9	0.4	0.6	0.5
Comparison	abcdef	abcde	abcde	abcde
Percent < EAR (7.9 mg/d)	6.9	15	0.7	0.2
Zinc, mg	8.3	9.8	10.8	9.8
Standard error	0.5	0.4	0.4	0.4
Comparison	abdefg	abcdef	bcde	abcdef
Percent < EAR (3.0 mg/d)	39	33	16	27

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
141	119	73	94
719	647	598	434
28	37	34	30
adefg	aefg	aefg	h
0	0	2.4	0.8
228	183	168	129
7	8	8	7
abcde	afg	fg	h
85	100	100	98
404	369	429	242
28	23	61	24
aefg	aefg	abdefgh	gh
73	71	65	98
6.7	5.2	5.1	3.5
0.3	0.2	0.3	0.2
acde	acfg	acfg	h
97	100	98	100
12.3	10.5	8.9	6.9
0.5	0.4	0.6	0.4
abcdef	aefg	fgh	gh
3.0	9.8	28	67
9.8	8.3	6.7	4.9
0.4	0.4	0.4	0.3
abcdef	abdefg	afg	h
14.5	39	88	86

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-8 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Women 19 Through 50 Years of Age

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	634	762	937	825
Calcium, mg	623	753	764	732
Standard error	16	15	15	14
Comparison	aef[b]	bcd	bcd	bcd
Percent > AI (1,000 mg/d)	14	22	17	9.1
Magnesium, mg (19–30 y)	231	254	254	260
Standard error	7	6	6	7
Comparison	abcdef	abcde	abcde	abcd
Percent < EAR (255 mg/d)	65	50	51	48
Magnesium, mg (31–50 y)	265	287	277	263
Standard error	6	5	5	5
Comparison	abcd	abc	abcd	acd
Percent < EAR (265 mg/d)	50	36	41	52
Vitamin A, RAE	542	665	675	543
Standard error	20	21	18	15
Comparison	adef	bc	bc	adef
Percent < EAR (500 μg/d)	43	28	11	39
Vitamin E, mg α-tocopherol[c]	6.6	6.8	7.4	7.0
Standard error	0.2	0.2	0.2	0.2
Comparison	abcd	abcd	abcd	abcd
Percent < EAR (12 mg/d)	100	94	90	94
Iron, mg	12.3	13.9	13.2	13.1
Standard error	0.3	0.3	0.2	0.2
Comparison	acdef	bcd	abcd	abcd
Percent < EAR (8.1 mg/d)	5.7	0.7	3.4	0

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
648	455	253	326
650	607	542	404
15	17	19	17
aef	aefg	fg	h
6.6	9.3	3.5	0.3
229	210	184	156
6	6	7	8
abcef	aefg	fgh	gh
78	84	83	99
226	212	180	145
5	6	7	6
ef	ef	g	h
86	84	94	100
480	491	395	294
16	21	24	19
adefg	adefg	efg	h
55	51	71	86
5.5	5.3	4.8	3.6
0.1	0.2	0.2	0.2
efg	efg	efg	h
99	97	99	100
11.6	11.3	10.0	7.4
0.2	0.2	0.3	0.2
aef	aefg	fg	h
9.5	11.5	29	63

continued

TABLE J-8 Continued

Nutrient[a]	Percent of Energy from Added Sugars			
	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
Zinc, mg	9.5	10.4	10.1	10.0
Standard error	0.2	0.2	0.2	0.2
Comparison	abcde	abcd	abcd	abcd
Percent < EAR (6.8 mg/d)	8	2.2	10	10

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
8.8	8.4	7.4	5.5
0.2	0.2	0.2	0.2
aef	ef	g	h
13	29	42	77

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE J-9 Median Nutrient Intakes by Range of Percent of Daily Energy Intake from Added Sugars, Women 51 Years of Age and Older

	Percent of Energy from Added Sugars			
Nutrient[a]	0 ≤ x ≤ 5%	5 < x ≤ 10%	10 < x ≤ 15%	15 < x ≤ 20%
n	786	851	707	496
Calcium, mg	567	639	677	623
Standard error	13	13	14	15
Comparison	adef[b]	bcdef	bcdef	abcdef
Percent > AI (1,200 mg/d)	4.5	5.7	3.9	3.8
Magnesium, mg	235	257	255	241
Standard error	4	4	4	5
Comparison	adef	bcd	bcd	abcdf
Percent < EAR (265 mg/d)	63	54	55	61
Vitamin A, RAE	762	675	777	612
Standard error	24	20	23	25
Comparison	abch	abdeh	ach	bdefh
Percent < EAR (500 μg/d)	12	32	11	37
Vitamin E, mg α-tocopherol[c]	5.0	5.6	5.7	5.7
Standard error	0.1	0.1	0.1	0.2
Comparison	aef	bcdf	bcdf	bcdf
Percent < EAR (12 mg/d)	98	90	99	95
Iron, mg	11.1	12.4	12.4	12.1
Standard error	0.2	0.3	0.2	0.3
Comparison	adef	bcd	bcd	abcdf
Percent < EAR (5 mg/d)	1.1	1.2	0.2	0.8
Zinc, mg	8.0	8.8	8.8	8.2
Standard error	0.2	0.2	0.2	0.2
Comparison	adef	bcd	bcd	abcdf
Percent < EAR (6.8 mg/d)	35	30	22	34

[a] AI = Adequate Intake, EAR = Estimated Average Requirement, RAE = retinol activity equivalents.
[b] NA = data not available.
[c] Percent ranges of energy from added sugars have been assigned a letter (a–h). When ranges of intakes do not share the same letter, they are significantly different ($p < 0.5$).
[d] Estimates of mg of α-tocopherol were obtained by multiplying estimates of mg of α-tocopherol equivalents by 0.8.
NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. Individuals were assigned to ranges of energy intake from added sugars based on unadjusted Day 1 intakes. Estimates of nutrient intake were adjusted using the Iowa State University method and data from the subsample of individuals with Day 2 recalls

20 < x ≤ 25%	25 < x ≤ 30%	30 < x ≤ 35%	> 35%
296	141	76	80
567	551	414	424
19	27	27	40
abdef	abdefh	gh	fgh
3.1	0.2	1.0	1.1
216	214	154	160
5	8	8	9
aef	adef	gh	gh
75	95	92	98
583	529	403	543
30	40	46	75
bdefh	defgh	fgh	abcdefgh
38	45	69	6
4.7	5.4	3.7	3.1
0.2	0.4	0.3	0.2
aefg	abcdef	egh	gh
97	97	100	100
10.3	10.6	7.9	7.8
0.3	0.5	0.5	0.4
aef	adef	gh	gh
3.5	0.3	16	7.0
7.2	7.6	6.0	5.1
0.2	0.3	0.4	0.3
aefg	adefg	efgh	gh
47	37	67	89

providing estimates of usual intake. Medians, standard errors, and percents below or above the Dietary Reference Intakes were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom.

DATA SOURCES: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994; National Cancer Institute's Pyramid Servings Database for NHANES III; and U.S. Department of Health and Human Services, National Center for Health Statistics and University of Minnesota Nutrition Coordinating Center's Carotenoid Database for NHANES III (vitamin A data only).

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

K

Data Comparing Carbohydrate Intake to Intake of Other Nutrients from the Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998

TABLE K-1 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Children 1 Through 3 Years of Age, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	18	379	1,579
Total energy (kcal)		1,306	1,402
Standard error		25	13
Carbohydrate (g)		135.0	178.0
Standard error		2.7	1.6
Carbohydrate (% energy)		41.3	51.1
Standard error		0.3	0.2
Fiber (g)		6.4	8.7
Standard error		0.2	0.1
Fat (g)		61.0	55.8
Standard error		1.3	0.6
Fat (% energy)		41.9	34.8
Standard error		0.3	0.2
Saturated fat (g)		26.1	22.4
Standard error		0.6	0.3
Saturated fat (% energy)		17.8	14.1
Standard error		0.2	0.1

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
1,428	353	20
1,385	1,253	
13	24	
206.0	213.0	
1.9	4.2	
59.7	68.2	
0.2	0.3	
10.0	10.3	
0.1	0.3	
44.9	31.5	
0.5	0.8	
28.7	22.0	
0.2	0.4	
17.3	11.7	
0.2	0.3	
11.1	8.3	
0.1	0.1	

continued

TABLE K-1 Continued

Nutrient	Carbohydrate Intake as Percentage of Total Energy		
	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
Fatty acid 18:2 (g)		6.9	7.6
Standard error		0.2	0.1
Fatty acid 18:2 (% energy)		4.8	4.8
Standard error		0.1	0.1
Thiamin (mg)		1.03	1.17
Standard error		0.02	0.01
Riboflavin (mg)		1.81	1.77
Standard error		0.04	0.02
Niacin (mg)		11.4	13.5
Standard error		0.3	0.2
Vitamin B_6 (mg)		1.10	1.31
Standard error		0.03	0.02
Vitamin B_{12} (μg)		4.11	3.38
Standard error		0.10	0.05
Folate (μg)		166	205
Standard error		5	3
Vitamin C (mg)		57	84
Standard error		2	2
Iron (mg)		8.6	10.6
Standard error		0.2	0.1
Zinc (mg)		8.0	7.9
Standard error		0.2	0.1
Calcium (mg)		972	877
Standard error		28	11

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of free-

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
6.7	4.9	
0.1	0.2	
4.3	3.4	
0.1	0.1	
1.19	1.12	
0.01	0.02	
1.65	1.44	
0.02	0.03	
13.5	12.6	
0.2	0.3	
1.37	1.38	
0.02	0.03	
2.9	2.28	
0.05	0.08	
222	219	
3	6	
114	131	
2	5	
11.3	11.5	
0.2	0.3	
7.2	6.4	
0.1	0.2	
769	623	
10	17	

dom. Children fed human milk or who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE K-2 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Children 4 Through 8 Years of Age, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	16	288	1,620
Total energy (kcal)		1,824	1,801
Standard error		32	15
Carbohydrate (g)		188.0	231.0
Standard error		3.4	1.9
Carbohydrate (% energy)		41.4	51.5
Standard error		0.4	0.2
Fiber (g)		10.4	11.9
Standard error		0.3	0.2
Fat (g)		86.4	71.1
Standard error		1.8	0.7
Fat (% energy)		42.0	34.9
Standard error		0.3	0.1
Saturated fat (g)		32.5	26.7
Standard error		0.7	0.3
Saturated fat (% energy)		15.8	13.1
Standard error		0.2	0.1
Fatty acid 18:2 (g)		12.2	10.6
Standard error		0.4	0.1
Fatty acid 18:2 (% energy)		5.9	5.2
Standard error		0.1	0.1
Thiamin (mg)		1.37	1.48
Standard error		0.03	0.02
Riboflavin (mg)		1.95	1.99
Standard error		0.04	0.02
Niacin (mg)		18.9	18.5
Standard error		0.5	0.2
Vitamin B_6 (mg)		1.46	1.55
Standard error		0.04	0.02
Vitamin B_{12} (μg)		4.68	4.20
Standard error		0.15	0.07
Folate (μg)		218	257
Standard error		6	4
Vitamin C (mg)		65	81
Standard error		3	2
Iron (mg)		11.9	13.4
Standard error		0.3	0.2
Zinc (mg)		10.7	9.9
Standard error		0.3	0.1
Calcium (mg)		948	903
Standard error		28	11

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 43 degrees of free-

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
1,562	275	8
1,715	1,626	
13	34	
254.0	277.0	
2.0	4.8	
59.3	67.6	
0.2	0.4	
12.0	12.3	
0.1	0.4	
56.6	42.2	
0.5	1.1	
29.4	23.1	
0.1	0.3	
20.7	15.3	
0.2	0.4	
10.7	8.4	
0.1	0.2	
8.9	7.1	
0.1	0.2	
4.6	3.8	
0.0	0.1	
1.50	1.36	
0.01	0.04	
1.94	1.72	
0.02	0.05	
17.6	15.2	
0.2	0.4	
1.61	1.45	
0.02	0.04	
3.46	2.58	
0.05	0.10	
275	255	
4	9	
105	114	
2	5	
13.8	12.5	
0.2	0.4	
9.0	7.4	
0.1	0.2	
836	741	
10	23	

dom. Children fed human milk or who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE K-3 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Boys 9 Through 18 Years of Age, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	8	115	484
Total energy (kcal)		2,476	2,512
Standard error		88	45
Carbohydrate (g)		262.0	319.0
Standard error		9.6	5.9
Carbohydrate (% energy)		42.5	50.9
Standard error		0.7	0.3
Fiber (g)		13.9	15.6
Standard error		0.8	0.4
Fat (g)		115.0	101.0
Standard error		4.6	2.0
Fat (% energy)		40.1	35.5
Standard error		0.5	0.3
Saturated fat (g)		41.5	36.4
Standard error		1.8	0.8
Saturated fat (% energy)		14.8	12.7
Standard error		0.3	0.2
Fatty acid 18:2 (g)		17.4	15.2
Standard error		0.9	0.4
Fatty acid 18:2 (% energy)		6.4	5.3
Standard error		0.2	0.1
Thiamin (mg)		1.84	1.92
Standard error		0.08	0.04
Riboflavin (mg)		2.35	2.44
Standard error		0.10	0.05
Niacin (mg)		25.3	25.1
Standard error		1.0	0.6
Vitamin B_6 (mg)		1.91	2.02
Standard error		0.08	0.05
Vitamin B_{12} (μg)		6.19	5.50
Standard error		0.32	0.16
Folate (μg)		232	278
Standard error		13	8
Vitamin C (mg)		87	88
Standard error		7	4
Iron (mg)		16.0	17.7
Standard error		0.7	0.4
Zinc (mg)		14.3	14.1
Standard error		0.6	0.3
Calcium (mg)		1,105	1,091
Standard error		61	27

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
343	61	8
2,467	2,335	
55	114	
370.0	391.0	
8.5	20.3	
59.7	66.1	
0.5	0.9	
16.6	17.6	
0.5	1.3	
80.0	60.0	
2.1	3.4	
28.9	23.5	
0.4	0.8	
28.0	20.9	
0.7	1.3	
10.1	8.2	
0.2	0.3	
12.7	10.6	
0.4	0.7	
4.5	4.1	
0.1	0.2	
2.13	2.07	
0.06	0.13	
2.47	2.44	
0.07	0.16	
25.5	25.1	
0.7	1.6	
2.10	2.33	
0.07	0.18	
4.70	4.40	
0.17	0.45	
329	356	
11	29	
126	143	
6	15	
19.3	20.7	
0.6	1.3	
12.3	11.2	
0.4	0.8	
1,043	958	
31	62	

were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Boys who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE K-4 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Men 19 Through 50 Years of Age, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	173	686	1,088
Total energy (kcal)	2,707	2,650	2,588
Standard error	92	47	32
Carbohydrate (g)	203.0	277.0	324.0
Standard error	7.3	5.1	4.1
Carbohydrate (% energy)	30.3	42.2	50.5
Standard error	0.7	0.4	0.3
Fiber (g)	13.1	16.7	18.2
Standard error	0.6	0.4	0.3
Fat (g)	125.0	112.0	97.0
Standard error	4.5	2.4	1.4
Fat (% energy)	42.6	37.4	33.4
Standard error	0.8	0.3	0.2
Saturated fat (g)	43.2	38.5	32.6
Standard error	1.7	0.9	0.5
Saturated fat (% energy)	14.6	12.7	11.1
Standard error	0.3	0.1	0.1
Fatty acid 18:2 (g)	20.0	18.9	17.0
Standard error	1.0	0.5	0.3
Fatty acid 18:2 (% energy)	6.7	6.2	5.8
Standard error	0.3	0.1	0.1
Thiamin (mg)	1.67	1.86	1.93
Standard error	0.07	0.04	0.03
Riboflavin (mg)	2.29	2.22	2.22
Standard error	0.09	0.04	0.03
Niacin (mg)	30.9	29.8	28.6
Standard error	1.2	0.6	0.4
Vitamin B_6 (mg)	2.35	2.15	2.11
Standard error	0.09	0.05	0.03
Vitamin B_{12} (μg)	7.90	7.60	5.50
Standard error	0.40	0.31	0.15
Folate (μg)	257	261	287
Standard error	12	6	5
Vitamin C (mg)	69	81	97
Standard error	5	3	3
Iron (mg)	16.3	17.6	18.3
Standard error	0.6	0.4	0.3
Zinc (mg)	18.0	15.8	13.7
Standard error	0.8	0.4	0.2
Calcium (mg)	858	885	910
Standard error	41	24	17

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
493	84	9
2,431	2,082	
43	94	
360.0	365.0	
6.9	15.4	
59.2	69.3	
0.5	1.3	
19.8	19.9	
0.5	1.6	
77.0	46.4	
1.6	3.1	
28.0	19.0	
0.3	1.0	
25.5	14.5	
0.7	1.1	
9.2	5.2	
0.1	0.4	
13.9	9.1	
0.4	0.7	
5.0	3.7	
0.1	0.3	
1.96	1.84	
0.04	0.15	
2.13	1.89	
0.05	0.16	
26.2	23.7	
0.6	1.7	
2.09	2.08	
0.06	0.18	
4.40	3.37	
0.17	0.36	
309	310	
9	30	
115	126	
5	14	
18.7	17.5	
0.4	1.3	
12.0	10.1	
0.3	0.8	
850	724	
24	56	

were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Men who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE K-5 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Men 51 Years of Age and Older, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	156	604	903
Total energy (kcal)	2,059	2,081	2,035
Standard error	75	36	26
Carbohydrate (g)	153.0	213.0	255.0
Standard error	6.2	3.8	3.4
Carbohydrate (% energy)	30.6	41.1	50.1
Standard error	0.8	0.3	0.3
Fiber (g)	11.2	15.3	17.6
Standard error	0.6	0.4	0.3
Fat (g)	98.0	91.0	78.0
Standard error	4.4	1.9	1.2
Fat (% energy)	42.7	39.0	34.2
Standard error	0.8	0.4	0.3
Saturated fat (g)	31.9	30.1	25.6
Standard error	1.6	0.7	0.5
Saturated fat (% energy)	14.1	12.9	11.2
Standard error	0.4	0.2	0.1
Fatty acid 18:2 (g)	16.9	15.9	13.7
Standard error	1.0	0.4	0.3
Fatty acid 18:2 (% energy)	6.9	6.7	6.0
Standard error	0.3	0.1	0.1
Thiamin (mg)	1.42	1.59	1.68
Standard error	0.07	0.03	0.03
Riboflavin (mg)	1.84	1.94	1.97
Standard error	0.08	0.04	0.03
Niacin (mg)	25.7	24.2	23.9
Standard error	1.2	0.5	0.4
Vitamin B_6 (mg)	1.85	1.84	1.93
Standard error	0.09	0.04	0.03
Vitamin B_{12} (μg)	6.07	5.60	5.50
Standard error	0.37	0.19	0.20
Folate (μg)	202	245	272
Standard error	10	6	5
Vitamin C (mg)	70	70	93
Standard error	7	3	3
Iron (mg)	13.4	14.7	16.4
Standard error	0.6	0.3	0.3
Zinc (mg)	13.8	12.7	11.5
Standard error	0.7	0.3	0.2
Calcium (mg)	618	716	761
Standard error	36	17	15

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
494	106	16
1,954	1,757	
35	56	
287.0	300.0	
4.9	10.1	
58.8	67.9	
0.4	0.7	
20.2	21.6	
0.5	1.1	
59.0	38.7	
1.4	1.8	
27.2	20.1	
0.3	0.7	
18.5	12.8	
0.5	0.7	
8.5	6.7	
0.1	0.4	
11.7	6.9	
0.3	0.4	
5.3	3.5	
0.1	0.2	
1.81	1.59	
0.04	0.07	
1.97	1.82	
0.05	0.08	
23.6	20.4	
0.5	1.0	
2.08	2.09	
0.05	0.13	
4.30	3.70	
0.18	0.38	
303	305	
9	19	
128	110	
5	7	
17.6	16.2	
0.4	0.9	
10.9	8.6	
0.3	0.3	
727	746	
18	32	

were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Men who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE K-6 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Girls 9 Through 18 Years of Age, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	6	108	401
Total energy (kcal)		1,893	1,824
Standard error		71	34
Carbohydrate (g)		196.0	229.0
Standard error		6.9	4.5
Carbohydrate (% energy)		42.2	50.6
Standard error		0.9	0.4
Fiber (g)		10.6	11.6
Standard error		0.5	0.3
Fat (g)		87.8	73.0
Standard error		3.1	1.6
Fat (% energy)		40.8	35.4
Standard error		0.5	0.4
Saturated fat (g)		31.3	25.9
Standard error		1.4	0.6
Saturated fat (% energy)		14.7	12.5
Standard error		0.3	0.2
Fatty acid 18:2 (g)		14.3	11.7
Standard error		0.7	0.3
Fatty acid 18:2 (% energy)		6.7	5.6
Standard error		0.3	0.1
Thiamin (mg)		1.22	1.38
Standard error		0.06	0.03
Riboflavin (mg)		1.74	1.77
Standard error		0.07	0.04
Niacin (mg)		19.3	18.4
Standard error		0.9	0.4
Vitamin B_6 (mg)		1.43	1.43
Standard error		0.07	0.04
Vitamin B_{12} (μg)		4.63	3.91
Standard error		0.30	0.14
Folate (μg)		177	205
Standard error		9	6
Vitamin C (mg)		54	73
Standard error		4	3
Iron (mg)		12.2	12.9
Standard error		0.6	0.3
Zinc (mg)		11.0	10.2
Standard error		0.6	0.3
Calcium (mg)		796	795
Standard error		41	22

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
401	90	7
1,853	1,838	
36	68	
275.0	315.0	
5.8	12.1	
59.3	68.5	
0.3	0.7	
13.4	13.9	
0.4	0.8	
61.5	45.5	
1.4	2.1	
29.3	22.0	
0.3	0.6	
21.4	15.3	
0.5	0.8	
10.2	7.3	
0.1	0.3	
9.9	7.8	
0.3	0.4	
4.7	3.9	
0.1	0.2	
1.46	1.43	
0.04	0.07	
1.73	1.72	
0.05	0.08	
18.3	16.5	
0.5	0.9	
1.53	1.49	
0.04	0.08	
3.55	2.63	
0.14	0.20	
237	249	
8	17	
95	128	
4	11	
13.6	13.2	
0.4	0.7	
8.9	7.9	
0.2	0.5	
743	781	
21	45	

were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Girls who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE K-7 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Women 19 Through 50 Years of Age, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	109	497	924
Total energy (kcal)	1,656	1,721	1,743
Standard error	63	34	22
Carbohydrate (g)	128.0	176.0	220.0
Standard error	5.1	3.7	2.8
Carbohydrate (% energy)	31.4	41.0	50.6
Standard error	0.8	0.4	0.3
Fiber (g)	9.0	11.1	13.0
Standard error	0.5	0.3	0.2
Fat (g)	81.3	77.0	67.0
Standard error	3.6	1.8	1.1
Fat (% energy)	43.9	39.8	34.0
Standard error	0.9	0.4	0.2
Saturated fat (g)	27.5	25.7	22.4
Standard error	1.4	0.7	0.4
Saturated fat (% energy)	14.7	13.3	11.3
Standard error	0.5	0.2	0.1
Fatty acid 18:2 (g)	13.7	13.8	12.0
Standard error	0.8	0.4	0.3
Fatty acid 18:2 (% energy)	7.4	7.0	6.0
Standard error	0.3	0.2	0.1
Thiamin (mg)	1.10	1.22	1.34
Standard error	0.06	0.03	0.02
Riboflavin (mg)	1.45	1.47	1.55
Standard error	0.07	0.03	0.02
Niacin (mg)	18.7	19.2	19.0
Standard error	1.0	0.4	0.3
Vitamin B_6 (mg)	1.30	1.37	1.45
Standard error	0.07	0.03	0.02
Vitamin B_{12} (μg)	4.76	4.52	3.75
Standard error	0.38	0.20	0.11
Folate (μg)	152	174	214
Standard error	8	5	4
Vitamin C (mg)	45	60	75
Standard error	4	3	2
Iron (mg)	10.2	11.5	12.8
Standard error	0.5	0.3	0.2
Zinc (mg)	10.7	9.8	9.4
Standard error	0.6	0.2	0.2
Calcium (mg)	634	607	635
Standard error	42	16	12

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
626	176	37
1,666	1,442	1,344
24	48	91
247.0	248.0	284.0
3.8	8.4	17.4
59.1	68.6	80.9
0.3	0.6	1.3
14.0	13.6	14.2
0.3	0.8	1.5
51.8	33.6	18.5
1.0	1.4	2.1
27.8	20.9	11.9
0.3	0.6	0.9
17.1	10.2	5.5
0.4	0.5	0.7
9.1	6.3	3.5
0.1	0.2	0.3
9.7	7.4	3.4
0.2	0.4	0.4
5.1	4.6	2.1
0.1	0.2	0.2
1.38	1.27	1.47
0.03	0.06	0.15
1.59	1.37	1.55
0.03	0.07	0.19
18.5	16.2	15.4
0.4	0.8	1.7
1.53	1.40	1.74
0.04	0.08	0.20
3.28	2.14	2.88
0.13	0.18	0.57
231	237	341
6	14	45
93	92	128
4	7	22
13.2	12.1	14.4
0.3	0.7	1.8
8.6	6.9	7.1
0.2	0.4	0.8
659	540	505
16	29	57

were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Women who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

TABLE K-8 Median Nutrient Intakes by Carbohydrate Intake as Percentage of Total Energy, Women 51 Years of Age and Older, United States, CSFII (1994–1996, 1998)

	Carbohydrate Intake as Percentage of Total Energy		
Nutrient	< 35%	35 ≤ to < 45%	45 ≤ to < 55%
n	77	438	861
Total energy (kcal)	1,394	1,464	1,528
Standard error	72	26	19
Carbohydrate (g)	104.0	147.0	193.0
Standard error	5.8	2.8	2.5
Carbohydrate (% energy)	29.6	40.3	51.0
Standard error	0.9	0.4	0.3
Fiber (g)	7.5	11.2	13.3
Standard error	0.6	0.3	0.2
Fat (g)	71.0	66.2	57.9
Standard error	4.5	1.4	0.9
Fat (% energy)	45.1	40.4	33.6
Standard error	1.2	0.4	0.3
Saturated fat (g)	23.7	21.5	18.7
Standard error	1.6	0.5	0.3
Saturated fat (% energy)	15.3	13.1	10.8
Standard error	0.6	0.2	0.1
Fatty acid 18:2 (g)	11.3	12.3	10.8
Standard error	1.0	0.4	0.2
Fatty acid 18:2 (% energy)	6.9	7.4	6.2
Standard error	0.4	0.2	0.1
Thiamin (mg)	1.01	1.13	1.25
Standard error	0.06	0.03	0.02
Riboflavin (mg)	1.26	1.40	1.53
Standard error	0.06	0.03	0.02
Niacin (mg)	17.1	17.8	17.9
Standard error	1.0	0.4	0.3
Vitamin B_6 (mg)	1.20	1.32	1.42
Standard error	0.07	0.03	0.02
Vitamin B_{12} (μg)	3.38	3.93	3.94
Standard error	0.27	0.19	0.14
Folate (μg)	139	177	209
Standard error	11	5	4
Vitamin C (mg)	45	62	82
Standard error	5	3	2
Iron (mg)	9.2	10.8	11.8
Standard error	0.5	0.2	0.2
Zinc (mg)	8.2	8.9	8.3
Standard error	0.5	0.2	0.1
Calcium (mg)	449	527	586
Standard error	28	15	11

NOTE: Data are limited to individuals who provided complete and reliable 24-hour dietary recalls on Day 1 and Day 2. Individuals were assigned to ranges of energy intake from carbohydrates based on unadjusted 2-day average intakes. Estimates of nutrient intake were adjusted using the Iowa State University method to provide estimates of usual intake. Medians and standard errors were obtained using C-Side. Standard errors

55 ≤ to < 65%	65 ≤ to < 75%	≥ 75%
620	147	18
1,422	1,272	
22	40	
210.0	219.0	
3.3	6.9	
59.1	69.2	
0.4	0.7	
15.3	17.6	
0.3	0.8	
43.4	28.1	
0.8	1.2	
27.1	19.4	
0.3	0.5	
13.7	8.2	
0.3	0.4	
8.6	5.7	
0.1	0.2	
8.4	5.8	
0.2	0.3	
5.3	3.9	
0.1	0.2	
1.28	1.30	
0.03	0.05	
1.51	1.42	
0.03	0.06	
17.2	16.2	
0.3	0.7	
1.54	1.65	
0.03	0.07	
3.06	2.58	
0.10	0.20	
232	263	
6	12	
102	123	
3	7	
12.3	13.0	
0.3	0.6	
7.8	7.1	
0.2	0.3	
604	558	
14	27	

were estimated via jackknife replication. Each standard error has 43 degrees of freedom. Women who reported no food intake for a day were excluded from the analysis.
DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service.
SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics, 2001.

L

Options for Dealing with Uncertainties

Methods for dealing with uncertainties in scientific data are generally understood by working scientists and require no special discussion here except to point out that such uncertainties should be explicitly acknowledged and taken into account whenever a risk assessment is undertaken. More subtle and difficult problems are created by uncertainties associated with some of the inferences that must be made in the absence of directly applicable data; much confusion and inconsistency can result if they are not recognized and dealt with in advance of undertaking a risk assessment.

The most significant inference uncertainties arise in risk assessments whenever attempts are made to answer the following questions (NRC, 1994):

- What sets of hazard and dose–response data (for a given substance) should be used to characterize risk in the population of interest?
- If animal data are to be used for risk characterization, which endpoints for adverse effects should be considered?
- If animal data are to be used for risk characterization, what measure of dose (e.g., dose per unit body weight, body surface, or dietary intake) should be used for scaling between animals and humans?
- What is the expected variability in dose–response between animals and humans?
- If human data are to be used for risk characterization, which adverse effects should be used?
- What is the expected variability in dose–response among members of the human population?

- How should data from subchronic exposure studies be used to estimate chronic effects?
- How should problems of differences in route of exposure within and between species be dealt with?
- How should the threshold dose be estimated for the human population?
- If a threshold in the dose–response relationship seems unlikely, how should a low-dose risk be modeled?
- What model should be chosen to represent the distribution of exposures in the population of interest when data relating to exposures are limited?
- When interspecies extrapolations are required, what should be assumed about relative rates of absorption from the gastrointestinal tract of animals and of humans?
- For which percentiles on the distribution of population exposures should risks be characterized?

At least partial, empirically based answers to some of these questions may be available for some of the nutrients under review, but in no case is scientific information likely to be sufficient to provide a highly certain answer; in many cases there will be no relevant data for the nutrient in question.

It should be recognized that for several of these questions, certain inferences have been widespread for long periods of time; thus, it may seem unnecessary to raise these uncertainties anew. When several sets of animal toxicology data are available, for example, and data are not sufficient for identifying the set (i.e., species, strain, and adverse effects endpoint) that best predicts human response, it has become traditional to select that set in which toxic responses occur at the lowest dose (the most sensitive set). In the absence of definitive empirical data applicable to a specific case, it is generally assumed that there will not be more than a tenfold variation in response among members of the human population. In the absence of absorption data, it is generally assumed that humans will absorb the chemical at the same rate as the animal species used to model human risk. In the absence of complete understanding of biological mechanisms, it is generally assumed that, except possibly for certain carcinogens, a threshold dose must be exceeded before toxicity is expressed. These types of long-standing assumptions, which are necessary to complete a risk assessment, are recognized by risk assessors as attempts to deal with uncertainties (NRC, 1994).

A past National Research Council (NRC) report (1983) recommended adoption of the concepts and definitions that have been discussed in this report. The NRC committee recognized that throughout a risk assessment, data and basic knowledge will be lacking and risk assessors will be faced with several scientifically plausible options (called inference options by the NRC) for dealing with questions such as those presented above. For

example, several scientifically supportable options for dose scaling across species and for high- to low-dose extrapolation will exist, but there will be no ready means to identify those that are clearly best supported. The NRC committee recommended that regulatory agencies in the United States identify the needed inference options in risk assessment and specify, through written risk assessment guidelines, the specific options that will be used for all assessments. Agencies in the United States have identified the specific models to be used to fill gaps in data and knowledge; these have come to be called *default options* (EPA, 1986).

The use of defaults to fill knowledge and data gaps in risk assessment has the advantage of ensuring consistency in approach (the same defaults are used for each assessment) and minimizing or eliminating case-by-case manipulations of the conduct of risk assessment to meet predetermined risk management objectives. The major disadvantage of the use of defaults is the potential for displacement of scientific judgment by excessively rigid guidelines. A remedy for this disadvantage was also suggested by the NRC committee: risk assessors should be allowed to replace defaults with alternative factors in specific cases of chemicals for which relevant scientific data are available to support alternatives. The risk assessors' obligation in such cases is to provide explicit justification for any such departure. Guidelines for risk assessment issued by the U.S. Environmental Protection Agency (EPA, 1986), for example, specifically allow for such departures.

The use of preselected defaults is not the only way to deal with model uncertainties. Another option is to allow risk assessors complete freedom to pursue whatever approaches they judge applicable in specific cases. Because many of the uncertainties cannot be resolved scientifically, case-by-case judgments without some guidance on how to deal with them will lead to difficulties in achieving scientific consensus, and the results of the assessment may not be credible.

Another option for dealing with uncertainties is to allow risk assessors to develop a range of estimates based on application of both defaults and alternative inferences that, in specific cases, have some degree of scientific support. Indeed, appropriate analysis of uncertainties seems to require such a presentation of risk results. Although presenting a number of plausible risk estimates has the advantage that it would seem to more faithfully reflect the true state of scientific understanding, there are no well-established criteria for using such complex results in risk management.

The various approaches to dealing with uncertainties inherent in risk assessment are summarized in Table L-1.

As can be seen in the nutrient chapters, specific default assumptions for assessing nutrient risks have not been recommended. Rather, the approach calls for case-by-case judgments, with the recommendation that the basis

for the choices made be explicitly stated. Some general guidelines for making these choices are, however, offered.

REFERENCES

EPA (U.S. Environmental Protection Agency). 1986. Proposed guidelines for carcinogen risk assessment; Notice. *Fed Regis* 61:17960–18011.

NRC (National Research Council). 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press.

NRC. 1994. *Science and Judgment in Risk Assessment*. Washington, DC: National Academy Press.

TABLE L-1 Approaches for Dealing with Uncertainties in a Risk Assessment Program

Program Model	Advantages
Case-by-case judgments by experts	Flexibility; high potential to maximize use of most relevant scientific information bearing on specific issues
Written guidelines specifying defaults for data and model uncertainties (with allowance for departures in specific cases)	Consistent treatment of different issues; maximization of transparency of process; resolution of scientific disagreements possible by resorting to defaults
Presentation of full array of estimates by assessors from all scientifically plausible models	Maximization of use of scientific information; reasonably reliable portrayal of true state of scientific understanding

Disadvantages
Potential for inconsistent treatment of different issues; difficulty in achieving consensus; need to agree on defaults
Possible difficulty in justifying departure or achieving consensus among scientists that departures are justified in specific cases; danger that uncertainties will be overlooked
Highly complex characterization of risk, with no easy way to discriminate among estimates; size of required effort may not be commensurate with utility of the outcome

M

Nitrogen Balance Studies Used to Estimate the Protein Requirements in Adults

TABLE M-1 Nitrogen Balance Studies Used to Estimate the Protein Requirements in Adults

Reference	Country	Study Type[a]
Agarwal et al., 1984	India	Primary estimation
Atinmo et al., 1988b	Nigeria	Primary estimation
Bourges and Lopez-Castro, 1982	Mexico	Primary estimation
Cheng et al., 1978	Chile	Primary estimation + test
Clark et al., 1972	United States	Primary estimation
Dutra de Oliveira and Vannucchi, 1984	Brazil	Primary estimation
Egana et al., 1992	Chile	Primary estimation
Egun and Atinmo, 1993b	Nigeria	Primary estimation
Fajardo et al., 1981	Columbia	Primary estimation
Hussein, 1984	Egypt	Primary estimation
Inoue et al., 1981	Japan	Primary estimation
Istfan et al., 1983b	United States	Primary estimation
Kaneko et al., 1988	Japan	Primary estimation
Ozalp et al., 1984a	Turkey	Primary estimation
Scrimshaw et al., 1983	United States	Primary estimation
Thomas et al., 1979	United States	Primary estimation
Tontisirin et al., 1981b	Thailand	Primary estimation
Uauy et al., 1978b	United States	Primary estimation
Yanez et al., 1982	Chile	Primary estimation
Young et al., 1984	United States	Primary estimation

Subjects	Age (y)	Protein Source
6 men, 5 women	25–39	Vegetable: rice, wheat
15 men	19–21	Mixed: beef, rice
11 men	15–30	Animal: milk + vegetable: corn, beans
14 men	23–29 60–73	Mixed: milk, wheat, soy
5 men, 1 woman	22–26	Mixed: milk, wheat, rice
9 men	18–28	Vegetable: rice, beans
14 men	18–31	Animal: egg + vegetable: lupin
12 women	21–32	Mixed: rice, wheat, beef
12 men, 2 women	21–26	Mixed: meat, wheat, potatoes + vegetable: rice, beans, potatoes
8 women	18–27	Mixed
21 men	19–28	Animal: fish + vegetable: soy + mixed: fish, soy
8 men	18–21	Vegetable: soy
12 women	18–24	Mixed
11 men	19–26	Mixed: wheat, yogurt
22 men	18–23	Animal: milk + vegetable: soy
7 women	18–23	Vegetable: cottonseed
13 men	19–27	Animal: egg
7 men, 7 women	68–84	Animal: egg
15 men	20–31	Mixed: wheat, milk + animal: egg
15 men	20s	Animal: egg + vegetable: soy

continued

TABLE M-1 Continued

Reference	Country	Study Type[a]
Huang and Lin, 1982	China	Secondary estimation
Inoue et al., 1973	Japan	Secondary estimation
Kaneko and Koike, 1985	Japan	Secondary estimation + energy
Komatsu et al., 1983	Japan	Secondary estimation
Wayler et al., 1983	United States	Secondary estimation
Xuecun et al., 1984	China	Secondary estimation
Young et al., 1973	United States	Secondary estimation
Young et al., 1975	United States	Secondary estimation
Zanni et al., 1979	United States	Secondary estimation + obligatory
Atinmo et al., 1985	Nigeria	Obligatory
Bodwell et al., 1979	United States	Obligatory
Bricker and Smith, 1951	United States	Obligatory
Calloway and Margen, 1971	United States	Obligatory
Huang et al., 1972	China	Obligatory
Inoue et al., 1974		Obligatory
Nicol and Phillips, 1976a	Nigeria	Obligatory
Scrimshaw et al., 1972	United States	Obligatory
Scrimshaw et al., 1976	United States	Obligatory
Tontisirin et al., 1981a	Thailand	Obligatory
Uauy et al., 1978a	United States	Obligatory
Uauy et al., 1982	Chile	Obligatory + energy
Young and Scrimshaw, 1968	United States	Obligatory
Atinmo et al., 1988a	Nigeria	Test
Bourges et al., 1984	Mexico	Test
Campbell et al., 1994	United States	Test
Castaneda et al., 1995	United States	Test
Dutra de Oliveira et al., 1981	Brazil	Test
Egun and Atinmo, 1993a	Nigeria	Test
Gersovitz et al., 1982	United States	Test
Istfan et al., 1983a	United States	Test
Nicol and Phillips, 1976b	Nigeria	Test
Oddoye and Margen, 1979	United States	Test
Ozalp et al., 1984b	Turkey	Test
Ozalp et al., 1984c	Turkey	Test
Tontisirin et al., 1984	Thailand	Test
Uauy et al., 1984	Chile	Test
Xuecun et al., 1984	China	Test
Yanez and Uauy, 1984	Chile	Test
Young et al., 1984	United States	Test

[a] Primary estimation = studies designed to estimate requirement by feeding a number of individuals several different intake levels; test = studies not designed to estimate requirement, usually involving long experimental periods for a single level; energy = studies designed to study the effects of varying energy intake; secondary estimation =

Subjects	Age (y)	Protein Source
41 men	20–29	Animal: egg + mixed
25 men	20–27	Animal: egg + vegetable: rice
15 women	18–22	Animal: egg
28 men	19–30	Animal: amino acids (egg)
34 men	18–26	Animal: beef + animal: milk + mixed: beef, soy
10 men	26–41	Mixed: rice, wheat, pork, egg
19 men	18–28	Animal: egg
15 men	18–24	Animal: beef + vegetable: wheat
6 men	63–77	Animal: egg white
15 men	19–39	
13 men, 11 women	19–52	
25 women	19–30	
13 men	21–37	
50 men	20–32	
9 men	Young	
9 men	21–30	
83 men	18–26	
11 women	67–91	
4 men	21–25	
8 men	68–72	
8 men	24–31	
8 men	17–22	
12 men	22–29	Mixed: beef, rice
20 men	19–25	Vegetable: corn, beans
8 men, 4 women	56–80	Mixed: milk, egg, vegetable
12 women	66–79	Mixed: milk, vegetable
14 men	17–26	Mixed: rice, beans, meat, milk
11 women	21–30	Mixed: rice, wheat, beef
7 men, 8 women	70–99	Animal: egg
6 men	18–26	Vegetable: soy
17 men	21–30	Vegetable: rice
12 men	23–30	Animal: egg + mixed: egg, soy
49 men	19–30	Mixed: wheat, yogurt
15 men	19–28	Mixed: wheat, yogurt
12 men	19–26	Mixed: rice, fish
53 men	18–19	Mixed: wheat, rice, milk
6 men	24–45	Mixed: rice, wheat, pork, egg
8 men	19–33	Mixed: wheat, rice, milk
32 men	20s	Animal: egg + vegetable: soy

studies that present only mean data or studied different individuals at each intake level; obligatory = studies that examined responses to zero or very low nitrogen intake.
SOURCE: Adapted from Rand et al. (2003).

REFERENCES

Agarwal KN, Bhatia BD, Agarwal DK, Shanker R. 1984. Assessment of protein energy needs of Indian adults using short-term nitrogen balance methodology. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp 89–95.

Atinmo T, Mbofung CMF, Hussain MA, Osotimehin BO. 1985. Human protein requirements: Obligatory urinary and faecal nitrogen losses and the factorial estimation of protein needs of Nigerian male adults. *Br J Nutr* 54:605–611.

Atinmo T, Egun G, Mbofung CMF. 1988a. Long-term evaluation of the adequacy of habitual diets to provide protein needs of adult Nigerian men. *Br J Nutr* 60:459–466.

Atinmo T, Mbofung CMF, Egun G, Osotimehin B. 1988b. Nitrogen balance study in young Nigerian adult males using four levels of protein intake. *Br J Nutr* 60:451–458

Bodwell CE, Schuster EM, Kyle E, Brooks B, Womack M, Steele P, Ahrens R. 1979. Obligatory urinary and fecal nitrogen losses in young women, older men, and young men and the factorial estimation of adult human protein requirements. *Am J Clin Nutr* 32:2450–2459.

Bourges H, Lopez-Castro BR. 1982. Protein requirements of young adult men fed a Mexican rural diet. *Arch Latinoam Nutr* 32:630–649.

Bourges H, Lopez-Castro B, Tovar A, Calerón P, Torres N, Villarreal M. 1984. Nitrogen balance response of young male adults fed predicted requirement levels of a Mexican rural diet. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 157–160.

Bricker ML, Smith JM. 1951. A study of the endogenous nitrogen output of college women, with particular reference to use of the creatinine output in the calculation of the biological values of the protein of egg and of sunflower seed flower. *J Nutr* 44:553–573.

Calloway DH, Margen S. 1971. Variation in endogenous nitrogen excretion and dietary nitrogen utilization as determinants of human protein requirement. *J Nutr* 101:205–216.

Campbell WW, Crim MC, Dallal GE, Young VR, Evans WJ. 1994. Increased protein requirements in elderly people: New data and retrospective reassessments. *Am J Clin Nutr* 60:501–509.

Castaneda C, Dolnikowski GG, Dallal GE, Evans WJ, Crim MC. 1995. Protein turnover and energy metabolism of elderly women fed a low-protein diet. *Am J Clin Nutr* 62:40–48.

Cheng AH, Gomez A, Bergan JG, Lee TC, Monckeberg F, Chichester CO. 1978. Comparative nitrogen balance study between young and aged adults using three levels of protein intake from a combination wheat-soy-milk mixture. *Am J Clin Nutr* 31:12–22.

Clark HE, Howe JM, Magee JL, Malzer JL. 1972. Nitrogen balances of adult human subjects who consumed four levels of nitrogen from a combination of rice, milk and wheat. *J Nutr* 102:1647–1654.

Dutra de Oliveira JE, Vannucchi H. 1984. The protein requirements of Brazilian rural workers: Studies with a rice and bean diet. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 111–118.

Dutra de Oliveira JE, Vannucchi H, Duarta RMF. 1981. Evaluation of the nutritive value of a rice-and-bean-based diet for agricultural migrant workers in Brazil. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo: United Nations University Press. Pp. 98–102.

Egana JI, Uauy R, Cassorla X, Barrera G, Yanez E. 1992. Sweet lupin protein quality in young men. *J Nutr* 122:2341–2347.

Egun GN, Atinmo T. 1993a. A metabolic nitrogen balance study for 40 d and evaluation of the menstrual cycle on protein requirement in young Nigerian women. *Br J Nutr* 70:449–457.

Egun GN, Atinmo T. 1993b. Protein requirement of young adult Nigerian females on habitual Nigerian diet at the usual level of energy intake. *Br J Nutr* 70:439–448.

Fajardo LF, Bolanos O, Acciarri G, Victoria F, Restrepo J, Ramirez AB, Angel LM. 1981. Protein requirements for young Colombian adults consuming local diets containing primarily animal or vegetable protein. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo: United Nations University Press. Pp. 54–62.

Gersovitz M, Motil K, Munro HN, Scrimshaw NS, Young VR. 1982. Human protein requirements: Assessment of the adequacy of the current Recommended Dietary Allowance for dietary protein in elderly men and women. *Am J Clin Nutr* 35:6–14.

Huang P-C, Lin CP. 1982. Protein requirements of young Chinese male adults on ordinary Chinese mixed diet and egg diet at ordinary levels of energy intake. *J Nutr* 112:897–907.

Huang P-C, Chong HE, Rand WM. 1972. Obligatory urinary and fecal nitrogen losses in young Chinese men. *J Nutr* 102:1605–1614.

Hussein MA. 1984. Protein requirements of Egyptian women. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 102–106.

Inoue G, Fujita Y, Niiyama Y. 1973. Studies on protein requirements of young men fed egg protein and rice protein with excess and maintenance energy intakes. *J Nutr* 103:1673–1687.

Inoue G, Fujita Y, Kishi K, Yamamoto S, Niiyama Y. 1974. Nutritive values of egg protein and wheat gluten in young men. *Nutr Rep Int* 10:201.

Inoue G, Takahashi T, Kishi K, Komatsu T, Niiyama Y. 1981. The evaluation of soy protein isolate alone and in combination with fish in adult Japanese men. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo: United Nations University Press. Pp. 77–87.

Istfan N, Murray E, Janghorbani M, Evans MJ, Young VR. 1983a. The nutritional value of a soy protein concentrate (STAPRO-3200) for long-term protein nutritional maintenance in young men. *J Nutr* 113:2524–2534.

Istfan N, Murray E, Janghorbani M, Young VR. 1983b. An evaluation of the nutritional value of a soy protein concentrate in young adult men using the short-term N-balance method. *J Nutr* 113:2516–2523.

Kaneko K, Koike G. 1985. Utilization and requirement of egg protein in Japanese women. *J Nutr Sci Vitaminol* 31:43–52.

Kaneko K, Ishikawa K, Setoguchi K, Koike G. 1988. Utilization and requirement of dietary protein taking into account the dermal and miscellaneous nitrogen losses in Japanese women. *J Nutr Sci Vitaminol* 34:459–467.

Komatsu T, Kishi K, Yamamoto T, Inoue G. 1983. Nitrogen requirement of amino acid mixture with maintenance energy in young men. *J Nutr Sci Vitaminol* 29:169–185.

Nicol BM, Phillips PG. 1976a. Endogenous nitrogen excretion and utilization of dietary protein. *Br J Nutr* 35:181–193.

Nicol BM, Phillips PG. 1976b. The utilization of dietary protein by Nigerian men. *Br J Nutr* 36:337–351.

Oddoye EA, Margen S. 1979. Nitrogen balance studies in humans: Long-term effect of high nitrogen intake on nitrogen accretion. *J Nutr* 109:363–377.

Ozalp I, Ozguc M, Tokol S, Koksal G, Tasci N, Soysal G. 1984a. Nitrogen balances of young Turkish adults on graded levels of protein intake. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 107–110.

Ozalp I, Ozguc M, Tokol S, Tasci N, Baysal A. 1984b. Short-term nitrogen balances of 49 young Turkish adults on estimated mean requirement intake levels of protein. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 161–163.

Ozalp I, Ozguc M, Tokol S, Tasci N, Baysal A, Coskin T. 1984c. Nitrogen balances of 15 Turkish young adults on a safe level of protein intake for 15 days. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 96–101.

Rand WM, Pellett PL, Young VR. 2003. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. *Am J Clin Nutr* 77:109–127.

Scrimshaw NS, Hussein MA, Murray E, Rand WM, Young VR. 1972. Protein requirements of man: Variations in obligatory urinary and fecal nitrogen losses in young men. *J Nutr* 102:1595–1604.

Scrimshaw NS, Perera WDA, Young VR. 1976. Protein requirements of man: Obligatory urinary and fecal nitrogen losses in elderly women. *J Nutr* 106:665–670.

Scrimshaw NS, Wayler AH, Murray E, Steinke FH, Rand WM, Young VR. 1983. Nitrogen balance response in young men given one of two isolated soy proteins or milk proteins. *J Nutr* 113:2492–2497.

Thomas MR, Ashby J, Sneed SM, O'Rear LM. 1979. Minimum nitrogen requirement from glandless cottonseed protein for nitrogen balance in college women. *J Nutr* 109:397–405.

Tontisirin K, Sirichakawal PP, Valyasevi A. 1981a. Obligatory nitrogen losses of adult Thai males. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo: United Nations University Press. Pp. 126–130.

Tontisirin K, Sirichakawal PP, Valyasevi A. 1981b. Protein requirements of adult Thai males. In: Torun B, Young VR, Rand WM, eds. *Protein-Energy Requirements of Developing Countries: Evaluation of New Data.* Tokyo: United Nations University Press. Pp. 88–97.

Tontisirin K, Thongprasert K, Valyasevi A. 1984. Long-term evaluation of the adequacy of habitual diets to provide protein needs for adult Thai men. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 126–138.

Uauy R, Scrimshaw NS, Rand WR, Young VR. 1978a. Human protein requirements: Obligatory urinary and fecal nitrogen losses and the factorial estimation of protein needs in elderly males. *J Nutr* 108:97–103.

Uauy R, Scrimshaw NS, Young VR. 1978b. Human protein requirements: Nitrogen balance response to graded levels of egg protein in elderly men and women. *Am J Clin Nutr* 31:779–785.

Uauy R, Yanez E, Ballester D, Barrera G, Guzman E, Saitua MT, Zacarias I. 1982. Obligatory urinary and faecal nitrogen losses in young Chilean men given two levels of dietary energy intake. *Br J Nutr* 47:11–20.

Uauy R, Yanez E, Velasco N, Egana JI. 1984. Short-term evaluation of the capacity of a Chilean mixed diet to meet protein energy needs of a group of young adult males. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 164–172.

Wayler A, Queiroz E, Scrimshaw NS, Steinke FH, Rand WM, Young VR. 1983. Nitrogen balance studies in young men to assess the protein quality of an isolated soy protein in relation to meat proteins. *J Nutr* 113:2485–2491.

Xuecun C, Taian Y, Xunjiu Y, Jiguo B, Zhisheng H. 1984. Protein requirements of Chinese male adults. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 96–101.

Yanez E, Uauy R. 1984. Long-term evaluation of the capacity of a Chilean mixed diet to meet the protein energy requirements of young adult males. In: Rand WM, Uauy R, Scrimshaw NS, eds. *Protein-Energy Requirement Studies in Developing Countries: Results of International Research.* Tokyo: United Nations University Press. Pp. 147–153.

Yanez E, Uauy R, Ballester D, Barrera G, Chavez N, Guzman E, Saitua MT, Zacarias I. 1982. Capacity of the Chilean mixed diet to meet the protein and energy requirements of young adult males. *Br J Nutr* 47:1–10.

Young VR, Scrimshaw NS. 1968. Endogenous nitrogen metabolism and plasma free amino acids in young adults given a 'protein-free' diet. *Br J Nutr* 22:9–20.

Young VR, Taylor YS, Rand WM, Scrimshaw NS. 1973. Protein requirements of man: Efficiency of egg protein utilization at maintenance and submaintenance levels in young men. *J Nutr* 103:1164–1174.

Young VR, Fajardo L, Murray E, Rand WM, Scrimshaw NS. 1975. Protein requirements of man: Comparative nitrogen balance response within the submaintenance-to-maintenance range of intakes of wheat and beef proteins. *J Nutr* 105:534–542.

Young VR, Puig M, Queiroz E, Scrimshaw NS, Rand WM. 1984. Evaluation of the protein quality of an isolated soy protein in young men: Relative nitrogen requirements and effect of methionine supplementation. *Am J Clin Nutr* 39:16–24.

Zanni E, Calloway DH, Zezulka AY. 1979. Protein requirements of elderly men. *J Nutr* 109:513–524.

Biographical Sketches of Panel and Subcommittee Members

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GEORGE A. BROOKS, Ph.D., is a professor of integrative biology at the University of California at Berkeley and specializes in the areas of exercise physiology and metabolism. His research is intended to elaborate the pathways and controls of lactic acid formation and removal during and after exercise and to study the integration of carbohydrates, lipids, and amino and fatty acids into the carbon flux sustaining exercise. To study these problems in detail, isotope tracer, biochemical, and molecular techniques have been developed and are used extensively. Additionally, the effects of acute and chronic bouts of exercise, gender, hypoxia, and perturbations in oxygen transport on energy fluxes and associated cellular organelles, membranes, and enzyme systems are under investigation. Dr. Brooks is responsible for articulating the "Crossover Concept" describing the balance of carbohydrate and lipid used during physical exercise, as well as for discovery of the "Cell-Cell" and "Intracellular Lactate Shuttles" that describe the pivotal role of lactate in intermediary metabolism.

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ALICIA L. CARRIQUIRY, Ph.D., is an associate professor in the Department of Statistics at Iowa State University. Since 1990, Dr. Carriquiry has been a consultant for the U.S. Department of Agriculture (USDA) Human Nutrition Information Service. She has also consulted to the U.S. Environmental Protection Agency and the National Pork Producers Council and is an affiliate for the Law and Economics Consulting Group. At present, Dr. Carriquiry is investigating the statistical issues associated with the Third National Health and Nutrition Examination Survey (NHANES III) and she has recently completed reports on improving USDA's food intake surveys and methods to estimate adjusted intake, and biochemical measurement distributions for NHANES III. Dr. Carriquiry is the current president of the International Society for Bayesian Analysis and is an elected member of the International Statistical Institute. She is editor of *Statistical Science*

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ALICE H. LICHTENSTEIN, D.Sc., is a senior scientist and director of the Cardiovascular Nutrition Research Laboratory at the Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University and the Stanley N. Gershoff professor of nutrition science and policy at the Gerald J. & Dorothy R. Friedman School of Nutrition Science & Policy at Tufts University. Dr. Lichtenstein earned her D.Sc. at Harvard University and received her postdoctoral training at the Cardiovascular Institute at Boston University School of Medicine. Dr. Lichtenstein has served on many committees of the American Society of Nutritional Sciences and the American Heart Association, where she currently serves as vice-chair of the Nutrition Committee. She is on the editorial boards of *Atherosclerosis* and *Journal of Lipid Research* and on the editorial advisory boards of *Nutrition in Clinical Care* and the *Tufts University Health & Nutrition*. She recently served on the 2000 Dietary Guidelines Advisory Committee. Her research interesting include the areas of plasma lipoprotein response to dietary modification with respect to fatty acids, protein, phytoestrogens, and plant sterols, and the effect of diet on lipoprotein kinetic behavior. She is specifically interested in the response of older, moderately hypercholesterolemic individual to dietary modification with the intent to decrease risk of developing cardiovascular disease.

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Index

A

Absorption of nutrients. *See* Bioavailability; Intestinal absorption; *individual nutrients*
Acceptable Macronutrient Distribution Ranges (AMDRs). *See also individual nutrients and life-stage groups*
  defined, 14-15, 28, 39, 772, 941
  evidence considered for, 15-16, 769
  rationale for, 14, 28, 784
  uses, 29, 941, 945, 946, 948-949
Adaptation, nutritional
  amino acid metabolism, 618, 619
  basal metabolism, 201
  to carbohydrate-free diet, 277-278, 293
  defined, 149, 973
  in energy balance, 149-151, 201, 220, 223-224, 452
  glucose metabolism, 277-278
  growth impairment as, 151, 220, 437
  to high-fat diets, 452
  pregnancy and lactation, 34, 47, 197, 290, 291, 650
  to protein metabolism, 47, 276, 279, 605, 611, 650, 657, 694
  to starvation, 277-279, 605
  weight as, 150
Adequate Intakes (AIs). *See also individual macronutrients and life-stage groups*
  criteria used to derive, 7-8, 10-11, 44-46
  defined, 3, 22, 26
  derivation of, 28, 31, 32, 47
  extrapolation between other age groups, 26-27, 31-32, 34, 46, 47, 283
  indicators used to set, 28
  methods used to set, 44-46, 47, 280-283, 385-390, 456-457, 460-461, 464, 465, 466-470, 471-472, 619-621, 662-665
  prevalence of intakes above, 789
  RDA compared, 6, 26-27
  uncertainty in, 26, 44
  uses, 26, 936, 939-940, 944-945, 946, 948
Adiposity, 125, 130, 189, 200, 220, 379, 832. *See also* Body fat content
Adolescents, ages 9 through 18 years. *See also* Puberty/pubertal development
  added sugars, 1206-1209, 1216-1219
  ages 9 through 13 years, 35, 386, 463-464, 470, 624-627, 631, 665, 673-674, 769, 1126-1129, 1138-1143, 1172-1173, 1178-1181, 1206-1207, 1216-1217, 1232-1233, 1238-1239
  ages 14 through 18 years, 35, 193, 201-202, 292, 293, 386, 389-390, 463-464, 465-466, 470, 471-472, 674-675, 729, 769, 1128-1129, 1143-1145, 1181-1183, 1208-1209, 1218-1219, 1232-1233, 1238-1239
  AIs, 26-27, 33, 385-386, 388-389, 463-464, 470, 471-472, 632-633
  AMDRs, 769, 816, 844, 945

amino acids, 664-670, 673-675, 702-703
aortic fatty streaks, 815
aspartame, 702-703
BMR, 178-179
body composition and size, 142, 178, 181, 626-629
bone mineralization, density, and mass, 66, 180
brain development, 288-289
carbohydrate, 284-285, 292, 1232-1233, 1238-1239
EARs, 33, 46-47, 284, 292, 293, 632, 664-669, 673-675
EERs, 175, 176-182, 193, 201-202, 216-219
energy intakes, 473, 474, 1206-1209, 1216-1219, 1232-1233, 1238-1239
extrapolation of data from adult values, 26-27
factorial methods, 628, 631
fat (total dietary), 459, 945, 1232-1233, 1238-1239
fatty acids, 456, 1232-1233, 1238-1239
fiber, 385-386, 388-389, 391, 394, 1232-1233, 1238-1239
glucose metabolism, 288-289
growth and development, 33, 142, 175, 177, 181, 182, 459, 654
lactation, 293, 389-390, 465-466, 471-472, 659
maintenance requirement, 667
nitrogen balance studies, 624-627, 632, 664-666
nutrient intakes with added sugars, 1206-1209, 1216-1219
obese or overweight, 181, 216-219, 312, 459, 1172-1173, 1178-1183, 1200, 1202
physical activity, 176-181, 182, 880, 883, 902-907, 911-912, 924, 1126-1129, 1138-1145, 1172-1173, 1178-1183
polyunsaturated fatty acids, 463-464, 465-466, 469-470, 471-472
pregnancy, 48, 193, 201-202, 292, 389, 465, 471-472, 650-652, 654-655
protein, 624-629, 631, 632-633, 665, 670, 769
RDAs, 285, 292, 293, 631-632, 655, 670, 673-675
reference weights and heights, 35, 136-137, 176, 178, 659, 670, 983
saturated fatty acids, 474, 835, 1232-1233, 1238-1239
special considerations, 216-219
sugar intakes, 312, 323, 1206-1209, 1216-1219
TEE, 176, 178, 181, 1126-1129, 1138-1145, 1172-1173, 1178-1183, 1200, 1202
trans fatty acids, 456
vitamin and mineral intakes, 1232-1233, 1238-1239
weight, 216-219, 650, 652, 653, 655
Adults, ages 19 years and older. *See also* Age/aging; Lactation; Pregnancy
added sugars, 295, 788-789, 1210-1215, 1220-1225
ages 19 through 50 years, 35, 46, 184, 186-189, 205-213, 286, 288, 292, 293, 296, 323, 371, 388, 389, 447, 450-452, 464, 471-472, 548, 614, 633-645, 648, 695, 887, 983-984, 701, 703, 720, 727, 729, 730, 1146-1159, 1164-1167, 1184-1187, 1190-1195, 1210-1211, 1220-1223, 1234-1235, 1240-1241
ages 51 years and older, 33-34, 66, 138, 143-144, 289, 296, 303, 358, 371, 388, 396, 398, 447, 450-452, 464, 548-549, 602, 603, 608, 634, 660, 661, 697, 704, 711, 723, 725, 734, 736-737, 841, 887, 922, 1150-1153, 1158-1163, 1186-1191, 1194-1199, 1214-1215, 1224-1225, 1236-1237, 1242-1243
AIs, 26, 33-34, 387-388, 464-466, 470-472
allergies, 692
AMDRs, 285, 769, 809, 826, 844, 941
amino acids, 594, 599, 607, 613, 614, 668, 669, 670-680, 686-688, 690-691, 692, 703, 720, 726
bioavailability of nutrients, 34
BMI, 35, 36, 121, 124-130, 131, 310, 1078-1087, 1098-1103
body composition data, 1078-1103
body fat content, 111, 124-125, 126, 128-130, 131, 1078-1101
bone mineral density, 66
brain utilization of glucose, 285-289
carbohydrates, 265, 277, 285-289, 294-295, 769, 809, 1234-1237, 1240-1243
catabolic stress, 594
CHD risk, 303, 366, 387-388, 777-784, 797-798

cholesterol, 548-549
dental caries, 296
diabetes (type 2), 268, 388, 784-785
dietary intakes, 294-295, 602, 695, 697, 1234-1237, 1240-1243
EARs, 33, 34, 46-47, 285-289, 292, 293, 633, 643-644, 646-649, 668, 670-679
EERs, 121, 124-130, 183-189
energy expenditure, 108, 116, 122-123, 131, 138, 140-141, 143-144
energy intakes, 474, 647, 1234-1237, 1240-1243
energy metabolism, 33, 54, 108, 116, 289
extrapolation of data to infants and children, 25, 26-27, 34, 46, 47, 284
fat (dietary), 459-460, 769, 809, 1234-1237, 1240-1243
fiber, 354, 358, 366, 387-389, 396, 398, 788, 809, 1234-1237, 1240-1243
glucose metabolism, 285-289, 388, 784-785
high fat, low carbohydrate diets, 792-810
hyperinsulinemia, 784-785
low fat, high carbohydrate diets, 772-792
malnutrition, 608
methodological considerations, 47-48
monounsaturated fatty acids, 432
nitrogen balance studies, 275, 287, 618, 633-643, 661
nutrient intakes with sugars, 1210-1215, 1220-1225
obese and overweight, 122-123, 792-797, 1184-1199, 1201
peak bone mass, 33
physical activity, 66, 138, 143-144, 183-184, 186-189, 883, 895-903, 911-912, 1184-1199
polyunsaturated fatty acids, 433, 435, 464, 470-472, 478
protein, 287-288, 595, 602, 605, 608, 611-612, 633-649, 660, 661, 668, 686-688, 690-691, 692, 695, 769, 841
RDAs, 33, 47, 265, 289-290, 292, 293, 603, 644-645, 649, 667-669, 679-680
reference heights and weights, 35, 124, 125, 126, 128-130, 983-984
renal function, 34
reserve capacity and functioning, 33-34
saturated fatty acids, 474, 835, 1234-1237, 1240-1243
special considerations, 202-213, 220
sugar intakes, 323, 789, 792, 1210-1213, 1220-1225
TEE, 161-164, 183, 203, 1146-1165, 1184-1199, 1200-1201
vitamin and mineral intakes, 1234-1237, 1240-1243
weight and height, 143, 183, 184, 220, 1078-1081, 1088-1091
weight maintenance, 773-777
Adverse effects. *See also individual nutrients*
defined, 84, 973
insufficient evidence of, 102-103, 970-971
nutrient–nutrient interactions, 85, 95
Aerobics Center Longitudinal Study, 912
African Americans
breast cancer, 379
energy expenditure, 145-146, 179
fiber, 379
pubertal development, 33
Age/aging. *See also* Adolescents; Adults; Children; Infants; Life-stage groups
BMR, 131, 143
carbohydrate–lipid oxidation balance, 922
energy expenditure, 117, 143-144, 157, 158, 159-161, 181, 183
and energy requirements, 183, 647
fat absorption, 447, 450-452
glucose metabolism, 289
insulin resistance, 62
physical activity, 143-144, 922, 924
and protein reserve, 595, 602, 640-641, 642
reporting of dietary intakes, 117
RMR, 143
sensitivity to nutrient toxicity, 92
and sugar intakes, 323
TEF, 134, 143, 165, 171, 179
weight gain, 143, 167
Alanine (dispensable), 276, 591, 593, 594, 596, 597, 604, 605, 606, 696-697, 736, 992-993
Alaska Natives, 275, 284, 693
Albumin, 304-305, 430, 602, 609, 610
Alcohol
dietary intakes, 49, 110, 1064-1065
energy contribution, 109, 771, 1064-1065
and fatty acid oxidation, 109, 453

by life stage and gender group, 1064-1065
oxidation rate, 108-109
TEF, 109-110
Alcoholics and alcoholism, 110, 704
Aldosterone, 543
Allergic reactions, 295, 396, 397, 399
α-Ketoglutarate, 604, 605
α-Linoleic acid. *See also* Polyunsaturated fatty acids, *n*-3
AIs, 8-9, 11, 423, 466-472, 834, 944-945
AMDRs, 15-16, 770, 834-835
and CHD, 427, 770, 827, 828, 829
deficiency, 9, 423, 427, 439-440, 443-445, 470, 472
dietary intakes, 478, 834
food sources, 478, 771, 834
function, 423, 427, 435, 445, 466
interaction with linoleic acid, 447, 453-455, 472, 825
and learning behavior, 439, 445
metabolism, 434-435, 445-446, 468, 472
parenteral nutrition and, 444
protective effects, 427, 770
sources, 427, 447
supplementation, 444
and vision, 439, 440, 468
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 483
Altitude, and energy expenditure, 149
Amino acids. *See also* Protein; *individual amino acids*
absorption, 621
adaptations in metabolism, 618, 619
adverse effects of, 696, 697-698, 701-703, 705-708, 711-712, 713-717, 720, 721-723, 724-726, 727, 729, 730-733, 734-735
AIs, 662-663
alcoholism and, 704
animal studies, 671, 696, 697-698, 701-702, 703, 705, 707-708, 711-712, 713-714, 720, 721-722, 724, 725-726, 727, 729, 730-732, 734-735
and appetite or eating behavior, 707, 709, 710, 713, 730, 731-732
and asthma, 716-717
and behavior, 697, 701, 713, 714, 721, 727, 729
bioavailability, 685
and body fat, 713
and brain chemistry, 704-705, 707, 709, 710, 711, 714, 721, 731, 732, 734, 735
branched-chain, 604, 616, 660, 704-711; *See also* Isoleucine, Leucine, Valine
and cancer, 54, 698-699, 700, 708, 710, 711, 713, 719, 722, 732, 843
and carbohydrates, 275, 276, 701, 731, 732-733
carbon metabolism, 605-607
catabolism, 278, 594, 603-608, 616, 617, 704, 712
and CHD risk, 726
chemistry, 590, 592-593
Chinese restaurant syndrome, 714, 715-716
composition of proteins, 279, 621, 666, 682, 685-686
deficiency, 662
deposition rate, 672-675
dermal effects, 733-734, 735
developmental studies, 708-710, 724, 732
diabetes and, 704
dietary intakes, 692, 696, 697, 700, 701, 704, 711, 712, 720, 721, 723, 725, 727, 729, 730, 731, 734, 736, 992-1027
digestibility, 621
direct amino acid oxidation method, 615-617, 618, 619, 670-671, 676-678
dose–response assessment, 697, 699-700, 703, 711, 712, 717, 719, 720, 723, 725, 726, 728, 729, 730, 731, 733-734, 736
EARs, 589, 619, 664-679, 680-681, 688
excretion, 604
factorial estimate, 614, 666-669
food sources, 48, 712-713, 714
free, 596-597, 599, 602, 603, 620, 692, 721
function, 9, 38, 589, 590, 696, 697, 701, 704-705, 712, 720-721, 725, 729, 731, 734, 736
and gastrointestinal disturbances, 698, 700, 714, 720, 722, 724, 726, 733
genotoxicity, 720
gluconeogenesis from, 276, 278, 288-289, 604, 606
and growth, 598, 607, 665, 666, 669, 697, 701, 707, 710, 713, 719, 720, 721, 724, 725, 728

hazard identification, 696-699, 700, 701-703, 704-710, 711-717, 718-719, 720, 721-723, 724-726, 727, 729, 730-733, 734-735
and herpes infections, 724
high-protein diets and, 712
homeostasis, 595-598
hormonal effects, 715
human studies, 608-699, 702-703, 705-706, 712, 714-715, 720, 722-723, 724-725, 726, 727, 729, 730, 731-733, 735
imbalances in, 707, 708-709, 710, 726
and immune function, 697-698, 699
indicator amino acid oxidation method, 617-619, 670-671, 676, 677, 678
indicators for estimating requirements, 613-619
individual variability in requirements, 614, 665-666, 679
insulin sensitivity, 696, 701, 705, 710
intake assessment, 736-737
interactions with other nutrients, 721-723, 725, 726, 731
by life stage and gender group, 662-682, 992-1027
limiting, 602, 611, 614, 669, 685, 689, 690, 691
and lipid profiles, 721, 724
liver function and, 704, 705, 721
losses, 601, 614
low-protein diets, 697, 707, 709, 721, 731-732
maintenance, 666, 667-669, 672-675
and malnutrition, 704
maple syrup urine disease, 704, 706
metabolic disorders, 697, 700, 704, 705, 706, 710, 714, 727, 728, 735
metabolic pathways, 597-598, 600, 617, 660, 697, 701, 704, 705, 717, 719, 724, 726, 728-729, 731
neurological effects, 696, 699, 701-702, 703, 704-705, 706, 711, 714, 715, 717, 718, 719, 727, 728, 733
nitrogen balance studies, 612, 613-614, 618, 662, 664-666, 670-671, 676, 677, 678, 688
nitrogen metabolism, 278, 603-605, 718, 720
nitrogen utilization through nonprotein pathways, 607-608
nutritional and metabolic classification, 593-594
and obesity, 701, 704, 732
opthalmologic effects, 711, 714, 720, 722, 729, 734, 735, 736
parenteral nutrition and, 699, 705, 714, 718, 719, 722-723
and physical exercise, 702, 705-706
planning and assessing intakes, 961-963
plasma amino acid response method, 614-615, 670-671
precursors of nonprotein products, 608
protective effects, 726
quality of protein source, 661, 662, 684-690, 721
RDAs, 47, 672-675, 679-680, 681, 682
reproductive effects, 701, 712, 713, 715
research recommendations, 737-738
risk characterization, 737
scoring, 14, 589, 662, 685, 686-691
selection of indicators for estimating requirements, 613-619
and somnolence, 698, 700, 722, 733
special considerations, 728
and starvation, 693, 704
supplementation, 695-735
synthesis, 275, 701, 712, 717, 723, 729, 734
and taste and smell acuity, 722
teratogenic effects, 708, 728
trauma and, 596, 605
24-hour amino acid balance method, 616-617, 670-671, 676, 677
ULs, 695-737
variance in requirements, 688
and weight, 697, 698, 700, 707, 709, 713, 721, 724, 730, 731-732, 734
Amino sugars, 684
Ammonia, 56, 375, 377, 603, 604, 605, 684, 697, 714, 717-718, 719
Amylopectin, 267-268, 269, 272
Amylose, 267, 272
Animal studies
advantages, 94-95, 97
amino acids, 671, 696, 697-698, 701-702, 707-708, 711-712, 713-714, 720, 721-722, 724, 725-726, 727, 729, 730-732, 734-735
carbohydrate, 40, 275
cholesterol, 548, 562
colon cancer, 377

dose-response assessment, 96, 98, 100
extrapolation of data from, 40, 87, 95, 97, 98, 100, 101, 492, 562, 1245-1246
fat, 40
fiber, 351, 361, 377
hazard identification, 94-95, 96, 696, 697-698, 701-702, 707-708, 711-712, 713-714, 721-722, 724, 725-726, 727, 729, 730-732, 734-735
nitrogen balance studies, 671
polyunsaturated fatty acids, 444-445, 492
pregnant animals, 709, 726
protein, 40
relevance of, 39, 40, 94, 96, 703, 705, 711, 727
uncertainties in, 100, 1245-1246
Apolipoprotein A-I, 61
Apolipoprotein B100, 503
Apolipoprotein CH, 429
Apolipoprotein E, 544
Apoproteins, 429
Apoptosis, 55, 833, 837-838
Appetite, 383, 707, 709, 710, 713, 730, 731-732, 795
Arabinose, 345
Arachidonic acid, 425, 426, 433-434, 435, 438, 439, 440, 442, 443, 444, 446-447, 453-454, 455-456, 465, 469, 472, 476, 478, 824, 838
Arginase, 605
Arginine (dispensable), 591, 593, 594, 597, 605, 608, 697-700, 709, 712, 717, 724, 736, 994-995
Arginine glutamate, 714
Arginionsuccinic acid synthetase, 697, 700
Arizona Wheat-bran Fiber Trial, 374
Arteriosclerosis, 130, 842
Asians, obese, 352
Asparagine (dispensable), 591, 593, 594, 700
Aspartame, 695, 702-703, 727
Aspartic acid/aspartate (dispensable), 591, 592, 593, 594, 597, 604, 605, 608, 695, 709, 736, 996-997
Association of Official Analytical Chemists International, 340, 344
Assessment of nutrient intakes
added sugars, 957
AI and, 939-940, 944-945
AMDR and, 941, 945
amino acids, 960-963
biochemical approach, 944
carbohydrate, 956-957
cut-point method, 943
EAR and, 938-939, 943-944
energy, 48, 225, 954-956
fat, 959
fiber, 957-958
of groups, 16-18, 941-945
of individuals, 937-941
polyunsaturated fatty acids, 959-960
probability approach, 942-943, 944
protein, 960-961
RDA and, 938-939, 944
UL and, 940, 945
Asthma, 396, 399, 716-717
Atherogenic dyslipidemia, 777
Atherogenic lipid profile, 802
Atherogenic lipoprotein phenotype, 777, 782
Atherosclerosis, 59, 485-486, 546, 548, 549, 560, 562, 563, 823-824, 826, 836-837, 840
Atherosclerosis Risk in Communities Study, 563
Athletes, 115. *See also* Physical activity
amino acid supplements, 702, 706
endurance training, 660
energy balance, 221-223, 452
high-carbohydrate diet, 452
high-fat diet, 452
lipoprotein profile, 61
low fat, high carbohydrate diet, 773
protein, 660-661
resistance training, 660
runners, 61, 773
skeletal health, 66
Autoimmune diseases, 487

B

Balance studies. *See also* Nitrogen balance studies
cholesterol, 543-544
defined, 40
limitations of, 40-41, 617, 676
methionine, 677
24-hour amino acid method, 616-617
zinc bioavailability, 394
Basal energy expenditure (BEE)
defined, 112
DLW data, 1104-1202
fat-free mass and, 128, 186
gender differences, 141, 217

and MET rate, 888
obese and overweight individuals, 217
prediction, 114, 171, 178-179, 186, 205, 217
Schofield equations, 171, 178-179, 186
and weight, 116, 141, 150, 183, 184, 186, 206-213, 888
Basal metabolic rate (BMR), 25
adaptations, 201
adolescents, 178-179
aging and, 131, 143
altitude and, 149
body composition and size and, 131, 141
and carbohydrates, 196
children, 141, 171, 1114-1121
climate and, 148
defined, 112
and energy expenditure, 112-114, 115, 131, 141, 164-165, 171, 178-179, 185, 188-190, 195
and energy requirement, 164-165, 171, 178-179, 185, 188-190, 195-196
ethnic differences, 146
FFM and, 139
gender differences, 141
infants, 164-165, 1106-1114
lactation, 195-196
measurement, 165, 171, 185, 188
menstrual cycle and, 140, 141
pregnancy, 185, 188-191, 291
protein balance and, 598
sedentary individuals, 115
Basal requirement, 24
Beans. *See* Legumes
Behavior. *See also* Eating behavior
amino acid intake and, 697, 701, 713, 714, 721, 727, 729
breastfed infants, 621
learning, 439, 445, 446, 447, 697, 713, 729
polyunsaturated fatty acids and, 439, 445, 446, 447
sugar intake and, 295-296, 323
Bengal gram, 366-367
β_3-Adrenergic receptor gene, 145
β-Glucans (dietary or functional fiber), 345, 355-356
β-Hydroxybutyrate, 285, 430
Bioavailability of nutrients
age/aging and, 447, 450-452
amino acids, 685
balance studies and, 394
defined, 93, 973
factors affecting, 29-30, 93-94, 271, 281
fat intake and, 424, 785, 788-792
fiber consumption and, 29, 94, 348, 351-352, 369, 382, 391, 394-395, 397-398, 838
in human milk, 431, 447, 621, 944
in infant formula, 26, 31, 45, 431, 940, 944, 946
nutrient–nutrient interactions and, 93, 271, 281, 424
and risk assessment, 93-94, 98
from supplements, 29, 93, 94
Biomarkers of disease, 41
Bladder cancer, 708, 710
Bleeding time, 492-493
Blood pressure. *See also* Hypertension
amino acids and, 735
fiber and, 60
physical activity and, 60
polyunsaturated fatty acids and, 59, 829
trans fatty acids and, 504
weight and, 204
Body composition and size. *See also* Body fat content; Fat-free mass; Fat mass; Obesity and overweight
adolescents, 142, 178, 181
adults, 1078-1103
and BMR, 131, 141
CLA and, 836-837
and energy expenditure, 65, 112, 117, 131-135, 138, 139, 141
gender differences, 128, 142, 1078-1103
genetic factors, 144, 146
NHANES III data, 124, 125, 130, 982, 1078-1103
pregnancy and, 188, 191-192
protein deposition, 626-629, 644
and reporting of dietary intakes, 117
research recommendations, 225, 240
and sensitivity to nutrients, 92
and TEE, 132
undernutrition and, 220
Body fat content. *See also* Body Mass Index; Fat mass
adults, 111, 124-125, 126, 128-130, 131, 1078-1101
amino acid intake and, 713
bioimpedance data, 124
BMI and, 121, 124-125, 126, 128-130, 1080-1087, 1098-1101

and cancer, 379
gender differences, 1078-1101
height and, 125, 128-130, 1078-1081, 1088-1089
infants, 142, 621
obesity, 126
physical activity and, 57, 61, 139, 180, 181
protein intake and, 843
reserves, 111, 220
and triceps skinfold, 125, 128, 1080-1081, 1086-1087, 1092-1093, 1100-1101
and waist circumference, 1084-1085, 1094-1099
and weight, 1090-1091
Body Mass Index (BMI)
adults, 35, 36, 121, 124-130, 131, 310, 1078-1087, 1098-1103
and body fat content, 121, 124-125, 126, 128-130, 1080-1087, 1098-1101
and cancer, 238-239
and CHD, 124, 232-233
children, 35, 36, 65, 130-131, 216, 814, 1114-1121
and chronic disease, 224, 226-239, 303
cutoffs, 121, 126
defined, 121
and diabetes type 2, 124, 226-229
fat intake and, 814
fiber consumption and, 352, 379, 383, 384
gender differences, 125-129, 1078-1087, 1098-1103
glycemic index and, 313
healthy, 121, 124, 126
and height, 1080-1081
as indicator of energy requirement, 121, 124-131
infants, 1106-1114
methodological issues, 121, 124-125
and mortality, 484
obesity, 126, 204, 216, 310, 313
PAL and, 220, 223, 814, 911
previous median vs. new median, 35
protein intake and, 843
reference heights and weights and, 35, 36, 124, 125, 126, 127-130
saturated fatty acid intake and, 484
sugar intake and, 65, 310, 313, 316-319
and triceps skinfold, 1080-1081, 1086-1087, 1100-1101
waist circumference used with, 124-125, 127, 1080-1081, 1084-1085, 1098-1099, 1102-1103
and weight, 1080-1081
Body weight. *See* Weight
Bogalusa Heart Study, 307, 310, 314-315, 792-793, 815
Bone mineral density, 66, 180, 276, 928
Brain
amino acids, 704-705, 707, 709, 710, 711, 714, 721, 724, 731, 732, 734, 735
carbohydrate utilization, 38, 265, 273, 276, 277, 278, 279, 280, 284, 285-289, 430
chemistry, 704-705, 707, 709, 710, 711, 714, 721, 731, 732, 734, 735
cholesterol synthesis by infants, 545, 548
glucose metabolism, 38, 265, 273, 276, 277, 279-280, 285-289
macronutrients needed by, 771
pituitary adenomas, 396
polyunsaturated fatty acid deficiency and, 444-445, 466, 468
Bran, 350, 353, 355, 356, 359, 367, 368, 371, 372, 378, 394, 395, 838
Breast cancer
arginine and, 698-699, 700
BMI and, 238-239
case-control studies, 54, 378
cholesterol intake and, 568, 574-575
conjugated linoleic acid and, 837, 838
cross-cultural studies, 54, 377-378
epidemiological studies, 54
fat intake and, 54, 55, 486, 512-513, 808, 843
fiber intake and, 56, 377-380
intervention studies, 378-379
monounsaturated fatty acid intake and, 819
physical activity and, 57
polyunsaturated fatty acids and, 825, 833
prospective studies, 378
protein intake and, 843-844
sugar intake and, 319-320
Breastfeeding. *See also* Human milk; Infants; Lactation
and energy expenditure, 165
recommendations, 31, 45, 171, 281, 662
Butyrate, 56, 348, 349, 361, 371, 375

C

Calcium, 281, 391, 394, 431, 592, 789, 790-793, 811, 812, 813, 835, 838, 840, 841, 1204-1211, 1214-1221, 1224-1225, 1228-1243
Canada
dietary intake data, 295, 473, 479, 481, 692, 1066-1075
fiber definitions and guidelines, 340, 349
Food Guide to Healthy Eating, 771
human milk intake and composition, 172-173
physical activity recommendations, 883
Canadian National Institute of Nutrition, 979
Canadian Paediatric Society, 31, 32, 45, 46
Canadian Society of Exercise Physiology, 883
Cancer. *See also individual histological sites*
amino acids and, 54, 698-699, 700, 708, 710, 711, 713, 719, 722, 732, 843
BMI and, 238-239
body fat and, 379
carbohydrate intake and, 55, 319-321
cholesterol and, 54, 568, 570-579
CLA and, 427
energy intake and, 54
evidence about dietary factors, 53
fat intake and, 54-55, 375, 376, 484, 486, 512-513, 808
fiber intake and, 54, 55-56, 319, 321, 339, 373-380, 396, 398
glycemic index of foods and, 310-311, 319, 321
high fat, low carbohydrate diets and, 808
hormone-related, 56
monounsaturated fatty acids and, 55, 486, 819
physical activity and, 56-57
polyunsaturated fatty acids and, 54, 824-825, 833-834
protective effect of nutrients, 54, 55, 819, 833-834
protein intake and, 54, 843-844
sugars and, 54, 55, 319-320, 321, 323
Caproic acid, 425
Caprylic acid, 425
Carbohydrate, dietary. *See also* Glucose; Glycemic index; High fat, low carbohydrate diets; Low fat, high carbohydrate diets; Starch; Sugar; *individual life-stage groups*
adaptation to starvation, 277-278, 293
adverse effects of overconsumption, 295-323
aging and, 289
AIs, 32, 280-283, 944
AMDRs, 15, 285, 769, 785, 809, 816
amino acids and, 275, 276, 701, 731, 732-733
animal derived, 342; *See also* Fiber
and BMR, 196
brain utilization, 38, 265, 273, 276, 277, 278, 279, 280, 284, 285-289, 430
Canada, 295, 1068-1069
and cancer, 55, 319-321
and CHD, 59, 303, 797, 798-799, 800-801
classification, 265-266
clinical effects of inadequate intakes, 275-276
compared to other nutrient intakes, 1226-1243
and dental caries, 296-297
and diabetes type 2, 63, 302, 303, 306-307, 785
dietary intakes, 46, 65, 265, 294-295, 770-771, 943, 944, 1032-1035, 1068-1069, 1226-1243
digestion, 272
EARs, 4, 6, 277-280, 284, 285-289, 290-293
energy contribution, 280, 281, 294-295, 770-771, 813, 1034-1035, 1226-1243
epidemiological studies, 783, 785, 800-801
fatty acid synthesis, 275, 277, 433
food sources, 265, 280-281, 294, 771
function, 4, 38, 265
and growth, 280-281, 922-923
hazard identification, 295-321
high-carbohydrate diets, 295, 297, 438, 769, 772-792, 795
in human milk, 281-283, 292
intake assessment, 323
intervention studies, 785, 786-787
intestinal absorption, 60, 272-273, 281, 323, 369
by life stage and gender group, 6, 280-293, 988-991, 1032-1033, 1068-1069
and lipid oxidation, 917-923
and lipid profile, 275, 277, 278-279, 297-303, 781, 782-784
low carbohydrate diets, 293, 430, 784, 792-810

malabsorption, 397
and mental health, 276
metabolism, 38, 64, 190, 196, 273-275, 424
and micronutrient inadequacies or excesses, 812, 816, 1226-1243
and obesity, 65, 275, 307, 310-319, 769
and physical activity, 64, 318-319, 452, 917-923
planning intakes, 956-957, 964
RDAs, 4, 6, 47, 265, 285, 289-290, 292, 293
research recommendations, 323-324
special considerations, 283, 293
TEF, 110, 114
total, 63, 956-957
Carbohydrate-free diet, 277-278, 281, 287-288, 289, 293, 701
Carbon metabolism, 605-607
Carboxymethylcellulose gum, 367, 382
Carboxypeptidases, 599
Cardiac arrhythmias, 59, 60, 427, 829, 927
Cardiovascular disease. *See also* Atherosclerosis; Coronary artery disease; Coronary heart disease
cholesterol intake, 546, 548, 549, 560, 562
lipid profile and, 302, 562-569
monounsaturated fatty acids and, 485-486
physical exercise and, 60-61, 927
Carnitine, 430, 607, 608, 723, 724
Carnosine, 721
Carotenoids, 424, 785, 792-793
Catecholamines, 608, 735
Caucasians
carbohydrate-free diet, 275
energy expenditure, 145-146
pubertal development, 33
Cell growth and proliferation, 55
Cell surface adhesion proteins, 490
Cellulose (dietary or functional fiber), 344-345, 348, 350, 351, 356, 358, 359, 367, 371, 372, 382, 390, 394
Centers for Disease Control and Prevention, 130, 216
Cereals and cereal fiber, 55-56, 359, 363, 364, 369, 370, 373, 377, 378, 380-381, 387, 388, 394, 399, 788
Chicago Western Electric Study, 562, 826-827, 828
Children, ages 1 through 8 years. *See also* Life-stage groups; Toddlers
added sugars, 294, 812-813, 816, 1204-1205
AIs, 26-27, 32, 34, 385-386, 463, 469-470
allergies, 692
AMDRs, 769, 816, 826, 844, 941, 945
amino acids, 25, 589, 614, 619, 664-670, 672-673, 686, 687, 689, 702-703, 720
aortic fatty streaks, 815
aspartame, 702-703
BMI, 35, 36, 65, 130-131, 216, 310, 814, 1114-1127, 1128-1139
BMR, 141, 171, 1114-1121
bone mass, 66
brain development, 284, 286-287, 288-289, 608-609
carbohydrates, 65, 265, 284-285, 294, 295, 769, 813, 1226-1231
chronic disease risk in adulthood, 130, 814-815
congenital defects of amino acids, 619, 697
constipation, 370-371, 385-386
dental caries, 296
derivation of DRIs, 32
diarrhea, 438
EARs, 25, 32, 34, 46-47, 284, 631, 664-669, 672-673
EERs, 107, 130-131, 168-170, 171, 174-177, 216-219
energy expenditure, 116, 134-135, 138, 141, 146, 148, 161-164, 174, 1114-1127
energy intakes, 54, 65, 170, 386, 473, 474, 814, 1226-1231
epilepsy, 284
extrapolation of data from adults to, 25, 26-27, 34, 47, 284
factorial method, 628, 631, 666-669
fat (dietary), 437, 438, 441, 459, 769, 810, 814-816, 945, 1226-1227, 1230-1231
fatty acids, 456, 1228-1231
fiber, 370-371, 385-386, 1226-1227, 1230-1231
glucose metabolism, 286-287, 288-289
growth, 32, 47, 134, 142, 151, 167-168, 174, 175, 221, 222, 437, 441, 456, 459, 609, 611, 810-811, 839-840, 922-923
high fat, low carbohydrate diets, 814-816

hyperactivity, 295
hypercholesterolemia, 811
lipid profiles, 811, 814-815
low fat, high carbohydrate diets, 438, 810-814
malnutrition, 167, 608-609, 839
methodological considerations, 25, 47-48
micronutrient intakes with macronutrients, 220, 811-814, 816, 1204-1205, 1228-1231
nitrogen balance studies, 624-627, 664-666
of obese parents, 133
obesity or overweight, 65, 130, 134, 140, 153, 216-219, 307, 310, 312-313, 459, 811, 814, 923, 1168-1179, 1200, 1202
PAL, 166, 1122-1127, 1128-1139, 1168-1179
phenylketonuria, 619
physical activity, 66, 138, 140, 146, 171, 174, 880, 883, 902-907, 911-912, 924
polyunsaturated fatty acids, 438, 444, 463, 469-470
protein, 25, 284, 608-609, 611, 624-629, 631, 667-669, 686, 687, 689, 692, 769, 811, 839-840
RDAs, 25, 34, 47, 265, 285, 631-632, 670, 672-673
saturated fatty acids, 474, 816, 835, 1226-1227, 1230-1231
special considerations, 216-219
stunting, 151, 217, 220, 221, 222, 811, 840
sugar intakes, 307-310, 813-814, 1204-1205
TEE, 134-135, 148, 161-164, 166, 174, 217, 1114-1127, 1128-1139, 1168-1179, 1200, 1202
TEF, 134, 171
toddlers (1 to 3 years), 32, 35, 130, 132-135, 166, 167-170, 284, 285, 386, 463, 470, 626-628, 631, 632, 664, 672, 686, 687, 689, 769, 816, 1106-1123, 1128-1129, 1226-1231
trans fatty acids, 456
UL derivation for, 34
underweight, 130, 811
urea synthesis defects, 699
wasting, 840
weight control, 216-219
weights and heights, reference, 34, 35, 130, 132-137, 176, 178, 983
Chinese restaurant syndrome, 715-716
Chitin and chitosan (functional fiber), 345, 351-352, 384, 395-396
Chloride, 725
Cholesterol (dietary)
absorption, 4, 60, 359, 369, 543-544, 561
animal studies, 548, 562
adverse effects of, 549, 558-573
balance studies, 543-544
and cancer, 54, 568, 570-579
and cardiovascular disease, 546, 548, 549, 560, 562
and CHD, 58, 542, 548, 562-569, 572, 573, 836
and diabetes type 2, 563
dietary intake, 549, 550-559, 563, 960, 1058-1059
dose–response assessment, 568-573
epidemiological studies, 562-569
food sources, 48, 544, 545, 546-549, 836
function, 4, 542, 543
hazard identification, 549-568
high cholesterol diets, 545, 836
by life stage and gender group, 546-549, 1058-1059
and lipid profile, 544-545, 548-562, 563, 568-569, 573
and lipoprotein metabolism, 544-545, 548-562, 563, 568-569, 573
low cholesterol diets, 546, 561, 835
metabolism, 4, 429, 544-546, 562
oxidation products, 545-546
reducing intakes, 836
research recommendations, 574-575, 578
risk characterization, 573-574
Cholesterol (plasma/serum total), 572. *See also* HDL cholesterol; LDL cholesterol
amino acids and, 721, 724
and cardiovascular disease, 546, 548, 549, 560, 562
and CHD, 58, 542, 548, 562-569, 572, 573, 836
cholesterol intakes and, 550-561
fat intake and, 58, 544, 550-559, 560, 809
fiber intake and, 4, 59-60, 339, 351, 352, 354, 355, 356, 357, 358-359, 360, 361, 365-368
genetic factors, 58, 544, 545, 546, 561-562
glycemic index and, 302

interindividual variation, 560-561, 562
monounsaturated fatty acids and, 58, 486, 817-818
polyunsaturated fatty acids and, 58, 59, 560
protein intake and, 60, 840
saturated fatty acid intake and, 481, 482, 560, 561, 809
trans fatty acids and, 58, 494-495
Chronic diseases. *See also individual diseases*
BMI and, 224, 226-239, 303
body weight gain and, 224, 226-239
fat-related risks, 437-438, 460
knowledge gaps on intake relationships to, 771-772, 970
physical activity and, 912-917
preventive effects of macronutrients, *See* Protective effects of macronutrients
protein intakes and, 694
Chylomicrons, 429, 430, 432, 543, 544
Citric acid cycle, 430, 606
Citrulline, 604, 607, 717
Climate, and energy expenditure and requirements, 146-149
Collagen, 593, 595, 729
Colon cancer
ammonia and, 375, 377
animal studies, 377
BMI and, 238-239
cholesterol intake and, 568, 576-577
colonic adenomas, 56, 238-239, 321, 371, 374, 375-376, 398
epidemiological studies, 373-374
fat intake and, 54, 55, 371, 486, 514-515, 808
fiber intake and, 55-56, 321, 348, 373-377
glycemic index of diet and, 310-311, 321
intervention studies, 374-375, 376-377
markers for, 374
monounsaturated fatty acids and, 819
physical activity and, 56-57
polyunsaturated fatty acids and, 833
protein intake and, 843
risk factors, 373
Colon health, fiber and, 55-56, 339, 348, 358, 370-377, 385-386, 388
Colonic adenomas, 56, 238-239, 321, 371, 374, 375-376, 398
Colorectal cancer, 54, 55, 321, 486, 514-515, 808, 833, 837
Conjugated linoleic acid (CLA)
and body composition, 836-837
and cancer, 427, 836-838
dietary intakes, 481
evidence considered for estimating requirements, 447
food sources, 480-481
function, 428-429
metabolism, 428
protective effects, 428, 836-838
supplements, 837
Constipation, 353, 355, 358, 370-371, 372, 379, 385-386, 388
Continuing Survey of Food Intakes by Individuals
adjustments to data, 49-50
dietary intake data, 294-295, 314-315, 391, 457, 461, 473, 474, 477, 478, 480, 549, 695, 788, 790-791, 799, 943, 1028-1065, 1226-1243
survey design, 49
Copper, 721, 723, 790-791
Cori cycle, 287, 607
Corn syrups, 266, 294
Coronary artery disease, 60-61, 434, 563, 815, 842-843. *See also* Coronary heart disease
Coronary heart disease
amino acids and, 726
aortic fatty streaks during childhood and, 815
BMI and, 124, 232-233
carbohydrate intake and, 59, 303, 797, 798-799, 800-801
cholesterol intake and, 58, 542, 548, 562-569, 572, 573, 836
epidemiological studies, 362-365, 562-569, 797-798, 800-801, 817, 820-821, 826-828
fat intake and, 58-59, 437-438, 460, 769, 797-799, 802
fiber intake and, 59-60, 322, 339, 356, 362-368, 369, 387-388, 389, 563
gender and, 363, 364
genetic factors, 57
glycemic index and, 303, 308-311
high fat, low carbohydrate diets, 797-802, 814-815
homocysteine and, 726
intervention studies, 365-368, 798-799, 817-818, 821, 828-831

lipid profile and, 57, 60, 356, 481-484, 542, 548-549, 562-569, 573, 798-799, 815
low fat, high carbohydrate diets and, 437-438, 772, 777-784
monounsaturated fatty acids and, 58-59, 817-818
obesity and overweight and, 130, 815
physical activity and, 60, 797, 886-887, 924
polyunsaturated fatty acids and, 59, 62-63, 427, 434, 455, 492, 770, 798-799, 820-821, 826-831
pregnancy, 389
protein and, 60
prothrombotic markers, 799, 802
randomized controlled clinical trials, 828-829
risk factors, 57, 563
saturated fatty acids and, 422, 481-484, 797, 798, 799
sugar intake and, 303, 800-801
trans fatty acids and, 58, 423, 504, 510-513
tricylglycerol and, 57-58, 59, 437
Cortisol, 189, 715
Creatine/creatinine, 603, 604, 607, 608, 609, 620, 647, 684, 697, 842
Critical endpoints, 93, 98, 99, 101, 102
Cysteine/cystine (dispensable), 589, 591, 592, 593, 594, 601, 607, 608, 614, 663-665, 666, 668, 672-675, 677, 678, 679-682, 683, 685, 686, 687, 689, 711-712, 736, 998-999

D

Data and database issues
adjustments to survey data, 49-50
critical data set, 98
dietary intake data, 49-50, 117
for dose–response assessment, 98, 101-103
quality and completeness of data, 2-3, 40, 43, 44, 46, 85, 86, 90, 97, 99, 180, 479, 969
research needs, 969-971
selection for dose-response assessment, 90, 98
statistical analysis, 612-613
uncertainties in, 86, 99, 1246
validation of dietary intake data with, 117
Dehydration, 926-927
Dental caries, 61-62, 296-297, 323
Department of Health Survey of British School Children, 307-310, 314-317, 792-793
Depletion-repletion studies, 40-41
Dermal effects of amino acids, 733-734, 735
Dermatitis, 5, 442, 444, 460
Developmental effects. *See also* Growth and development
of amino acids, 708-710, 724, 732
of functional fiber, 396
of *n*-3 polyunsaturated fatty acid deficiency, 444-447
Dextrose, 295
Diabetes mellitus, type 1, 268, 275
Diabetes mellitus, type 2
adults, 268, 388, 784-785
and amino acids, 704
BMI and, 124, 226-229
carbohydrate intake and, 63, 302, 303, 306-307, 785
cholesterol intake and, 563
epidemiological studies, 380-381, 785, 803, 832
fat intake and, 62-63, 437-438, 460, 802-808
fiber intake and, 63, 352-353, 354, 355, 359-360, 380-382, 388
gender differences, 380, 381
genetic factors, 62
glycemic index and, 63, 302, 304-307, 308-309, 322
glycemic response, 268, 271
HDL cholesterol and, 308-309
high fat, low carbohydrate diets and, 802-808
insulin resistance, 63, 275, 303, 306-307, 308-312, 784-785
intervention studies, 381-382, 785, 786-787, 806-807, 832-833
lipid profile, 308-309
low fat, high carbohydrate diets and, 437-438, 772, 784-785
monounsaturated fatty acids and, 819
obesity and overweight and, 802, 803
physical activity and, 63-64
polyunsaturated fatty acids and, 494, 821, 832-833
protective effects of nutrients, 380-381
risk factors, 57, 62, 563
saturated fatty acids and, 484-485
sugar intakes and, 303

Diabetes Prevention Program Research Group, 806-807
Dialysis, 722
Diammonium citrate, 594
Diarrhea, 397, 398, 438, 693
Diet and Reinfarction Trial (DART), 828
Dietary and Nutritional Survey of British Adults, 314-315, 316-317, 318-319
Dietary Approaches to Stop Hypertension diet, 798
Dietary intakes. *See also individual nutrients*
  adjustment of data, 49-50, 103, 938, 941-942, 943
  assessment of, 88-89, 90, 118, 323, 436
  and bioavailability, 940, 944
  breast-fed infants, 45, 624, 939-940
  Canadian, 1066-1075
  and chronic disease, 970
  corroboration of, 437
  day-to-day variations in, 49, 938, 940, 941-942, 943
  energy density of foods and, 794-796
  food composition databases, 48, 49-50, 941
  food frequency questionnaires, 939
  food quotient from, 120
  form of, 96 n.2
  gender differences, 265, 294, 473, 474, 692, 988-1065
  menu samples, 392-393
  methodological issues, 42, 48, 49-50, 110, 116, 117-118, 307, 312, 313, 322, 563, 624, 643, 936-937
  self-reported, 42, 48-49, 64, 117-118, 307, 479, 938
  sources of data, 49-50
  underreporting, 42, 49, 110, 117-118, 313, 643, 794, 936-937, 944, 956
  using data from, 937-939, 940
Dietary Intervention Study in Children (DISC), 812, 814
Dietary Reference Intakes (DRIs)
  applicable population, 30, 202
  assessment applications, 16-18, 23-24, 936, 937-941
  categories, 2, 22-28; *See also* Acceptable Macronutrient Distribution Ranges; Adequate Intakes; Estimated Average Requirements; Recommended Dietary Allowance; Tolerable Upper Intake Levels
  criteria for, 3, 5-13, 21-22, 44
  defined, 2, 3, 21-22
  extrapolation from other age groups, 26-27, 31-32, 34, 101, 982-984
  framework, 36, 979-981
  group applications, 16-18, 23-24, 941-945, 947-949
  individual applications, 26, 30, 937-941, 946
  origin, 978-979
  parameters for, 29-36; *See also* Life-stage groups; Reference weights and heights
  planning applications, 24, 936, 946-949
  rationale for, 1, 978-979
  sources of data, 2-3, 36, 43-44; *See also* Methodological considerations
  uses, 16-18, 28, 936-966
  WHO/FAO/WHO approach compared, 24
Direct amino acid oxidation (DAAO) method, 615-617, 618, 619, 670-671, 676-678
Disaccharides, 265, 266, 272, 281, 342
Diverticular disease, 371-372, 388
Docosahexanoic acid (DHA), 9, 55, 59, 62, 427, 435, 439, 440, 443, 444-446, 447, 453, 455-456, 466, 468, 469, 470, 471, 472, 478, 487, 492, 494, 770, 826, 828, 829, 833, 1056-1057
Docosapentaenoic acid, 426, 427, 1054-1055
Dose–response assessment. *See also individual nutrients*
  animal studies, 96, 98, 100
  components and process, 87-88, 95
  critical endpoint, 93, 98, 99, 101, 102
  data quality and completeness, 98, 101-103
  data selection, 90, 98
  defined, 974
  derivation of UL, 90, 98, 101
  human studies, 98
  LOAEL/NOAEL identification, 90, 98, 99-100, 102
  special considerations, 100, 101
  uncertainty assessment, 98, 100-101
Doubly labeled water method
  advantages, 120
  BEE predictions, 1104-1202
  data analysis and assumptions for equations, 43, 154-157, 183

description of database, 151-157
EAR determination, 47
factorial method compared, 119
inclusion/exclusion criteria, 152-154
methodological issues, 120-121, 152, 198
normative database, 151-153, 154-155
overweight and obese database, 153, 156-157
prediction equations, 154-157
pregnant women, 193, 196-197, 290
representativeness of sample, 152
statistical analysis of studies, 43
TEE predictions, 116, 117, 119-121, 122-123, 138-139, 141, 151-157, 166, 174, 193, 198-199, 201, 291, 1104-1202
validation of dietary intake data with, 117
whole-body calorimetry results compared, 120, 122-123
Duodenal ulcer, 370, 372

E

Eating behavior
amino acid supplementation and, 707, 709, 710, 713, 730, 731-732
appetite sensations and, 795
cognitive factors, 796
energy density of foods and, 794-796
palatability of foods and, 795, 809
Eating disorders, 928
Eicosanoic acid, 426
Eicosanoids
metabolism, 9, 55, 423, 434, 454, 825, 833, 838
proinflammatory, 59
Eicosapentanoic acid (EPA), 9, 55, 59, 62, 427, 435, 439, 443, 453-454, 460, 466, 469, 470, 471-472, 478, 487, 492-493, 494, 770, 826, 828, 829, 832, 833, 1052-1053
Eicosatrienoic acid, 439, 440, 442
Elaidic acid, 427, 436, 495
Endometrial cancer, 56, 57, 379, 844
Endorphins, 916
Endothelial function, 59
Energy balance, 107, 111-112, 164
adaptation, 149-151, 201, 220, 223-224, 452
negative, 213-215
physical activity and, 4, 5, 57, 65, 116, 138, 143, 157-161, 184, 221-223, 452, 884-912
research recommendations, 225, 240, 323-324
and weight, 65, 150, 212, 214, 220
Energy density of foods and, 64, 794-796
Energy expenditure. *See also* Basal energy expenditure; Resting energy expenditure; Total energy expenditure; *individual life-stage groups*
age/aging and, 117, 143-144, 157, 158, 159-161, 181, 183
altitude and, 149
BMR and, 112-114, 115, 131, 141, 164-165, 171, 178-179, 185, 188-190, 195
body composition and size and, 65, 112, 131-135, 138, 139, 141
climate and, 147-148
environment and, 147-148, 149
ethnicity and, 145-146
factors affecting, 131-151, 165
gender differences, 108, 114, 132, 140-141, 143, 148, 157, 158, 217
genetics and, 144-145
and growth rate, 134, 164, 190-192
height and, 157, 159-161
lactation and, 116, 198-199
measurement of, 118-121, 122-123, 140
obesity and overweight and, 111, 122-123, 133-135, 138, 140, 209, 212, 216-219
of physical activity (EEPA), 115-116, 117, 133, 138-140, 141, 143-144, 145-146, 147, 183, 190, 209, 212, 884-913
postexercise, 139
pregnancy, 189, 193
research recommendations, 225, 240
RMR and, 112, 131, 132, 141, 148, 165
TEF and, 114, 115, 116, 150, 165, 171
and thermoregulation, 114
weight and, 132, 135, 141, 150, 159-161, 183, 184, 186, 206-213, 215, 889, 891-895, 951
Energy intake. *See also* Acceptable Macronutrient Distribution Ranges; *individual macronutrients and life-stage groups*
adaptation to, 149-151, 201, 220, 223-224, 452

adverse effects of overconsumption, 54, 57, 110, 223-239
alcohol contribution, 109, 771, 1064-1065
assessment, 48, 225, 954-956
Canada, 1066-1075
and cancer, 54
energy density of foods and, 64, 794-796
environment and, 150
FAO/WHO/UNU recommendations, 170
and glycemic index of foods, 269, 313, 320, 322
for groups, 952-954, 955-956
hazard identification, 223-224
indicators of adequacy or inadequacy, 110-111
of individuals, 949-952, 955
interrelationships of nutrients, 39, 103, 770-771, 964
intra-individual variability, 111
by life stage and gender group, 1028-1031, 1034-1035, 1040-1041, 1062-1067, 1072-1075
and obesity, 54, 65, 111, 307, 310, 312, 313, 322, 794
planning, 949-954, 963
research recommendations, 225
restricted, 54
sugar contribution, 65, 118, 273, 307, 310, 313, 314-315, 770
total, 1034-1035
underreporting, 42, 49, 117-118, 643, 794, 956
and weight, 223-224, 793-794, 951-952
yields from substrates, 108-110
Energy metabolism, 289
Energy mobilization from tissues, 199-200
Energy requirements. *See also* Estimated Energy Requirements
accommodation, 151
adaptation, 150
age/aging and, 183, 647
athletes, 221-223
BMI and, 121, 124-131
BMR and, 164-165, 171, 178-179, 185, 188-190, 195-196
brain, 278
climate and, 146-147, 149
environment and, 146-147
factors affecting, 131-151
FAO/WHO/UNU criteria, 111-112
genetics and, 144
for growth, 45, 116-117, 142, 166-168, 174, 177, 181, 190-192, 441
measurement, 160-161
nutrient requirements compared, 110-111
obesity and overweight and, 110, 132-133, 135, 138, 202-213, 216-219
physical activity and, 38, 138-140, 157-161, 166, 171, 174, 175, 176-181, 182, 183-184, 190, 197-198
pregnancy, 290
research recommendations, 225
restoration of normal weight, 220-221
special considerations, 202-223
TEF and, 165, 171, 190, 196-197
thermoregulation and, 165-166
total, 200-201
weight and, 112, 183, 184, 220
Environment
altitude, 149
climate, 146-149
and energy expenditure and requirements, 146-149
Eosinophilia-myalgia syndrome (EMS), 733
Eosinophilic fasciitis, 733, 734
Epidemiological studies. *See also* Observational studies
analytic studies, 41, 42
breast cancer, 54
carbohydrates, 783, 785, 800-801
CHD, 362-365, 562-569, 797-798, 800-801, 817, 820-821, 826-828
cholesterol, 562-569
colon cancer, 373-374
diabetes risk, 380-381, 785, 803, 832
fiber and disease prevention, 343-344, 362-365, 368, 373-374, 380-381, 382-383
glucose metabolism, 380-381
hazard identification, 95, 96
high fat, low carbohydrate diets, 792-794, 797-798, 803
hyperlipidemia prevention, 362-365
hypertension prevention, 362-365
insulin sensitivity, 380-381
limitations, 41, 42, 95, 322
low fat, high carbohydrate diets, 783, 785
methodological issues, 40, 41-42, 322, 569
monounsaturated fatty acids, 817

obesity risk, 792-794, 796-797
physical activity, 912-917
polyunsaturated fatty acids, 820-821, 826-828, 832
satiety and weight maintenance, 382-383
sugar and chronic disease, 800-801
trans fatty acids, 510-515
Esophageal cancer, 844
Estimated Average Requirements (EARs). *See also individual nutrients and life-stage groups*
coefficient of variation, 24-25
cut-point method, 943, 952
data quality and completeness, 969
defined, 3, 22-23
derivation of, 28, 34, 47, 631
evidence considered for, 46-47, 277-280, 284, 285-293, 646-648, 656-659, 664-669
extrapolation on body-weight basis, 34, 44, 45, 47
factorial method, 631
indicators of adequacy, 6, 28, 110
method used to set, 23, 46-47, 624-629, 635, 637-639, 666-669, 681-682, 981-982
prevalence of intakes below, 789
and RDA, 23, 24
reported energy intakes and, 117-118
standard deviation, 24-25, 629
uses, 23-24, 688, 936, 938-939, 943-944, 947-948
Estimated Energy Requirements (EERs). *See also* Energy requirements; *individual life-stage groups*
averaging for group members, 953-954
criteria for, 5
defined, 3, 4, 22, 107, 202
derivation of, 107, 116-117, 168-170, 174-177, 181-182, 184-185, 193-197, 201-203
evidence considered in determining, 116, 164-168, 171-174, 177-181, 183-184, 185, 188-193, 195-201
gender differences, 169-170, 176-179, 185, 202-203
indicator selection for, 117-131
by life stage and gender group, 5, 164-223
menu samples, 392-393
methodological issues, 202-203
for reference person, 952-953
special considerations, 30, 202-223
TEE and, 149-150, 166, 168-169, 174, 176, 181, 183, 188, 193, 200-201, 202, 208
uses, 951, 952-953
Estrogen, 56, 378-380, 543, 921
Ethanolamine phosphoglycerides, 435
Ethnicity. *See* Race/ethnicity; *individual ethnic groups*
EURAMIC study, 827
European Center Prevention Organization Study, 398
Excretion. *See also individual nutrients*
Explorers, high-protein diets, 693
Exposure
acceptable or tolerable, 86-87
assessment, 88-89, 90
duration of, 96, 99
route of, 96, 98, 713

F

Factor VII activity, 369, 799
Factorial approach, 25, 118-119
amino acids, 614, 666-669
children, 628, 631, 666-669
DLW method compared, 119
PAL evaluation, 118, 899-902
protein, 610-611
TEE, 116
Fat (dietary), total. *See also* Fatty acids; High fat; Lipids and lipid metabolism; Low fat; Phospholipids; Triacylglycerol or triacylglyceride
absorption, 4, 60, 339, 351-352, 369, 375, 429, 442, 447, 450-452
adaptation to, 452
adverse effects of, 58, 481
AIs, 4, 9, 32, 456-457
and alcohol metabolism, 453
AMDRs, 15, 422, 423, 440, 481, 769, 785, 809, 816, 945
animal studies, 40
assessment of intakes, 959
balance, 441, 452
and bioavailability of vitamins, 424, 785, 788-792
and BMI, 814
and cancer, 54-55, 371, 375, 376, 484, 486, 512-515, 808

carbohydrate ratio, 437
and CHD, 58-59, 437-438, 460, 769, 797-799, 802
and chronic disease risk, 437-438, 460
and diabetes type 2, 62-63, 437-438, 460, 802-808
dietary intakes, 46, 49, 64, 118, 457, 473, 959, 1038-1041, 1070-1071, 1226-1227
energy contribution, 64, 109, 424, 430, 437, 441, 473, 769, 771, 814, 1040-1041, 1070-1071, 1226-1227
evidence considered for estimating requirements, 440-441
excretion, 431, 447
factors affecting requirements, 447, 450-452
fiber and, 4, 351-352, 367, 369, 375, 376, 808
food sources, 48, 54, 280, 424, 448-451, 457, 473
function, 4, 38, 424-425
gastric emptying, 438
gender differences, 473
genetic factors, 452
and glucose intolerance, 802-808
and glycemic index of foods, 269
glycerol metabolism, 289, 430, 784-785, 802-909
and growth, 280, 437, 441, 457, 459
high fat diets, 452, 769, 772, 792-810
inadequate intakes, 437-438
and insulin sensitivity, 62, 303, 430, 437, 438, 802-808
intervention studies, 64, 794-796
by life stage and gender group, 9, 456-460, 1038-1039, 1040-1041, 1070-1071
and lipid profile, 58, 429, 437, 483, 544, 550-559, 560, 777-782, 809, 815
low fat diets, 359, 366, 375, 378-379, 438, 442, 772-792
malabsorption, 442, 452
and metabolic syndrome, 802
and micronutrient intakes, 808-809, 816
and obesity, 64, 459, 460, 772, 773-776, 792-797, 802, 803, 814
oxidation, 452, 810, 832, 922
physical activity and, 430, 452, 773
planning intakes, 959
polyunsaturated intake and, 58
protein and, 60, 271, 693
research recommendations, 324, 505, 514
saturated fat intake and, 58, 799
special considerations, 457
stores, 595; *See also* Body fat
TEF, 114
and weight, 441, 452, 773-776, 809
Fat-free mass
energy expenditure and, 112, 113, 128, 131, 186, 212
height and, 125, 128-130
measurement, 121
and metabolic rate, 131, 139
physical activity and, 139, 923
and protein status, 609
puberty and, 142
Fat mass, 121, 125, 128-130, 142, 814, 923
Fat-soluble vitamins, 94
Fatigue, 706, 733, 920
Fatty acids. *See also* Fat, total; Monounsaturated fatty acids; Polyunsaturated fatty acids; Saturated fatty acids, *n*-3; *Trans* fatty acids
alcohol consumption and, 453
from carbohydrates, 275, 277, 433
categories, 424
dietary intakes, 1228-1243
energy contribution, 349, 1228-1243
from fiber, 348, 361, 371, 372
food sources, 48
function, 38, 424-425
integrated dietary planning, 964
metabolism, 189, 275, 277, 348, 361, 371, 372, 425, 430-431, 453
oxidation, 166, 279, 430, 432, 440, 453, 920
storage, 430
transport, 429, 430, 432
Federation of American Societies for Experimental Biology, 713, 716
FELS Longitudinal Study, 174, 181
Female athlete triad, 928
Fetus
amino acids, 708-709, 732
congenital defects, 728
energy cost of tissue deposition, 190-192
energy expenditure, 185, 437
fatty acid metabolism, 433, 436, 445
glucose metabolism, 189-190, 290-292, 910
hypoxemia, 910
intrauterine growth delay, 728
neural tube defects, 726
protein, 839

Fiber, dietary or functional, 957-958. *See also individual sources of fiber*
absorption, metabolism and excretion, 348-349
adverse effects of, 377, 391-395
allergic reactions, 396, 397, 399
animal studies, 351, 361, 377
and appetite, 383
and *Bacteriodes*, 357
between-country studies, 377-378
and *Bifidobacteria*, 354
and BMI, 352, 379, 383, 384
C-peptide response, 353, 361
Canadian guidelines, 340, 349
and cancer, 54, 55-56, 319, 321, 339, 348, 373-380, 396, 398
case-control studies, 378
characteristics, 341-342
and CHD, 59-60, 322, 339, 356, 362-368, 369, 387-388, 389, 563
clinical effects of inadequate intake, 361-362
and colon health, 55-56, 321, 339, 348, 358, 370-377, 385-386, 388
definitions, 4, 339, 340-341, 342-343
description of, 344-347
developmental effects, 396
and diabetes type 2, 63, 352-353, 354, 355, 359-360, 380-382, 388
dietary, 4, 339, 340-343, 344, 345, 346, 347, 348, 349, 355, 361-369, 370-384, 385-387, 390, 391, 394-395, 771, 788, 808, 838
diverticular disease prevention, 371-372, 388
and duodenal ulcer, 370, 372
energy contribution, 348, 349, 371, 372, 383, 385, 386, 388, 788
epidemiological studies, 343-344, 362-365, 368, 373-374, 380-381, 382-383
and estrogen, 56, 378-380
evidence considered for estimating requirement for, 362-384
examples of, 343
and fat absorption, 4, 339, 351-352, 367, 369, 375, 376
fatty acid metabolism, 348, 361, 371, 372
fermentation of, 56, 348, 355, 371, 372, 375
function, 38
functional, 4, 339, 340, 341, 342, 343-344, 345, 346-347, 348-350, 355, 369, 361-362, 365, 366, 367, 369, 370, 371, 372, 374, 377, 379, 382, 388, 391, 395-399
and gastric emptying, 4, 63, 65, 339, 348, 360, 370, 379, 382, 383
and gastrointestinal health, 348, 350, 351, 352, 353-354, 355, 356, 357-358, 360-361, 370-372, 396-397, 398, 839
genotoxicity, 396
glucose response, 63, 339, 350, 351, 352-353, 354, 355-356, 357, 359-360, 361, 380-382, 383, 388
and glycemic index of foods, 322, 360, 361, 380-381, 382
hazard identification for, 395-399
health benefits, 343
high fat diets and, 808
high-fiber diets, 297, 374, 378-379, 383, 788, 839
and hyperlipidemia prevention, 355, 362-368
and hypertension, 60, 362-368, 369
insulin response, 60, 63, 297, 306-307, 339, 351, 353, 355-356, 360, 380-382, 388
intervention studies, 344, 351, 358, 365-368, 374-377, 378-379, 381-382, 383-384
and *Lactobacillus*, 357
and laxation, 339, 350, 351, 352, 353-354, 355, 356, 357-358, 360-361, 370-371, 372, 385-386, 388
and lipid metabolism, 297, 350, 351, 352, 354, 355, 356-357, 358-359, 360, 361, 365-366, 388
and lipid profile, 4, 59-60, 339, 351, 352, 354, 355, 356, 357, 358-359, 360, 361, 365-368
low-fiber diets, 367, 838
measures of efficacy, 344, 350
methodological problems with trials, 376-377
and micronutrient absorption, 4, 29, 94, 348, 351-352, 369, 382, 391, 394-395, 397-398, 838
nutrition labeling, 340, 344
and obesity, 65, 352, 370, 382-384
physiological role, 343, 349-361
properties, 339

prospective studies, 378
protective effects, 55-56, 59, 63, 322, 339, 348, 363, 367-368, 369, 372, 374, 375, 376-380
research recommendations, 399-400
and satiety, 65, 348, 382-384, 388
sources, 48, 56, 341-342, 344, 349, 350, 390, 771
special considerations, 395
supplements, 60, 361, 365, 366, 370, 371, 372, 374, 383, 394, 398
synthetic fibers, 342, 349-351
USDA database, 344, 346
and water intake, 398
and weight control, 65, 339, 351-352, 370, 382-384
Fiber, total (dietary + functional)
AIs, 4, 7-8, 322, 339, 369, 372, 384-385, 386, 389-390, 944-945
and cancer, 56, 373
definition, 4, 339, 340
and diabetes type 2, 382
dietary intakes, 339, 387, 391, 392-393, 1036-1037, 1226-1227
expression of requirement, 384-385
by life stage and gender group, 7-8, 384-390, 1036-1037
menu samples, 392-393
planning intakes, 957-958, 964
Fibrinolysis, 60
Fish and fish oil, 55, 59, 826-828, 832
Fluoride, 297
Folate/folic acid, 375, 726, 789, 790-791, 808, 812, 816, 1228-1243
Food. *See also* Thermic effect of food
additives, 90, 350, 366, 391
allergies, 692
amino acid composition, 683-686, 689-690
energy-dense, nutrient-poor, 302, 312, 794-796
palatability, 425, 795, 808, 809
plant- vs. animal-derived, 771
safety, 86-90, 104
supplementation trials, 654
Food and Agriculture Organization, 84, 110, 621, 634, 648, 684
Food Guide Pyramid, 266, 267, 391, 771
Food quotient, 119-120
Food sources. *See also individual nutrients*
determination of, 50
Formulas, infant
amino acids, 731, 733
bioavailability of nutrients from, 26, 31, 45, 431, 940, 944, 946
carbohydrates, 280, 283
cholesterol, 545, 548-549
FAO/WHO/UNU recommendations, 621
fat (total), 280-281, 448-451, 457
fatty acids, 461, 463, 466, 468, 479
protein, 280-281, 621
Fortified foods, 27, 85, 91-92. *See also* Formulas, infant
Fructans (dietary or functional fiber), 341, 342
Fructooligosaccharides (dietary or functional fiber), 345-346, 353-354, 396-397, 838
Fructosamine, 304-307
Fructose, 59, 266, 267, 268, 273, 274, 276, 294, 295, 297, 298-301, 302, 809, 813
Fructose-1-phosphate aldolase deficiency, 809
Fruits and vegetables, fiber and, 56, 363, 371, 373, 374, 375, 378, 388, 394, 788

G

Galactomannans, 345, 352
Galactose, 266, 273-274, 276, 281
Galacturonic acid, 345
Gallbladder disease, 234-235
γ-Linoleic acid, 426, 446, 476, 477, 824
Gastric emptying
amino acids, 615
energy density of food and, 795
fat, 438
fiber and, 4, 63, 65, 339, 348, 360, 370, 379, 382, 383
Gastrointestinal distress, fiber intake and, 394-395, 396-397, 398
Gastrointestinal health
amino acid supplementation and, 698, 700, 714, 720, 722, 724, 726, 733
fiber and, 348, 350, 351, 352, 353-354, 355, 356, 357-358, 360-361, 370-372, 396-397, 398, 839
protein intake and, 844
Gender differences. *See also* Men; Women
added sugars, 988-991
amino acids, 673-675, 732, 992-1027

BMI, 125-129, 1078-1087, 1098-1103
body composition and size, 128, 142, 1078-1103
body fat, 1078-1101
and carbohydrate–lipid oxidation balance, 921
cardiovascular disease, 60
dietary intakes, 265, 294, 473, 474, 692, 988-1065
EER, 169-170
energy expenditure, 108, 114, 132, 140-141, 143, 148, 157, 158, 217
energy intake, 473
fat (dietary), 473
fiber, 386, 387, 389, 391
growth velocity, 33, 142, 175, 922-923
linoleic acid, 463-464
metabolic rate, 141
monounsaturated fatty acids, 474
nutrient intakes with added sugars, 1203-1225
physical activity, 921
polyunsaturated fatty acids, 8, 463-464, 470, 471, 478
protective effects of nutrients, 60
puberty onset, 33
reporting of dietary intakes, 117
saturated fatty acids, 474
weight and heights, reference, 35
Genetic factors
body composition and size, 144, 146
cancer, 55
CHD, 57
cholesterol, 58, 544, 545, 546, 561-562
diabetes mellitus, type 2, 62
energy expenditure, 144-145
energy requirements, 144
fat balance, 452
obesity, 146, 452, 784
Genetic markers of disease, 41
Genotoxicity, 396, 720
Glucagon, 189, 277
Glucated hemoglobin (HbA_{1c}), 308-309, 322
Glucoamylase, 272
Glucocorticoids, 602
Gluconeogenesis
amino acids and, 276, 278, 288-289, 604, 606
carbohydrate-free diet and, 275-276, 277, 287-288
energy cost of, 114
glycerol from fat and, 278-279, 289, 292-293, 430
in infants, 280
insulin and, 274
pregnancy and, 189
protein and, 278, 284, 287-288, 293
starvation and, 277
Glucoregulatory hormones, 57
Glucose, 266, 345
in human milk, 282-283
intestinal absorption, 63, 273, 383
transporters, 273
Glucose–alanine cycle, 607
Glucose–glutamine, 607
Glucose metabolism. *See also* Gluconeogenesis; Insulin response
adaptation, 277-278
adolescents, 288-289
adults, 285-289, 388, 784-785
altitude and, 149
for brain utilization, 38, 265, 273, 276, 277, 279-280, 285-289
children, 286-287, 288-289
energy yields, 109, 274
epidemiological studies, 380-381
fat intake and, 289, 430, 784-785, 802-909
fiber and, 63, 339, 350, 351, 352-353, 354, 355-356, 357, 359-360, 361, 380-382, 383, 388
glycemic index of foods and, 63, 268, 306, 322
high fat, low carbohydrate diets and, 437, 802-808
infants, 280, 281, 288-289
intervention studies, 381-382
intracellular utilization, 274
lactation and, 196
and lipogenesis, 59
low fat, high carbohydrate diets and, 438, 784-785
and ketosis, 276, 277, 278-279, 280, 281, 284, 287, 289, 290-291, 430
methodological issues, 280
monounsaturated fatty acids and, 819
muscle uptake, 63, 430
obesity and, 204, 802
physical activity and, 60, 921
polyunsaturated fatty acids and, 821, 822-823

pregnancy and, 189-190
and protein requirement, 278, 605
saturated fatty acids and, 484-485
weight loss and, 204
Glutamate, 591, 593, 594, 596, 604, 605, 606, 608, 697, 701, 703, 709, 712, 717. *See also* Monosodium glutamate
Glutamic acid (dispensable), 592, 593, 594, 596, 597, 712-718, 728, 736, 1000-1001
Glutaminase, 717
Glutamine (dispensable), 591, 593, 594, 596, 605, 607, 706, 717-719
Glutamine synthetase, 717
Glutathione, 607, 608, 620
Glycemic index (GI), 321-323
amount of food ingested and, 268
and BMI, 313
calculation, 268, 307
and cancer risk, 310-311, 319, 321
and carbohydrate metabolism, 304-307
and CHD risk, 303, 308-311, 322
definition, 268
and diabetes type 2, 63, 302, 304-307, 308-309, 322
digestability of foods and, 269
and energy intake, 269, 313, 320, 322
fiber and, 322, 360, 361, 380-381, 382
food characteristics and, 269-270
food values, 268, 270
and glucated hemoglobin (HbA_{1c}), 308-309, 322
and glucose metabolism, 63, 268, 306, 322
and HDL cholesterol, 308-309, 322
high-GI diets, 302, 306-307, 313, 318, 323
and hunger and satiety, 313
and insulin sensitivity, 63, 306-307, 308-312, 322
and lipid metabolism, 269, 270-271, 297, 302-303, 304-308, 322
low-GI diets, 304-307, 313, 321-322
of mixed meals, 270-271
methodological issues, 322
and obesity, 313, 322-323
palatibility of foods and, 272
and physical activity, 318-319
utilization, 269-272
and weight loss, 313
Glycemic load, 269-272, 303, 322, 380-381
Glycemic response, 63, 268, 322
of diabetics, 268, 271
to fiber, 63, 352
palatability of foods and, 795
Glyceraldehyde, 274
Glycerol, 289, 292-293. *See also* Triacylglycerol or triacylglyceride
Glycine (dispensable), 591, 593, 596, 597, 607, 608, 678, 719-720, 729, 731, 736, 1002-1003
Glycogen
amino acids and, 705
food sources, 265-266
repletion, 64, 924
storage, 273, 276, 281, 595-596
synthesis and utilization, 274, 277, 920, 921, 923
Glycoprotein, 692
Glycosis-tricarboxylic acid (TCA) pathway, 605, 606
Greenland Eskimos, 275, 284, 493, 494, 826
Growth and development. *See also individual life-stage groups*
adaptation, 151, 220, 437
amino acids and, 598, 607, 665, 666, 669, 697, 701, 707, 710, 713, 719, 720, 721, 724, 725, 728
carbohydrates and, 280-281, 922-923
catch-up in children, 221, 222, 840
children, 32, 47, 134, 142, 151, 167-168, 174, 175, 221, 222, 437, 441, 456, 459, 609, 611, 810-811, 839-840
defined, 177
and EAR derivation, 47
and EER derivation, 116, 166-168, 174, 181
energy expenditure and, 134, 164, 190-192
energy requirements, 45, 116-117, 142, 166-168, 174, 177, 181, 190-192, 441
fat intake and, 280, 437, 441, 457, 459
formula-fed infants, 280-281, 448-451, 457
gender differences, 33, 142, 175, 922-923
impaired, 151, 217, 220, 221, 222, 437, 721, 811, 839-840
lipid metabolism, 922-923
low fat, high carbohydrate diets and, 810-811
maternal and fetal tissues, 92, 190-192
measurement precision, 142
physical activity and, 922-923

polyunsaturated fatty acids and, 444-447, 453, 460
protein intake and, 280-281, 608-609, 654, 683, 811, 839-840
puberty and, 142, 922
stunting, 151, 217, 220, 221, 222, 811, 840
undernutrition and, 220, 221, 222
velocity, 33, 47, 142, 151, 166-168, 181
Growth hormone, 277, 699, 715, 724, 923
Guar gum, 63, 352-353, 355-356, 365, 366, 382, 396
Gums (dietary or functional fiber), 345, 355, 365, 367, 369, 388, 391, 396. *See also* Guar gum

H

Hawaiian natives, 798
Hazard identification. *See also individual nutrients*
animal data, 94-95, 96, 696, 697-698, 701-702, 707-708, 711-712, 713-714, 721-722, 724, 725-726, 727, 729, 730-732, 734-735
asthma, 716-717
behavior, 295-296
cancer, 319-321
causality, 94, 96, 102
Chinese restaurant syndrome, 715-716
components of, 87, 94-98
data sources, 96-97
defined, 87, 975
dental caries, 296-297
developmental studies, 708-710
diabetes, 303, 306-307
evaluation process, 95
human studies, 94, 696, 698-699, 702-703, 705-706, 712, 714-715, 722-723, 724-725, 726, 727, 729, 730, 732-733, 735
insulin sensitivity, 303, 306-307
maple syrup urine disease, 706
metabolic considerations, 705
obesity, 307, 311-313, 314-319
pharmacokinetic and metabolic data, 96-97, 98
physical activity, 318-319
HDL cholesterol. *See also* Lipids and lipid metabolism
carbohydrate intake and, 59, 781-784
and CHD, 57
cholesterol intake and, 549-562, 563, 568-569
in diabetes, 308-309
fat intake and, 437, 483, 777-782
fiber intake and, 354, 357, 358, 359, 361, 366
glycemic index and, 302, 303, 308-309, 322
hazard identification, 549, 560-562
lipoprotein lipase activity and, 61
low fat, high carbohydrate diets and, 777-781
monounsaturated fatty acid intake and, 817-818
physical exercise and, 60, 61
polyunsaturated fatty acids and, 820, 821, 822-823, 826, 828, 830-831
protective effect, 560
saturated fatty acids and, 483
sugar intake and, 298-301, 302
trans fatty acids and, 495-503
transport, 543, 544
Health Canada, 349, 481, 883, 979
Health Professionals Follow-Up Study, 321, 363, 364, 368, 371-372, 375-376, 377, 387, 562, 563, 827
Healthy People 2000, 882
Heart disease. *See also* Cardiovascular disease; Coronary heart disease
carbohydrate intake and, 59
fiber intake and, 59-60
physical activity and, 60-61
protein intake and, 60
Heat of combustion, 108, 109
Height. *See also* Reference weights and heights
BMI and, 1080-1081
and body composition, 125, 128-130, 1078-1081, 1088-1089
catch-up growth, 221
and energy expenditure, 157, 159-161
Heme, 607, 608
Hemicelluloses (dietary fiber), 345, 348, 390
Hemoglobin, 595, 720-721
Hepatic lipase activity, 61
Hepatomegaly, 721
Heterocyclic amines, 379
High fat, high carbohydrate diet, 367
High fat, high protein diet, 275

High fat, low carbohydrate diets, 103
added sugars, 810, 816
adults, 792-810
AMDRs, 809, 816
cancer risk, 808
CHD risk, 797-802, 814-815
children, 814-816
diabetes (type 2) risk, 802-808
energy intakes, 793-795
epidemiological studies, 792-794, 797-798, 803
fat excess, 808-809
and glucose intolerance, 437, 802-808
hyperinsulinemia, 802-808
intervention studies, 794-796, 798-799, 803-807
metabolic syndrome, 802-808
and micronutrient inadequacy or excess, 808-809, 816
obesity risk, 792-797, 814
saturated fatty acid intakes, 799-802
sugar inadequacy, 809
High-fiber diets, 297, 374, 378-379, 383, 788, 839
High fructose corn syrup, 294, 295
High glycemic index diets, 302
Hippuric acid, 604
Histidine (indispensable), 589, 591, 592, 593, 597, 604, 662, 663-665, 666, 668, 672-675, 678-682, 686, 687, 689, 709, 712, 720-723, 736, 1004-1005
Homocysteine, 302, 726
Homovanillic acid, 735
Honolulu Heart Program, 562
Human chorionic somatomammotropin, 189
Human milk. *See also* Breastfeeding; Formulas, infant; Infants; Lactation
amino acid content, 598, 607, 621, 657, 663, 664-665, 686, 687
and behavioral development, 621
bioavailability of nutrients, 431, 447, 621, 944
carbohydrate content, 281-283, 292
cholesterol, 546-549
energy content, 171, 172-173, 199, 457, 461, 468, 474, 477
energy cost of synthesis, 195-196
energy output, 199
fat content, 281, 431, 456, 458-459, 468
fiber content, 385
and immune function, 621
monounsaturated fatty acids, 474, 477
nonprotein nitrogen content, 620, 657, 658
nutritional adequacy, 31, 447, 456, 662, 663
polyunsaturated fatty acids, 447, 461, 462-463, 466, 467
protein content, 620, 622-623, 657, 658, 686, 687
saturated fatty acids, 474, 475-476
trans fatty acids, 479, 480
volume of intake, 31, 45, 171, 172-173, 281, 456, 663
Human studies. *See also* Balance studies
advantages, 91, 98
amino acids, 608-699, 702-703, 705-706, 712, 714-715, 720, 722-723, 724-725, 726, 727, 729, 730, 731-733, 735
controlled, 40
dose–response assessment, 98
feeding trials, 40-41
limitations of, 40-41, 94
Hunger, 117, 313, 732, 795, 796
Hydrogenated fat, 427-428, 436, 455, 456, 479, 495, 498-504, 836
5-Hydroxyindoleacetic acid, 732
Hydroxylysine, 593
3-Hydroxy-3-methylglutaryl coenzyme A, 545
Hydroxyproline, 592-593, 728-729
Hyperactivity, 295
Hyperammonemia, 699, 714, 718
Hypercalciuria, 694, 841
Hyperchloremic acidosis, 698
Hypercholesteremia, 276, 352, 355, 356, 358, 359, 366, 367, 494, 495, 721, 811, 842
Hyperglutamic acidemia, 718
Hyperglycemia, 275, 353, 815
Hyperinsulinemia, 130, 784-785, 802-808, 832
Hyperkalemia, 699
Hyperlipidemia, 130, 302, 304-308, 322, 323, 355, 362-368
Hyperlipoproteinemia, 359
Hyperphenylalaninemia, 728
Hypertension, 57, 735
BMI and, 124, 230-231
fiber and, 60, 362-368, 369
polyunsaturated fatty acids and, 59
protective effects of nutrients, 59, 362-368
risk factors, 130

Hyperthermia, 910, 926-927
Hypertriacylglyceridemia or hypertriacylglycerolemia, 59, 297, 323
Hypoalbuminemic malnutrition, 608
Hypoenergetic diet, 311
Hypoglycemia, 295, 910
Hyponatremia, 699
Hypothermia, 927
Hypothermogenicity, 696
Hypoxia, 149

I

Ileostomy patients, 357
Imino acids, 591, 592
Immune function, 57, 396, 439, 487-492, 697-698, 699, 839
Immunosuppression, 492
Indian Experiment of Infarct Survival, 828
Indicator amino acid oxidation (IAAO) method, 617-619, 670-671, 676, 677, 678
Indicators of nutrient adequacy. *See also specific indicators, nutrients, and life stages*
  methodological considerations, 43
  risk reduction-based
Infants, 0-12 months. *See also* Formulas, infant; Human milk; Life-stage groups
  ages 0 through 6 months, 31, 35, 44, 45, 169, 199, 201, 281, 283, 385, 456-457, 461, 468, 619-623, 662-665
  ages 7 through 12 months, 31-32, 35, 45-46, 169, 199, 283, 385, 457, 461, 468, 624-630, 664-670, 672
  AIs, 4, 26, 30-32, 44-46, 280-283, 456-457, 460-461, 466-469, 619-623, 662-665, 944, 946
  amino acids, 30, 45, 594, 598, 607, 614, 619, 621, 662-670, 672, 686, 687, 719, 722-723, 724, 726
  birth weight, 456, 471, 650, 654, 719, 731, 811, 839, 840, 910
  BMI, 1106-1114
  BMR, 164-165, 1106-1114
  body fatness, 142, 621
  brain development, 280, 288-289, 291, 445, 448-451, 466, 468, 545, 548, 608-609
  carbohydrate, 30, 32, 46, 280-283, 288-289, 291
  cholesterol, 545-549
  dietary intakes, 30, 46, 170, 171, 199, 457, 624
  EARs, 46, 624-629, 664-670, 672
  EERs, 32, 45, 46, 164-171
  energy expenditure and deposition, 116, 122-123, 164, 167
  extrapolation of data from adults to, 46, 47
  extrapolation of data from younger to older infants, 31-32
  factorial modeling, 624, 628
  fat, 4, 30, 32, 46, 432, 437, 456-459, 769, 816
  fiber, 385
  formula-fed, 26, 31, 45, 165, 166, 168, 280-281, 283, 446-447, 448-451, 454, 461, 463, 466, 468, 621
  glucose metabolism, 280, 281, 288-289
  growth, 30, 45, 142, 164, 166-168, 280-281, 436, 437, 445, 446-447, 448-451, 457, 460, 465, 468, 472, 607, 609, 611, 630, 669, 982
  hyperammonemic, 699
  language development, 447
  malnutrition, 165, 167, 608-609
  methodological considerations, 44-46
  milk consumption, 26
  monounsaturated fatty acids, 432
  newborn, 92, 142, 165, 166, 291, 433, 594, 595, 598, 603
  nitrogen balance studies, 624-627
  of overweight mothers, 134
  on parenteral nutrition, 722-723
  phenylketonuria, 728
  physical activity, 166
  polyunsaturated fatty acids, 30, 46, 433, 435, 438, 439, 440, 445-447, 448-451, 454, 460-463, 472
  premature, 122-123, 165, 166, 167, 280, 435, 445, 447, 456, 469, 594, 607, 609, 719, 731, 840, 910
  protein, 30, 45, 46, 595, 602, 603, 608-609, 611, 619-630, 669, 686, 687
  RDAs, 31, 629-630, 672
  recommended food sources, 26, 31, 32, 45, 46
  saturated fatty acid, 431
  sleepiness, 733

special considerations, 45, 283, 457, 461, 463, 469, 621-623
TEE, 166, 168, 169, 170, 1106-1114
thermic effect of food, 165
thermoregulation, 165-166
trans fatty acids, 456
visual development, 448-451
weight and height, reference, 35, 132-135, 1106-1114
weight gain, 46, 621
zinc, 722-723
Inflammatory disorders, 824
Institute of Medicine, 45, 46
Insulin resistance, 2, 62, 63, 189, 275, 291, 303, 306-307, 308-312, 320, 784-785, 802-808, 921. *See also* Diabetes mellitus
Insulin Resistance Atherosclerosis Study, 803
Insulin response. *See also* Hyperinsulinemia
age/aging and, 62
amino acids, 696, 701, 705, 710
and cancer, 320
to carbohydrate intake, 268, 269, 273, 274, 275, 277, 303, 320, 437
and diabetes, type 2, 63, 275, 303, 306-307, 308-312, 784-785
epidemiological studies, 380-381
to fat, 62, 303, 430, 437, 438, 484-485, 802-808
fiber intake and, 60, 63, 297, 306-307, 339, 351, 353, 355-356, 360, 380-382, 388
to glucose metabolism, 268, 273, 274
glycemic index of foods and, 63, 269, 306-307, 308-312, 322
hazard identification, 303, 306-307
intervention studies, 381-382
metabolic syndrome, 802
obesity and, 62, 303, 784, 802, 803
oral contraceptives and, 921
parenteral nutrition, 438
physical activity and, 60, 62, 63, 303, 803, 921
pregnancy and, 189, 291
to protein intake, 279, 602
sensitivity of, 62, 63, 189, 291, 303, 306-307, 308-312, 322
to undernutrition, 220
Insulin-like growth factors, 320
Interactions of dietary factors
adverse, 85, 95
amino acids, 721-723, 725, 726, 731
and bioavailability, 93, 271, 281, 424
and blood pressure
fatty acids, 453-456
methodological issues, 41-42, 53, 376-377
Intermediate density lipoproteins, 545
Intervention studies
breast cancer, 378-379
carbohydrate, 785, 786-787
CHD, 365-368, 798-799, 817-818, 821, 828-831
colon cancer, 374-375, 376-377
confounding of dietary factors, 376-377
design features, 43
diabetes mellitus (type 2), 381-382, 785, 786-787, 806-807, 832-833
of dietary patterns, 43
fiber and disease prevention, 344, 351, 365-368, 374-377, 378-379, 381-382, 383-384
glucose response, 381-382, 803-807
high fat, low carbohydrate diets, 794-796, 798-799, 803-807
hyperlipidemia prevention, 365-368
hypertension prevention, 365-368
insulin response to fat intake, 803-807
low *n*-9 monounsaturated fatty acid diets, 817-818
meta-analyses, 58, 777, 798
methodological issues, 43, 376-377
obesity, 311, 773-776, 794-796, 797
polyunsaturated fatty acids, 821, 828, 830-831, 832-833
satiety and weight maintenance, 383-384
timing of, 376
Intestinal absorption. *See also individual nutrients*
active transport, 273
aging and, 447, 450-452
estrogen, 378
facilitated diffusion, 273
fiber intake and, 60, 348, 378, 383
glucose, 382, 383
monosaccharides, 272-273
and sensitivity to nutrient toxicity, 92
slowing, 323
Intestinal metabolic dysfunction, 594
Intestinal obstruction, 395, 398
Inuits, 275

Inulin (dietary or functional fiber), 341, 345, 353-354, 390, 391, 394, 397, 838
Iowa Women's Health Study, 307, 363
Irritable bowel syndrome, 353-354, 358, 395
Iron, 391, 394, 398, 725, 771, 789, 790-793, 812, 813, 840, 981, 982, 1204-1211, 1214-1221, 1224-1225, 1228-1243
Isoleucine (indispensable), 589, 591, 593, 597, 662, 663-665, 666, 668, 669, 672-675, 678, 679-682, 686, 687, 689, 704-711, 736, 1006-1007
Isomaltose, 272

J

Joint FAO/WHO Expert Committee on Food Additives, 90, 713

K

KANWU study, 485
Karaya gum, 367, 382, 838
Keratin, 592
Ketoacids and ketosis, 276, 277, 278-279, 280, 281, 284, 287, 289, 290-291, 430, 604, 605, 704
Kidney stones, 841-842
Krebs-Henseleit cycle, 604-605, 606

L

Lactase, 272, 592
Lactate, 276
Lactation. *See also* Breastfeeding; Human milk
  adaptation to, 34, 47, 197, 290, 291, 650
  adolescents, 201, 293, 388-389, 465-466, 471-472, 659
  AIs, 34, 388-389, 465-466, 471-472
  amino acids, 681-682
  BMR, 195-196
  and body weight, 199-200, 201
  carbohydrates and, 196
  derivation of DRIs for, 34, 48
  EARs, 34, 292-293, 656-659, 681
  EERs, 107, 116-117, 195-202
  and energy ependiture, 116, 198-199
  energy mobilization, 34, 199-200
  fiber, 388-389
  milk energy output, 172-173, 199
  physical activity, 197-198, 199, 1166-1167
  polyunsaturated fatty acids, 465-466, 471-472
  protein, 840
  RDAs, 293, 659, 682
  stage of, 172-173
  TEE, 116, 198-199, 201, 1166-1167
  TEF, 196-197
  total energy requirements, 200-201
  ULs, 92
Lactose, 266, 267, 268, 272, 273, 281, 282-283, 292, 813
Lactulose, 397
Lauric acid, 58, 425, 483
Laxation, fiber consumption and, 339, 350, 351, 352, 353-354, 355, 356, 357-358, 360-361, 370-371, 372, 385-386, 388
LDL cholesterol. *See also* Lipoprotein metabolism
  carbohydrate intake and, 781, 782-784, 797
  and CHD risk, 57, 481-484, 542, 548-549, 573, 798-799, 815
  children, 815
  cholesterol intake and, 544-545, 548-562, 563, 568, 569, 573
  fiber intake and, 59, 351, 352, 355, 356, 357, 358, 359, 361, 365-366, 367-368
  glycemic index and, 302
  hazard identification, 549, 560-562
  low fat, high carbohydrate diets and, 777-781
  monounsaturated fatty acids and, 58, 486, 817-818
  polyunsaturated fatty acids and, 58-59, 821, 822-823, 828, 830-831
  protein intake and, 60
  saturated fatty acids and, 58, 422, 432, 481-484, 798-799
  sugar intake and, 297-301, 302
  trans fatty acids and, 58, 423, 494-503, 504
Legumes, 365, 366, 370, 382, 390
Leucine (indispensable), 589, 591, 593, 596, 597, 617, 618, 650, 660, 663-665, 666, 668, 671-682, 686, 687, 689, 704-711, 736, 1008-1009
Leukotrienes, 434, 454, 824, 838
Life-stage groups. *See also* Adolescents; Adults; Children; Infants; Toddlers
  alcohol, 1064-1065

amino acids, 662-682, 992-1027
carbohydrates, 6, 280-293, 988-991, 1032-1033, 1068-1069
categories, 30-34
cholesterol, 546-549, 1058-1059
EERs by, 5, 164-223
energy, 1028-1031, 1034-1035, 1040-1041, 1062-1067, 1072-1075
fat (total) by, 9, 456-460, 1038-1041, 1070-1071
fiber, 384-390, 1036-1037
intakes by, 988-1065
monounsaturated fatty acids, 1044-1045
polyunsaturated fatty acids, 11, 460-466, 820, 1046-1057
protein (total) by, 619-662, 1060-1063, 1074-1075
saturated fatty acids, 1042-1043, 1072-1073
and toxicological sensitivities, 97-98
weights and heights, reference
Lignin (dietary fiber), 344, 346, 350, 356
Limit dextrins, 272
Linoleic acid. *See also* α-Linoleic acid; Conjugated linoleic acid
absorption, 431
AIs, 5, 8, 10, 423, 460-461, 463-466, 770, 822, 825, 944
AMDRs, 15, 770, 825-826
and cancer, 825
and CHD, 821
deficiency, 4-5, 423, 426, 438, 464
dietary intakes, 8, 478, 1044-1045
food sources, 771
function, 38, 423, 426-427
in infant formula, 461, 463
interaction with α-linoleic acid, 447, 453-455, 472, 825
by life stage and gender group, 10, 460-466
and lipid peroxidation, 824, 838
metabolism, 433, 434, 440, 442, 453, 455-456, 476, 838
protective effects of, 821
supplementation, 442, 444
trans fatty acids and, 455-456
Lipids and lipid metabolism
aging and, 922
amino acids and, 724, 731
carbohydrates and, 275, 277, 278-279, 297-303, 781, 782-784, 917-923
cardiovascular disease, 302, 562-569
and CHD, 57, 60, 356, 481-484, 562-569
fatty acids and, 424-425, 430-431, 493
fiber and, 297, 350, 351, 352, 354, 355, 356-357, 358-359, 360, 361, 365-366, 388
glycemic index of diet and, 269, 270-271, 297, 302-303, 304-308
and growth and development, 922-923
peroxidation, 493, 504, 823-824, 838
physical activity and, 430, 917-923
sugars and, 297-302
thermoregulation and, 166
weight loss and, 204
Lipolysis, 277
Lipoprotein (a), 503
Lipoprotein lipase activity, 61
Lipoprotein metabolism, 61, 369, 429, 436, 438, 544-545, 548, 562, 563, 568-569, 573, 815. *See also* Cholesterol; HDL cholesterol; LDL cholesterol
Liver
alcohol dehydrogenase, 108-109
disease, 705
function, 92, 704, 705, 721
Locust bean gum, 367, 382
Longevity, composition of energy sources and, 39
Low density lipoprotein (LDL), 431. *See also* LDL cholesterol
oxidation, 504, 823-824
Low fat, high carbohydrate diets
added sugars, 788-789, 812-813
adults, 772-792
and cancer risk, 772
CHD risk, 437-438, 772, 777-784
children, 438, 810-814
diabetes (type 2) risk, 437-438, 772, 784-785
and diarrhea, 438
epidemiological studies, 783, 785
fat oxidation, 810
fiber, 367, 788
glucose intolerance risk, 784-785
and growth, 810-811
high monounsaturated fatty acid diet compared, 817
and hunger, 795
hyperinsulinemia, 784-785
hypocaloric diets, 772

intervention studies, 311, 773-776, 777, 785, 786-787
isocaloric diets, 772, 773, 777
and lipid levels, 777-781
and micronutrient inadequacy or excess, 785, 788-789, 811-814
and obesity, 769, 773-776, 777
and physical activity, 773
protein intake and, 843
total sugars, 789, 792, 813-814
and weight, 772, 773-777
Low glycemic index diets, 304-307
Low-protein diets, 648, 667, 697, 707, 709, 721, 731-732, 839-840
Lowest-Observed-Adverse-Effect Level (LOAEL), 90, 98, 100-101, 224, 569, 975
Lung cancer, 54-55, 319, 486, 568, 570-573, 808, 837, 844
Luteinizing hormone, 715
Lyon Diet Heart Study, 829
Lysine (indispensable), 589, 591, 593, 597, 602, 608, 614, 616, 617, 618, 650, 661, 663-665, 666, 668, 669-670, 671-682, 685, 686, 687, 689, 692, 723-725, 736, 1010-1011

M

Macronutrients. *See also* Carbohydrate; Fat; Protein
brain requirements, 771
defined, 108
imbalances and chronic diseases, 771
integrated planning of intakes, 936-966
Magnesium, 394, 789, 790-791, 813, 838, 1204-1211, 1214-1221, 1224-1225
Malabsorption syndrome, 30
Malnutrition, 167, 437, 595, 608-610, 704, 839. *See also* Starvation
Malondialdehyde, 711
Malonyl coenzyme A, 274
Maltase, 272
Maltodextrin, 360
Maltose, 266, 272
Mannitol, 266
Mannose, 345
Maple syrup urine disease, 704, 706
Masai, 275
Melanin, 608
Men. *See also* Gender differences
carbohydrate intakes compared to other nutrients, 1232-1237
CHD, 363, 364
cholesterol, 354
diabetes type 2, 380, 381
fiber, 363, 364, 380, 381
lipoprotein profile, 61
nutrient intakes with sugars, 1208-1213
PAL, 893
protein intakes, 695
reference weights and heights, 125
TEE, 147
Menstrual cycle, 140, 141, 921, 928
Mental health, 151, 276, 720, 913, 916
Mental retardation, 728
Menus, sample, 392-393
Metabolic alkalosis, 699
Metabolic disorders, 697, 700, 704, 705, 706, 710, 714, 727, 728, 735
Metabolic equivalent, 975
Metabolic syndrome, 802
Metabolism. *See also* Basal metabolic rate; Glucose metabolism; Lipids and lipid metabolism; *individual nutrients*
cellular uptake of nutrients, 273
eiconasanoid, 55
glycogen synthesis and utilization, 274
insulin, 275
intracellular utilization of sugars, 273-274
physical activity and, 138
splanchnic, 600, 717
Methionine (indispensable), 589, 591, 593, 594, 597, 608, 614, 663-665, 666, 668, 672-675, 677, 678, 679-682, 685, 686, 687, 689, 711, 723, 725-726, 736, 1012-1013
Methodological issues. *See also* Data and database issues; Indicators of nutrient adequacy
AI derivation for infants, 44-46
in balance studies, 40-41, 617, 676
BMI, 121, 124-125
brain blood flow methods, 280
children, 25, 47-48
confounding and bias, 41-42, 376-377, 451, 484, 643
data sources, 39-44
depletion–repletion studies, 40-41

in dietary intake estimates, 42, 48, 49-50, 110, 116, 117-118, 307, 312, 313, 322, 563, 624, 643, 936-937
direct amino acid method, 616-617, 618
DLW method, 120-121, 152, 198
EARs for children and adults, 25, 46-47
epidemiological evidence, 40, 41-42, 322, 569
experimental studies, 40
extrapolation from animal studies, 40, 87, 95, 97, 98, 100, 101, 492, 562, 703, 705, 1245-1246
extrapolation from other age groups, 25, 26-27, 31-32, 34, 44, 46, 47, 101, 283
extrapolation from short periods to 24 hours, 616
factorial approach, 25, 116, 118, 611, 981
generalizability of studies, 41, 42, 100, 118
glycemic index calculation, 307
growth measurement, 142
human feeding studies, 40-41
indicator amino acid oxidation method, 618, 619
interactions of dietary factors, 41-42, 53, 376-377
intervention studies, 42-43, 376-377, 725
Monte Carlo approach, 981-982
multicollinearity, 42
nitrogen balance method, 611-612, 635, 643, 644, 688
in nutrient intake estimates, 41-42, 48-49, 941-945
observational studies, 40, 41-42
plasma amino acid response method, 615
pregnant and lactating women
randomized clinical trials, 40, 42-43, 376-377
research needs, 969-970
in risk assessment, 91-94, 100
single treatment vs. multitreatment parallel designs, 492
supplementation trials, 43
weighing the evidence, 3, 43-44, 94
weight maintenance in overweight and obese adults, 202-204
Methylcellulose (dietary fiber), 341
Mevalonic acid, 545
Mohawk Indians, 146
MONICA Study, 316-317, 318-319, 790-793
Monosaccharides, 59, 265, 266, 272, 276, 281, 297, 342
Monosodium glutamate, 695, 712-713, 715-717
Monounsaturated fatty acids (cis isomer). *See also individual fatty acids*
absorption, 432
adverse effects of overconsumption, 485-486
AMDR, 820
and cancer risk, 55, 486, 819
and cardiovascular disease, 485-486
and CHD risk, 58-59, 817-818
and diabetes, 819
dietary intakes, 474, 1044-1045
energy contribution, 474, 478
epidemiological studies, 817
evidence considered for estimating requirements, 441, 460
excretion, 433
food sources, 426, 474, 478, 816, 819-820
function, 4, 426, 432, 460
and glucose metabolism, 819
hazard identification, 485-486
high *n*-9 fatty acid diets, 820
insulin sensitivity, 806
intervention studies, 817-818
by life stage and gender groups, 1044-1045
and lipid profile, 58, 486, 817-818
low *n*-9 fatty acid diets, 817-820
metabolism, 4, 423, 432-433
and micronutrient inadequacy, 819-820
n-9, 460
protective effects, 816-817, 819
research recommendations, 505
Montreal Diet Dispensary, 654
Mortality
BMI and, 484
saturated fatty acids and, 484
MSG Symptom Complex, 714, 715-717
Mucins, 592, 601, 683
Multiple Risk Factor Intervention Trial, 827, 914-915
Myosin, 593, 595
Myristic acid, 58, 425, 483
Myristoleic acid, 426

N

N-Methyl-D-aspartate, 711
National Cholesterol Education Program, 798
National Health and Nutrition Examination Survey III, 36, 46
  adjustments to data, 49-50
  at-risk-for-overweight category, 130
  body composition data, 124, 125, 130, 982, 1078-1103
  dietary intake data, 283, 295, 473, 474, 624, 701, 704, 711, 712, 720, 721, 723, 725, 727, 729, 730, 731, 734, 789, 792, 812, 988-1027
  Epidemiological Follow-up Study, 827
  lipid profiles, 302
  survey design, 49
  underreporting of energy intakes, 49
National Institutes of Health, 121
National Nutrition Monitoring System, 936
National Nutritious Food Basket, 481
National Research Council, 87
Nationwide Food Consumption Survey, 314-315, 318-319, 474, 790-793
Navajo Indians, 173
Nervonic acid, 426
Netherlands Cohort Study, 378
Neural development, 444-447
Neural tube defects, 726
Neurological effects. *See also* Brain
  amino acids, 696, 699, 701-702, 703, 704-705, 706, 711, 714, 715, 717, 718, 719, 727, 728, 733
Neurotransmitters, 704-705, 707, 709, 710, 711, 714, 731, 732, 734
Niacin, 731, 790-791, 813-814, 1228-1243
Nicotinamide adenine dinucleotide, 453
Nicotinic acid, 608, 792-793
Nitric oxide, 608
Nitrogen. *See also* Protein
  amino acid utilization through nonprotein pathways, 607-608, 684
  balance, 275, 279, 287, 594, 611, 694, 718
  carbohydrate-free diets and, 275
  content in dietary protein, 590
  factorial method, 610-611, 624, 628, 629
  host-colon nitrogen cycle, 600
  individual variation, 612-613, 634, 635, 649
  losses, 598, 600-601, 610-611, 612, 625, 634, 635, 644, 646, 650, 667, 668, 671, 682-683
  maintenance requirement, 667-669
  median requirement, 635, 637-638
  metabolism, 278, 598, 603-605, 718, 720
  nonprotein, 607-608, 620
  and potassium balance, 650-653
  protein conversion factor, 684-685
  protein/nitrogen ratio, 684-685
  quality as protein source, 611, 684-685
  sources, 594
Nitrogen balance studies
  adolescents, 624-627, 632, 664-666
  adults, 275, 287, 618, 633-643, 661
  amino acids, 612, 613-614, 618, 662, 664-666, 670-671, 676, 677, 678, 688
  animals, 671
  children, 624-627, 664-666
  data analysis, 639, 677
  energy intake estimates and, 647, 648
  factor analysis, 639-643
  infants, 624-627
  limitations, 611-612, 618, 635, 643, 644, 688
  meta analysis, 643, 644, 646, 648, 691
  older adults, 646-648
  pregnant women, 650-653, 654-655
  protein, 611-613, 633-635, 639, 642-643, 650-653, 654-655, 684, 691, 693, 1250-1253
  statistical analysis of data, 612-613, 635, 638, 639, 642-643, 666
  younger adults, 633-635, 639, 642-643
No-Observed-Adverse-Effect Level (NOAEL), 90, 98, 100, 101, 975
Non-Hodgkin's lymphoma, 844
Norepinephrine, 277, 735, 916
Normative Aging Study, 484
Normative requirement, 24
Nuclear peroxisome proliferator activating receptors, 425
Nurses' Health Study, 306-307, 363, 368, 376, 377, 387, 563, 827-828, 842
Nutrient intakes. *See also* Dietary intakes
  added sugar intakes and, 788-789, 790-793, 1203-1225
  adjusting for day-to-day variation, 29, 49-50
  assessment of, 42, 48-49, 937-945
  bioavailability and, 29-30

biochemical assessment, 944
calculation of, 941-945
carbohydrate compared to other nutrients, 1226-1243
carbohydrate intake and micronutrients, 812, 816, 1226-1243
chronic intakes above the UL, 104, 105
high fat, low carbohydrate diets and, 808-809, 816
low fat, high carbohydrate diets and, 785, 788-789, 811-814
methodological considerations, 41, 42, 46, 48-49, 941-945
probability approach, 942-943, 944
special considerations, 30
Nutrient requirements, energy requirements compared, 110-111
Nutrition Canada Survey, 983
Nutrition labels, 267, 340, 341

O

Oat products, 60, 355-356, 365, 366, 368, 378, 382, 394
Obesity and overweight
abdominal, 62, 64, 379, 802
as adaptation, 150
adolescents, 313, 815, 1172-1173, 1178-1183, 1202
adults, 153, 310-313, 814, 1184-1199, 1201
amino acids and, 701, 704, 732
appetite sensations and, 795
BEE, 217
BMI, 126, 204, 216, 310, 313
body fat content, 126
carbohydrate intake and, 65, 275, 307, 310-319, 769
and CHD risk, 130, 815
children, 65, 130, 134, 140, 153, 216-219, 307, 310, 312-313, 459, 811, 814, 923, 1168-1179, 1200, 1202
children of obese parents, 133
and diabetes type 2, 802, 803
DLW database, 153, 156-157, 202
energy density of foods and, 794-796
and energy expenditure, 111, 122-123, 133-135, 138, 140, 209, 212, 216-219
energy intakes, 54, 65, 111, 307, 310, 312, 313, 322, 794
and energy requirements, 110, 132-133, 135, 138, 202-213, 216-219
epidemiological studies, 792-794, 796-797
fat intake and, 64, 459, 460, 769, 772, 773-776, 792-797, 802, 803, 814
fiber intake and, 65, 352, 370, 382-384
genetic factors, 146, 452, 784
glucose metabolism, 204, 802
glycemic index and, 313, 322
health risks, 64, 130, 204, 224
high fat, low carbohydrate diets and, 769, 792-797
insulin resistance, 62, 303, 784, 802, 803
intervention studies, 311, 773-776, 794-796, 797
lipid metabolism, 204
management, 204
mechanisms for, 794-796
palatability of foods and, 795
physical activity and, 56, 65, 133, 140, 181, 209, 212, 1168-1182, 1184-1199
polyunsaturated fatty acids and, 832
pregnancy, 191
prevalence, 773
protein intake and, 694, 843
and reference weights and heights, 982
resting metabolic rate, 133, 135, 137
risk factors, 64, 65
saturated fatty acids and, 484
sugar intake, 307, 310-313, 314-319, 323
susceptible populations, 134
TEE, 133, 153, 156-157, 202-204, 209-213, 1168-1182, 1184-1199, 1201-1202
TEF, 133-134, 143
and underreporting of energy intakes, 42, 64, 65, 313, 938
weight loss, 204, 209, 212, 219, 311, 313, 370
weight maintenance, 202-209, 216-219, 382-383, 384, 732
weight regain following weight loss, 135
Observational studies. *See also* Epidemiological studies
methodological issues, 40, 41-42, 94
Oleic acid, 426, 431, 432-433, 436, 439, 442, 455, 483, 486, 495, 819
Oligofructose (dietary or functional fiber), 353-354, 390, 391, 396-397
Oligosaccharides (dietary or functional fiber), 265, 272, 341, 342, 344, 592
Olive oil, 55
Opthalmologic effects, 711, 714, 720, 722, 729, 734, 735, 736

Oral and pharynx cancer, 844
Oral contraceptives, 921
Ornithine, 697
Osteoarthritis, 236-237
Osteoporosis, 841, 928
Ovarian cancer, 56, 379
Oxaloacetate, 604, 701
Oxysterols, 545-546

P

Palmitic acid, 58, 425, 431, 432, 483
Palmitoleic acid, 426, 486
Pampas indigenous people, 275
Pancreatic
  cancer, 57
  disease, 395
  lipase, 429, 431
Parenteral nutrition, 438, 442, 444, 460, 469, 699, 705, 714, 718, 719, 722-723
Pathobiological Determinants of Atherosclerosis in Youth Study, 815
Pectins (dietary and/or functional fiber), 63, 346, 348, 352, 356-357, 365, 366, 369, 371, 382, 388, 390, 391, 394, 397-398
Phenylalanine (indispensable), 589, 591, 593, 596, 597, 616, 617, 618, 663-665, 666, 668, 671-682, 686, 687, 689, 695, 703, 709, 726, 727-728, 734, 736, 1014-1015
Phenylketonuria, 619
Phosphatidylethanolamine, 444
Phosphatidylserine, 435, 444
Phospholipids, 425, 429, 433, 434
Phosphorus, 789, 790-791, 812, 813
Physical activity. *See also individual life-stage groups*
  adaptations in, 197, 201, 220, 922
  adverse effects of excessive activity, 180, 926-929
  age and, 143-144
  amino acids and, 918
  and appetite, 884
  and BMI, 880, 884
  and body fat, 57, 61, 139, 180, 181
  Canadian recommendations, 883, 913
  and cancer, 56-57
  and cardiovascular health, 60-61, 882, 887-888, 913, 927
  and CHD risk, 60, 886-887, 924
  and chronic disease prevention, 912-917
  climate and, 147, 148
  cycling, 184, 190, 895
  daily living activities, 886, 895, 898-899, 902-903
  data limitations, 180
  defined, 179, 881
  and diabetes mellitus type 2, 63-64
  DLW studies, 880, 881, 911
  duration, 138, 139, 183, 884, 918, 920-921
  elderly individuals, 138, 922
  energy expenditure of, 115-116, 117, 133, 138-140, 141, 143-144, 145-146, 147, 183, 190, 209, 212, 884-913
  and energy requirements, 38, 138-140, 157-161, 166, 171, 174, 175, 176-181, 182, 183-184, 190, 197-198
  epidemiological studies, 912-917
  and fat balance, 57, 60, 452
  and fatigue, 920, 921
  fidgeting, 118-119, 139-140, 902
  gender differences, 140-141, 182
  genetic influences, 145
  and glucose metabolism, 60
  glycemic index and, 318-319
  and growth and development, 922-923
  health benefits, 180-181, 912-917
  history of recommendations, 882-883, 913
  and immune function, 57
  insulin response, 60, 62, 63, 303, 803, 921
  intensity, 139, 140, 148, 183, 190, 884, 885-886, 904-905, 910, 918-920, 921, 922
  leisure activities, 885, 896-897, 900-901, 912-913
  and lipid balance, 57, 60, 61, 452, 913, 917-923
  and mental health, 151, 881, 913, 916
  metabolic equivalents, 884-887, 888, 896-899, 903, 906, 917
  and mortality rates, 912-917
  obese and overweight individuals, 56, 65, 133, 140, 181, 209, 212, 1168-1182, 1184-1199
  and obesity, 56, 65, 784, 923
  and PAL, 884-912
  prevention of adverse effects, 928-929
  protective effects of, 56, 62
  protein requirements, 660-661, 918, 920

recommended, 4, 56, 880, 882-883, 910, 911-912, 913, 926, 928-929
reported, 184
research recommendations, 225, 829
residual effects of, 112, 139
and skeletal health, 66, 180, 928
sleeping, 118
special considerations, 660-661
spontaneous nonexercise activity, 139-140, 146
TEF and, 884, 886, 895
trends in, 881-882
walking, 115, 116, 140, 158, 161, 183-184, 190, 881, 889-894, 895, 903, 906-909, 912, 913, 927
and weight control, 209, 452, 888, 908
Physical activity level (PAL)
active lifestyle, 158, 162-163, 895-899, 900-903
age/aging and, 143
BEE and, 887, 888, 895
BMI and, 220, 223, 814, 911
and BMR, 115, 902
body weight and, 116, 184, 889, 891-895
calculation, 887-889
categories, 157-161, 162-163, 164, 183
and chronic disease risk reduction, 914-917
defined, 116, 174, 887
DLW studies, 895
evaluation of, 118, 180, 895-909
exercise program, 209
gender differences, 903, 904-905
and glycemic index of foods, 318
impact of activities on, 884-912
intensity of physical activity and, 138, 184, 887-889, 904-905
low-active lifestyle, 158, 162-163, 183, 895-899
measurement, 174
reference activity, 889
RMR and, 917
sedentary, 115, 118-119, 140, 183, 200, 895-899
TEE and, 157-161, 162-163, 164, 884, 887, 906-909
very active lifestyle, 115, 138, 158-159, 162-163, 895-899
Physical exercise
adaptations in program, 928
age and, 922, 924
amino acid supplements and, 702, 705-706
athletes, 115, 138, 139, 180, 918, 924, 925
and body composition, 922, 923, 924
carbohydrate balance and, 64, 318-319, 452, 917-923, 924-925
and carbohydrate/electrolyte beverages, 924-925
and cardiovascular events, 927
defined, 881
and dehydration, 926-927
duration, 918, 920-921
endurance (aerobic), 61, 138, 140, 143, 318, 452, 660, 882, 916, 917, 918, 923, 924
energy expenditure for, 884, 924
excess post-exercise oxygen consumption, 112, 139
female athlete triad, 928
gender differences, 921, 928
and growth and development, 180, 922-923
and hyperthermia, 910, 926-927
and hypothermia, 927
intensity, 918-920, 921, 922, 925
and lipid oxidation, 917-923
overuse injuries, 926
physical education in schools, 923, 924
pregnancy and, 907, 908-911
recovery from illness and, 922
resistance exercise, 223, 661, 925, 928
running, 115, 138, 184, 223, 892, 893, 894, 926
treadmill, 184, 913
and weight, 61, 115-116, 213-215, 452, 773
Physical fitness
defined, 179-180, 881
endurance (aerobic) training and, 923
intensity of exercise and, 140
objectives, 883
pregnancy and, 907-908
resistance exercise and, 925, 928
and spontaneous physical activity, 139
supplementation of water and nutrients, 925-926
Physicians' Health Study, 827, 828
Phytochemicals, 369, 379, 391, 394, 395, 788
Pima Indians, 134, 146, 804-807
Pituitary adenomas, 396
Planet Health, 318-319

Planning nutrient intakes
AI and, 946, 948
AMDR and, 946, 948-949
carbohydrate, 956-957, 964
EAR and, 947-948
energy, 949-956, 963, 964
fat, 959
fiber, 957-958, 964
of groups, 947-949, 952-954
of individuals, 946, 949-952
integrated example, 963-964, 965
polyunsaturated fatty acids, 959-960, 964
protein and amino acids, 946, 961, 964
RDA and, 946
saturated fatty acids, *trans* fatty acids, and cholesterol, 960
UL and, 946, 947-948
Plant sterols, 544
Plasma amino acid response method, 614-615, 670-671
Poland and United States Collaborative Study on Cardiovascular Epidemiology, 484
Polydextrose (dietary or functional fiber)
adverse effects, 398
characteristics, 341, 346-347
laxation, 357
and lipid concentrations, 357
uses, 36
Polyp Prevention Trial, 374
Polysaccharides, 265, 341, 342, 343, 344, 350, 377
Polyunsaturated fatty acids, *n*-3. *See also* α-Linoleic acid; *other individual fatty acids*
absorption, 434
adverse effects of, 63, 487-494
AMDRs, 834-835
animal studies, 444-445, 492
and bleeding time, 492-493
and blood pressure, 829
and body fat, 832
and cancer, 54, 55, 833-834
and carbohydrate utilization, 832
and cardiovascular disease, 59, 455
and CHD, 59, 62-63, 455, 492, 826-827, 828-829
deficiency, 439-440, 443-447, 454-455, 469, 834
and diabetes, 494, 832-833
dietary intakes, 478, 959-960, 944, 1048-1057
epidemiological studies, 826-828, 832
evidence considered for estimating requirements, 443-447
excretion, 435
food sources, 478, 771
function, 8, 443, 444-445, 446, 466, 468, 469
and glucose metabolism, 833
and growth, 444-447, 468, 469, 471
hazard identification, 487-493
high-intake diets, 834
and immune function, 443, 487-492, 834
and insulin sensitivity, 832-833
interaction of *n*-6 and, 453-454
intervention studies (nonclinical), 828, 830-831, 832-833
and learning behavior, 445, 446, 447
by life stage and gender group, 11, 466-473, 1048-1049
and lipid profile, 826, 828, 830-831
low intake diets, 826-834
metabolism, 434-435, 439, 445-447, 453-456, 466
n-6:*n*-3 ratio, 8, 434, 439, 446-447, 454-455, 472, 834
and neural development and function, 443, 444-445, 446, 466, 468, 469
and obesity, 832
oxidative damage, 493, 832
parenteral nutrition and, 443, 454-455, 469
protective effects of, 55, 826-834
randomized controlled clinical trials, 446, 828-829
research recommendations, 509, 514
special considerations, 469, 471-472, 494
and stroke risk, 59, 492-493, 827-828, 829, 834
supplements, 455, 471-472, 487-491, 492-493, 494, 828, 829, 832, 833
and total fat, 58
trans fatty acid impact, 455-456
vegetarian diets, 466
and vision, 443, 444, 445, 446
Polyunsaturated fatty acids, *n*-6. *See also* Linoleic acid; *other specific fatty acids*
absorption, 433
adverse effects of overconsumption, 486, 825
adverse effects of underconsumption, 821-822

AIs, 461, 944-945
AMDRs, 486, 825-826
and cancer risk, 54, 824-825
and CHD, 59, 434, 798-799, 820-821
deficiency, 8, 438-439, 442, 454-455, 460, 463, 464, 785
and diabetes risk, 821
dietary intakes, 442, 478, 944, 959-960
energy contribution, 478, 821
epidemiological studies, 820-821
evidence considered for estimating requirements, 442-443
excretion, 434
food sources, 476, 822
function, 426-427
and glucose metabolism, 821
high-intake diets, 823-825
and immune function, 439
and inflammatory disorders, 824
interaction of *n*-3 and, 453-454
intervention studies, 821
by life stage and gender group, 10, 460-466
and lipid peroxidation, 823-824
and lipid profile, 59, 798-799, 820-821, 822-824
low fat diets and, 785
low intake diets, 820-823
metabolism, 8, 433-434, 442, 443, 453-456, 476
n-6:*n*-3 ratio, 8, 434, 439, 442, 446-447, 454-455, 472, 834
parenteral nutrition and, 438, 442, 444, 454-455, 460, 464
primary, 426
requirement, 38
research recommendations, 508-509
special considerations, 461, 463
trans fatty acid impact, 455-456
Potassium, 650-653, 725, 838
Prealbumin, 609, 610
Pregnancy. *See also* Lactation
adaptation to, 34, 47, 197, 290, 291, 650
adolescents, 48, 193, 201-202, 292, 389, 465, 471-472, 650-652, 654, 655
AIs, 34, 47, 388, 465, 471-472
amino acids, 680-681, 709, 724, 726, 732, 735
animal studies, 709, 726
BMR, 185, 188-191, 291
body composition, 188, 191-192
carbohydrates, 188
cervical ripening, 472
CHD risk, 389
derivation of DRIs for, 34, 47-48
DLW studies, 193, 196-197, 290
EARs, 34, 47, 290-292, 650-655, 680
EERs, 107, 116-117, 185, 188-194, 437
energy metabolism, 47, 185, 188-189, 193, 194-195, 197, 290
fat (dietary), 290, 437
fiber, 353, 388
food supplementation trials, 654
glucose metabolism, 189-190, 290-291
growth of maternal and fetal tissues, 92, 190-192, 194-195
insulin resistance, 189, 291
multiparous, 656
nitrogen balance studies, 650-653, 654-655
obesity and overweight, 191
obligatory fetal transfer, 47
physical activity, 190, 197, 907-911, 1164-1165
polyunsaturated fatty acids, 465, 471-472
potassium balance, 650-653
protein, 839
RDA, 292, 656, 680-681
special considerations, 656
supplements, 654, 656, 726
TEE, 116, 193, 197, 290, 1164-1165
thermic effect of food, 190
ULs, 92
weight, 47-48, 188, 190, 191, 192, 196, 650, 652, 653, 655, 709, 726, 732, 908, 910
Prolactin, 189, 715
Proline (dispensable), 592, 593, 607, 697, 712, 717, 728-729, 736, 1016-1017
Prospective studies, breast cancer and dietary fiber, 378
Prostaglandins, 434, 838
Prostate cancer, 54, 55, 56, 57, 321, 379, 486, 568, 578-579, 808, 819, 825, 833-834, 837, 844
Protease, 602
Protective effects
α-linoleic acid, 427, 770
amino acids, 726
cancer prevention, 54, 55, 819, 833-834
CLA, 428, 836-838
diabetes type 2, 380-381

fiber, 55-56, 59, 63, 322, 339, 348, 363, 367-368, 369, 372, 374, 375, 376-380
Protein. *See also* Amino acids; Nitrogen
absorption, 114, 599-600, 609
adaptations to metabolism of, 47, 293, 596, 605, 611, 650, 657, 694
adverse effects of, 692-694
age/aging and, 595, 602, 640-641, 642
AIs, 619-621
allergies, 692
AMDR, 15, 769, 844
amino acid content, 279, 621, 666, 682, 685-686
and amino acid homeostasis, 595-598
assessment of nutritional status, 609-610
and birth weight, 840
and blood pressure, 60, 843
and BMR, 598
body composition and, 626-629, 644, 843
body reserve, 595-596, 602, 609
and cancer, 54, 843-844
catabolism, 278, 284
and CHD, 60
chemistry, 590-592
chronic disease risk, 694
climate and, 640-641, 642
clinical effects of inadequate intake, 608-609
complete, 691
and coronary artery disease, 694, 842-843
deficiency, 601-602, 608-610, 620, 662, 840
degradation, 602
deposition rates, 626-629, 665, 666, 669, 837
dietary intakes, 589, 596, 602-603, 624, 662, 692, 1060-1063, 1074-1075
digestion and digestability, 9, 589, 592, 599-600, 621, 662, 682-684, 688-690
dose–response assessment, 694
EARs, 12-13, 624-629, 631, 637, 643-644, 646-649, 650-654
efficiency of utilization, 666
energy contribution, 109, 589, 605, 647, 648, 771, 1062-1063, 1074-1075
factorial method, 624, 628, 629, 633, 657, 658
FAO/WHO recommendations, 648
fat intake and, 60, 271, 693
food sources, 48, 280-281, 620, 622-623, 640-641, 643, 691, 771
food supplementation trials, 654
function, 9, 38, 589, 590
gastrointestinal effects, 694
gender difference, 640-641, 643, 644
and gluconeogenesis, 278, 284, 287-288, 293
and glycemic index of foods, 269
and growth, 280-281, 608-609, 654, 683, 811, 839-840
hazard identification, 692-694
high-protein diets, 692-694, 712, 841-844
and immune function, 609, 621, 839
incomplete, 691
insulin response, 279
intake assessment, 695, 960-961
intestinal losses, 600-601
and kidney stones, 694, 841-842
by life stage and gender group, 12-13, 603, 619-662, 1060-1063, 1074-1075
and lipid profile, 60, 840, 843
low-protein diets, 648, 667, 697, 707, 709, 721, 731-732, 839-840
maintenance (homeostasis), 595-597, 598-599, 601-602, 625-627, 630, 632, 657, 660, 668, 683, 684
metabolism, 597-598, 609, 650, 657, 724
methods used to estimate requirements, 635, 637-639
micronutrient availability, 840, 841
nitrogen balance, 9, 279, 287, 611-613, 624-625, 632, 633-644, 650, 654-655, 684, 691, 693, 1250-1253
nitrogen/protein ratio, 684-685
and obesity, 694, 843
and osteoporosis, 694, 841
oxidation, 109
physical activity and, 660-661
planning diets, 946, 961, 964
quality, 14, 60, 589, 608, 611, 621, 643, 661-662, 682-691, 697, 721, 811, 840
RDAs, 9, 12-13, 25, 47, 278, 589, 612-613, 629-630, 631-633, 644-645, 649, 656, 659, 844, 946
and renal function, 609, 694, 842
research recommendations, 737
risk characterization, 695
selection of indicators for estimating requirements, 610-613
special considerations, 621, 656, 660-662
sugar intakes and, 790-791
supplementation, 654, 656, 692, 694, 840

synthesis, 114, 601-602, 603, 708-709
thermic effect of, 110, 114
total, 619-662
turnover, 598, 601, 602-603, 611, 650, 655, 705
ULs, 692-695
urea production, 594, 601, 603, 604-605, 611, 620, 650, 657, 671, 684, 693-694
vegetarians, 661-662, 840
and weight, 644, 647, 650, 652, 653, 654, 655
Protein digestibility corrected amino acid score (PDCAAS), 688-690
Protein–energy malnutrition, 608-610, 704, 839, 840
Protein-free diet, 278, 635, 648, 667, 683
Psyllium (functional fiber), 347, 348, 356, 357-360, 365, 366, 371, 374-375, 388, 398-399, 693-694
Puberty/pubertal development
age at onset, 33, 983
developmental changes, 177
growth spurt, 142
racial/ethnic differences, 33
Purine nucleotide cycle, 604, 605
Pyrimidine nucleotides, 620
Pyruvate, 604, 605

R

Race/ethnicity. *See also* African Americans; Caucasians
and BMR, 146
and energy expenditure, 145-146
and pubertal development
and reporting of dietary intakes, 117
Raffinose, 265, 342
Randomized clinical trials, 42-43, 828-829
Recommended Dietary Allowance (RDA)
AIs compared, 6, 26-27
coefficient of variation, 24-25, 47, 285, 289, 292, 293, 630, 632-633, 645, 656, 670, 679, 682
criteria used to derive, 6
defined, 3, 22, 23, 24, 285, 289-290, 292, 293, 629
derivation, 285, 629-630, 633, 644-645, 649, 656, 679, 682
EAR and, 23, 24
method used to set, 24-25, 34, 47, 981-982
not established, 107
replacement with DRIs, 1, 936-937
uses, 24, 25, 26, 936, 938-939, 944, 946
Recommended Nutrient Intakes (RNIs), 31, 936-937
Reference weights and heights
and BMI, 35, 36, 124, 125, 126, 127-130
derivation of earlier values, 982-984
and energy requirements, 183
new, 35, 36, 982
use of, 34, 47, 659
Renal cancer, 844
Renal failure, 842
Renal function, 92
Reproductive effects, 701, 712, 713, 715
Requirement, defined, 21-22, 39
Research recommendations. *See also individual nutrients*
adverse effects, 970-971
amino acids, 737-738
approach to setting, 968
body composition and size, 225, 240
carbohydrates, 323-324
cholesterol, 574-575, 578
chronic disease relationships to intakes, 970
data and database issues, 969-971
energy, 225, 240, 323-324
fat (total), 324, 505, 514
fiber, 399-400
major information gaps and, 18, 44, 969-971
methodology, 969-970
monounsaturated fatty acids, 505
physical activity, 225, 829
polyunsaturated fatty acids, 508-509, 514
priorities, 18, 971
protein, 737
requirements, 969
saturated fatty acids, 505
trans fatty acids, 514
Resistant dextrins (dietary or functional fiber), 341, 347, 360
Resistant starch (dietary or functional fiber), 268, 342, 344, 347, 348, 360-361, 366, 371, 376-377, 378, 382, 384, 390, 399
Respiratory quotient (RQ), 109, 119-120, 189, 196, 279, 291, 832
Resting energy expenditure (REE), 112, 114, 128, 133, 141, 212

Resting metabolic rate (RMR)
aging and, 143
body composition and size and, 131, 135, 138, 144
energy expenditure, 112, 131, 132, 141, 148, 165
FFM and, 113, 139
gender differences, 141
lactation and, 195
menstrual cycle and, 141
weight and, 113, 133, 135
Retinol, 792-793
Retinol binding protein, 609, 610
Rheumatoid arthritis, 487, 722, 824
Riboflavin, 790-791, 835, 840, 1228-1243
Risk assessment models. *See also* UL modeling
application to nutrients, 27, 91-94
basic concepts, 86-87
bioavailability considerations, 93-94, 98
defined, 86, 976
environmental chemicals vs. nutrients, 91
EPA guidelines, 1246
and food safety, 86-90, 104
limitations, 100
nutrient–nutrient interactions, 93
process, 87-89, 97-98
sensitivity of individuals, 89, 92-93, 97-98, 100, 101
thresholds, 89-90
uncertainties, 86, 87, 91-92, 100, 1244-1249
Risk characterization, 86, 89, 90, 976
Risk management, 87, 89, 104, 976

S

Satiety, 65, 313, 348, 382-384, 388, 794, 795, 796, 843
Saturated fatty acids. *See also individual fatty acids*
absorption, 431-432
adverse effects of overconsumption, 481-485
and BMI, 484
and cancer, 484
and CHD risk, 422, 481-484, 797, 798, 799
and diabetes (type 2) risk, 484-485
dietary intake, 474, 960, 1042-1043, 1072-1073, 1076-1077, 1226-1227
energy contribution, 474, 835, 1072-1073, 1226-1227
evidence considered for estimating requirements, 441, 460
excretion, 432
food sources, 424, 425, 474, 475-476, 771, 835, 836
function, 4, 422, 425, 432, 460, 484-485
and glucose tolerance, 484, 485
hazard identification, 481-485
high-intake diets, 836
and insulin sensitivity, 62, 484-485, 806
by life stage and gender group, 1042-1043, 1072-1073
and lipid profile, 422, 432, 481-484, 560, 561, 809, 835
low intake diets, 835
metabolism, 4, 432
and micronutrient intakes, 835
and mortality incidence, 484
in nonvegetarian diets, 1076
and obesity, 484
properties, 424
reducing intakes, 836
research recommendations, 505
and total fat, 58, 424
in vegetarian diets, 835, 1076
Schizophrenia, 720
Scottish Heart Health Study, 316-317, 318-319, 790-793
Selenium, 444
Sensitive subpopulations. *See also* Special considerations
identification of, 97-98
Septicemia, 609, 705
Serine (dispensable), 591, 593, 594, 597, 604, 608, 711, 719, 729-730, 736, 1018-1019
Serotonin, 608, 706, 731, 732, 916
Seven Countries Study, 562, 817, 826, 827
Seventh Day Adventists, 363, 835
Skeletal health, physical activity and, 66
Skin cancer, 837
Sleeping metabolic rate (SMR), 112, 118, 140, 147, 165, 195
Snack foods, 118, 732-733
Socioeconomic status, and reporting of dietary intakes, 117
Sodium, 725
Soft drinks, 312-313, 789
Soldiers, 148, 223

Somnolence, 698, 700, 722, 733
Sorbitol, 266
Special considerations. *See also individual nutrients and life-stage groups*
athletes, 221-223, 660-661
chronic diseases, 494
disabled individuals, 30, 660
dose–response assessment, 100, 101
drug interactions, 494
identification of, 92, 102
infant formula, 45, 283, 457, 461, 463, 469, 621
irritable bowel syndrome, 395
linoleic acid:α-linoleic acid ratio, 472
low carbohydrate diets, 293
muscle wasting diseases, 660
negative energy balance, 213-215
overweight and obesity, 202-213, 216-219
phenylketonuria, 728
physical activity, 660-661
twin pregnancy, 656
undernutrition, 220, 221
vegetarians, 661-662
weight maintenance, 202-204, 216-219
weight reduction, 209, 212, 213-215, 219
weight restoration, 220-221
Special Turku Coronary Risk Factor Intervention Project, 811
Specific Dynamic Action. *See* Thermic effect of food
Stachyose, 265, 342
Starch. *See also* Resistant starch
and cancer risk, 321
definition, 267-268
and dental caries, 296
digestion and digestibility, 269, 272
energy yields, 109
food sources, 265-266, 294
glycemic index, 323
insulin sensitivity, 303
lipogenesis, 59, 298-301, 302
slow release vs. fast release, 382
Starvation, 276, 277-279, 284, 430, 437, 595, 605, 609, 693, 704
Stearic acid, 58, 425, 431, 432, 483-484
Sterol-coenzyme A desaturase, 837
Sterol regulatory element-binding protein, 545, 562
Stroke, 59, 230-231, 492-493, 827-828
Stunting, 221, 701
Sucrase, 272, 592
Sucrose, 109, 266, 272, 274, 283, 294, 295, 297, 298-301, 302, 303, 311, 319, 345
Sugar, 323
added, 16, 65, 118, 266-267, 294, 295, 303, 312, 314-315, 318-319, 323, 770, 788-789, 790-793, 810, 812-813, 816, 957, 988-991, 1203-1225
adverse effects of, 295, 319-321
alcohols, 266, 341, 342
behavioral effects, 295-296, 323
and BMI, 65, 310, 313, 316-319
and cancer risk, 55, 319-320, 321, 323
and CHD risk, 303, 800-801
definition, 266-267
and dental caries, 61-62, 296-297, 323
and diabetes type 2, 303
dietary intakes, 118, 266, 294-295, 323, 988-991, 1206-1209, 1216-1219
digestion, 272
energy intake from, 65, 118, 273, 307, 310, 313, 314-315, 770
epidemiological studies, 800-801
extrinsic, 266, 297, 812
food sources, 266-267, 294, 312-313
glycemic index, 323
in high fat, low carbohydrate diets, 810
and insulin sensitivity, 303
intake assessment, 323
intestinal absorption, 273
intrinsic, 265
lipogenicity, 59, 297-302, 323
in low fat, high carbohydrate diets, 788-789, 790-793
maximal intake levels, 16, 810, 816
and micronutrient intake levels, 788-789, 790-793, 809, 812, 1203-1225
and obesity, 307, 310-313, 314-319, 323
substitutes, 346, 695, 702-703, 727
total, 313, 314-315, 316-317, 789, 792, 809, 813-814
uses, 266
Sugar beet fiber, 383, 394, 838
Supplements, dietary. *See also individual nutrients*
bioavailability considerations, 29, 93, 94
chronic consumption, 719, 727
clinical trials, 27-28, 85
data sources on intakes, 941
fiber, 345
impurities in, 733

intake assessment, 88-89, 104
physical exercise and, 925-926
ULs and, 27, 85, 91-92, 104

T

Tarahumara Indians, 546, 561
Taste and smell acuity, 722
Taurine, 608
Teratogens, 708, 728
Testosterone, 543
Thermic effect of food (TEF). *See also individual nutrients*
age/aging and, 134, 143, 165, 171, 179
alcohol, 109-110
defined, 109-110, 114
and energy expenditure, 114, 115, 116, 150, 165, 171
and energy requirements, 165, 171, 190, 196-197
fat, 114
infants, 165
lactation and, 196-197
obesity and overweight and, 133-134, 143
pregnancy and, 190
protein, 110, 114
Thermoregulation, 114, 116, 165-166
Thiamin, 790-791, 1228-1243
Threonine (indispensable), 589, 591, 593, 597, 601, 604, 615, 618, 661, 663-665, 666, 668, 671-682, 683, 686, 687, 689, 692, 723, 730-731, 736, 1020-1021
Threonine dehydrogenase, 678
Thrombosis, 427
Thromboxanes, 434, 454, 826
Thyroid hormones, 608
Thyroid stimulating hormone, 715
Toddlers, ages 1 through 3 years. *See* Children
Tolerable Upper Intake Levels (ULs). *See also* UL modeling
applicable population, 84, 89
criteria and proposed values, 12-13
defined, 3, 22, 23, 27-28, 84, 99
derivation of, 27, 85-86, 90, 96, 98, 101, 102
extrapolation on body-weight basis, 34, 47, 85, 86, 101
fortification of foods and, 27, 85
not established for macronutrients, 101-104, 107, 224, 694, 770, 940, 946
offsetting benefits reduction, 103
supplement use and, 27, 85, 88-89, 91-92
uses, 27, 84, 85, 936, 940, 945, 947-948
Total energy expenditure (TEE). *See also* Energy expenditure
approach used to determine, 151-164, 202-203
body composition and size and, 132
coefficients and standard errors, 1200-1202
components of, 112-116
data analysis and assumptions for equations, 154-157
defined, 116
DLW data, 116, 117, 119-121, 122-123, 138-139, 141, 151-157, 166, 174, 193, 198-199, 201, 291, 1104-1202
EEPA, 115-116, 117, 133, 138-140, 143-144, 145-146, 147-148
EER derivation, 149-150, 166, 168-169, 174, 176, 181, 183, 186, 193-195, 201, 202-203, 208
equations for normal-weight children, 161-164, 1200
factorial approach, 116, 118-119
gender differences, 166, 174, 202-203, 204, 206-213, 217, 218-219
menstrual cycle and, 141
for obese and overweight individuals, 133, 153, 156-157, 202-204, 209-213, 1168-1182, 1184-1199, 1201-1202
PAL categories, 116, 157-161, 162-163, 164, 1122-1199
regression on variables, 159-161, 164, 214
reported energy intake and, 117-118
RMR and, 132, 148
TEF and, 116
underfeeding studies, 213-215
uses, 951
whole-body calorimetry measurements, 120, 122-123, 140
Toxicity
age and sensitivity to, 92
mechanisms of action, 97
Trans fatty acids
absorption, 436
adverse effects of, 436, 455-456, 494-505
and blood pressure, 504, 506-509
and cancer, 512-515
and cardiovascular disease, 503

and cerebrovascular disease, 503
and CHD risk, 58, 423, 504, 510-513
controlled feeding trials, 496-499
dietary intakes, 436, 479, 835, 960
energy contribution, 479, 480
epidemiological studies, 510-515
evidence considered for estimating requirements, 447, 473
excretion, 437
and fetal and infant growth, 436, 455
food sources, 48, 427-428, 436, 455, 479, 480, 495, 836
free-living trials, 500-503
function, 427-428
hazard identification, 494-504
and hemostatic factors, 504, 506-509
high-intake diets, 836
and LDL oxidation, 504, 506-509
and lipid profile, 58, 423, 494-503, 504
low-intake diets, 835
and Lp(a), 496-503, 510-511
measuring intakes, 436
metabolism, 436-437
and polyunsaturated fatty acid metabolism metabolism, 455-456
properties, 424, 427
reducing intakes, 836
research recommendations, 514
transport, 436
Transamination, 604, 704, 712
Transferrin, 609, 610
Trauma, 596, 605
Trehalose, 266
Triacylglycerol or triacylglyceride. *See also* Fat, total; Lipids and lipid metabolism
amino acid intake and, 724
carbohydrate intakes and, 59, 275, 783
and CHD risk, 57-58, 59, 437
fat intake and, 777-781
fiber intake and, 60, 351, 354, 356, 357, 359, 360, 361, 367-368, 369
food sources, 473
gluconeogenesis, 275, 278
glycemic index and, 302, 322
glycerol content, 278, 279
hydrolysis of, 429
lipoprotein metabolism and, 61, 278
low fat, high carbohydrate diets and, 777-781
lypolysis, 431
monounsaturated fatty acid intake and, 817-818
physical exercise and, 60
polyunsaturated fatty acids and, 59, 820, 821, 822-823, 826, 828, 830-831
protein intake and, 60, 843
sugar intake and, 297-301
synthesis, 431, 432, 439
very low density lipoprotein, 430, 431, 439
Tricarboxylic acid (TCA) cycle, 274
Triceps skinfold measurements, 125, 128, 1080-1081, 1086-1087, 1092-1093, 1100-1101
Trisaccharides, 272
Trypsin, 599
Tryptophan (indispensable), 589, 591, 593, 608, 616, 663-665, 666, 668, 672-675, 677, 678, 679-682, 686, 687, 689, 692, 704, 705, 706, 707, 709, 710, 726, 731-734, 736, 1022-1023
24-Hour amino acid balance method, 616-617, 670-671, 676, 677
2000 Dietary Guidelines for Americans, 124, 267
Typhoid vaccine, 488-489, 491
Tyrosine (conditionally indispensable), 589, 591, 593, 594, 597, 608, 617, 619, 663-665, 666, 668, 671-682, 686, 687, 689, 703, 704, 707, 709, 710, 726, 727, 734-736, 1024-1025
Tyrosinemia II, 735

U

Ubiquitin-protease system, 602
UCP1 gene, 145
UK National Diet and Nutrition Survey of Children, 314-315, 790-791
UL modeling. *See also* Dose–response assessment; Risk assessment models
critical endpoint, 93, 98, 99, 101, 102
data selection, 98
hazard identification, 94-98
mathematical models, 85-86
nutrient intake assessment, 104
risk characterization, 86, 89, 90, 104-105
uncertainty assessment, 89, 98, 100-101
Ulcerative colitis, 348, 371
Uncertainties
in AIs, 26, 44
amino acid scoring patterns, 688
approaches for dealing with, 1244-1249

assessment, 89, 98, 100-101
case-by-case judgments, 1246-1247, 1248-1249
in data, 86, 99, 1246
default options, 1246, 1248-1249
dose–response assessment, 98, 100-101
in exposure routes, 98
extrapolation from one age group to another, 101
range of estimates applied to, 1246, 1248-1249
in risk assessment, 86, 87, 91-92, 100-101, 102-103, 1244-1249
Uncertainty factors
defined, 90, 977
for energy intake, 224
inferences from experimental animal studies, 100, 1245-1246
LOAEL instead of NOAEL, 100-101
selection of, 87, 99, 100
sensitivity of individuals, 100
sources of uncertainty in, 100-101
subchronic NOAEL to predict chronic NOAEL, 101
use, 90, 91
Undernutrition, 130, 220
Underweight, 121, 130, 190, 811
United Kingdom Department of Health, 266
United Nations University, 621, 634
United States
fiber definitions, 340
human milk intake and composition, 172-173
physical activity recommendations, 882-883
Urea, 114, 594, 601, 603, 604-605, 611, 620, 650, 657, 671, 684, 693-694, 699, 712
Uric acid, 603, 604
Urinary C-peptide, 322, 353, 361
U.S. Department of Agriculture, 49, 124, 266, 294, 344, 346, 391, 479, 771, 882
U.S. Department of Health and Human Services
dietary intake survey data, 49
Office of Disease Prevention and Health Promotion, 1
2000 Dietary Guidelines, 124, 882-883
U.S. Department of Health, Education, and Welfare, 882
U.S. Environmental Protection Agency, 1246

V

Vaccenic acid, 426, 428
Valine (indispensable), 589, 591, 593, 597, 663-665, 666, 668, 672-675, 677, 678, 679-682, 686, 687, 689, 704-711, 726, 736, 1026-1027
Vegetables. *See* Fruits and vegetables
Vegetarians, 372, 466, 661-662, 835, 975, 1077
Very low density lipoprotein (VLDL), 61, 430, 439, 545
remnant, 431, 544
Vision, 439, 440, 468, 711, 714, 720, 722, 729
Vitamin A, 424, 609, 785, 788, 789, 790-793, 811, 812, 813, 1204-1211, 1214-1221, 1224-1225
Vitamin B_6, 771, 785, 788, 789, 790-793, 1228-1243
Vitamin B_{12}, 771, 785, 789, 790-791, 813, 835, 1228-1243
Vitamin C, 771, 788, 789, 790-791, 808, 813, 816, 1228-1243
Vitamin D, 424, 790-791, 811, 812, 840, 841
Vitamin E, 424, 444, 493, 785, 789, 790-793, 811, 812, 813, 829, 1204-1211, 1214-1221, 1224-1225
Vitamin K, 424, 788
VLDL cholesterol, 843

W

Waist circumference, 124-125, 127, 1080-1081, 1084-1085, 1094-1099, 1102-1103
Water
and laxation, 370, 398
physical exercise and, 925-926
Weight. *See also* Obesity and overweight; Reference weights and heights; Underweight; *individual life-stage groups*
adaptation, 150
adjustment of DRIs based on, 34
adults, 143, 183, 184, 220, 1078-1081, 1088-1091
age/aging and, 143, 167
amino acids and, 697, 698, 700, 707, 709, 713, 721, 724, 730, 731-732, 734

BEE and, 116, 141, 150, 183, 184, 186, 206-213, 888
BMI and, 1080-1081
body fat and, 1090-1091
and chronic disease, 224, 226-229
and diabetes type 2, 802
energy balance and, 65, 150, 212, 214, 220
and energy expenditure, 116, 132, 135, 141, 150, 157, 159-161, 183, 184, 186, 206-213, 215, 216-219, 889, 891-895, 951
energy intake and, 121, 223-224, 793-794, 951-952
and energy requirements, 112, 183, 184, 220
epidemiological studies, 382-383
fat intake and, 441, 452, 773-776, 809
fiber intake and, 65, 339, 351-352, 370, 382-384
gain, 47-48, 110, 121, 143, 144, 167, 186, 223-224, 226-229, 452, 650, 652, 653, 654, 655, 697, 698, 709, 730-732, 734, 802, 951-952
gender differences, 1078-1081, 1088-1091
genetic factors, 144, 452
hypocaloric vs. isocaloric diets, 772
intervention studies, 311, 383-384
loss, 61, 65, 121, 199-200, 204, 209, 212, 215, 217, 219, 225, 311, 313, 351-352, 370, 383, 721, 843, 951
low fat, high carbohydrate diets, 311, 773-777
maintenance, 149, 202-209, 216-219, 382-383, 441, 773-777, 951-952
measurement confounding, 202-204
metabolic rate and, 112, 113, 135, 138
overeating and, 121, 151
physical exercise and, 61, 115-116, 213-215, 452, 773
pregnancy, 47-48, 188, 190, 191, 192, 196, 650, 652, 653, 655, 709
protein (nitrogen) and, 598, 612, 843
rapid loss, 217
recommended, 117
regain after loss, 135
restoration, 220-221
stabilization, 138
and TEE, 159-161
velocity, 142
Whites. *See* Caucasians
Whole-body calorimetry, 120, 122-123
Women. *See also* Gender differences; Lactation; Pregnancy
bone mineral density, 841, 928
calcium, 789, 841
carbohydrate intakes compared to other nutrients, 1238-1243
CHD, 363, 364
colon cancer, 373
diabetes type 2, 380, 381
energy expenditure, 140
fiber, 363, 364, 373, 380, 381
glycemic load, 303
menopause, 141, 143, 921
metabolic rate, 140, 141
nutrient intakes with added sugars, 1218-1225
oral contraceptives, 921
physical activity, 138, 140, 894, 913, 921, 928
premenopausal, 140, 141
protein intakes, 695, 841
reference weights and heights, 126
weight control, 352, 773
Women's Health Initiative Observational Study, 913
World Cancer Research Fund, 321
World Health Organization, 84, 110, 121, 621, 634, 648, 684, 913

X

Xylose, 345

Y

Youth Risk Behavior Study, 923

Z

Zinc, 221, 391, 394, 397-398, 705, 721-723, 771, 785, 789, 790-793, 812, 813-814, 840, 1204-1209, 1212-1219, 1222-1225, 1228-1243
Zutphen Elderly Study, 381, 483, 826, 827

Summary Tables, Dietary Reference Intakes

Recommended Intakes for Individuals, Vitamins 1320
Recommended Intakes for Individuals, Elements 1322
Recommended Intakes for Individuals, Total Water and Macronutrients 1324
Acceptable Macronutrient Distribution Ranges 1325
Additional Macronutrient Recommendations 1325
Tolerable Upper Intake Levels (UL), Vitamins 1326
Tolerable Upper Intake Levels (UL), Elements 1328
Estimated Average Requirements for Groups 1330

Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Vitamins
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Vitamin A (μg/d)[a]	Vitamin C (mg/d)	Vitamin D (μg/d)[b,c]	Vitamin E (mg/d)[d]	Vitamin K (μg/d)	Thiamin (mg/d)
Infants						
0–6 mo	400*	40*	5*	4*	2.0*	0.2*
7–12 mo	500*	50*	5*	5*	2.5*	0.3*
Children						
1–3 y	**300**	**15**	5*	**6**	30*	**0.5**
4–8 y	**400**	**25**	5*	**7**	55*	**0.6**
Males						
9–13 y	**600**	**45**	5*	**11**	60*	**0.9**
14–18 y	**900**	**75**	5*	**15**	75*	**1.2**
19–30 y	**900**	**90**	5*	**15**	120*	**1.2**
31–50 y	**900**	**90**	5*	**15**	120*	**1.2**
51–70 y	**900**	**90**	10*	**15**	120*	**1.2**
> 70 y	**900**	**90**	15*	**15**	120*	**1.2**
Females						
9–13 y	**600**	**45**	5*	**11**	60*	**0.9**
14–18 y	**700**	**65**	5*	**15**	75*	**1.0**
19–30 y	**700**	**75**	5*	**15**	90*	**1.1**
31–50 y	**700**	**75**	5*	**15**	90*	**1.1**
51–70 y	**700**	**75**	10*	**15**	90*	**1.1**
> 70 y	**700**	**75**	15*	**15**	90*	**1.1**
Pregnancy						
14–18 y	**750**	**80**	5*	**15**	75*	**1.4**
19–30 y	**770**	**85**	5*	**15**	90*	**1.4**
31–50 y	**770**	**85**	5*	**15**	90*	**1.4**
Lactation						
14–18 y	**1,200**	**115**	5*	**19**	75*	**1.4**
19–30 y	**1,300**	**120**	5*	**19**	90*	**1.4**
31–50 y	**1,300**	**120**	5*	**19**	90*	**1.4**

NOTE: This table (taken from the DRI reports, see www.nap.edu) presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a] As retinol activity equivalents (RAEs). 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b] As cholecalciferol. 1 μg cholecalciferol = 40 IU vitamin D.

[c] In the absence of adequate exposure to sunlight.

[d] As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements.

[e] As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not NE).

[f] As dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folic acid

Riboflavin (mg/d)	Niacin (mg/d)[e]	Vitamin B_6 (mg/d)	Folate (μg/d)[f]	Vitamin B_{12} (μg/d)	Pantothenic Acid (mg/d)	Biotin (μg/d)	Choline (mg/d)[g]
0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
0.5	**6**	**0.5**	**150**	**0.9**	2*	8*	200*
0.6	**8**	**0.6**	**200**	**1.2**	3*	12*	250*
0.9	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
1.3	**16**	**1.3**	**400**	**2.4**	5*	25*	550*
1.3	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
1.3	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
1.3	**16**	**1.7**	**400**	**2.4**[h]	5*	30*	550*
1.3	**16**	**1.7**	**400**	**2.4**[h]	5*	30*	550*
0.9	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
1.0	**14**	**1.2**	**400**[i]	**2.4**	5*	25*	400*
1.1	**14**	**1.3**	**400**[i]	**2.4**	5*	30*	425*
1.1	**14**	**1.3**	**400**[i]	**2.4**	5*	30*	425*
1.1	**14**	**1.5**	**400**	**2.4**[h]	5*	30*	425*
1.1	**14**	**1.5**	**400**	**2.4**[h]	5*	30*	425*
1.4	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
1.4	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
1.4	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*	550*

from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

[g] Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

[h] Because 10 to 30 percent of older people may malabsorb food-bound B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with B_{12} or a supplement containing B_{12}.

[i] In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet.

[j] It is assumed that women will continue consuming 400 μg from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001); *and Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Elements
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Calcium (mg/d)	Chromium (µg/d)	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)
Infants							
0–6 mo	210*	0.2*	200*	0.01*	110*	0.27*	30*
7–12 mo	270*	5.5*	220*	0.5*	130*	**11**	75*
Children							
1–3 y	500*	11*	**340**	0.7*	**90**	**7**	**80**
4–8 y	800*	15*	**440**	1*	**90**	**10**	**130**
Males							
9–13 y	1,300*	25*	**700**	2*	**120**	**8**	**240**
14–18 y	1,300*	35*	**890**	3*	**150**	**11**	**410**
19–30 y	1,000*	35*	**900**	4*	**150**	**8**	**400**
31–50 y	1,000*	35*	**900**	4*	**150**	**8**	**420**
51–70 y	1,200*	30*	**900**	4*	**150**	**8**	**420**
> 70 y	1,200*	30*	**900**	4*	**150**	**8**	**420**
Females							
9–13 y	1,300*	21*	**700**	2*	**120**	**8**	**240**
14–18 y	1,300*	24*	**890**	3*	**150**	**15**	**360**
19–30 y	1,000*	25*	**900**	3*	**150**	**18**	**310**
31–50 y	1,000*	25*	**900**	3*	**150**	**18**	**320**
51–70 y	1,200*	20*	**900**	3*	**150**	**8**	**320**
> 70 y	1,200*	20*	**900**	3*	**150**	**8**	**320**
Pregnancy							
14–18 y	1,300*	29*	**1,000**	3*	**220**	**27**	**400**
19–30 y	1,000*	30*	**1,000**	3*	**220**	**27**	**350**
31–50 y	1,000*	30*	**1,000**	3*	**220**	**27**	**360**
Lactation							
14–18 y	1,300*	44*	**1,300**	3*	**290**	**10**	**360**
19–30 y	1,000*	45*	**1,300**	3*	**290**	**9**	**310**
31–50 y	1,000*	45*	**1,300**	3*	**290**	**9**	**320**

NOTE: This table presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

Manganese (mg/d)	Molybdenum (μg/d)	Phosphorus (mg/d)	Selenium (μg/d)	Zinc (mg/d)	Potassium (g/d)	Sodium (g/d)	Chloride (g/d)
0.003*	2*	100*	15*	2*	0.4*	0.12*	0.18*
0.6*	3*	275*	20*	**3**	0.7*	0.37*	0.57*
1.2*	**17**	**460**	**20**	**3**	3.0*	1.0*	1.5*
1.5*	**22**	**500**	**30**	**5**	3.8*	1.2*	1.9*
1.9*	**34**	**1,250**	**40**	**8**	4.5*	1.5*	2.3*
2.2*	**43**	**1,250**	**55**	**11**	4.7*	1.5*	2.3*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.5*	2.3*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.5*	2.3*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.3*	2.0*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.2*	1.8*
1.6*	**34**	**1,250**	**40**	**8**	4.5*	1.5*	2.3*
1.6*	**43**	**1,250**	**55**	**9**	4.7*	1.5*	2.3*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.5*	2.3*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.5*	2.3*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.3*	2.0*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.2*	1.8*
2.0*	**50**	**1,250**	**60**	**12**	4.7*	1.5*	2.3*
2.0*	**50**	**700**	**60**	**11**	4.7*	1.5*	2.3*
2.0*	**50**	**700**	**60**	**11**	4.7*	1.5*	2.3*
2.6*	**50**	**1,250**	**70**	**13**	5.1*	1.5*	2.3*
2.6*	**50**	**700**	**70**	**12**	5.1*	1.5*	2.3*
2.6*	**50**	**700**	**70**	**12**	5.1*	1.5*	2.3*

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001); and *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Total Water and Macronutrients

Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Total Water[a] (L/d)	Carbo-hydrate (g/d)	Total Fiber (g/d)	Fat (g/d)	Linoleic Acid (g/d)	α-Linolenic Acid (g/d)	Protein[b] (g/d)
Infants							
0–6 mo	0.7*	60*	ND	31*	4.4*	0.5*	9.1*
7–12 mo	0.8*	95*	ND	30*	4.6*	0.5*	**11.0+**
Children							
1–3 y	1.3*	**130**	19*	ND[c]	7*	0.7*	**13**
4–8 y	1.7*	**130**	25*	ND	10*	0.9*	**19**
Males							
9–13 y	2.4*	**130**	31*	ND	12*	1.2*	**34**
14–18 y	3.3*	**130**	38*	ND	16*	1.6*	**52**
19–30 y	3.7*	**130**	38*	ND	17*	1.6*	**56**
31–50 y	3.7*	**130**	38*	ND	17*	1.6*	**56**
51–70 y	3.7*	**130**	30*	ND	14*	1.6*	**56**
> 70 y	3.7*	**130**	30*	ND	14*	1.6*	**56**
Females							
9–13 y	2.1*	**130**	26*	ND	10*	1.0*	**34**
14–18 y	2.3*	**130**	26*	ND	11*	1.1*	**46**
19–30 y	2.7*	**130**	25*	ND	12*	1.1*	**46**
31–50 y	2.7*	**130**	25*	ND	12*	1.1*	**46**
51–70 y	2.7*	**130**	21*	ND	11*	1.1*	**46**
> 70 y	2.7*	**130**	21*	ND	11*	1.1*	**46**
Pregnancy							
14–18 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
19–30 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
31–50 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
Lactation							
14–18 y	3.8*	**210**	29*	ND	13*	1.3*	**71**
19–30 y	3.8*	**210**	29*	ND	13*	1.3*	**71**
31–50 y	3.8*	**210**	29*	ND	13*	1.3*	**71**

NOTE: This table presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake. The plus (+) symbol indicates a change from the prepublication copy due to a calculation error.

[a] *Total* water includes all water contained in food, beverages, and drinking water.

[b] Based on g protein per kg of body weight for the reference body weight, e.g., for adults 0.8 g/kg body weight for the reference body weight.

[c] Not determined.

SOURCES: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005); *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Acceptable Macronutrient Distribution Ranges
Food and Nutrition Board, Institute of Medicine, National Academies

	Range (percent of energy)		
Macronutrient	Children, 1–3 y	Children, 4–18 y	Adults
Fat	30–40	25–35	20–35
n-6 Polyunsaturated fatty acids[a] (linoleic acid)	5–10	5–10	5–10
n-3 Polyunsaturated fatty acids[a] (α-linolenic acid)	0.6–1.2	0.6–1.2	0.6–1.2
Carbohydrate	45–65	45–65	45–65
Protein	5–20	10–30	10–35

[a] Approximately 10 percent of the total can come from longer-chain *n*-3 or *n*-6 fatty acids.

SOURCE: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005).

Dietary Reference Intakes (DRIs): Additional Macronutrient Recommendations
Food and Nutrition Board, Institute of Medicine, National Academies

Macronutrient	Recommendation
Dietary cholesterol	As low as possible while consuming a nutritionally adequate diet
Trans fatty acids	As low as possible while consuming a nutritionally adequate diet
Saturated fatty acids	As low as possible while consuming a nutritionally adequate diet
Added sugars	Limit to no more than 25% of total energy

SOURCE: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005).

Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels (UL[a]), Vitamins
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Vitamin A (μg/d)[b]	Vitamin C (mg/d)	Vitamin D (μg/d)	Vitamin E (mg/d)[c,d]	Vitamin K	Thiamin
Infants						
0–6 mo	600	ND[f]	25	ND	ND	ND
7–12 mo	600	ND	25	ND	ND	ND
Children						
1–3 y	600	400	50	200	ND	ND
4–8 y	900	650	50	300	ND	ND
Males, Females						
9–13 y	1,700	1,200	50	600	ND	ND
14–18 y	2,800	1,800	50	800	ND	ND
19–70 y	3,000	2,000	50	1,000	ND	ND
> 70 y	3,000	2,000	50	1,000	ND	ND
Pregnancy						
14–18 y	2,800	1,800	50	800	ND	ND
19–50 y	3,000	2,000	50	1,000	ND	ND
Lactation						
14–18 y	2,800	1,800	50	800	ND	ND
19–50 y	3,000	2,000	50	1,000	ND	ND

[a] UL = The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, and carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b] As preformed vitamin A only.

[c] As α-tocopherol; applies to any form of supplemental α-tocopherol.

[d] The ULs for vitamin E, niacin, and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two.

[e] β-Carotene supplements are advised only to serve as a provitamin A source for individuals at risk of vitamin A deficiency.

Ribo-flavin	Niacin (mg/d)[d]	Vitamin B_6 (mg/d)	Folate (μg/d)[d]	Vitamin B_{12}	Pantothenic Acid	Biotin	Choline (g/d)	Carote-noids[e]
ND	ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND	ND
ND	10	30	300	ND	ND	ND	1.0	ND
ND	15	40	400	ND	ND	ND	1.0	ND
ND	20	60	600	ND	ND	ND	2.0	ND
ND	30	80	800	ND	ND	ND	3.0	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND
ND	30	80	800	ND	ND	ND	3.0	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND
ND	30	80	800	ND	ND	ND	3.0	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND

[f] ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels (UL[a]), Elements
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Arsenic[b]	Boron (mg/d)	Calcium (g/d)	Chromium	Copper (μg/d)	Fluoride (mg/d)	Iodine (μg/d)	Iron (mg/d)	Magnesium (mg/d)[c]
Infants									
0–6 mo	ND[f]	ND	ND	ND	ND	0.7	ND	40	ND
7–12 mo	ND	ND	ND	ND	ND	0.9	ND	40	ND
Children									
1–3 y	ND	3	2.5	ND	1,000	1.3	200	40	65
4–8 y	ND	6	2.5	ND	3,000	2.2	300	40	110
Males, Females									
9–13 y	ND	11	2.5	ND	5,000	10	600	40	350
14–18 y	ND	17	2.5	ND	8,000	10	900	45	350
19–70 y	ND	20	2.5	ND	10,000	10	1,100	45	350
> 70 y	ND	20	2.5	ND	10,000	10	1,100	45	350
Pregnancy									
14–18 y	ND	17	2.5	ND	8,000	10	900	45	350
19–50 y	ND	20	2.5	ND	10,000	10	1,100	45	350
Lactation									
14–18 y	ND	17	2.5	ND	8,000	10	900	45	350
19–50 y	ND	20	2.5	ND	10,000	10	1,100	45	350

[a] UL = The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for arsenic, chromium, silicon, potassium, and sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b] Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements.

[c] The ULs for magnesium represent intake from a pharmacological agent only and do not include intake from food and water.

[d] Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to supplements.

[e] Although vanadium in food has not been shown to cause adverse effects in humans,

Manganese (mg/d)	Molybdenum (μg/d)	Nickel (mg/d)	Phosphorus (g/d)	Potassium	Selenium (μg/d)	Silicon[d]	Sulfate	Vanadium (mg/d)[e]	Zinc (mg/d)	Sodium (g/d)	Chloride (g/d)
ND	ND	ND	ND	ND	45	ND	ND	ND	4	ND	ND
ND	ND	ND	ND	ND	60	ND	ND	ND	5	ND	ND
2	300	0.2	3.0	ND	90	ND	ND	ND	7	1.5	2.3
3	600	0.3	3.0	ND	150	ND	ND	ND	12	1.9	2.9
6	1,100	0.6	4.0	ND	280	ND	ND	ND	23	2.2	3.4
9	1,700	1.0	4.0	ND	400	ND	ND	ND	34	2.3	3.6
11	2,000	1.0	4.0	ND	400	ND	ND	1.8	40	2.3	3.6
11	2,000	1.0	3.0	ND	400	ND	ND	1.8	40	2.3	3.6
9	1,700	1.0	3.5	ND	400	ND	ND	ND	34	2.3	3.6
11	2,000	1.0	3.5	ND	400	ND	ND	ND	40	2.3	3.6
9	1,700	1.0	4.0	ND	400	ND	ND	ND	34	2.3	3.6
11	2,000	1.0	4.0	ND	400	ND	ND	ND	40	2.3	3.6

there is no justification for adding vanadium to food and vanadium supplements should be used with caution. The UL is based on adverse effects in laboratory animals and this data could be used to set a UL for adults but not children and adolescents.

f ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001); *and Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Estimated Average Requirements for Groups
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	CHO (g/d)	Protein (g/kg/d)	Vit A (μg/d)[a]	Vit C (mg/d)	Vit E (mg/d)[b]	Thiamin (mg/d)	Riboflavin (mg/d)	Niacin (mg/d)[c]	Vit B_6 (mg/d)
Infants									
7–12 mo		1.0							
Children									
1–3 y	100	0.87	210	13	5	0.4	0.4	5	0.4
4–8 y	100	0.76	275	22	6	0.5	0.5	6	0.5
Males									
9–13 y	100	0.76	445	39	9	0.7	0.8	9	0.8
14–18 y	100	0.73	630	63	12	1.0	1.1	12	1.1
19–30 y	100	0.66	625	75	12	1.0	1.1	12	1.1
31–50 y	100	0.66	625	75	12	1.0	1.1	12	1.1
51–70 y	100	0.66	625	75	12	1.0	1.1	12	1.4
> 70 y	100	0.66	625	75	12	1.0	1.1	12	1.4
Females									
9–13 y	100	0.76	420	39	9	0.7	0.8	9	0.8
14–18 y	100	0.71	485	56	12	0.9	0.9	11	1.0
19–30 y	100	0.66	500	60	12	0.9	0.9	11	1.1
31–50 y	100	0.66	500	60	12	0.9	0.9	11	1.1
51–70 y	100	0.66	500	60	12	0.9	0.9	11	1.3
> 70 y	100	0.66	500	60	12	0.9	0.9	11	1.3
Pregnancy									
14–18 y	135	0.88	530	66	12	1.2	1.2	14	1.6
19–30 y	135	0.88	550	70	12	1.2	1.2	14	1.6
31–50 y	135	0.88	550	70	12	1.2	1.2	14	1.6
Lactation									
14–18 y	160	1.05	885	96	16	1.2	1.3	13	1.7
19–30 y	160	1.05	900	100	16	1.2	1.3	13	1.7
31–50 y	160	1.05	900	100	16	1.2	1.3	13	1.7

NOTE: This table presents Estimated Average Requirements (EARs), which serve two purposes: for assessing adequacy of population intakes and as the basis for calculating Recommended Dietary Allowances (RDAs) for individuals. EARs have not been established for vitamin D, vitamin K, pantothenic acid, biotin, choline, calcium, chromium, fluoride, manganese, or other nutrients not yet evaluated via the DRI process.

[a] As retinol activity equivalents (RAEs). 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b] As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements.

Folate (μg/d)[a]	Vit B_{12} (μg/d)	Copper (μg/d)	Iodine (μg/d)	Iron (mg/d)	Magnesium (mg/d)	Molybdenum (μg/d)	Phosphorus (mg/d)	Selenium (μg/d)	Zinc (mg/d)
				6.9					2.5
120	0.7	260	65	3.0	65	13	380	17	2.5
160	1.0	340	65	4.1	110	17	405	23	4.0
250	1.5	540	73	5.9	200	26	1,055	35	7.0
330	2.0	685	95	7.7	340	33	1,055	45	8.5
320	2.0	700	95	6	330	34	580	45	9.4
320	2.0	700	95	6	350	34	580	45	9.4
320	2.0	700	95	6	350	34	580	45	9.4
320	2.0	700	95	6	350	34	580	45	9.4
250	1.5	540	73	5.7	200	26	1,055	35	7.0
330	2.0	685	95	7.9	300	33	1,055	45	7.3
320	2.0	700	95	8.1	255	34	580	45	6.8
320	2.0	700	95	8.1	265	34	580	45	6.8
320	2.0	700	95	5	265	34	580	45	6.8
320	2.0	700	95	5	265	34	580	45	6.8
520	2.2	785	160	23	335	40	1,055	49	10.5
520	2.2	800	160	22	290	40	580	49	9.5
520	2.2	800	160	22	300	40	580	49	9.5
450	2.4	985	209	7	300	35	1,055	59	10.9
450	2.4	1,000	209	6.5	255	36	580	59	10.4
450	2.4	1,000	209	6.5	265	36	580	59	10.4

[c] As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan.

[d] As dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folic acid from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001), and *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005). These reports may be accessed via www.nap.edu.