TOXICOLOGICAL PROFILE FOR FORMALDEHYDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-447-1544 (to be replaced by 1-888-42-ATSDR in 1999) or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://atsdr1.atsdr.cdc.gov:8080

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for formaldehyde. The panel consisted of the following members:

1. Carson Conaway, Research Scientist, American Health Foundation, Valhalla, New York 10595;

2. John Egle, Jr., Professor, Department of Pharmacology and Toxicology, Medical College of Virginia, Smith Bldg., Room 656, Richmond, VA 23219; and

3. Vincent Garry, Director, Environmental Medicine, University of Minnesota, 421 29th Ave., SE Minneapolis, MN 55414.

These experts collectively have knowledge of formaldehyde's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about formaldehyde and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Formaldehyde has been found in at least 26 of the 1,428 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with formaldehyde may increase. This is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to formaldehyde, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS FORMALDEHYDE?

Formaldehyde is a colorless, flammable gas at room temperature. It has a pungent, distinct odor and may cause a burning sensation to the eyes, nose, and lungs at high concentrations. Formaldehyde is also known as methanal, methylene oxide, oxymethylene, methylaldehyde, and oxomethane. Formaldehyde can react with many other chemicals, and it will break down into methanol (wood alcohol) and carbon monoxide at very high temperatures.

Formaldehyde is naturally produced in very small amounts in our bodies as a part of our normal, everyday metabolism and causes us no harm. It can also be found in the air that we breathe at home and at work, in the food we eat, and in some products that we put on our skin. A major source of formaldehyde that we breathe every day is found in smog in the lower atmosphere. Automobile exhaust

from cars without catalytic converters or those using oxygenated gasoline also contain formaldehyde. At home, formaldehyde is produced by cigarettes and other tobacco products, gas cookers, and open fireplaces. It is also used as a preservative in some foods, such as some types of Italian cheeses, dried foods, and fish. Formaldehyde is found in many products used every day around the house, such as antiseptics, medicines, cosmetics, dish-washing liquids, fabric softeners, shoe-care agents, carpet cleaners, glues and adhesives, lacquers, paper, plastics, and some types of wood products. Some people are exposed to higher levels of formaldehyde if they live in a new mobile home, as formaldehyde is given off as a gas from the manufactured wood products used in these homes.

Formaldehyde is used in many industries. It is used in the production of fertilizer, paper, plywood, and urea-formaldehyde resins. It is present in the air in iron foundries. It is also used in the production of cosmetics and sugar, in well-drilling fluids, in agriculture as a preservative for grains and seed dressings, in the rubber industry in the production of latex, in leather tanning, in wood preservation, and in photographic film production. Formaldehyde is combined with methanol and buffers to make embalming fluid. Formaldehyde is also used in many hospitals and laboratories to preserve tissue specimens.

1.2 WHAT HAPPENS TO FORMALDEHYDE WHEN IT ENTERS THE ENVIRONMENT?

Most of the formaldehyde you are exposed to in the environment is in the air. Formaldehyde dissolves easily in water, but it does not last a long time in water and is not commonly found in drinking water supplies. Most formaldehyde in the air also breaks down during the day. The breakdown products of formaldehyde in air include formic acid and carbon monoxide. Formaldehyde does not seem to build up in plants and animals, and although formaldehyde is found in some food, it is not found in large amounts. You will find more information about where formaldehyde comes from, how it behaves, and how long it remains in the environment in Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO FORMALDEHYDE?

You are exposed to small amounts of formaldehyde in the air. It occurs from both natural and man made sources although combustion is the largest source. If you live in an unpopulated area, you may be exposed to about 0.2 parts per billion (ppb) of formaldehyde in the air outdoors. In suburban areas, you may be exposed to about 2–6 ppb of formaldehyde. If you live in a heavily populated area or near some industries, you may be exposed to 10–20 ppb. You may also be exposed to higher levels of formaldehyde during rush hour commutes in highly populated areas because it is formed in automobile and truck exhaust.

There is usually more formaldehyde present indoors than outdoors. Formaldehyde is released to the air from many home products and you may breath in formaldehyde while using these products. Latex paint, fingernail hardener, and fingernail polish release a large amount of formaldehyde to the air. Plywood and particle board, as well as furniture and cabinets made from them, fiberglass products, new carpets, decorative laminates, and some permanent press fabrics give off a moderate amount of formaldehyde. Some paper products, such as grocery bags and paper towels, give off small amounts of formaldehyde. Because these products contain formaldehyde, you may also be exposed on the skin by touching or coming in direct contact with them. You may also be exposed to small amounts of formaldehyde in the food you eat. You are not likely to be exposed to formaldehyde in the water you drink because it does not last a long time in water.

Many other home products contain and give off formaldehyde although the amount has not been carefully measured. These products include household cleaners, carpet cleaners, disinfectants, cosmetics, medicines, fabric softeners, glues, lacquers, and antiseptics. You may also breath formaldehyde if you use unvented gas or kerosene heaters indoors or if you or someone else smokes a cigar, cigarette, or pipe indoors. The amount of formaldehyde in mobile homes is usually higher than it is in conventional homes because of their lower air turnover.

People who work at or near chemical plants that make or use formaldehyde can be exposed to higher than normal amounts of formaldehyde. Doctors, nurses, dentists, veterinarians, pathologists, embalmers, workers in the clothing industry or in furniture factories, and teachers and students who handle preserved specimens in laboratories also might be exposed to higher amounts of formaldehyde. The National

Institute for Occupational Safety and Health (NIOSH) estimates that 1,329,332 individuals in the United States have had the potential for occupational exposure to formaldehyde.

1.4 HOW CAN FORMALDEHYDE ENTER AND LEAVE MY BODY?

Formaldehyde can enter your body after you breath it in, drink or eat it, or when it comes in contact with your skin. Formaldehyde is quickly absorbed from the nose and the upper part of your lungs. When formaldehyde is eaten and drunk, it is also very quickly absorbed. Very small amounts are probably absorbed from formaldehyde that comes in contact with your skin. Once absorbed, formaldehyde is very quickly broken down. Almost every tissue in the body has the ability to break down formaldehyde. It is usually converted to a non-toxic chemical called formate, which is excreted in the urine. Formaldehyde can also be converted to carbon dioxide and breathed out of the body. It can also be broken down so the body can use it to make larger molecules needed in your tissues, or it can attach to deoxyribonucleic acid (DNA) or to protein in your body. Formaldehyde is not stored in fat.

1.5 HOW CAN FORMALDEHYDE AFFECT MY HEALTH?

Formaldehyde is irritating to tissues when it comes into direct contact with them. Some people are more sensitive to the effects of formaldehyde than others. The most common symptoms include irritation of the eyes, nose, and throat, along with increased tearing, which occurs at air concentrations of about 0.4–3 parts per million (ppm). NIOSH states that formaldehyde is immediately dangerous to life and health at 20 ppm. One large study of people with asthma found that they may be more sensitive to the effects of inhaled formaldehyde than other people; however, many studies show that they are not more sensitive. Severe pain, vomiting, coma, and possible death can occur after drinking large amounts of formaldehyde. Skin can become irritated if it comes into contact with a strong solution of formaldehyde.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have

the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Several studies of laboratory rats exposed for life to high amounts of formaldehyde in air found that the rats developed nose cancer. Some studies of humans exposed to lower amounts of formaldehyde in workplace air found more cases of cancer of the nose and throat (nasopharyngeal cancer) than expected, but other studies have not found nasopharyngeal cancer in other groups of workers exposed to formaldehyde in air. The Department of Health and Human Services (DHHS) has determined that formaldehyde may reasonably be anticipated to be a human carcinogen (NTP). The International Agency for Research on Cancer (IARC) has determined that formaldehyde is probably carcinogenic to humans. This determination was based on specific judgements that there is limited evidence in humans and sufficient evidence in laboratory animals that formaldehyde can cause cancer. The Environmental Protection Agency (EPA) has determined that formaldehyde is a probable human carcinogen based on limited evidence in humans and sufficient evidence in laboratory animals. More information on the health effects of formaldehyde can be found in Chapter 2.

1.6 HOW CAN FORMALDEHYDE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Children and adults are likely to be exposed to formaldehyde in the same way. The most common way for children to be exposed to formaldehyde is by breathing it. Children may also be exposed by wearing some types of new clothes or cosmetics. A small number of studies have looked at the health effects of formaldehyde in children. It is very likely that breathing formaldehyde will result in nose and eye irritation (burning feeling, itchy, tearing, and sore throat). We do not know if the irritation would occur at lower concentrations in children than in adults. Studies in animals suggest that formaldehyde will not cause birth defects in humans. Inhaled formaldehyde or formaldehyde applied to the skin is not likely to be transferred from mother to child in breast milk or to reach the developing fetus.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO FORMALDEHYDE?

If your doctor finds that you have been exposed to significant amounts of formaldehyde, ask if children may also be exposed. When necessary your doctor may need to ask your state department of public health to investigate.

Formaldehyde is usually found in the air. Formaldehyde levels are also higher indoors than outdoors. Opening windows or using a fan to bring in fresh air is the easiest way to lower formaldehyde levels in the home and reduce the risk of exposure to your family.

Removing formaldehyde sources from the house will also reduce the risk of exposure. Since formaldehyde is found in tobacco smoke, not smoking or smoking outside will reduce exposure to formaldehyde. Unvented heaters, such as portable kerosene heaters, also produce formaldehyde. If you do not use these heaters in your home or shop, you help to prevent the build up of formaldehyde indoors.

Formaldehyde is found in small amounts in many consumer products including antiseptics, medicines, dish-washing liquids, fabric softeners, shoe-care agents, carpet cleaners, glues, adhesives, and lacquers. If you or a member of your family uses these products, providing fresh outdoor air when you use them, this will reduce your exposure to formaldehyde. Some cosmetics, such as nail hardeners, have very high levels of formaldehyde. If you do not use these products in a small room, or if you have plenty of ventilation when you use them, you will reduce your exposure to formaldehyde. If your children are not in the room when you use these products, you will also reduce their exposure to formaldehyde.

Formaldehyde is emitted from some wood products such as plywood and particle board, especially when they are new. The amount of formaldehyde released from them decreases slowly over a few months. If you put these materials in your house, or buy furniture or cabinets made from them, opening a window will lower formaldehyde in the house. The amount of formaldehyde emitted to the house will be less if the wood product is covered with plastic laminate or coated on all sides. If it is not, sealing the unfinished sides will help to lower the amount of formaldehyde that is given off.

Some permanent press fabrics emit formaldehyde. Washing these new clothes before use will usually lower the amount of formaldehyde and reduce your family's risk of exposure.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO FORMALDEHYDE?

We have no reliable test to determine how much formaldehyde you have been exposed to or whether you will experience any harmful health effects.

More information about medical tests for formaldehyde can be found in Chapter 2.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the NIOSH.

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for formaldehyde include the following:

Several international, national, and state authorities have established regulations or guidelines for the use and production of formaldehyde. OSHA has established the permissible exposure limit (PEL) 8-hour time-weighted average (TWA) at 0.75 ppm and the 15-minute Short-Term Exposure Limit (STEL) at 2 ppm. The EPA sets regulations for reporting quantities used and how much formaldehyde can legally be produced from automobile exhaust; the FDA also has regulations about the use of formaldehyde in the food you eat.

Non-enforceable guidelines have also been established for formaldehyde. The American Conference of Governmental and Industrial Hygienists (ACGIH) has established a ceiling limit for occupational exposure (Threshold Limit Value [TLV]) of 0.4 ppm. NIOSH has a recommended exposure limit for occupational exposure (8-hour TWA) of 0.016 ppm, and a 15-minute ceiling limit of 0.1 ppm.

More information about the federal and state regulations and guidelines for formaldehyde can be found in Chapter 7.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: (800) 447-1544
Fax: (404) 639-6359

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of formaldehyde. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure— inhalation, oral, and dermal; and then by health effect—death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods—acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of

exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of formaldehyde are indicated in Tables 2-1, 2-4, and 2-5 and Figures 2-1 and 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for formaldehyde. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990c), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Formaldehyde vapors used in controlled-exposure inhalation studies can be generated by heating commercial formalin, aqueous solutions containing 30–50% formaldehyde by weight plus methanol or other substances to inhibit intrinsic polymerization, or by heating solid paraformaldehyde, a formaldehyde polymer. Unless noted otherwise, inhalation studies used in the preparation of this profile provided clear evidence that formaldehyde was the only added gas in the experimental atmosphere.

2.2.1.1 Death

Reports of deaths in humans from short-term inhalation exposure to formaldehyde were not located. Increased rates of cancer-related mortality associated with occupational exposure to formaldehyde have been found in some epidemiological studies, but not in others. A more thorough discussion of available epidemiological studies is available in Section 2.2.1.8.

Repeated exposure to formaldehyde vapors at 40 ppm, 6 hours/day, 5 days/week for up to 13 weeks produced 80% mortality in B6C3F1 mice, whereas mice exposed with the same protocol to 20 ppm showed no mortalities within the exposure period (Maronpot et al. 1986). Deaths occurred predominately in the fifth and sixth week of exposure and were associated with ataxia, severe body weight depression, and inflammation and metaplasia in the nasal cavity, larynx, trachea, and lungs. Deaths were attributed to occlusive tracheal lesions and/or prominent seropurulent rhinitis (Maronpot et al. 1986).

In other intermediate duration inhalation bioassays, no exposure-related deaths or early mortalities were found in Wistar rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), in F344 rats, Cynomolgus monkeys, or Golden Syrian hamsters exposed to up to 2.95 ppm, 22 hours/day, 7 days/week for 26 weeks (Rusch et al. 1983), or in Wistar rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 4, 8, or 13 weeks and subsequently observed for 117 weeks without exposure (Feron et al. 1988). No exposure-related maternal or fetal deaths occurred in studies that exposed pregnant Sprague-Dawley rats to up to 10 ppm formaldehyde, 6 hours/day on gestation days

6 through 15 (Martin 1990) or up to 40 ppm, 6 hours/day on gestation days 6 through 20 (Saillenfait et al. 1989).

In chronic inhalation bioassays, increased mortality (compared with controls) was found in Sprague-Dawley rats exposed to 14.2 ppm formaldehyde, 6 hours/day, 5 days/week for up to 588 days (Albert et al. 1982), in F344 rats exposed to 5.6 or 14.3 ppm (but not 2 ppm), 6 hours/day, 5 days/week for up to 24 months (Kerns et al. 1983b; Swenberg et al. 1980), in F344 rats exposed to 15 ppm (but not to 0.7, 2, 6, or 10 ppm) 6 hours/day, 5 days/week for 24 months (Monticello et al. 1996), and in F344 rats exposed to 15 ppm (but not to 0.3 or 2 ppm), 6 hours/day, 5 days/week for up to 28 months (Kamata et al. 1997). In general, observations of increased mortality in the rat bioassays occurred after about one year of exposure and were associated with the development of nasal squamous cell carcinomas. Golden Syrian hamsters exposed to 10 ppm formaldehyde, 5 hours/day, 5 days/week for life showed a small, but statistically significant, increase in mortality compared with controls, but no increased incidence of nasal tumors and only a minimal (5% versus zero in controls) increased incidence of hyperplasia or metaplasia in the nasal epithelium (Dalbey 1982). No exposure-related increased mortality was found in B6C3F1 mice exposed to up to 14.3 ppm for 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b).

The LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE							
Systemic							
1	Human (anatomy students)	3 hr	Resp		1.88 (nose irritation; increase in FEV_1 & $FEFR_{25-75}$ during class period less than in controls)		Akbar-Khanzadeh and Mlynek 1997
			Ocular		1.88 (eye irritation)		
2	Human (anatomy students)	2-3 hr	Resp		1.24 (nose irritation; 1.2% decrease in FEV_3 during class period)		Akbar-Khanzadeh et al. 1994
			Ocular		1.24 (eye irritation)		
3	Human (normal)	4 hr	Resp		0.2 (3/16 nasal irritation)		Andersen and Molhave 1983
			Ocular		0.2 (3/16 eye irritation)		
4	Human (normal)	6 min	Ocular		0.35 (decreased eye irritation response time in 5/12)		Bender et al. 1983
5	Human (normal)	90 min	Resp		1 (4/9 nasal congestion)		Day et al. 1984
			Ocular		1 (8/9 eye irritation)		

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
6	Human (w/health complaints)	90 min	Resp		1 (3/9 nasal congestion)		Day et al. 1984
			Ocular		1 (7/9 eye irritation)		
7	Human (w/contact dermatitis)	2 hr	Resp		0.4 (3/13 nasal irritation & sneezing)		Gorski et al. 1992
			Ocular		0.4 (3/13 eye irritation)		
8	Human (normal)	2 hr	Resp		0.4 (1/5 nasal irritation)		Gorski et al. 1992
			Ocular	0.4			
9	Human (healthy & asthmatics)	1 hr	Resp		3 (nose/throat irritation; dec FEV_1 >10% in 5/38)		Green et al. 1987
			Ocular		3 (eye irritation)		
10	Human (particle-board workers)	8 hr	Resp		0.69 (small decrease in FEFR during workshift)		Horvath et al. 1988
11	Human (non-preexposed)	2 hr	Resp		0.4 (increased eosinophils & protein in nasal lavage fluid)		Krakowiak et al. 1998
12	Human (asthmatics)	2 hr	Resp		0.4 (increased eosinophils & protein in nasal lavage fluid)		Krakowiak et al. 1998

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
13	Human (normal)	3 hr	Resp	1	2	(7/19 with nose/throat irritation)		Kulle et al. 1987; Kulle 1993
			Ocular	0.5	1	(4/19 with eye irritation)		
14	Human (purported asthmatics)	30 min	Resp	1	2	(12/230 w/decreased PEFR > 15%)		Nordman et al. 1985
15	Human (w/contact dermatitis)	2 hr	Resp		0.4 [b]	(increased eosinophils and protein in nasal lavage fluid, increased itching, sneezing, and congestion)		Pazdrak et al. 1993
16	Human (healthy)	2 hr	Resp		0.4	(increased eosinophils & protein in nasal lavage fluid, increased itching, sneezing, and congestion)		Pazdrak et al. 1993
17	Human (healthy)	30 min	Resp		3	(small average decreases in FEV, FVC, & FEV_3)		Sauder et al. 1986
			Ocular		3	(increase in eye irritation)		
18	Human (normal)	35 min	Resp	0.5	1.2	(nasal irritation)		Weber-Tschopp et al. 1977
			Ocular	0.5	1.2	(eye irritation)		
19	Human (healthy)	40 min/d	Resp		2	(5/15 nasal irritation)		Witek et al. 1986; Witek et al. 1987
			Ocular		2	(8/15 eye irritation)		

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
20	Human (asthmatics)	40 min/d	Resp		2 (5/15 nasal irritation)		Witek et al. 1986; Witek *et al. 1987*
			Ocular		2 (8/15 eye irritation)		
21	Monkey (Rhesus)	5 d 6 hr/d	Resp			6 M (hyperplasia & squamous metaplasia in nasal epithelium, extending to trachea & carina)	Monticello et al. 1989
			Cardio	6 M			
			Gastro	6 M			
			Hepatic	6 M			
			Renal	6 M			
			Endocr	6 M			
			Ocular		6 M (mild lacrimation and conjunctival hyperemia)		
			Bd Wt	6 M			
22	Rat (Sprague-Dawley)	4 hr	Resp			10 M (ciliary destruction and cell separation in naso- and maxillo-turbinates, celluar swelling throughout turbinates, mucous releasing goblet cells in naso-turbinates)	Bhalla et al. 1991
23	Rat (Wistar)	3 d 2 x/day 8 hr	Resp			3.6 M (necrosis, hyperplasia and squamous metaplasia in nasal respiratory epithelium and rhinitis)	Cassee and Feron 1994

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
24	Rat (Fischer- 344)	10 min	Resp		31.7 (RD_{50})		Chang et al. 1981
25	Rat (Fischer- 344)	1 or 5 d 6 hr/d	Resp			15 M (increased nasal epithelial cell turnover; degeneration and sloughing of epithelial cells, necrobiotic cells with inclusions, hyperplasia, and focal neutrophil infiltration in nasal cavity, severe ulcerative rhinitis)	Chang et al. 1983
26	Rat (Sprague-Dawley)	4 d 6 hr/d	Resp		10 (clinical signs of nasal irritation)		Dinsdale et al. 1993
			Ocular		10 (clinical signs of eye irritation)		
27	Rat (Fischer- 344)	6 hr	Resp			128 (bloody nasal discharge and pulmonary edema)	Kamata et al. 1996b
28	Rat (Fischer- 344)	1, 2, or 4 d 6 hr/d	Resp			6 (hypertrophy in nasal passages)	Monteiro-Riviere and Popp 1986
29	Rat (Fischer- 344)	1, 4, or 9 d 6hr/d	Resp	2 M		6 M (nasal epithelial cell necrosis; neutrophil infiltration; epithelial hyperplasia; squamous metaplasia; increased cell proliferation)	Monticello et al. 1991

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
30	Rat (Fischer- 344)	once 10 min - 6 hr	Resp	2 M	15 M (decreased nasal mucous flow and ciliary activity)		Morgan et al. 1986a
31	Rat (Fischer- 344)	1, 2, 4, 9, or 14 d 5 d/wk 6 hr/d	Resp	0.5 M	2 M (minimal mucostasis)	6 M (severe mucostasis and nasal ulcerations)	Morgan et al. 1986c
			Ocular	0.5 M	2 M (eye irritation)		
32	Rat (Wistar)	3 d 8 hr/d	Resp			5 M (increases in nasal cell turnover rates; squamous metaplasia with cellular hyperplasia)	Wilmer et al. 1987
33	Rat (Wistar)	3 d 8 x 30 min/d	Resp			10 M (increased nasal epithelial cell turnover rates; squamous metaplasia with cellular hyperplasia)	Wilmer et al. 1987
34	Mouse (B6C3F1)	10 min	Resp		4.9 (RD_{50})		Chang et al. 1981
35	Mouse (B6C3F1)	1 or 5 d 6 hr/d	Resp			15 M (increased nasal respiratory epithelial cell turnover; mild to serious rhinitis and focal degeneration of the respiratory epithelium; congestion of the olfactory blood vessels, focal erosion and ulceration; hyperplasia)	Chang et al. 1983

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
36	Mouse (Swiss-Webster)	10 min	Resp		3.1 (RD_{50})		Kane & Alarie 1977
37	Gn Pig (Hartley)	2 hr	Resp	3.4 M	9.4 M (increased airway resistance)		Swiecichowski et al. 1993
38	Gn Pig (Hartley)	8 hr	Resp	0.1	0.3 M (increased airway resistance)		Swiecichowski et al. 1993
	Immunological/Lymphoreticular						
39	Human	3 hr		1.0			Pross et al. 1987
40	Human	3 hr		1.0			Pross et al. 1987 (UFFI)
41	Mouse (BALB/c)	10d 6 hr/d			1.6 (increased IgE response to inhaled ovalbumin)		Tarkowski and Gorski 1995
42	Gn Pig (Dunkin-Hartley)	5d 8 hr/d			0.25 (10/12 with allergic response to ovalbumin vs. 3/12 in controls)		Riedel et al. 1996
	Neurological						
43	Human	5.5 hr			0.12 (decreased performance on short term memory tests)		Bach et al. 1990

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
44	Rat (Sprague-Dawley)	1-2 d 3 hr/d			5 M (decreased motor activity; increased concentrations of 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenyl- acetic acid, & dopamine in the hypothalamus)		Boja et al. 1985
45	Rat (Fischer- 344)	once 10 min - 6 hr			15 M (restlessness)		Morgan et al. 1986a
	INTERMEDIATE EXPOSURE						
	Death						
46	Rat (Fischer- 344)	9 mo 5d/wk 6hr/d				15 M (significantly reduced survival after 9 months)	Kamata et al. 1997
47	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d				40 (80% mortality)	Maronpot et al. 1986

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
48	Monkey (Rhesus)	6 wk 5 d/wk 6 hr/d	Resp			6 M (in the nasal epithelium: loss of goblet cells & cilia; epithelial hyperplasia; squamous metaplasia; neutrophil inflammatory response; erosion of the metaplastic epithelium; increased cell proliferation in nasal transitional epithelium, nasal passage epithelium, trachea & carina. Larynx/trachea/carina: loss of cilia, goblet cells, mild epithelial hyperplasia, early squamous metaplasia.)	Monticello et al. 1989
			Cardio	6 M			
			Gastro	6 M			
			Musc/skel	6 M			
			Hepatic	6 M			
			Renal	6 M			
			Endocr	6 M			
			Ocular		6 M (mild lacrimation and conjunctival hyperemia)		
			Bd Wt	6 M			

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
49	Monkey (Cynomolgus)	26 wk 7 d/wk 22 hr/d	Resp	0.98[c]		2.95 M (hoarseness; nasal congestion and discharge; increased incidence of squamous metaplasia and hyperplasia in the nasoturbinates)	Rusch et al. 1983
			Bd Wt	2.95			
50	Rat (Wistar)	13 or 52 wk 5 d/wk 6 hr/d	Resp	1 M		10 M (rhinitis; hyperplasia and metaplasia of nasal epithelium)	Appelman et al. 1988
			Cardio	10 M			
			Gastro	10 M			
			Hemato	10 M			
			Hepatic	10 M			
			Renal	1 M	10 M (increased incidence of oliguria)		
			Endocr	10 M			
			Ocular	10 M			
			Bd Wt	1 M	10 M (10% decrease in body weight)		
51	Rat (Fischer- 344)	81 d 5 d/wk 6 hr/d	Resp	2 M	6 M (increased DNA-protein crosslinkage in lateral, medial & posterior meatuses of the nose)		Casanova et al. 1994

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
52	Rat (Fischer- 344)	6 wk 5 d/wk 6 hr/d	Resp	2 M		6 M (nasal epithelial cell necrosis; neutrophil infiltration; epithelial hyperplasia; squamous metaplasia; increased cell proliferation)	Monticello et al. 1991
53	Rat (Fischer- 344)	26 wk 7 d/wk 22 hr/d	Resp	0.98		2.95 (increased incidence of: nasal squamous metaplasia & hyperplasia; basal cell hyperplasia; rhinitis)	Rusch et al. 1983
			Bd Wt	0.98 M 2.95 F	2.95 M (average 13% decreased body weight)		
54	Rat (Sprague-Dawley)	gd 6-20 15 d 6 hr/d	Bd Wt	20 F		40 F (51% decrease in maternal weight gain)	Saillenfait et al. 1989
55	Rat (Wistar)	4 wk 5 d/wk 8 hr/d	Resp			5 M (nasal cavity squamous metaplasia with cellular hyperplasia; minimal to moderate rhinitis)	Wilmer et al. 1987
56	Rat (Wistar)	4 wk 5 d/wk 8 x 30 min/d	Resp			10 M (increased cell turnover rates; thinning & disarrangement of the nasal epithelium; squamous metaplasia with cellular hyperplasia; minimal to moderate rhinitis)	Wilmer et al. 1987

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
57	Rat (Wistar)	13 wk 5 d/wk 8 hr/d	Resp	2 M			Wilmer et al. 1989
58	Rat (Wistar)	13 wk 5 d/wk 8x 30 min/d	Resp	2 M		4 M (increased cell proliferating rates in nasal epithelium; squamous metaplasia with basal cell hyperplasia in nasal epithelium)	Wilmer et al. 1989
59	Rat (Wistar)	13 wk 5 d/wk 6 hr/d	Resp	1		10 (metaplasia, with keratinization of the epithelial lining the larynx; cell turnover, squamous metaplasia & hyperplasia in the nasal turbinates)	Woutersen et al. 1987
			Cardio	20			
			Gastro	20			
			Hemato	20			
			Hepatic	10 M 20 F	20 M (increased plasma AST, ALT, and ALP levels)		
			Renal	20			
			Endocr	20			
			Ocular	20			
			Bd Wt	10 M 20 F	20 (18.2% decrease in body weight)		
60	Rat (Wistar)	3 mo 5 d/wk 6 hr/d	Resp	1 M		10 M (increased nasal squamous metaplasia and rhinitis)	Woutersen et al. 1989

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
61	Rat (Wistar)	13 wk 5 d/wk 6 hr/d	Resp	1	3 (disarranged and hyperplastic nasal epithelial cells; increased cell proliferation)		Zwart et al. 1988
			Bd Wt	3			
62	Mouse (B6C3F1)	3 wk 5 d/wk 6 hr/d	Hemato		15 F (decrease in the absolute number of monocytes)		Dean et al. 1984
			Bd Wt	15 F			
63	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	2 M 4 F		4 M 10 F (squamous metaplasia; keratinization; suppurative inflammatory and serous exudate; & epithelial degeneration in nasal sections; dyspnea)	Maronpot et al. 1986
			Cardio	40			
			Gastro	40			
			Musc/skel	40			
			Hepatic	40			
			Renal	40			
			Endocr	40			
			Dermal	20	40 (loss of skin elasticity)		
			Ocular	40			
			Bd Wt	10 M 20 F	20 M (18% decrease in body weight)	40 M (50% decrease in body weight) 40 F (33% decrease in body weight)	

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
64	Hamster (Golden Syrian)	26 wk 7 d/wk 22 hr/d	Resp	2.95			Rusch et al. 1983
			Bd Wt	2.95			
	Immunological/Lymphoreticular						
65	Monkey (Rhesus)	6 wk 5 d/wk 6 hr/d		6			Monticello et al. 1989
66	Rat (Fischer- 344)	13 or 52 wk 5 d/wk 6 hr/d		10			Appelman et al. 1988
67	Rat (Wistar)	13 wk 5 d/wk 6 hr/d		20			Woutersen et al. 1987
68	Mouse (B6C3F1)	3 wk 5 d/wk 6 hr/d			15 F (increased ability of macrophages to release reactive oxygen intermediates)		Adams et al. 1987
69	Mouse (B6C3F1)	3 wk, 5 d/wk 6 hr/d		15 F			Dean et al. 1984
70	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		40			Maronpot et al. 1986
	Neurological						
71	Rat (Wistar)	13 or 52 wk 5 d/wk 6 hr/d		10 M			Appelman et al. 1988

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
72	Rat (Wistar)	13 wk 5 d/wk 6 hr/d		10	20 (temporary uncoordinated movement & wall-climbing)		Woutersen et al. 1987
73	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		10	20 (listlessness, hunched appearance)	40 (ataxia)	Maronpot et al. 1986
	Reproductive						
74	Human	1 to 11 mo to several years		0.97 M			Ward Jr. et al. 1984
75	Rat (Sprague-Dawley)	15 d gd 6-20 6 hr/d		40 F			Saillenfait et al. 1989
76	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		20 F 40 M	40 F (decreased prominence of endometrial glands & stroma; decrease in ovarian luteal tissue)		Maronpot et al. 1986
	Developmental						
77	Rat (Sprague-Dawley)	15 d gd 6-20 6 hr/d		10	20 M (5% decrease in fetal weight)	40 (21% decrease in fetal weight)	Saillenfait et al. 1989
	Cancer						
78	Rat (Wistar)	4 wk 5 d/wk 6 hr/d				20 M (CEL: nasal tumors; squamous cell carcinoma & polypoid adenoma)	Feron et al. 1988

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
79	Rat (Wistar)	13 wk 5 d/wk 6 hr/d				10 M (CEL: nasal tumors; squamous cell carcinoma, cystic squamous cell carcinoma, carcinoma in situ and meloblastoma)	Feron et al. 1988
	CHRONIC EXPOSURE						
	Death						
80	Rat (Sprague-Dawley)	588 d 5 d/wk 6 hr/d				14.2 M (38% mortality)	Albert et al. 1982
81	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				15 M (decreased survival rate)	Monticello et al. 1996
82	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				5.6 M (significantly reduced survival after 17 months) 14.3 M F (significantly reduced survival after 12 months)	Swenberg et al. 1980, Kerns et al. 1983b;
83	Hamster (Golden Syrian)	lifetime 5 d/wk 5 hr/d				10 M (significantly reduced survival times)	Dalbey 1982

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
84	Human (plywood factory workers)	6.8 yr (range: 2-19 yr)	Resp		0.39 (increased lesions [nonciliated cells, metaplasia, dysplasia] in nasal epithelium samples)		Ballarin et al. 1992
85	Human (particleboard workers)	10.5 yr (range: 1-39 yr)	Resp		0.49 M (increased lesions [nonciliated cells, metaplasia, mild dysplasia] in nasal epithelium cells)		Edling et al. 1988
			Ocular		0.49 M (running eyes - 75%)		
86	Human (chemical workers)	7.3 yr (range: 1-36 yr)	Resp		0.24 [d] (increased lesions [nonciliated cells, metaplasia, mild dysplasia] in nasal epithelium samples)		Holmstrom et al. 1989c
87	Human (furniture factory workers)	7.3 yr (range: 1-36 yr)	Resp	0.2			Holmstrom et al. 1989c
88	Human (embalmers)	8.2 yrs (average, range not reported)	Resp		0.36 (increased reporting of symptoms of respiratory irritation)		Holness and Nethercott 1989
			Dermal		0.36 (increase in past skin problems and contact dermatitis)		
			Ocular		0.36 (increase in eye irritation)		

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
89	Human (particleboard workers)	10.3 yr (range <1-20 yr)	Resp		0.69	(increased reporting of respiratory symptoms)			Horvath et al. 1988
			Ocular		0.69	(increased reporting of itchy eyes and burning/watery eyes)			
90	Rat (Fischer- 344)	28 mo 5d/wk 6hr/d	Resp	0.3	2	(significant increased incidence of squamous cell metaplasia in nasal respiratory epithelium)	15	(hyperplasia or squamous metaplasia of nasal epithelium observed in all rats)	Kamata et al. 1997
			Gastro	15					
			Hemato	15					
			Musc/skel	15					
			Hepatic	15					
			Renal	15					
			Endocr	15					
			Bd Wt	2	15	(>10% decrease in body weight after 4 months)			
91	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d	Resp	2 M			6 M	(nasal inflammatory cell infiltrate; nasal epithelial hyperplasia & squamous metaplasia)	Monticello et al. 1996

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
92	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d	Resp		2	(restricted areas of dysplasia & metaplasia in nasal epithelium rhinitis)	5.6	(dyspnea; rhinitis, epithelial dysplasia and squamous metaplasia of nasal epithelium; epithelial hyperplasia or dysplasia or squamous metaplasia of the tracheal mucosa)	Swenberg et al. 1980, Kerns et al. 1983b
			Cardio	14.3					
			Gastro	14.3					
			Hemato	14.3					
			Musc/skel	14.3					
			Hepatic	14.3					
			Renal	14.3					
			Endocr	14.3					
			Ocular	14.3					
			Bd Wt	5.6	14.3	(approximate 10% decrease in body weight)			
93	Rat (Wistar)	28 mo 5 d/wk 6 hr/d	Resp	1 M			10 M	(increased squamous metaplasia and basal cell/ pseudoepithelial hyperplasia of the nasal epithelium; thinning & disarrangement of olfactory epithelium, & rhinitis)	Woutersen et al. 1989
			Bd Wt	1 M	10 M	(approximate 10% decrease in body weight)			

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
94	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d	Resp	2.0		5.6	(inflammatory, dysplastic & squamous metaplastic alterations of the nasal epithelium; serous rhinitis)	Kerns et al. 1983b
			Cardio	14.3				
			Gastro	14.3				
			Hemato	14.3				
			Musc/skel	14.3				
			Hepatic	14.3				
			Renal	14.3				
			Endocr	14.3				
			Ocular	14.3				
			Bd Wt	14.3				
95	Hamster (Golden Syrian)	lifetime 5 d/wk 5 hr/d	Resp			10 M	(hyperplastic & metaplastic areas in the nasal epithelium)	Dalbey 1982
	Immunological/Lymphoreticular							
96	Rat (Sprague-Dawley)	22 mo 5 d/wk 6 hr/d		12.6 F				Holmstrom et al. 1989b
97	Rat (Fischer- 344)	28 mo 5 d/wk 6 hr/d		15				Kamata et al. 1997
98	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d		14.3				Swenberg et al. 1980; Kerns et al. 1983b

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
99	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d		14.3			Kerns et al. 1983b
	Neurological						
100	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d		14.3			Swenberg et al. 1980, Kerns et al. 1983b
101	Mouse (B6C3F1)	24 mo 5 d/wk 6 hr/d		14.3			Kerns et al. 1983b
	Cancer						
102	Rat (Sprague-Dawley)	588 d 5 d/wk 6 hr/d				14.2 M (CEL: squamous cell carcinomas 10/100 rats)	Albert et al. 1982
103	Rat (Fischer- 344)	28 mo 5 d/wk 6 hr/d				15 (CEL: nasal squamous cell carcinoma in 13/32 rats)	Kamata et al. 1997
104	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				10 M (CEL: nasal tumors - 20/90 rats)	Monticello et al. 1996
105	Rat (Sprague-Dawley)	lifetime 5 d/wk 6 hr/d				14.8 M (CEL: nasal cavity tumors; 38/100 squamous cell carcinomas, 1/100 fibrocarcinoma, & 1/100 mixed carcinoma)	Sellakumar et al. 1985

Table 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
106	Rat (Fischer- 344)	24 mo 5 d/wk 6 hr/d				14.3	(CEL: squamous cell carcinomas of nasal cavity - 106/235 rats)	Swenberg et al. 1980, Kerns et al. 1983b

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an acute duration inhalation minimal risk level (MRL) of 0.04 ppm; concentration, 0.4 ppm, was divided by an uncertainty factor of 9 (3 for the use of a minimal LOAEL and 3 to account for variability among a group of potentially sensitive individuals).

[c]Used to derive an intermediate duration inhalation MRL of 0.03 ppm; concentration, 0.98 ppm, was divided by an uncertainty factor of 30 (3 for extrapolation from monkeys to humans and 10 to account for human variability).

[d]Used to derive chronic duration inhalation MRL of 0.008 ppm; concentration , 0.24 ppm, was divided by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 to account for human variability).

ALAT = alanine amino transferase; ALP = alkaline phosphatase; AST = aspartate amino transferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; FEFR = forced expiratory flow rate; FEFV = forced expiratory flow volume; FVC = forced vital capacity; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; GGT = gamma-glutamyl transpeptidase; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); mo = months; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; OR = odds ratio; Resp = respiratory; wk = week(s); x = times; yr = year(s)

Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation

Acute (≤14 days)

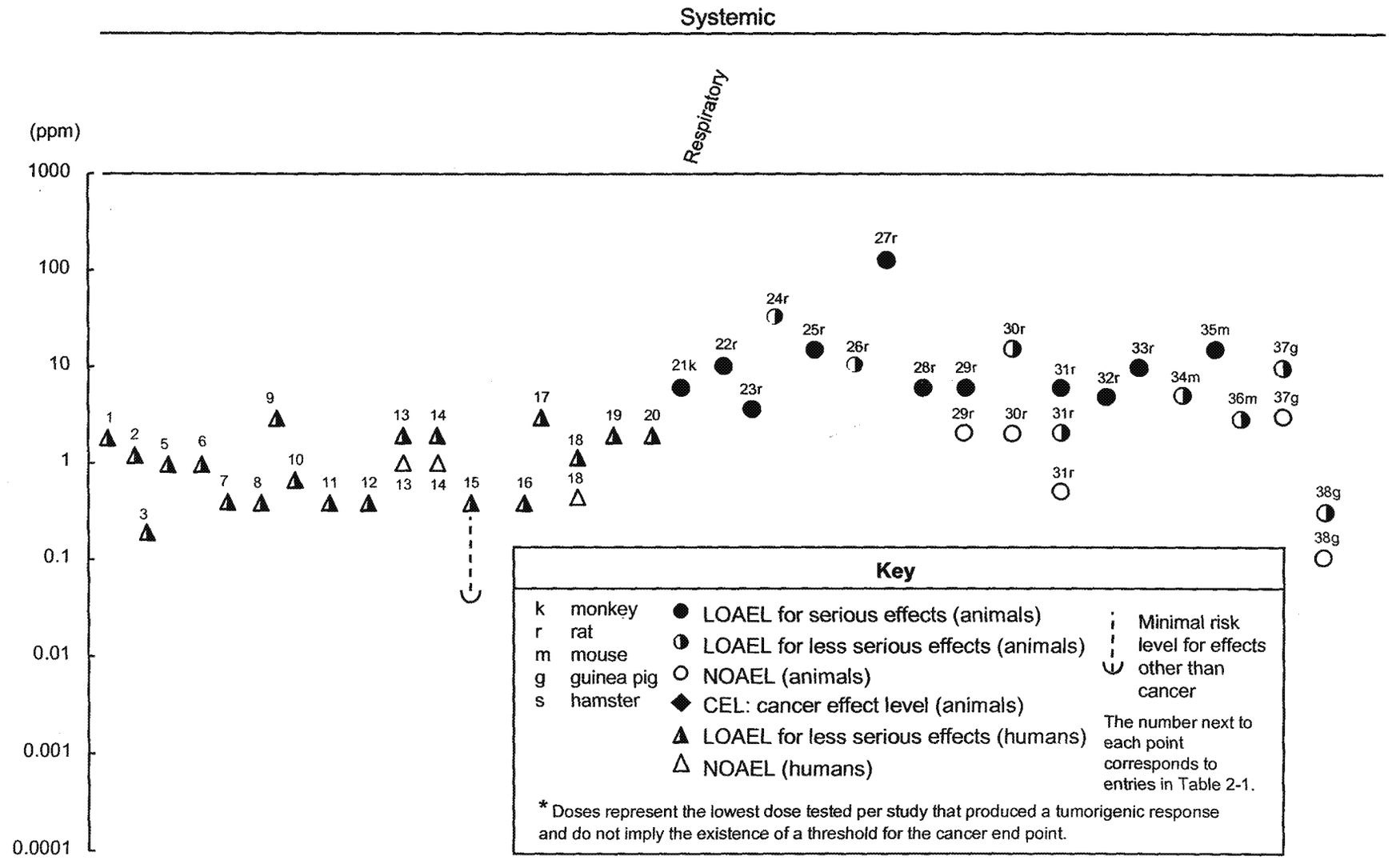
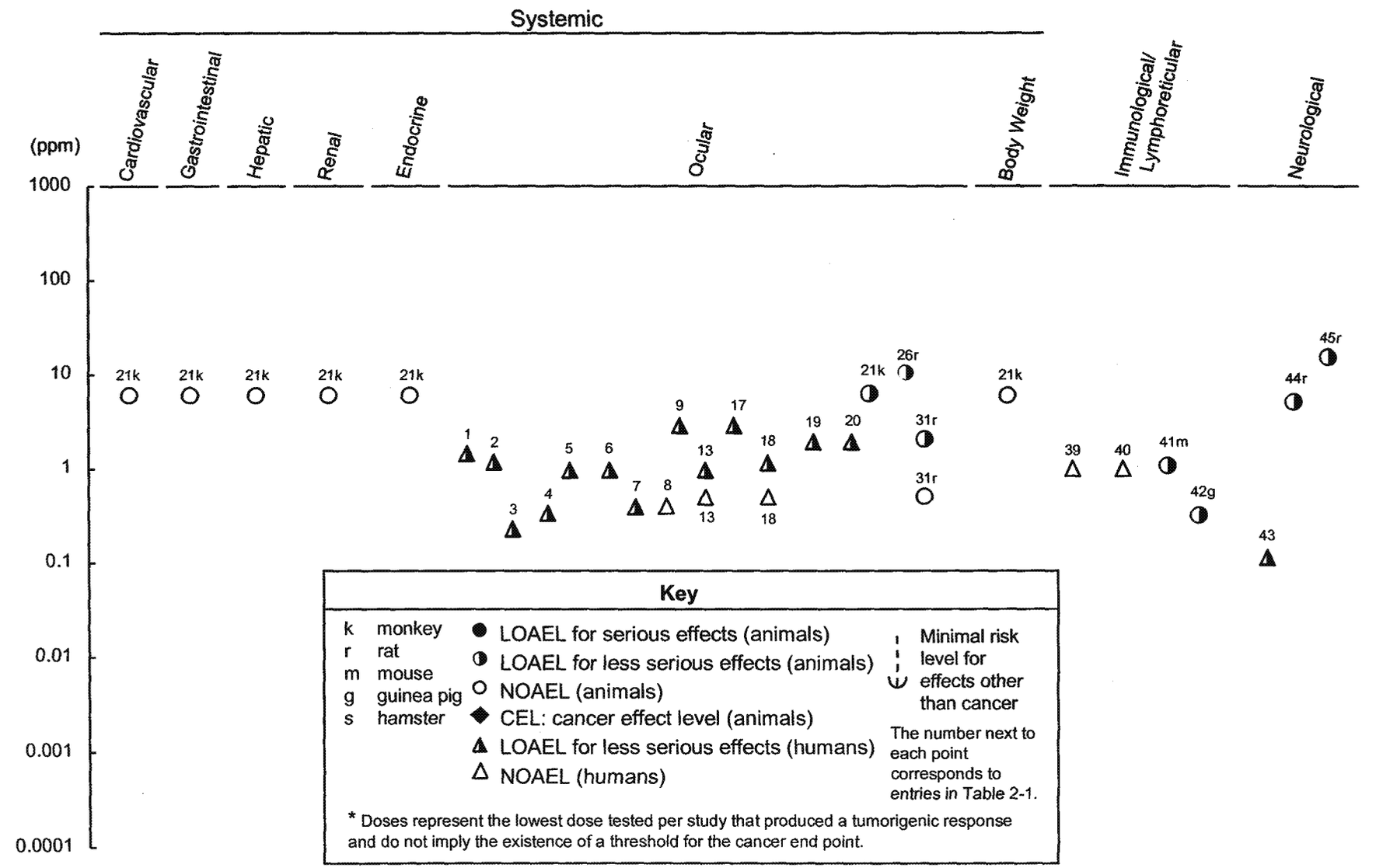


Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

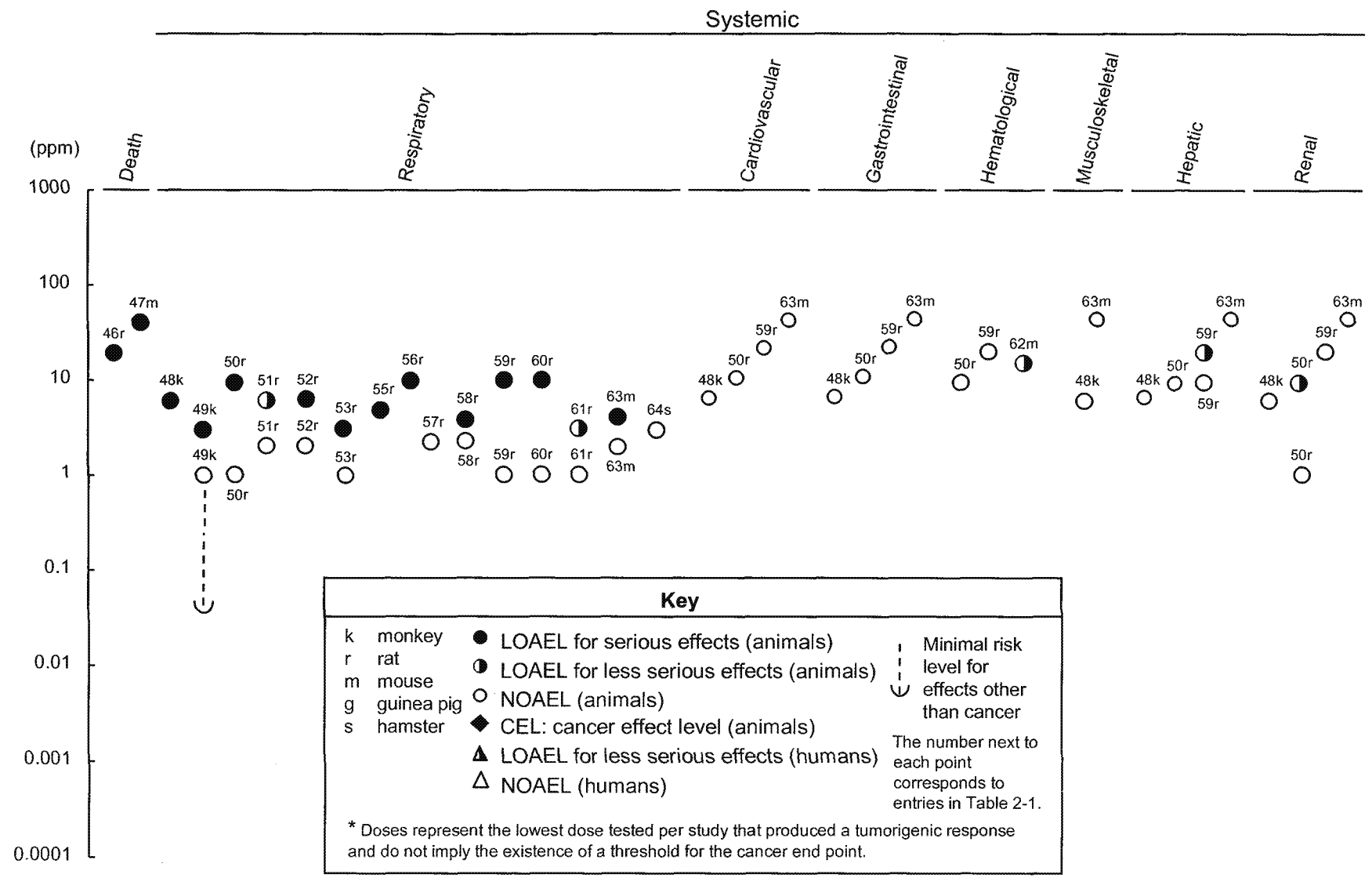
Acute (≤14 days)



ED_013348_00000124-00055

Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

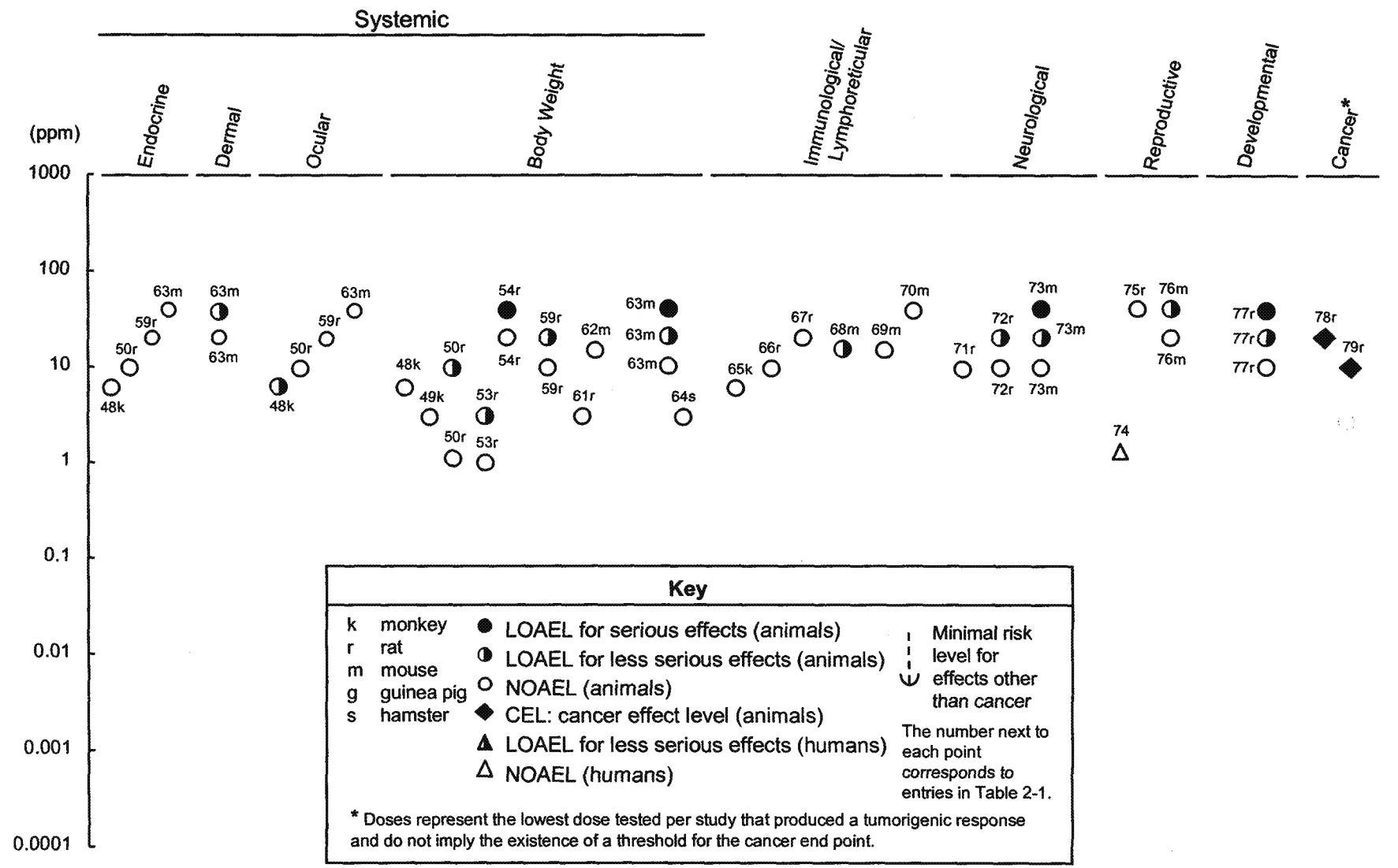
Intermediate (15-364 days)



ED_013348_00000124-00056

Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Intermediate (15-364 days)



ED_013348_00000124-00057

Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Chronic (≥365 days)

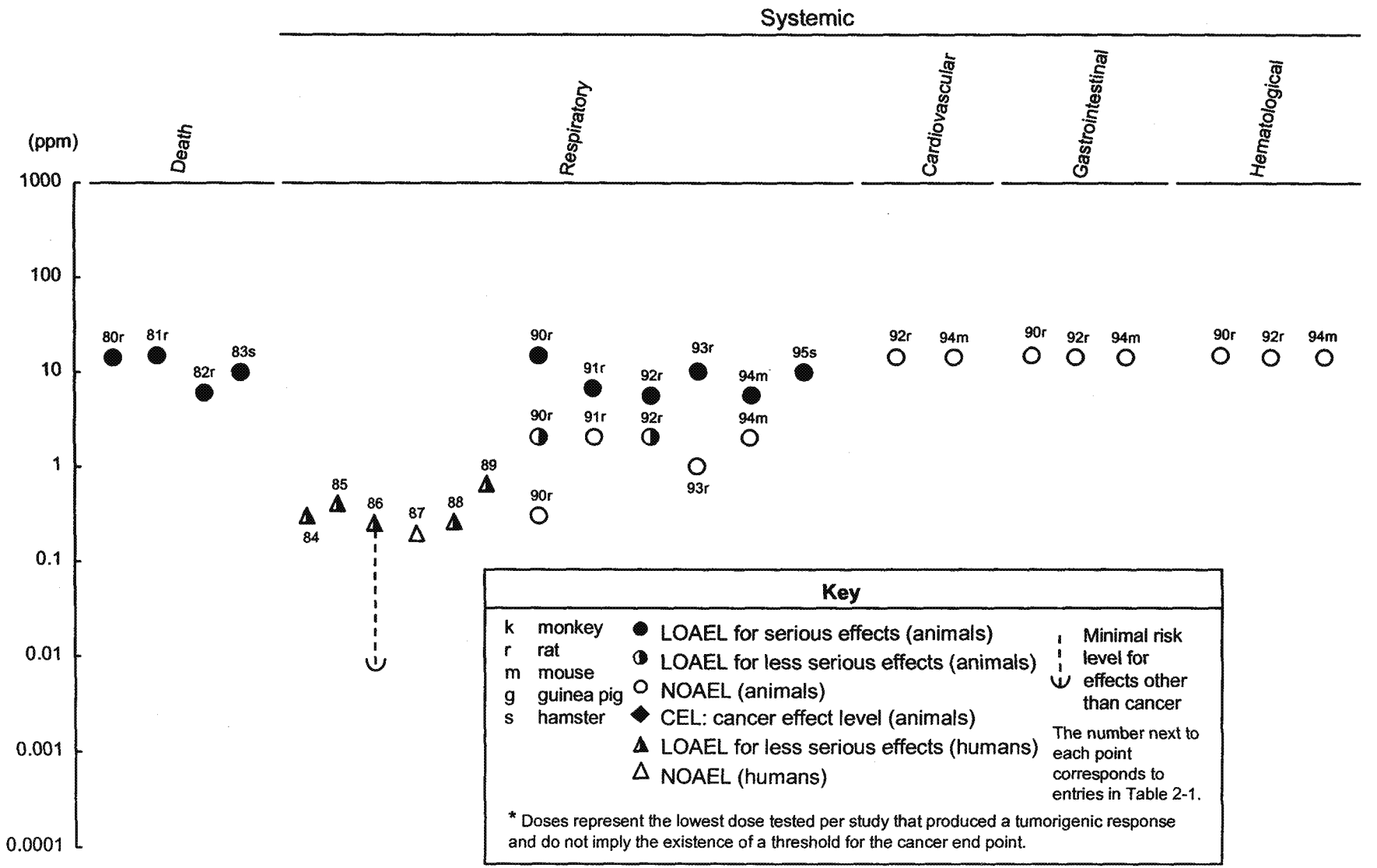
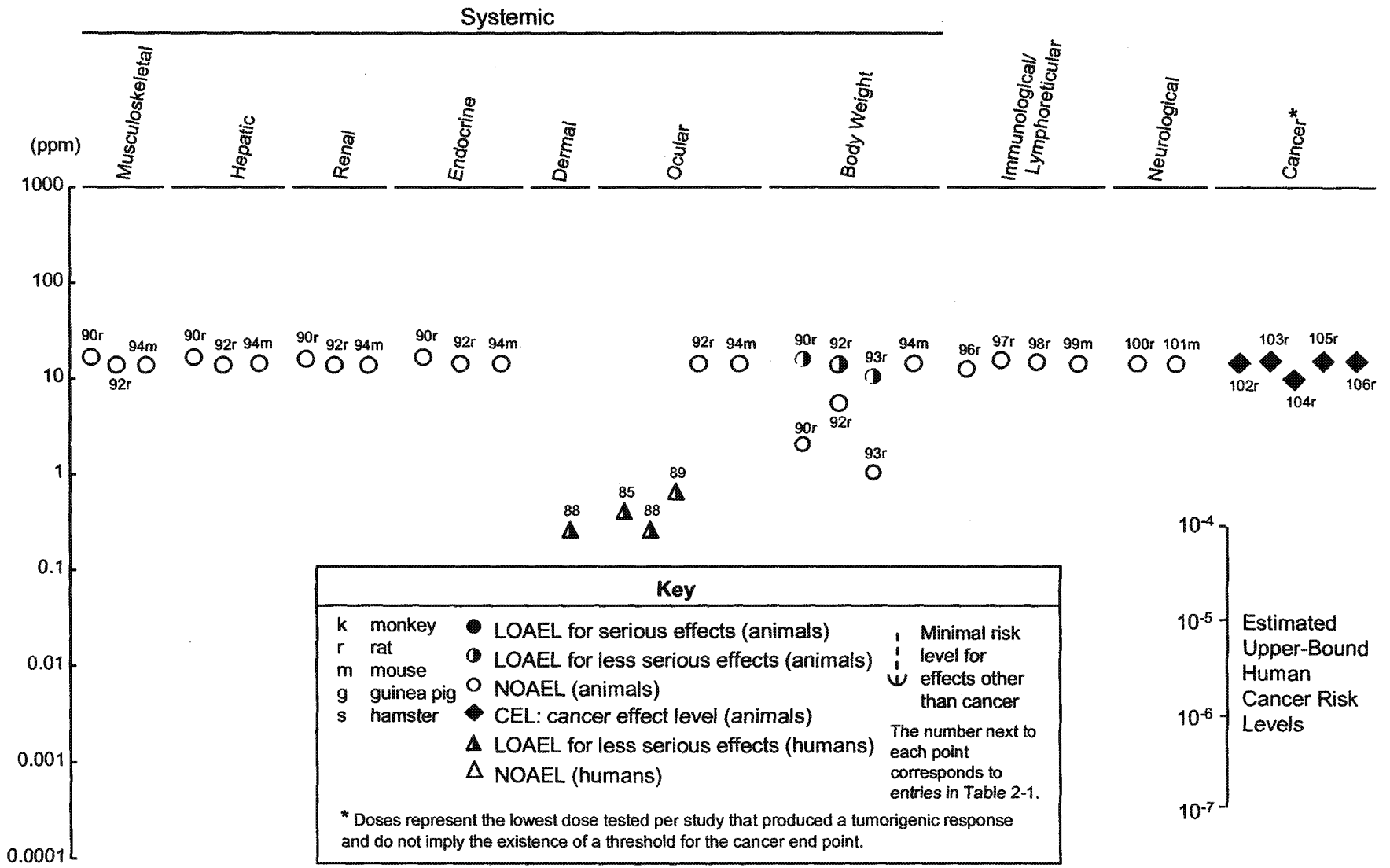


Figure 2-1. Levels of Significant Exposure to Formaldehyde - Inhalation (cont.)

Chronic (≥365 days)



Results from human and animal studies indicate that the critical target organs to airborne formaldehyde are the nose and the eyes, with the lungs being a secondary target at high exposure levels. Due to rapid, detoxifying metabolism of formaldehyde by most, if not all, cells, tissues, and organs distant from portals of entry are spared toxic effects from formaldehyde at concentrations normally expected to be encountered in the ambient or workplace atmosphere.

Respiratory Effects.

The respiratory tract, especially the upper respiratory tract, is a critical target of the toxicity of airborne formaldehyde as shown by acute controlled exposure human studies, by studies of humans exposed acutely or repeatedly under occupational or residential conditions, and by studies of animals (including primates) exposed by inhalation for acute, intermediate, and chronic durations.

Acute Controlled Exposure Human Studies. More than 15 published studies of respiratory function and/or irritation of the nose, eyes, and throat are available involving acute controlled exposure of volunteers, generally at formaldehyde concentrations 3 ppm. Recent reviews of these studies include those by ACGIH (1992), Krivanek and Imbus (1992), and Paustenbach et al. (1997).

Controlled exposure human studies have found that short-term inhalation exposures to concentrations ranging from 0.4 to 3 ppm can produce symptoms of mild to moderate irritation of the eyes, nose, and throat. The odor threshold for formaldehyde in humans has been reported to be 1 ppm (Leonardos et al. 1969), but others have noted that it may range as low as 0.05 ppm (ACGIH 1992). Descriptions follow of findings for irritation of the eyes, nose, and throat from a sampling of available controlled exposure studies of acute irritation, emphasizing studies that examined symptoms of irritation at the lower end of this concentration range (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Weber-Tschopp et al. 1977). Several of these studies reported that the initial severity of irritation lessened to some degree with continued exposure (Bender et al. 1983; Day et al. 1984; Green et al. 1987; Weber-Tschopp et al. 1977).

Weber-Tschopp et al. (1977) exposed a group of 33 healthy subjects for 35 minutes to concentrations of formaldehyde that increased during the period from 0.03 to 3.2 ppm; another group of 48 healthy subjects was exposed to 0.03, 1.2, 2.1, 2.8, and 4.0 ppm for 1.5 minute intervals. Eye and nose irritation were reported on a 1–4 scale (1=none to 4=strong) in both experiments, and eye blinking rate was measured in

the second experiment. Average indices of eye and nose irritation were increased in both experiments to a small, but statistically significant, extent at 1.2 ppm compared with indices for nonexposed controlled conditions. The published report of this study graphically showed average severity scores of about 1.3–1.4 for both indices at 1.2 ppm compared with 1.0–1.1 for nonexposed conditions. The average severity score was increased to a greater degree at higher concentrations, but was less than about 2.5 at the highest exposure concentration, 4 ppm. Average rates of eye blinking were not significantly affected at 1.2 ppm, but were statistically significantly increased at 2.1 ppm (about 35 blinks/minute at 2.1 ppm versus about 22 blinks/minutes under nonexposed conditions).

Andersen and Molhave (1983) exposed a group of 16 healthy subjects to 0.3, 0.5, 1.0, and 2.0 mg/m^3 (0.2, 0.4, 0.8, and 1.6 ppm) for 4-hour periods preceded by a nonexposed period of two hours. Subjects were asked to assess "discomfort" on a 0–100 scale ranging from 0=no discomfort to 100=intolerable discomfort (scores between 1 and 33 were rated as "slight discomfort"). Average peak discomfort scores for the group generally increased with exposure concentration, but the average discomfort score for the highest exposure concentration (1.6 ppm) never exceeded 18. Numbers of subjects who reported "No discomfort" ratings at the end of exposure periods were 7, 13, 10, and 6, respectively for 0.2, 0.4, 0.8, and 1.6 ppm; respective numbers of subjects reporting "conjunctival irritation and dryness in the nose and throat" were 3, 5, 15, and 15 of the 16 subjects exposed to each respective concentration. A statistical analysis of these data was not reported.

Bender et al. (1983) exposed groups of 5–28 healthy subjects to 0, 0.35, 0.56, 0.7, 0.9, or 1.0 ppm for 6-minute periods and asked them to note when they experienced eye irritation and to rate eye irritation on a 0–3 scale (0=none to 3=severe, with 1=slight). The subjects were selected from a larger group of subjects in a preliminary screening test as those who "responded to 1.3 and 2.2 ppm". Upper respiratory tract irritation was not rated in this study. Average initial severity scores for the five exposure concentrations in increasing order were 0.71, 0.79, 0.86, 0.80, and 1.56; no irritation was noted with "clean air" exposure. The median times to noting eye irritation (response time measured in seconds) generally decreased with increasing concentration as follows: 360 (clean air), 268, 217, 72, 119, and 78 seconds. Numbers of subjects who reported response times that were less than their clean air response time were: 5/12 at 0.35 ppm, 14/26 at 0.56 ppm, 4/7 at 0.7 ppm, 3/5 at 0.9 ppm, and 20/27 at 1.0 ppm. The elevation in percentage of subjects with shortened response time was only statistically significant at the 1 ppm level.

Kulle et al. (1987; Kulle 1993) exposed 19 healthy subjects to 0, 1.0, and 2.0 ppm for 3-hour periods and asked them to note symptoms of eye and nose/throat irritation and to rate severity on a 0–3 scale: 0=none; 1=mild (present but not annoying); 2=moderate (annoying); and 3=severe (debilitating). Ten of the subjects were also exposed to 0.5 ppm and nine were exposed to 3 ppm for 3-hour periods. The frequencies of subjects reporting eye irritation or nose/throat irritation increased with increasing exposure concentration, especially at concentrations 1 ppm. Under nonexposed conditions, 3/19 subjects noted mild nose/throat irritation and 1/19 noted mild eye irritation. At 0.5 ppm, 1/10 subjects noted mild nose/throat irritation, but none reported eye irritation. Frequencies for subjects with mild or moderate eye irritation were 4/19 at 1 ppm (1 was moderate), 10/19 at 2 ppm (4 were moderate), and 9/9 at 3 ppm (4 were moderate). The increased frequency for eye irritation (compared with controls) was statistically significant at 2 ppm. Frequencies for mild nose/throat irritation were 1/19 at 1 ppm, 7/19 at 2 ppm, and 2/9 at 3 ppm. Compared with control frequency for nose/throat irritation, only the response at 2 ppm was significantly elevated.

In a study of volunteers exposed to 1 ppm for 90 minutes, seven subjects reported eye irritation and three reported nasal congestion among nine subjects who had previously complained of health effects from exposure to urea-formaldehyde insulation in their homes (Day et al. 1984). A similar response to 1 ppm formaldehyde was noted among the other nine subjects in this study who had no previous complaints: eight reported eye irritation and four reported nasal congestion from the 90-minute exposure.

In groups of 15 healthy subjects and 15 asthmatics exposed to 2 ppm for 40 minutes while exercising, "mild" eye irritation (average severity scores of 1.1 and 1.6 on a 5-point scale ranging from 0=none to 4=incapacitating, with 1=mild) was reported by eight healthy and five asthmatic subjects (Schachter et al. 1986; Witek et al. 1986, 1987). Nasal irritation was reported by 5/15 healthy and 5/15 asthmatics subjects with average severity scores of 1.2 and 1.8, respectively.

Gorski and colleagues have reported that symptoms of upper respiratory tract irritation occurred in three studies comparing respiratory responses to 2-hour exposures to placebo or 0.5 mg formaldehyde/m^3 (0.4 ppm) in healthy, nonexposed subjects, in subjects with formaldehyde-sensitive contact dermatitis (Gorski et al. 1992; Pazdrak et al. 1993), and in formaldehyde-exposed workers with bronchial asthma (Krakowiak et al. 1998). Krakowiak et al. (1998) noted that, for these studies, formaldehyde vapors were generated by evaporating 10 μL of a 10% aqueous solution of formaldehyde in a 12-m, temperature- and humidity-controlled, exposure chamber. Measured airborne concentrations of formaldehyde ranged from

0.2 to 0.7 mg/m^3 with a mean of 0.5 mg/m^3 (0.4 ppm). Gorski et al. (1992) reported that, after exposure to 0.4 ppm, 1/5 healthy subjects and 3/13 subjects with formaldehyde-sensitive contact dermatitis experienced nose irritation, sneezing, or eye irritation. Similar exposure produced statistically significant increases in the average number and proportion of eosinophils and the concentration of albumin and total protein in nasal lavage fluid, both in groups of 9 sensitized subjects and in groups of 11 nonexposed subjects; the responses in the two groups were not significantly different (Pazdrak et al. 1993). Pazdrak et al. (1993) reported that exposure "caused itching, sneezing, and congestion", but did not indicate the number of subjects reporting these symptoms. In another experiment, exposure to 0.4 ppm also produced similar statistically significant increases in eosinophils and protein in nasal lavage fluid in other groups of 10 nonexposed subjects and 10 formaldehyde-exposed workers with bronchial asthma, and "caused sneezing, itching and congestion in all subjects" (Krakowiak et al. 1998). Pulmonary functions were also measured in each of these studies, but no exposure-related effects were found in any of the groups (see below). An acute inhalation MRL of 0.04 ppm was calculated as described in the footnote in Table 2-1 and in Appendix A based on the LOAEL (0.4 ppm) from the study by Pazdrak et al. (1993).

Formaldehyde-induced effects on human pulmonary function variables including forced vital capacity (FVC), forced expiratory volume in 1.0 seconds ($FEV_{1.0}$), peak expiratory flow rate (PEFR), and forced expiratory flowrate between 25 and 75% FVC ($FEFR_{25-75}$), have not been found as consistently as symptoms of eye and nose irritation at acute exposure levels in the range of 0.4–3 ppm. In controlled exposure studies, no statistically significant exposure-related effects on lung function measurements were found in 10 healthy subjects exposed to up to 2 ppm for 3 hours (Kulle et al. 1987; Kulle 1993), 15 healthy subjects exposed to 0 or 2 ppm for 40 minutes with or without exercise (Schachter et al. 1986; Witek et al. 1986), 15 formaldehyde-exposed laboratory workers exposed to 0 or 2 ppm for 40 minutes with or without exercise (Schachter et al. 1987), 15 asthmatic volunteers exposed to 0 or 2 ppm for 40 minutes with or without exercise (Witek et al. 1986, 1987), 18 subjects, 9 of whom had complaints of health effects from exposure to urea-formaldehyde foam insulation in their homes, exposed to 1 ppm for 90 minutes (Day et al. 1984), 16 healthy student volunteers exposed to up to 1.7 ppm for 4 hours (Andersen and Molhave 1983), 13 subjects with allergic dermal sensitivity to formaldehyde and 5 healthy subjects exposed to 0.4 ppm for 2 hours (Gorski et al. 1992), 10 formaldehyde-exposed textile or shoe manufacturing workers with purported bronchial asthma and 10 nonexposed healthy subjects exposed to 0.4 ppm for 2 hours (Krakowiak et al. 1998), 13 formaldehyde-exposed subjects, who previously reported symptoms of chest tightness, coughing, or wheezing, exposed to placebo or up to 3 ppm for 20 minutes (Reed and Frigas 1984), or 15 patients with documented severe bronchial

hyperresponsiveness (to histamine) exposed to room air and up to 0.7 ppm for 90 minutes (Harving et al. 1986, 1990).

A few controlled exposure studies have found only subtle or infrequent effects of acute exposure to low concentrations of formaldehyde on pulmonary function variables (Green et al. 1987; Nordman et al. 1985; Sauder et al. 1986). Nordman et al. (1985) measured PEFR, FVC, and FEV_1 during and after a 30-minute "challenge" exposure to placebo, 1 or 2 ppm in a group of 230 patients who had been occupationally exposed to formaldehyde and had reported respiratory symptoms consistent with asthma during a 6-year period. Patients were first challenged with 1 ppm; if no response was found, a second challenge of 2 ppm was given. Exposure-related drops in PEFR of 15% or greater in response to 2 ppm formaldehyde were found in 12/230 of the patients; one of these 12 subjects showed a response to 1 ppm. Formaldehyde concentrations were not measured during each test, but periodic checks of exposure concentrations indicated that challenge concentrations ranged from 0.8 to 0.9 ppm for the 1 ppm target and 1.7–2.0 ppm for the 2 ppm target. Nordman et al. (1985) concluded that pulmonary function sensitivity to formaldehyde, at concentrations of 1 to 2 ppm, is rare. Sauder et al. (1986) measured small, but statistically significant, decreases in FEV_1 (2% decrease) and $FEFR_{25-75}$ (7% decrease) after 30 minutes of exposure to 3 ppm, but not after 1 or 3 hours of exposure, in a group of nine healthy subjects who performed intermittent exercise during exposure and who served as their own controls. Green et al. (1987) measured statistically significant, but small, average deficits (2–3%) in FEV_1, FVC, and FEV_3 (but no change in $FEFR_{25-75}$) in a group of 22 exercising healthy subjects during and after 1 hour of exposure to 3 ppm, but found no significant deficits in a group of 16 asthmatic subjects similarly exposed. Among the 38 subjects in this study, five (13%; 2 normal and 3 asthmatic) displayed exposure-related percentage deficits in FEV_1 greater than 10%, but generally less than 15%.

Acute Occupational Exposure Human Studies. Numerous assessments of pulmonary function variables in formaldehyde-exposed workers during workday shifts have found, similar to findings from controlled exposure studies, either no effects or only small and subtle effects from formaldehyde exposure during a work period. Bracken et al. (1985) measured no significant changes in pulmonary function variables (FVC, FEV_1, and $FEFR_{25-75}$) during a workshift in which 10 laboratory technicians were exposed to estimated average formaldehyde concentrations ranging from 0.106±0.02 to 0.269±0.05 ppm. No significant differences in changes in pulmonary function variables across a workshift were found in groups of 22 embalmers exposed to an estimated mean concentration of 0.36±0.61 ppm (range 0.08–0.81 ppm) during a 2- to 3-hour embalming procedure compared with a nonexposed group of

13 subjects (Holness and Nethercott 1989) or in groups of 55 plywood workers exposed to estimated concentrations ranging from 0.22 to 3.48 ppm compared with a nonexposed group of 50 subjects (Malaka and Kodama 1990). Kilburn et al. (1985a) reported that decreases in FVC, FEV_1, and $FEFR_{25-75}$ occurred during a workshift in a group of fiberglass batt workers and not in a group of nonexposed hospital workers, but workplace air concentrations of formaldehyde were not assessed for the batt workers. Alexandersson and Hedenstierna (1989) reported that small, but statistically significant, declines in FEV_1/FVC and $FEFR_{25-75}$ occurred during a workshift in a group of 11 nonsmoking woodworkers, but not in 10 smokers, who were exposed to an estimated mean TWA formaldehyde concentration of 0.4±0.1 ppm. Alexandersson and Hedenstierna (1989) did not compare workshift changes in the exposed group to changes in a control group. Horvath et al. (1988) measured small, but statistically significant, average declines in $FEFR_{50}$, $FEFR_{75}$, and $FEFR_{25-75}$ during a workshift in a group of 109 particle board workers exposed to estimated TWA formaldehyde concentrations ranging from 0.17 to 2.93 ppm (mean 0.69 ppm), but no significant workshift change in these variables in a group of 254 nonexposed, food-processing workers. Median concentrations of airborne nuisance particulates (i.e., wood dust) in the particle board plant were 0.38 and 0.11 mg/m^3 for total and respirable particulates, respectively. Akbar-Khanzadeh et al. (1994) found no statistically significant differences in workshift changes in pulmonary function variables (FVC, FEV_1, FEV_3, and $FEFR_{25-75}$) in a group of 34 students exposed for 2- to 3-hour periods to an estimated TWA concentration of 1.24±0.61 ppm (range 0.07–2.94 ppm) in a gross anatomy laboratory compared with a nonexposed group of 12 subjects, except that the exposed group showed an average 1.2% decline in FEV_3 during exposure compared with a 1.3% increase in FEV_3 for the controls during a comparable period. In another group of 50 students exposed to formaldehyde-containing embalming fluid in a 3-hour gross anatomy laboratory and a control group of 36 nonexposed students in a 3-hour physiotherapy laboratory, pulmonary function variables increased during the 3-hour periods, but the average increases in FEV_1 and $FEFR_{25-75}$ for the exposed group (2.7% and 2.2%, respectively) were statistically significantly less than the average increases (5.2% and 9.3%, respectively) for the control group (Akbar-Khanzadeh and Mlynek 1997). Estimates of breathing zone formaldehyde concentrations in the anatomy laboratory ranged from 0.3 to 4.45 ppm with a mean of 1.88±0.96 ppm. In both studies by Akbar-Khanzadeh and colleagues, eye and nose irritation were reported by more than 70% of exposed subjects.

Repeated-Exposure Human Studies. Studies of formaldehyde-exposed humans with repeated exposure under occupational or residential conditions provide confirmatory evidence that formaldehyde can be irritating to the upper respiratory tract (Boysen et al. 1990; Edling et al. 1988; Garry et al. 1980;

Holmstrom et al. 1989c; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987), but only limited evidence that pulmonary functions may be adversely affected by repeated exposure to formaldehyde (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Krzyzanowski et al. 1990; Malaka and Kodama 1990).

Garry et al. (1980) surveyed 275 possible cases of formaldehyde exposure for which health complaints were registered during a 5-month period (February through June) in 1979 with the Minnesota Department of Health and measured formaldehyde air levels in living rooms and bedrooms of the subjects' residences. Formaldehyde concentrations ranged from approximately 0.1 to 3 ppm; approximate mean values for the 5 months were 0.65, 0.4, 0.2, 0.6, and 1.0 ppm. Eye, nose, and throat irritation was reported in about 75% of adults (age 18 years, n=102), 60% of children (age 3–12 years, n=30), and 60% of infants (n=36). Cough and wheeze reporting percentages were about 35% in adults, 70% in children, and 60% in infants. This study provided no information on the duration of exposure.

Ritchie and Lehnen (1987) surveyed approximately 2,000 people living in conventional and mobile homes and measured formaldehyde concentrations in air samples taken from two rooms in each residence. Subjects were selected from requests made to the Minnesota Department of Health for formaldehyde testing. Reporting percentages of subjects with eye irritation, nose/throat irritation, headaches, and skin rash were recorded for homes with formaldehyde concentrations classified as "low" (<0.1 ppm), "medium" (0.1 ppm– <0.3 ppm), or "high" (>0.3 ppm). In both conventional and mobile homes with air concentrations >0.3 ppm, more than 60% of subjects reported eye irritation, nose/throat irritation, or headache; with air concentrations between 0.1 and 0.3 ppm, respective reporting percentages ranged approximately from 10 to 20%, 15 to 20%, and 20 to 25%, depending on home type. Reporting percentages for homes with concentrations <0.1 ppm were less than 10% for each of these three symptoms. A major limitation associated with this study is that the participants, in order to be eligible for the study, complained about symptoms and were therefore a self-selected group with a potential bias.

Holness and Nethercott (1989) surveyed 84 funeral directors and apprentices exposed to an estimated mean concentration of 0.36±0.19 ppm (range 0.08–0.81 ppm) for an average of 8.2 years and 38 nonexposed control subjects. Embalmers reported that symptoms of irritation of the eyes, upper respiratory tract, and skin occurred during work more frequently than controls: chronic bronchitis

(20 versus 3%), shortness of breath (20 versus 3%), and nasal irritation (44 versus 16%) were among the most common respiratory complaints.

Horvath et al. (1988) surveyed 109 workers in a particle board and molded plastics plant for symptoms of respiratory tract irritation. The duration of exposure among exposed workers ranged from <1 year to 20 years, with a mean and median of 10.3 and 10 years, respectively. Estimates of formaldehyde air concentrations ranged from 0.17 to 2.93 ppm with a mean of 0.69 ppm. Nuisance particles (predominantly softwood dust) were also detected in the particle board area. The percentages of particle board workers reporting a number of symptoms of respiratory irritation over a workshift were statistically significantly greater than workshift reporting percentages for a nonexposed group of 264 food-processing workers: cough (34.9 versus 18.9%), chest pains (9.2 versus 2%), phlegm production (26.6 versus 9.8%), burning nose (28.4 versus 2%), stuffy nose (33.9 versus 14.2%), burning or watering eyes (39.5 versus 9.1%), itchy nose (21.1 versus 7.9%), and sore/burning throat (22 versus 3.9%).

Several studies have histologically examined nasal biopsy specimens in formaldehyde-exposed workers and observed epithelial lesions that are consistent with the irritant and reactive properties of formaldehyde (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c).

Edling et al. (1988) found histological evidence of epithelial damage in biopsied specimens from the nasal mucosa of 75 workers from two particle board processing plants and a laminate plant. From air measurements occasionally made during an 8-year period before the study, estimates of TWA concentrations were calculated ranging from 0.08 to 0.9 ppm. (A mean TWA concentration was not reported, but the midpoint of this range is 0.49 ppm). Peaks of up to 4.07 ppm were measured during the 8-year period. Air concentrations were qualitatively assessed as being "somewhat higher" during earlier periods. Wood dust air concentrations in the particle board plants ranged from 0.6 to 1.1 mg/m^3; air in the laminate plant was reported to be without wood dust. Employment durations ranged from 1 to 39 years with a mean of 10.5 years. Runny nose, nasal crusting, and runny eyes when at work were reported by 60 and 75% of the exposed subjects, respectively, but frequencies were not compared in the report with frequencies of symptoms for a control group of 25 nonexposed subjects. Little information was given about the selection of the control group, except that they were "selected with regard to age and smoking habits", however, 35% of exposed versus 48% of controls were smokers. Gross clinical examination showed that 25% of exposed workers had either swollen nasal mucosa or dry nasal mucosa; prevalence of this condition in the control group was not reported. Nasal mucosal biopsy sections were

assigned a score as follows: 0 - normal respiratory epithelium; 1 - loss of ciliated epithelium cells; 2 - mixed cuboid/squamous epithelium, metaplasia; 3 - stratified squamous epithelium; 4 - keratosis; 5 - keratosis with budding of epithelium; 6 - mild or moderate dysplasia; 7 - severe dysplasia; and 8 - carcinoma. Normal ciliated epithelium was found only in 3/75 exposed subjects; whereas a loss of ciliated cells and goblet cell hyperplasia was noted in 59/75 subjects, and 6/75 exposed subjects showed mild dysplasia. No subjects displayed severe dysplasia or carcinoma. Edling et al. (1988) did not report incidences of nasal lesions found in the control group, but did report that the average histological score for the exposed group (2.8) was statistically significantly greater than the control score (1.8). Histological scores did not increase with increasing employment duration in the exposed group. The authors reported that there was no difference in average histological scores between the exposed workers from the particle board plants, where confounding exposure to wood dust occurred, and those from the laminate plant without wood dust exposure. This observation supports the hypothesis that the observed nasal epithelial lesions were caused by formaldehyde and not by an interaction between formaldehyde and wood dust.

Holmstrom et al. (1989c) examined histological changes in nasal tissue specimens from a group of 70 workers in a chemical plant that produced formaldehyde and formaldehyde resins for impregnation of paper, a group of 100 furniture factory workers working with particle board and glue components, and a nonexposed, control group of 36 office workers in the same village as the furniture factories. Mean durations of employment in the groups were 10.4 years (sd 7.3, range 1–36 years) for the chemical workers and 9.0 years (sd 6.3, range 1–30 years) for the furniture workers. Estimates of personal breathing zone air concentrations ranged from 0.04 to 0.4 ppm (median 0.24±0.13 ppm) for the chemical workers, from 0.16 to 0.4 ppm (median 0.20±0.04 ppm) for the furniture workers, and from 0.07 to 0.13 ppm in the late summer for the office workers with a year-round office worker median reported as 0.07 ppm with no standard deviation. The mean wood dust concentration in the furniture factory was reported to have been between 1 and 2 mg/m^3. Nasal mucosa specimens were taken from the medial or inferior aspect of the middle turbinate. Histology scores were assigned to each specimen based on a 0–8 scale, identical to the scale used by Edling et al. (1988; described previously). Nasal histology scores ranged from 0 to 4 (mean 2.16, n=62) for the chemical workers, from 0 to 6 (mean 2.07, n=89) for the furniture workers, and from 0 to 4 (mean 1.46, n=32) for the office workers. The mean histological score for the chemical workers, but not the furniture workers, was significantly different from the control score, thus supporting the hypothesis that the development of the nasal lesions is formaldehyde-related and not obligatorily related to a possible interaction between formaldehyde and wood dust. The most

severe epithelial change found (light or moderate epithelial dysplasia) was found in two furniture workers. Among the chemical workers (not exposed to wood dust), loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium occurred more frequently than in the control group of office workers. Within both groups of formaldehyde-exposed workers, no evidence was found for associations between histological score and duration of exposure, index of accumulated dose, or smoking habit. A chronic inhalation MRL of 0.008 ppm was calculated as described in Table 2-1 and in Appendix A based on the minimal LOAEL of 0.24 ppm for mild nasal lesions in chemical factory workers in this study using an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability).

Boysen et al. (1990) histologically examined biopsy specimens from the nasal mucosa of 37 workers in a chemical plant that produced formaldehyde and formaldehyde resin and 37 age-matched, nonexposed controls. Exposed workers had been employed in the plant for more than 5 years (range 3–36 years, mean 20 years), had volunteered for the study, and represented about half of the workers in the plant. Controls were selected from office staff of two chemical plants, laboratory personnel from a hospital, and outpatients at an eye, ear, and nose clinic. Workers were classified into five exposure level groups based on "knowledge of the production process, recent measurements, and previous and present subjective sensations experienced by the workers". Exposure measurement data were not reported, but the exposure levels during the 1950s and 1960s were reported to have been "high". Workers in exposure level 1 (containing zero exposed workers) were defined as having occasional exposure (not daily) up to the level of olfactory detection. Twelve exposed workers reported frequent, but not daily, exposure that was irritating to the eyes or upper respiratory tract (exposure level 2), 17 workers reported daily exposure up to a level of olfactory detection (level 3), 5 reported daily exposure above the level of irritation (level 4), and 3 reported daily exposure inducing discomfort (level 5). The investigators surmised that concentrations between 0.5 and 2 ppm were associated with exposure levels 1–3, and that levels 4 and 5 were associated with concentrations >2 ppm. Biopsy samples were taken from the anterior curvature of the middle turbinate of the nasal cavity judged to have the best air flow. Specimen sections were assigned histology scores for the following findings: 1 for stratified cuboidal epithelium, 2 for mixed stratified cuboidal/stratified squamous epithelium, 3 for nonkeratinizing stratified squamous epithelium, 4 for keratinizing stratified squamous epithelium, and 5 for dysplasia. Numbers of subjects in the exposed group assigned histological scores ranging from 0 to 5 were: 3, 16, 5, 9, 1, and 3; respective numbers of subjects for the control group were: 5, 17, 10, 5, 0, and 0. The mean histological score for the exposed group (1.9) was statistically significantly greater than the mean for the controls (1.4). Much

of the difference in histological score between the exposed and control groups can be accounted for by three cases of dysplasia and one case of keratinizing stratified squamous epithelium in the exposed group; these lesions were not found in the nonexposed group. The workers with dysplasia were purported to have been exposed to concentrations in the range of 0.5–2.0 ppm and not to concentrations higher than 2 ppm.

Ballarin et al. (1992) examined smears of nasal respiratory mucosa cells sampled from the inner turbinate of 15 nonsmokers who were exposed to formaldehyde released from a urea-formaldehyde glue used in a plywood factory and 15 age- and sex-matched nonexposed clerks from outside of the factory. Estimates of formaldehyde air concentrations ranged from: 0.21 to 0.60 ppm (mean 0.39±0.20 ppm) in the warehouse where seven subjects worked, 0.08 to 0.14 ppm (mean 0.1±0.02 ppm) in the shearing press where six subjects worked, and 0.09 ppm (only one sample taken) in the sawmill area where two subjects worked. Mean wood dust concentrations for the three areas were 0.23±0.1 mg/m^3, 0.41±0.21 mg/m^3, and 0.73 mg/m^3, respectively. Exposed subjects worked at the factory for 2–19 years (mean 6.8±5.0 years). Nasal mucosal slides were scored as follows: normal cellularity, 1; number of mucus-secreting cells greater than ciliated cells, 1.5; hyperplasia, 2; squamous metaplasia, 2.5; mild dysplasia, 3; moderate dysplasia, 4; severe dysplasia, 5; and malignant cells, 6. In the exposed group, all subjects had a greater number of nonciliated than ciliated cells, 40% had hyperplasia, 67% had squamous metaplasia, and 6% slight dysplasia. In controls, 26% had normal cytology, 67% had more ciliated than nonciliated cells, 33% had hyperplasia, and 6% had squamous metaplasia. The mean cytology score for the exposed group (2.3±0.5) was reported to be statistically significantly greater than the control score (1.6±0.5). Also found in this study was a statistically significantly higher percentage of micronucleated mucosal cells in the exposed group compared with the control group (0.91%±0.47 versus 0.25%±0.22).

Studies of baseline pulmonary function variables (e.g., FVC, FEV_1, $FEFR_{25-75}$) that have found no abnormal average values for groups of workers repeatedly exposed to formaldehyde or no statistically significant exposure-related differences compared with referent, nonexposed workers include those of: 10 laboratory technicians employed for an average 7.7 years in workplaces with estimated mean concentrations ranging from 0.106±0.2 to 0.269±0.05 ppm (Bracken et al. 1985), 109 particleboard workers employed for an average 10.3 years (range <1–20 years) in a plant with estimated TWA concentrations ranging from 0.17 to 2.93 ppm (mean 0.69 ppm) (Horvath et al. 1988), and 64 embalmers (embalming for an average of 10 years) and 12 embalming apprentices (employed less than a year)

estimated to have been exposed to formaldehyde concentrations ranging from 0.08 to 0.81 ppm (mean 0.36±0.19 ppm) (Holness and Nethercott 1989).

Other studies have presented evidence for generally small or subtle formaldehyde-induced changes in pulmonary function variables with repeated occupational exposure (Alexandersson and Hedenstierna 1988, 1989; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990).

Using American Thoracic Society Criteria, Malaka and Kodama (1990) reported that the percentages of subjects with abnormal values for a number of pulmonary function variables (e.g., FEV_1 and $FEFR_{25-75}$) were significantly higher in a group of 93 plywood workers compared with a group of 93 nonexposed subjects. The plywood workers were employed for a mean of 6.2±2.4 years in workplaces with estimated formaldehyde air concentrations ranging from 0.22 to 3.48 ppm. The mean product of employment duration times workplace air formaldehyde concentration was 6.2 ppm/year (sd 2.72 ppm/year) for the exposed group of workers; division of this value by the average duration of employment (6.2 years) arrives at an estimated average exposure concentration of 1 ppm formaldehyde. Reported average respirable and total wood-dust concentrations in workplace air were 0.60 and 1.35 mg/m^3, respectively. Mean values of baseline FEV_1 and $FEFR_{25-75}$, after adjustment for dust exposure, were reportedly statistically significantly lower in the exposed group of workers compared with the nonexposed group (FEV_1 2.78 L [sd 0.41] versus 2.82 L [sd 0.3]; and FEF_{25-75} 3.14 L/second [sd 0.76] versus 3.44 L/second [sd 0.78]). Malaka and Kodama (1990) noted that although the small differences were statistically significant, their clinical significance was unclear.

Mean baseline measures of FVC and FEV_1 were significantly lower (by <10%) than reference values in a group of 21 woodworkers employed for an average of 11 years, but mean values of these variables did not decline significantly when measured 5 years later (Alexandersson and Hedenstierna 1989). Estimates of workplace air concentrations were 0.3±0.2 ppm at the beginning and 0.4±0.1 ppm at the end of the 5-year period.

Mean values for FVC and FEV_1 were significantly lower than reference values in a group of 38 workers exposed to formaldehyde and other solvents used in lacquer applications, but the difference was small (<5–10% change from reference values) (Alexandersson and Hedenstierna 1988). The workers in the lacquer-applying workplace were employed for an average of 7.8 years; estimates of formaldehyde concentrations in workplace air ranged from 0.2 to 2.1 ppm with a TWA mean of 0.3 ppm.

Mean values of FVC, FEV_1/FVC, and maximum mid-expiratory flow rate were significantly lower in a group of 37 anatomy and histopathology workers compared with values for a control group of 37 nonexposed workers from the same college (FVC 2.18 L versus 2.63 L; FEV_1/FVC 0.607 versus 0.787; flow rate 1.55 L/second versus 2.71 L/second) (Khamgaonkar and Fulare 1991). Employment durations were not reported in this study, but estimated formaldehyde air concentrations ranged from 0.036 to 2.27 ppm (mean 1.0±0.55 ppm) in the anatomy and histopathology workplaces compared with 0 to 0.52 ppm (mean 0.1±0.11 ppm) in the control workplaces. The study authors suggested that the apparent bronchoconstrictor effect of formaldehyde was due either to a direct effect of formaldehyde or a reflex response caused by irritation of the nose and throat.

Mean baseline PEFR declined by about 2% over a 10-week period in a group of 24 physical therapy students who dissected cadavers for 3-hour periods per week (Kriebel et al. 1993). Estimates of breathing zone formaldehyde concentrations ranged from 0.49 to 0.93 ppm (geometric mean 0.73±1.22 ppm). PEFR, the only pulmonary function variable measured in this study, was measured before and after each exposure period. Postexposure PEFR means were 1–3% lower than preexposure PEFR means during the first 4 weeks, but this difference was not apparent during the last 6 weeks. Fourteen weeks after the end of the 10-week period, the mean PEFR for the group returned to the preexposure baseline value.

Effect levels associated with formaldehyde-induced changes in pulmonary function variables in workers exposed to airborne formaldehyde concentrations generally less than 1 ppm are not included in Table 2-1 because the observed differences: are not of sufficient magnitude to be of obvious clinical significance, have not been observed consistently across studies, and may be confounded, in some cases, by the presence of wood dust particulates which may facilitate transport of adsorbed formaldehyde to deeper regions of the respiratory tract compared with low-level exposure to formaldehyde alone. In contrast, mild nasal epithelial lesions observed in formaldehyde-exposed workers: have been observed consistently across four studies (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c), do not appear to be confounded by exposure to wood dust (see Edling et al. 1988; Holmstrom et al. 1989c), and are consistent with results from animal toxicity, pharmacokinetic, and anatomical airflow studies indicating that, at concentrations 1 ppm, inhaled formaldehyde gas does not reach lower regions of the respiratory tract (see following review of animal inhalation toxicity studies and Sections 2.3 and 2.4).

A single study was located providing suggestive, but to date uncorroborated, evidence that elevated levels of formaldehyde in residential air may change pulmonary function variables in children, but not adults. Krzyzanowski et al. (1990) reported that children who lived in households with formaldehyde air concentrations greater than 0.06 ppm had greater prevalence rates of physician-diagnosed bronchitis or asthma compared with children who lived in households with concentrations less than 0.06 ppm. A statistically significant trend for increasing prevalence rate with increasing formaldehyde air concentration was found for households with environmental tobacco smoke, but the trend was not significant in households without tobacco smoke. A statistically significant trend was also found for decreasing PEFR values in children with increasing household formaldehyde air concentration. The clinical significance of these findings is uncertain (see Section 2.6 for more discussion).

Acute Inhalation Animal Studies. Studies in animals confirm that the upper respiratory tract is a critical target for inhaled formaldehyde and describe exposure-response relationships for upper respiratory tract irritation and epithelial damage in several species. Acute inhalation animal studies show that inhaled formaldehyde, at appropriate exposure concentrations, damages epithelial tissue in specific regions of the upper respiratory tract in rats, mice, and monkeys (Chang et al. 1983; Monticello et al. 1989, 1991; Morgan et al. 1986a, 1986c), that formaldehyde is a more potent sensory irritant in mice (Chang et al. 1981, 1983; Kane and Alarie 1977) than in rats (Chang et al. 1981, 1983), that lung damage from inhaled formaldehyde occurs at higher concentrations than those only affecting the upper respiratory tract (Kamata et al. 1996a, 1996b; Swiecichowski et al. 1993), that mice are less susceptible to formaldehyde-induced upper respiratory tract epithelial damage than rats (Chang et al. 1983), that rats and monkeys may be equally susceptible to epithelial damage from formaldehyde but display similar epithelial lesions in different regions of the upper respiratory tract (Monticello et al. 1989, 1991), and that formaldehyde induces bronchoconstriction and airway hyperreactivity in guinea pigs (Amdur 1960; Swiecichowski et al. 1993).

Formaldehyde-induced epithelial damage in the nasal cavity of rats (e.g., squamous metaplasia and hyperplasia) displays regional specificity (anterior regions of the nasal epithelium, posterior to the vestibule at the lowest effective concentrations) and occurs with acute exposures to concentrations generally greater than 2–6 ppm. Monticello et al. (1991) found no evidence for histological nasal epithelial damage in F344 rats exposed to 0.7 or 2 ppm, 6 hours/day for 1, 4, or 9 days, but damage was observed at 6, 10, and 15 ppm. Regions of epithelium showing histological lesions also showed increased rates of cellular proliferation at concentrations greater than 6 ppm (Monticello et al. 1991).

Site-specific damage to nasal epithelial cells after acute exposure (6 hours/day for 1 to 3 weeks) of F344 rats to formaldehyde was correlated with inhibition of mucociliary function (i.e., mucostasis) at concentrations of 2, 6, and 15 ppm, but no effects on these end points were found at 0.5 ppm (Morgan et al. 1986a, 1986c). Morgan et al. (1986c) reported that mucus flow was stopped after only 1 hour of exposure to 15 ppm in regions of the nasal epithelium that later developed lesions, and that this effect was still apparent 18 hours after exposure ceased. Other acute inhalation studies with rats (Bhalla et al. 1991; Cassee and Feron 1994; Monteiro-Riviere and Popp 1986; Wilmer et al. 1987) provide supporting evidence that short-term exposure to concentrations in excess of 2 ppm can damage nasal epithelial tissues in this species (see Table 2-1).

Upper respiratory tract epithelial lesions similar to those observed in rats have been observed in Rhesus monkeys exposed to 6 ppm, 6 hours/day, 5 days/week for 1 week; the regional distribution of these lesions was not restricted to the nasal cavity, as they were in rats exposed to 6 ppm (Monticello et al. 1991), but extended to the trachea and major bronchi (Monticello et al. 1989). Lesions were most severe in the nasal passages and were minimal in the lower airways (larynx, trachea, and carina). Regions of epithelium with lesions corresponded with regions in which high rates of cellular proliferation were measured. No evidence for lesions or changes in cell proliferation rates were found in the maxillary sinuses. Studies describing exposure-response relationships for upper respiratory tract epithelial damage in monkeys acutely exposed to inhaled formaldehyde were not located.

Inhaled formaldehyde is a more effective sensory irritant (i.e., stimulates trigeminal nerve endings and inhibits respiration rate and tidal volume) in mice than in rats (Chang et al. 1981; Kane and Alarie 1977), whereas nasal effects such as rhinitis and degeneration of respiratory epithelial cells are more severe in rats than in mice, and increased indices of cell proliferation in nasal epithelium are more frequent in rats than mice, after exposure to 15 ppm, 6 hours/day for 1 or 5 days (Chang et al. 1983). Measured RD_{50} values for mice (2.2–5.9 ppm; concentrations associated with a 50% decrease in respiratory rate) were much lower than RD_{50} values for rats (22.7–31.7 ppm) (Chang et al. 1981). Kane and Alarie (1977) reported a similar RD_{50} value, 3.1 ppm, for formaldehyde in mice. These results suggest that the lesser sensitivity of mice to formaldehyde-induced nasal tissue damage may be due, at least in part, to the mouse's ability to maintain decreased respiration rates and decreased tidal volumes in the presence of airborne formaldehyde, whereas the rat does not have this ability and thus sustains a greater degree of tissue damage.

Acute inhalation exposure to formaldehyde has been associated with tissue damage in the lungs only at much higher exposure concentrations than those affecting the nasal region alone. Histological and ultrastructural examination of lung tissue from rats exposed to 10 ppm, 6 hours/day for 4 days found no evidence for tissue injury, although these rats showed clinical signs of eye and nose irritations (Dinsdale et al. 1993). In addition, activities of alkaline phosphatase and γ-glutamyl transpeptidase in bronchoalveolar lavage fluid and lung tissue concentrations of cytochrome P-450 were not significantly elevated in exposed rats compared with control rats. These results indicate that very limited amounts of formaldehyde reach the lungs with exposure to 10 ppm. In contrast, Kamata et al. (1996a) reported that single 6-hour exposures of male F344 rats to 150 ppm formaldehyde induced histological changes throughout the nasal turbinates (including hyperkeratosis of the squamous epithelium in the vestibule, desquamation of the respiratory epithelium), the trachea (increased secretion and desquamation of mucosal cells), and the lung (hyperplasia of the alveolar wall and plasma-like secretions in the lung), whereas similar exposure to 15 ppm produced only slight hypersecretion of the nasal and tracheal mucosal epithelium. Kamata et al. (1996b) also noted that F344 rats exposed to 128 or 295 ppm formaldehyde for 6 hours showed bloody nasal discharge and pulmonary edema, indicating that, at these very high concentrations, formaldehyde can reach and damage lung tissue as well as nasal tissue.

Experiments with guinea pigs provide evidence that acute exposure to inhaled formaldehyde can influence lower airway resistance and hyperreactivity of the lungs (Amdur 1960; Swiecichowski et al. 1993). Amdur (1960) measured significantly increased airway resistance in guinea pigs exposed for 1 hour to formaldehyde concentrations as low as 0.3 ppm; the average increase in resistance was about 14, 29, and 43% over control values at 0.3, 1.2, and 3.6 ppm, respectively. Amdur suggested that the changes in resistance were due to bronchoconstriction. More recently, Swiecichowski et al. (1993) reported that pulmonary resistance was significantly increased in guinea pigs exposed to 9.4 ppm for 2 hours, but not in guinea pigs exposed to 3.4 ppm or lower for 2 hours. Longer duration exposure (8 hours) changed the exposure-response relationship; concentrations as low as 0.3 ppm produced significantly increased pulmonary resistance. Pulmonary sensitivity to acetylcholine was significantly increased by 2-hour exposures to concentrations 9.4 ppm and by 8-hour exposures to 0.3 ppm. No exposure-related epithelial damage or inflammatory response was detected by histological examinations of portions of the midtrachea.

Intermediate Inhalation Animal Studies. Results from intermediate-duration inhalation studies with rats (Appelman et al. 1988; Feron et al. 1988; Monticello et al. 1991; Rusch et al. 1983; Woutersen et al. 1987; Zwart et al. 1988), Rhesus monkeys (Monticello et al. 1989), Cynomolgus monkeys (Rusch et al. 1983), mice (Maronpot et al. 1986), and hamsters (Rusch et al. 1983) indicate that the nasal epithelium is the most sensitive target of inhaled formaldehyde. The studies support the hypothesis that mice and hamsters are less sensitive than rats and monkeys to formaldehyde-induced nasal damage (Maronpot et al. 1986; Rusch et al. 1983), show that formaldehyde-induced damage to the upper respiratory tract epithelium (hyperplasia and squamous cell metaplasia) has a wider regional distribution in Rhesus monkeys than in rats (Monticello et al. 1989, 1991), show that site-specific nasal lesions in both monkeys and rats corresponded to regions with high rates of cellular proliferation (Casanova et al. 1994; Monticello et al. 1989, 1991), indicate that damage to the respiratory epithelium is more concentration-dependent than duration-dependent (Wilmer et al. 1987, 1989), and show that concentrations of DNA-protein cross links are correlated with regional sites of formaldehyde-induced epithelial damage in the nose of rats (Casanova et al. 1994).

In a study designed to detect potential effects on tissues and organs distant from the nose and to describe exposure-response relationships for nasal lesions in rats exposed to between 1 and 20 ppm formaldehyde for intermediate durations, Woutersen et al. (1987) exposed groups of 10 male and 10 female Wistar rats to 0, 1, 10, or 20 ppm 6 hours/day, 5 days/week for 13 weeks. Sections of the lungs, trachea, larynx, and nose were microscopically examined in all rats; all other major organs and tissues were also examined microscopically in control and high-exposure groups. Exposure to 20 ppm produced severe and extensive keratinized squamous metaplasia of the nasal respiratory epithelium, focal degeneration and squamous metaplasia of the olfactory epithelium, and squamous metaplasia of the laryngeal epithelium (males only). No exposure-related lesions were found in other tissues or organs. Respiratory effects at 10 ppm were restricted to moderate squamous metaplasia of the nasal respiratory epithelium. Effects noted in the 1-ppm group were restricted to minimal focal hyperplasia and squamous metaplasia of the nasal respiratory epithelium found in three rats.

Zwart et al. (1988) exposed groups of male and female Wistar rats to formaldehyde at concentrations of 0, 0.3, 1, or 3 ppm, 6 hours/day, 5 days a week for 13 weeks to study details of formaldehyde-induced nasal tissue damage. Exposure-related nasal tissue histological changes were restricted to a small area of the anterior region of the nose normally covered with respiratory epithelium and were found only in the high-exposure group. Lesions were described as ranging from epithelial disarrangement to epithelial

hyperplasia and squamous metaplasia. After 3 days of exposure, increased rates of cellular proliferation, compared with controls, were found in the 1- and 3-ppm groups in epithelial regions where lesions were found after 13 weeks in the 3-ppm group. After 13 weeks of exposure, cellular proliferation rates were not increased in the lesion-laden regions of exposed rats, but were increased in more posterior regions of the nasal epithelium, most notably in rats exposed to 3 ppm. These results are consistent with the hypothesis that the change of mucus-covered respiratory epithelial cells to squamous epithelial cells is adaptive.

Appelman et al. (1988) exposed groups of male SPF Wistar rats to 0, 0.1, 1, or 10 ppm formaldehyde 6 hours/day, 5 days/week for 13 or 52 weeks. Within each exposure group, half of the animals had their nasal mucosa damaged by acute electrocoagulation prior to formaldehyde exposure. In groups without predamaged nasal mucosa, exposure-related effects were restricted to rhinitis and hyperplasia and metaplasia of the nasal respiratory epithelium in the 10-ppm group. Comprehensive histological examination of major tissues and organs in the control and 10-ppm groups revealed no other exposure-related lesions. Microscopic examination of nose sections from the 1- and 0.1-ppm groups without electrocoagulation revealed no exposure-related effects. Rats with predamaged nasal mucosa were more susceptible to the cytotoxic action of formaldehyde; at 52 weeks, focal squamous metaplasia of the nasal respiratory epithelium was found in rats exposed to 0.1 or 1 ppm formaldehyde.

Monticello et al. (1991) exposed groups of 36 male F344 rats to 0, 0.7, 2, 6, 10, or 15 ppm, 6 hours/day, 5 days/week for up to 6 weeks and labeled with tritiated thymidine prior to scheduled termination to determine rates of cellular proliferation in specific regions of the nasal epithelium. After 6 weeks of exposure to 10 or 15 ppm, epithelial hyperplasia and squamous metaplasia of the respiratory epithelium were located primarily in the nasoturbinates, just posterior to the nasal vestibule, with milder lesions extending into more posterior regions including the nasopharynx. Exposure to 6 ppm produced mild epithelial hyperplasia and squamous metaplasia that was restricted to the most anterior regions of the respiratory epithelium in the nasoturbinates. Statistically significant increases in cellular proliferation rates were measured in the groups exposed to 6 ppm or higher. Exposure-related effects on nasal epithelium were not found in the 2- or 0.7-ppm groups. Sites of cellular injury were well-correlated with sites of increased rates of cellular proliferation.

Casanova et al. (1994) exposed groups of male F344 rats to 0, 0.7, 2, 6, or 15 ppm 6 hours/day, 5 days/week for 81 days to examine the effect of preexposure to formaldehyde on the concentrations of

DNA-protein cross links formed in specific regions of nasal cavity epithelium in response to acute exposure to radiolabeled formaldehyde. DNA-protein cross link concentrations were approximately 6-fold higher in the mucosal lining of the lateral meatus (where formaldehyde-induced lesions develop) than in the mucosal lining of the medial and posterior meatus (where lesion development is less strong). Preexposure to formaldehyde at concentrations 2 ppm did not affect the formation of DNA-protein cross links, but at higher concentrations, pre-exposed rats showed decreased acute formation of DNA-protein cross links compared with rats without prior exposure to formaldehyde.

Monticello et al. (1989) exposed groups of three male Rhesus monkeys to 0 or 6 ppm formaldehyde, 6 hours/day, 5 days/week to compare respiratory responses to formaldehyde in primates with those in rodents. Comprehensive histological examination of respiratory tract tissues (and also extra-respiratory tissues) was conducted. Exposure-related lesions were confined to the epithelium of the upper respiratory tract and were described as mild hyperplasia and squamous metaplasia confined to particular regions of the transitional and respiratory epithelium of the nasal passages and the respiratory epithelium of the trachea and carina. Cellular proliferation rates were significantly elevated in damaged regions of the nasal epithelium. Nasal lesions seen in monkeys were similar to those reported in rats exposed to 6 ppm by a similar exposure protocol and duration in a companion study (Monticello et al. 1991) except that the lesions extended into the trachea in the monkeys. The lesions in the larynx, trachea, and carina of the formaldehyde-exposed primates included multifocal loss of cilia and goblet cells, mild epithelial hyperplasia, and early squamous metaplasia. Cell proliferation rates in the trachea and carina were increased as well. In both species, regions where lesions were found were well-correlated with regions in which high rates of cellular proliferation were measured (Monticello et al. 1989, 1991). The investigators suggested that the difference in the location of the lesions was due to different breathing patterns in the rat and monkey and differences in the anatomic structure of their respective nasal passages.

Rusch et al. (1983) histologically examined the lungs, trachea, and nasal turbinates of groups of 6 or 12 male Cynomolgus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Golden Syrian hamsters exposed to 0, 0.2, 0.98, or 2.95 ppm for 22 hours/day, 7 days/week for 26 weeks. Examination of other organs and tissues at necropsy for gross lesions revealed no exposure-related effects, but these tissues were not microscopically examined. Monkeys exposed to 2.95 ppm showed an increased incidence of hoarseness, congestion, and nasal discharge. Monkeys in the lower exposure groups showed a greater incidence of nasal discharge than control monkeys, but the discharge was "only a

minimal grade" and was noted sporadically throughout the study. The study authors judged that the nasal discharge at the two lowest exposure levels was not of biological significance. Body weights of exposed monkeys were not significantly different from body weights of controls. Monkeys and rats exposed to 2.95 ppm, but not the lower concentrations, showed a significantly increased incidence of squamous metaplasia and/or basal cell hyperplasia of the nasal cavity epithelium; the response was reported to be most clearly seen in both species in the mid-region of the nasoturbinates. No lesions were found in the most anterior sections of the nose or in the ethmoturbinates. Incidences of monkeys with squamous metaplasia/hyperplasia in nasal turbinate epithelium were 0/12, 0/6, 1/6, or 6/6 at 0, 0.2, 0.98, and 2.95 ppm, respectively. Respective incidences of rats with squamous metaplasia/hyperplasia were 5/77, 1/38, 3/36, and 23/37. The investigators made no mention of any difference in the regional distribution of the nasal lesions in rats and monkeys or of any histological changes in the trachea or lungs of the exposed monkeys or rats. Ultrastructural examinations were made of the nasal turbinates, trachea, and lungs from rats in the control and 0.98-ppm group; no exposure-related changes were found. No histological changes were found in the nasoturbinates, trachea, or lungs of the exposed hamsters compared with controls. An intermediate inhalation MRL of 0.03 ppm was calculated as described in Table 2-1 and in Appendix A based on the NOAEL of 0.98 ppm for nasopharyngeal irritation in Cynomolgus monkeys using an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Wilmer et al. (1987) investigated whether varying the exposure to formaldehyde (i.e., continuous versus intermittent) affected formaldehyde cytotoxicity to upper respiratory tract epithelium. Groups of male albino Wistar rats were exposed to 0, 5, or 10 ppm formaldehyde, 8 hours/day continuously, or to 10 or 20 ppm formaldehyde, 8 hours/day intermittently (30-minute exposure periods separated by 30-minute periods of nonexposure). Eighteen hours after the third day or fourth week of exposure, three rats from each group were injected with ^{3}H-thymidine, sacrificed, and their nasal cavities were processed and examined for cell turnover. After 4 weeks of exposure, cell turnover rates in nasal epithelium were significantly elevated in the rats exposed to 10 and 20 ppm intermittently, but not in rats exposed to 5 and 10 ppm continuously. The majority of cell labeling occurred in the naso- and maxillary turbinates. Focal thinning and disarrangement of the respiratory epithelium lining were noted in some of the 10-ppm and all of the 20-ppm rats. Squamous metaplasia with cellular hyperplasia was noted in some of the rats exposed to 5 ppm and in most of the rats exposed to 10 or 20 ppm. Minimum to moderate rhinitis was seen in each of the treatment groups. In a similar study, Wilmer et al. (1989) studied the same toxicological end points in male albino Wistar rats using lower concentrations of 0, 1, or 2 ppm

formaldehyde, 8 hours/day continuously, or 2 or 4 ppm formaldehyde, 8 hours/day intermittently (30-minute exposure periods separated by 30-minute periods of nonexposure), all groups were treated for 5 days/week for 13 weeks. After 13 weeks of exposure, there were no statistically significant differences between the 1 and 2 ppm (continuously dosed), the 2 ppm (intermittently dosed) groups, and the controls in cell turnover rates, however, the mean cell turnover rate after 13 weeks of exposure in the 4-ppm rats was 2.9-fold greater than that of control rats. Treatment-related histological changes were noted only in the 4-ppm intermittent exposure group. The changes consisted of increased disarrangement, hyperplasia, and squamous metaplasia with or without keratinization of the respiratory epithelium lining of the septum and nasoturbinates. The group continuously exposed to 2 ppm formaldehyde (i.e., the same total daily exposure as the 4-ppm intermittent group) did not exhibit an increased incidence of these lesions. These data suggest that the concentration of formaldehyde is more important in determining epithelial damage than the duration of exposure.

Maronpot et al. (1986) exposed groups of 10 male and 10 female B6C3F1 mice to formaldehyde 6 hours/day, 5 days/week for 13 weeks at concentrations of 0, 2, 4, 10, 20, or 40 ppm. Comprehensive histological examinations of major tissues and organs were conducted. Significant mortality and severe weight loss occurred in the 40-ppm group. Exposure-related lesions were restricted to the respiratory tract, except for hypoplasia of the uterus and ovaries in the 40-ppm group which were interpreted to be due to severe body weight loss. In the 40-ppm groups, squamous metaplasia, keratinization, suppurative inflammatory exudate, serous exudate, and mild degeneration of the epithelium were noted in nasal sections. Similar lesions were noted in the 20- and 10-ppm groups, although the severity declined with decreasing concentrations. Similar lesions were seen in only one male mouse at 4 ppm, and in none of the 4-ppm females; no such lesions were noted in either sex at exposures of 2 ppm. Squamous metaplasia, suppurative inflammation, and fibrosis was also noted in the trachea and larynx of most mice in the 40-ppm group; similar, though less severe, lesions were noted in the 20-ppm group. Lung lesions consisting of epithelial hyperplasia, suppurative inflammation, squamous metaplasia, and fibrosis were seen in some of the mice exposed to 40 ppm, but were not found in mice exposed to lesser concentrations.

Studies of pulmonary function variables in rats after intermediate-duration exposure to inhaled formaldehyde have not found marked, exposure-related effects (Dallas et al. 1985, 1986; Saldiva et al. 1985). Dallas and colleagues measured the change in minute volume produced by acute challenges with formaldehyde administered either intratracheally (Dallas et al. 1986) or by nosepiece (Dallas et al. 1985)

in rats exposed to 0, 0.5, 3 (nose-piece experiment only), or 15 ppm formaldehyde, 6 hours/day 5 days/week for 8 or 16 weeks. Responses to the acute challenge were compared with responses in age-matched, nonexposed rats. A slightly diminished minute volume response to the formaldehyde challenge was observed in the exposed rats (from the 15-ppm groups only) compared with the response in nonexposed rats with both types of challenge administration, but this was statistically significant only with nosepiece administration. Saldiva et al. (1985) found no statistically significant differences between a group of rats exposed to 5.7 ppm formaldehyde, 8 hours/day, 5 days/week for 5 weeks and a group of nonexposed rats in mean values for numerous pulmonary function variables including FEV in 1/4 second and several measures of forced expiratory flow rates.

Chronic Inhalation Animal Studies. Chronic-duration exposures to inhaled formaldehyde have also been studied in rats, mice, and hamsters. In rats exposed to concentrations 15 ppm, formaldehyde-induced effects were restricted to nonneoplastic and neoplastic lesions found primarily in anterior regions of the nasal epithelium, posterior to the vestibule (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Swenberg et al. 1980; Woutersen et al. 1989). Nonneoplastic damage to rat nasal epithelium occurred at concentrations as low as 2 ppm, 6 hours/day, 5 days/week (Kamata et al. 1997), whereas significantly increased incidences of neoplastic lesions (squamous cell carcinomas, squamous cell papillomas or polyploid adenomas) were found in rats generally at concentrations greater than 6 ppm (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Nonneoplastic damage to upper respiratory tract epithelium has also been observed in mice exposed to 5.6 ppm, 6 hours/day, 5 days/week for 2 years (Kerns et al. 1983b) and in hamsters exposed to 10 ppm, 5 hours/day, 5 days/week for life (Dalbey 1982). Nasal tumors similar to those found in formaldehyde-exposed rats were found in mice exposed to 14.3 ppm for 2 years (Kerns et al. 1983b), but were not found in formaldehyde-exposed hamsters (Dalbey 1982). See Section 2.2.1.8 for more details of neoplastic findings from these studies.

Male and female Fischer 344 rats were exposed to 0, 2, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b; Swenberg et al. 1980). The exposure period was followed by a 6-month observation period. Interim sacrifices were performed at 6, 12, 18, 24, 27 (3 months postexposure), and 30 months (6 months postexposure). In the 14.3-ppm treatment group, early mortalities occurred, rats tended to be dyspneic and emaciated, and many had facial swellings which were subsequently determined to be nasal cavity carcinomas. Microscopic lesions were limited to the nasal cavity and trachea, however, lesions were initially seen only in the ventral portion of the nasal

septum. As the study progressed, the lesions spread and became progressively more severe. In the low- and mid-dose groups, rhinitis, epithelial dysplasia, and squamous metaplasia developed over the course of the study. Occasionally, animals in the high-dose group exhibited minimal-to-mild epithelial hyperplasia or dysplasia or squamous metaplasia of the tracheal mucosa; these effects were not seen in the lower-dose groups and disappeared in the high-dose group during the postexposure periods. Malignant nasal tumors were found in 5.6- and 14.3-ppm rats (see Section 2.2.1.8). Neoplastic lesions were not found in other regions of the respiratory tract or in other organ systems.

Woutersen et al. (1989) investigated the effects of damage to the nasal mucosa on the induction of non-neoplastic tissue changes and tumors from long-term exposure to formaldehyde. Male and female Wistar rats were used, with 67% of all rats undergoing electrocoagulation of the nasal mucosa. Half of the animals were exposed to formaldehyde for 28 months and the other half for 3 months, all at doses of 0, 0.1, 1, or 10 ppm for 6 hours/day, 5 days/week. In undamaged noses in the 28-month study, histopathological changes were not seen in the 0.1 or 1 ppm groups; exposure to 10 ppm resulted in an increased incidence of squamous metaplasia and basal cell/pseudoepithelial hyperplasia of the respiratory epithelium, thinning and disarrangement of the olfactory epithelium, and rhinitis. In damaged nasal mucosa in the long-term study, exposure to all levels of formaldehyde resulted in squamous metaplasia. Rats exposed to formaldehyde vapors for 3 months (without electrocoagulation pretreatment) were sacrificed following a 25-month recovery period. Non-neoplastic nasal lesions with statistically significant increased incidences, compared with controls, were found only in the most anterior regions of the nasal cavity in 10-ppm rats: squamous metaplasia of the respiratory epithelium (17/26 compared with 3/26 in controls; $p<0.01$, Fisher exact test performed by Syracuse Research Corporation), and rhinitis (13/26 compared with 5/26; $p<0.05$, Fisher exact test performed by Syracuse Research Corporation). Nasal tumors were found only in the 10-ppm, 3-month-exposure group; one rat had a squamous cell carcinoma and one had a polypoid adenoma (see Section 2.2.1.8 for more details on neoplastic responses in this study).

Monticello et al. (1996) assessed the role of regional increases in nasal epithelial cell proliferation in the formation of formaldehyde-induced nasal neoplastic and non-neoplastic tissue damage in male Fischer 344 rats. Rats were exposed to 0, 0.7, 2, 6, 10, or 15 ppm formaldehyde, 6 hours/day, 5 days/week for 24 months. During the last 5 days of exposure prior to each interim sacrifice period (3, 6, 12, and 18 months), 6 rats per dose group were labeled with ^{3}H-thymidine via osmotic pumps to measure regional rates of cell proliferation in nasal cavity epithelium. No formaldehyde-induced non-

neoplastic lesions were found in the nasal cavities of rats from the 0.7- or 2-ppm groups. Non-neoplastic lesions in the 6-ppm group were limited to focal squamous metaplasia in the anterior region of the nasal cavity. In the 10- and 15-ppm groups, lesions seen included epithelial hypertrophy and hyperplasia, squamous metaplasia, inflammatory cell infiltration, nasal turbinate adhesions, and olfactory degeneration. These lesions occurred more frequently and with greatest severity in the 15-ppm group. Cell proliferation in nasal epithelium was not affected by formaldehyde exposures of 6 ppm or less; increases in the cell labeling index were significant at the 10- and 15-ppm exposure levels. Nasal tumors were found in the 6-, 10-, and 15-ppm groups (see Section 2.1.1.8).

Kamata et al. (1997) exposed groups of 32 male F344 rats by inhalation to formaldehyde concentrations of 0.3, 2, or 15 ppm, 6 hours/day, 5 days/week for up to 28 months. Two control groups of 32 rats were included: an inhalation chamber group ("0 ppm") inhaling 4.2 ppm methanol and a "room control, no-exposure group". Significantly increased mortality (after 9 months) and decreased body weights (after 4 months) were restricted to the 15-ppm group compared with the control groups. No exposure-related effects on hematological parameters were found. Comprehensive autopsies and histological examination of the pituitary, thyroid, nasal region, trachea, esophagus, stomach, intestine, prostate gland, spinal cord, and mesenteric lymph nodes found exposure-related effects only in the nasal cavities. Epithelial cell hyperplasia, hyperkeratosis, and squamous metaplasia were apparent in all exposure groups and were predominately restricted to the respiratory epithelium of nasal turbinates and maxilloturbinates, just posterior to the nasal vestibule. Incidences for epithelial cell hyperplasia with squamous cell metaplasia were 0/32, 0/32, 4/32, 7/32, and 29/32 in the 0-, room control-, 0.3-, 2-, and 15-ppm groups respectively; incidences for squamous cell metaplasia without epithelial cell hyperplasia were 0/32, 0/32, 1/32, and 5/32, respectively (this combination of lesions did not occur in the 15-ppm group). Nasal tumors squamous cell carcinomas and papillomas were found only in the 15-ppm group (see Section 2.2.1.8). Kamata et al. (1997) concluded that the study did not identify a NOAEL for nonneoplastic nasal lesions due to the finding of epithelial cell hyperplasia with squamous cell metaplasia in the 0.3-ppm group, but the incidences for nonneoplastic nasal lesions in the 0.3-ppm group were not statistically significantly different compared with the controls. In Table 2-1, 0.3 ppm is noted as a NOAEL for non-neoplastic lesions in the nasal epithelium.

Kerns et al. (1983b) exposed male and female B6C3F1 mice to 0, 2, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months, followed by a 6-month observation period. Interim sacrifices were performed at 6, 12, 18, 24, 27, and 30 months. Major tissues from each organ system in control and

high-exposure mice were examined histologically. Non-neoplastic nasal lesions were found in the 5.6- and 14.3-ppm groups of mice, most notably inflammatory, dysplastic, and squamous metaplastic changes in the respiratory epithelium. Minimal to moderate hyperplasia of the squamous epithelium lining the nasolacrimal duct and atrophy of the olfactory epithelium of the ethmoturbinates also were observed in the 5.6- and 14.3-ppm groups. At the end of exposure (24 months), nasal lesions were found in >90% of 14.3-ppm mice and "in a few" 5.6-ppm mice (incidence was not specified). Mice sacrificed 3 months postexposure showed regression of the formaldehyde-induced nasal epithelial lesions. At 24 months, mice in the 2-ppm group were "free of significant nasal lesions", but a few mice had serous rhinitis and minimal hyperplasia of the squamous epithelium lining the nasolacrimal duct. Two male mice in the 14.3-ppm group sacrificed at 24 months displayed squamous cell carcinomas in the nasal cavity similar to those found in rats. The number of mice sacrificed at 24 months was not specified in the published report, but the incidence was indicated to be significantly increased compared with controls. No other tumors were reported in exposed or control mice.

Dalbey (1982) exposed groups of male Golden Syrian hamsters to 0 (n=132) or 10 (n=88) ppm formaldehyde, 5 hours/day, 5 days/week for life (up to about 110 weeks). Exposed hamsters showed reduced survival time compared with controls. End points in this study were restricted to histopathological examinations of respiratory tract tissues. There was no evidence of rhinitis in treated animals, and no tumors were found in the respiratory tract of treated or control animals. Hyperplastic and metaplastic areas were seen in the nasal epithelium of 5% of the treated hamsters but were not seen in controls. Dalbey (1982) also exposed groups of 50 male hamsters to 0 or 30 ppm formaldehyde, 5 hours/day, 1 day/week for life. No respiratory tract tumors were reported to have been found in control or exposed animals, but Dalbey (1982) did not mention if the nasal epithelium was examined for non-neoplastic changes in these two groups of hamsters.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to formaldehyde.

No histological evidence for formaldehyde effects on cardiovascular tissues was found in intermediate-duration inhalation studies, using a 6 hour/day, 5 day/week exposure protocol, with mice exposed to up to 40 ppm for 13 weeks (Maronpot et al. 1986), Rhesus monkeys exposed to 6 ppm for 6 weeks (Monticello et al. 1989), rats exposed to up to 20 ppm for 13 weeks (Woutersen et al. 1987), or rats exposed to up to 10 ppm for 13 or 52 weeks (Appelman et al. 1988). Similarly, no evidence for

formaldehyde effects on cardiovascular tissues were found in chronic inhalation studies with rats or mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for 2 years (Kerns et al. 1983b). The only study located that examined cardiovascular function in animals exposed to airborne formaldehyde was a report that concluded that blood pressure and heart rate were not affected in anesthetized rats exposed for 1 minute to 1,628 ppm formaldehyde (Egle and Hudgins 1974).

Gastrointestinal Effects. Few studies regarding gastrointestinal effects after inhalation exposure were located. In humans, Kilburn (1994) describes vague gastrointestinal effects in four patients who had been occupationally exposed to formaldehyde for 14–30 years. Three of the patients were anatomists and were exposed to formalin; the fourth was a railroad worker who worked next to a wood-products factory that used large quantities of phenol-formaldehyde resins. Intestinal cramps with flatus and bloody stools was one of many nonspecific effects noted in this small population.

No histological evidence for formaldehyde effects on the gastrointestinal tract was found in intermediate-duration inhalation studies using a 6 hour/day, 5 days/week exposure protocol with mice exposed to up to 40 ppm for 13 weeks (Maronpot et al. 1986), Rhesus monkeys exposed to 6 ppm for 6 weeks (Monticello et al. 1989), rats exposed to up to 20 ppm for 13 weeks (Woutersen et al. 1987), or rats exposed to up to 10 ppm for 13 or 52 weeks (Appelman et al. 1988). Similarly, no evidence for formaldehyde effects on gastrointestinal tissues were found in chronic inhalation studies with rats exposed to up to 15 ppm, 6 hours/day, 5 days/week for 2 years or more (Kamata et al. 1997; Kerns et al. 1983b), or in mice exposed similarly (Kerns et al. 1983b).

Hematological Effects. Pross et al. (1987) evaluated the immunologic response of asthmatic subjects exposed to urea-formaldehyde foam insulation (UFFI) off-gas products. Subjects consisted of 23 individuals with a history of asthmatic symptoms attributed to UFFI and 4 individuals (controls) with asthma unrelated to UFFI by-products. Subjects were exposed to one of the following: room air (placebo) for 30 minutes; 1 ppm formaldehyde gas for 3 hours; UFFI particles (4 μm, 0.5 particles/mL) for 3 hours, commencing 48 hours after formaldehyde gas exposure; and UFFI off-gas products for 3 hours, commencing 48 hours after UFFI particle exposure. There were no significant alterations in any of the white blood cell populations when the four unexposed controls were compared to the subjects (who also lived in a home where UFFI is present) before or after being exposed to UFFI in the chamber. However, there was a significant increase in the percentage and absolute number of eosinophils and

basophils in the subjects (who also lived in UFFI-homes) after exposure to UFFI in the exposure chamber when compared to the white blood cell values obtained before chamber exposure to UFFI.

No exposure-related effects on hematological variables were found in rats exposed to up to 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), in rats exposed to up to 10 ppm, 6 hours/day, 5 days/week for up to 52 weeks (Appelman et al. 1988), in rats or mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for up to 24 months (Kerns et al. 1983b), or rats exposed to up to 15 ppm for 28 months (Kamata et al. 1997). Dean et al. (1984) reported that female mice exposed to up to 15 ppm for 6 hours/day, 5 days/week for 3 weeks showed a statistically significant decrease in absolute number of monocytes compared with control values, but no other hematological variable was affected by exposure in this study.

Musculoskeletal Effects. Few studies were located that described musculoskeletal effects of formaldehyde after inhalation exposure. Holness and Nethercott (1989) reported that muscle or joint stiffness was reported more frequently by a surveyed group of funeral directors and embalmers than in a referent nonexposed group (23 versus 5%), but reporting of similar symptoms has not been frequently encountered in other health surveys of formaldehyde-exposed groups of workers.

With 6-hours/day, 5-days/week exposure protocols, no formaldehyde-induced histological changes in muscle or skeletal tissue were found in mice exposed to up to 40 ppm for 13 weeks (Maronpot et al. 1986), in monkeys (bone marrow of sternum) exposed to 6 ppm for 6 weeks (Monticello et al. 1989), in rats (femur and muscle tissue) exposed to up to 15 ppm for 28 months (Kamata et al. 1997), or in rats or mice exposed to up to 14.3 ppm for 24 months (Kerns et al. 1983b).

Hepatic Effects. No studies were located that reported hepatic effects in humans following exposure to airborne formaldehyde.

Murphy et al. (1964) found increased activities of alkaline phosphatase in livers of rats exposed to 35 ppm formaldehyde for 18 hours and suggested that formaldehyde may be hepatotoxic. More recent animal studies, however, have found no consistent evidence for formaldehyde-induced hepatotoxicity. Woutersen et al. (1987) found statistically significant increased levels of aspartate amino transferase, alanine amino transferase, and alkaline phosphatase in plasma of rats exposed to 20 ppm, (but not to 10 or 1 ppm) 6 hours/day, 5 days/week for 13 weeks, but found no exposure-related microscopic lesions

in the livers of these rats. In another experiment from the same laboratory, Appelman et al. (1988) found no exposure-related changes in serum aspartate amino transferase, alanine amino transferase, or alkaline phosphatase in plasma, no changes in liver concentrations of total protein or reduced glutathione, and no hepatic histological changes in rats exposed to up to 10 ppm by the same protocol for 13 or 52 weeks. Kamata et al. (1997) also reported that no exposure-related changes were found, at several sampling dates, in activities of serum alkaline phosphatase, aspartate amino transferase, or alanine amino transferase in rats exposed to up to 15 ppm, 6 hours/day, 5 days/week for up to 28 months. In 15-ppm rats, absolute, but not relative, liver weights were statistically significantly decreased compared with controls. This effect appears to have been a secondary effect from decreased food consumption at this exposure level rather than a direct effect of formaldehyde on the liver. No histological liver changes were found in Rhesus monkeys exposed to 6 ppm formaldehyde, 6 hours/day, 5 days/week for 6 weeks (Monticello et al. 1989), in mice exposed to up to 40 ppm by a similar protocol for 13 weeks (Maronpot et al. 1986), or in rats or mice exposed to up to 14.3 ppm for 24 months (Kerns et al. 1983b). The weight of available evidence suggests that airborne formaldehyde may produce toxic effects on the liver only at high concentrations that may exceed metabolic and binding capacities in the respiratory tract.

Renal Effects. In the only report located regarding renal effects in humans after inhalation exposure to formaldehyde, Freestone and Bentley (1989) noted that renal failure occurred in a 68-year-old man who inhaled and/or ingested an undetermined amount of formaldehyde. He stated that he had inhaled formaldehyde for a sore throat, however, the medical staff believed that he may have gargled with the formaldehyde as well. Dopamine was administered until renal function improved and the man was released.

No evidence from histological examinations or blood chemistry monitoring for formaldehyde-induced kidney effects has been found in intermediate-duration inhalation studies with rats, Rhesus monkeys, or mice (Appelman et al. 1988; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987), or in chronic inhalation studies with rats and mice (Kamata et al. 1997; Kerns et al. 1983b). Appelman et al. (1988) noted that rats exposed to 10 ppm, 6 hours/day, 5 days/week for 52 weeks had "frequent oliguria". Kerns et al. (1983b) also measured urinalytic variables in rats and mice exposed to up to 14.3 ppm by a similar protocol for 24 months, but did not report a similar finding.

Endocrine Effects. No studies were located regarding endocrine effects in humans exposed to inhaled formaldehyde. No evidence from histological examinations or organ weight measurements for formaldehyde-induced effects on endocrine organs (e.g., pancreas, pituitary, adrenals, thyroid) has been found in intermediate-duration inhalation studies with rats, mice or Rhesus monkeys (Appelman et al. 1988; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987), or in chronic inhalation studies with rats or mice (Kamata et al. 1997; Kerns et al. 1983b).

Dermal Effects. Occupational exposures to formaldehyde have been associated with dermal irritation and the diagnosis of allergic contact dermatitis by patch testing. Reported historical percentages of subjects with skin problems showing positive responses to formaldehyde in patch tests performed by dermatologists using aqueous solutions with 1 or 2% formaldehyde include 7.8% in North America between 1992 and 1994 (Marks et al. 1995), 1.6% in a 1983–1984 Swedish study (Meding and Swanbeck 1990), 2.6% in a 1988–1989 European study (Menné et al. 1991), and 3.7% in a 1990–1994 Polish study (Kiec-Swierczynska 1996). Lack of case-specific exposure information for these patients precludes the determination of the degree to which sensitization may have been caused by direct dermal contact to formaldehyde in liquids or by contact with formaldehyde gas in air, but the widespread use of formaldehyde or formaldehyde-releasing chemicals in cosmetics and cleaning agents (Flyvholm 1991; Rastogi 1992) suggest that the dermal route of exposure may be the more important sensitizing route. Dermal effects in humans from exposure to formaldehyde are further discussed in Sections 2.2.3.2 and 2.2.3.3.

Acute controlled exposure studies of volunteers exposed to airborne formaldehyde at concentrations ranging from 0.4 to 3 ppm have not found increased reporting of skin irritation symptoms (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Weber-Tschopp et al. 1977). Eberlein-Konig et al. (1998), however, found subtle skin effects in seven subjects described as having formaldehyde atopic eczema compared with seven nonsensitized subjects. Exposure to 0.08 ppm formaldehyde for 4 hours in an exposure chamber induced increased transepidermal water loss, but not skin roughness, on the uncovered lower arms of subjects with atopic eczema; neither transepidermal water loss nor skin roughness were increased by similar exposure in a group of seven subjects without atopic eczema. Serum levels of eosinophil cationic protein and soluble interleukin-2 receptor were not increased by exposure in either group.

No evidence for formaldehyde-induced effects on the skin has been reported in intermediate-duration inhalation studies with rats, hamsters, Rhesus monkeys, or mice (Appelman et al. 1988; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987), or in chronic inhalation studies with rats or mice (Kamata et al. 1997; Kerns et al. 1983b), except that the highest concentration used in these studies (40 ppm used in the 13-week mouse study by Maronpot et al. 1986) produced severe clinical signs of toxicity in mice including mouth breathing, ataxia, and "loss of skin elasticity".

Ocular Effects. From occupational exposure experience and results in controlled acute inhalation exposure studies in humans, airborne formaldehyde is well-known as an eye irritant. Because formaldehyde-induced eye irritation and upper respiratory tract irritation have often been noted at similar exposure concentrations, results from survey studies of occupationally-exposed workers and controlled acute exposure studies in which subjects reported symptoms of eye irritation were discussed earlier in the Respiratory Effects part of this section.

Studies of animals exposed to airborne formaldehyde for intermediate and chronic durations have not found increased incidences of histological changes in the eyes of mice exposed to up to 40 ppm (Kerns et al. 1983b; Maronpot et al. 1986), rats exposed to up to 20 ppm (Appelman et al. 1988; Kerns et al. 1983b; Swenberg et al. 1980; Woutersen et al. 1987), or monkeys exposed to 6 ppm (Monticello et al. 1989). Kerns et al. (1983b) reported that ophthalmoscopic examinations revealed no exposure-related changes in rats or mice examined at several intervals during a 2-year period of exposure to concentrations as high as 14.3 ppm. Clinical signs of eye irritation during exposure, however, have been reported in monkeys ("mild lacrimation and conjunctival hyperemia") exposed to 6 ppm for up to 6 weeks (Monticello et al. 1989), in rats exposed to 10 ppm for up to 4 days (Dinsdale et al. 1993), and in rats ("ocular discharge") exposed to 2 to 15 ppm, but not to 0.5 ppm, for up to 3 weeks (Morgan et al. 1986c). Swenberg et al. (1980) described the development of a "unilateral ocular discharge" that was associated with the subsequent development of nasal tumors in rats exposed to 14.3 ppm; this discharge is likely distinct from the clinical signs of eye irritation noted in the other animal studies and in the human studies.

Body Weight Effects. Body weight effects have not been associated with formaldehdye exposure in humans, but exposure-response relationships have been described in animal studies.

Body weight decreases 10% of control values were observed in male rats exposed to 10 ppm, but not to 1 ppm, 6 hours/day, 5 days/week for 13 or 52 weeks (Appelman et al. 1988); in male rats exposed to 2.95 ppm, but not to 0.98 ppm, 22 hours/day, 7 days/week for 26 weeks (Rusch et al. 1983); in male rats exposed to 20 ppm, but not to 10 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987); in male mice exposed to 20 ppm, and female mice exposed to 40 ppm, 6 hours/day, 5 days/week for 13 weeks (Maronpot et al. 1986); in male and female rats exposed to 14.3 ppm, but not to 5.6 ppm, 6 hours/day, 5 days/week for 2 years (Kerns et al. 1983b); in male rats exposed to 15 ppm, but not to 2 ppm, 6 hours, 5 days/week for 4 to 28 months (Kamata et al. 1997); and in male rats exposed to 10 ppm, but not to 1 ppm, 6 hours/day, 5 days/week for 28 months (Woutersen et al. 1989).

No body weight effects were observed in Rhesus monkeys exposed to 6 ppm, 6 hours/day, for 5 days or 5 days/week for 6 weeks (Monticello et al. 1989), in female rats, Cynomolgus monkeys, or hamsters exposed to up to 2.95 ppm, 22 hours/day, 7 days/week for 26 weeks (Rusch et al. 1983), in female rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), or in mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b).

2.2.1.3 Immunological and Lymphoreticular Effects

As discussed previously in Section 2.2.1.2 (dermal effects from inhalation exposure), formaldehyde is commonly diagnosed as a dermal allergen worldwide. Lack of case-specific exposure information precludes determining the degree to which sensitization may have been caused by direct dermal contact to formaldehyde in liquids or by contact with formaldehyde gas in air, but the widespread use of formaldehyde or formaldehyde-releasing chemicals in cosmetics and cleaning agents (Flyvholm 1991; Rastogi 1992) suggest that the dermal route of exposure may be the more important sensitizing route. Dermal effects in humans from exposure to formaldehyde, including formaldehyde allergic contact dermatitis, are further discussed in Section 2.2.3.2 and 2.2.3.3.

Investigations into the possibility of immunologically-mediated respiratory responses in formaldehyde-exposed individuals reporting respiratory problems such as bronchial asthma have provided very limited positive evidence.

There are only a few available case reports of bronchial asthma suggestive of respiratory tract sensitization to formaldehyde gas including two renal dialysis nurses (Hendrick and Lane 1975, 1977;

Hendrick et al. 1982), a plastic moulder (Burge et al. 1985), a printer (Burge et al. 1985), a worker in a phenol formaldehyde manufacturing plant (Burge et al. 1985), and a carpenter (Lemiere et al. 1995). These cases of formaldehyde-exposed workers all displayed marked changes in FEV_1 or airflow rates in response to acute challenges with formaldehyde gas at exposure levels <3 ppm. Nordman et al. (1985) provided acute formaldehyde (2 ppm) challenges to 230 patients who had been occupationally exposed to formaldehyde and who had reported respiratory symptoms consistent with asthma, but found challenge-induced decreases in PEFR >15% in only 12 subjects. Although an immunologic-mediated response may be consistent with the observed airway responses, the mechanism of sensitization in these subjects is uncertain. Challenge-induced deficits in FEV_1 or airflow rates indicative of lower airway sensitization were not found in studies of: 9 subjects complaining of respiratory problems from urea-formaldehyde foam insulation in their homes who were challenged with 1–1.2 ppm formaldehyde for 90 minutes (Day et al. 1984); 10 formaldehyde-exposed textile or shoe manufacturing workers with purported bronchial asthma who were challenged with 0.41 ppm for 2 hours (Krakowiak et al. 1998); and 13 formaldehyde-exposed subjects who had previously reported asthma-like symptoms who were challenged with 0.1, 1, or 3 ppm for 20 minutes (Reed and Frigas 1984).

Several studies have examined serum for formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed humans (Dykewicz et al. 1991; Grammar et al. 1990; Kramps et al. 1989; Wantke et al. 1996a, 1996b). In general, the studies do not provide consistent evidence for a formaldehyde-induced allergic respiratory syndrome, but provide suggestive evidence that children may have an increased tendency to develop specific antibodies after exposure to low levels of formaldehyde in indoor air (Wantke et al. 1996a).

Formaldehyde-specific IgE antibodies could be detected in only 1/86 serum samples from four groups of formaldehyde-exposed subjects (Kramps et al. 1989). The groups included 28 subjects living or working in places with formaldehyde-containing construction materials (e.g., chipboard) and estimated formaldehyde concentrations ranging from 0.08 to 0.37 ppm, 18 occupationally exposed subjects from an anatomy laboratory and in other unspecified industries where air concentrations were not measured, 12 hospital attendants who worked with formaldehyde-sterilized hemodialysis equipment, and 28 hemodialysis patients treated with formaldehyde-sterilized equipment. Variable symptoms such as headache, eye irritation, and respiratory complaints were reported by 24/28 subjects in the construction-material group. The group of 18 occupationally exposed subjects reported nonspecific irritation of eyes and airways associated with their work; the subject with detected formaldehyde-specific IgE displayed no

allergic symptoms. The hospital attendants and hemodialysis patients reported no exposure-related symptoms. Durations of exposure or employment were not reported for the subjects in this study.

Grammer et al. (1990) studied the immunologic nature of formaldehyde sensitivity in 37 workers who complained of formaldehyde-related illness and were examined by a group of physicians. Blood samples were collected and assayed for IgE and IgG activity against formaldehyde and formaldehyde-human serum albumin (f-HSA). Fourteen workers had symptoms consistent with an irritant syndrome, another 14 had symptoms consistent with a possible irritant, and 9 had no work-related symptoms. Four workers also had symptoms consistent with formaldehyde allergy. None of the workers had IgG activity against formaldehyde. Five workers had antiformaldehyde IgE activity, but further testing revealed that the IgE lacked formaldehyde specificity. The authors concluded that in this group of workers, there was no evidence of an immunologically mediated response to formaldehyde.

Dykewicz et al. (1991) sought to determine whether IgE or IgG antibodies to formaldehyde were related to formaldehyde exposure or respiratory symptoms arising from such an exposure. The authors studied 55 hospital histology technicians, internal medicine residents, pathology residents, current smokers, subjects with known workplace exposure to formaldehyde, and controls with no history of formaldehyde exposure. Reported workplace formaldehyde concentrations were 0.2–0.64 ppm for pathology residents, 0.64 ppm for histology technicians, and 0.6–11 ppm for miscellaneous formaldehyde exposure scenarios. No workplace air concentrations were measured for the other occupations. Average years of occupational exposure to formaldehyde were 12.45 years for histology technicians, 0.38 years for medical residents, 3.21 years for pathology residents, and 18.34 years for 5 subjects exposed to miscellaneous workplaces with formaldehyde. Each subject was evaluated by questionnaire for the presence of upper- and lower-respiratory tract and ocular symptoms and formaldehyde-related illnesses. Blood samples were drawn from each subject and were analyzed for IgE and IgG reactivity with f-HSA. Three subjects had IgE against f-HSA; these three and two others had low levels of anti-f-HSA IgG. The presence of IgG and IgE antibodies to formaldehyde was not clearly related to formaldehyde exposure or pack-years of smoking. One subject had both IgE and IgG antibodies and also suffered from eye and respiratory symptoms when exposed to formaldehyde at his workplace. The authors concluded that they could not establish a relationship of IgE and IgG to formaldehyde exposure. They further concluded that if immunologically mediated rhinitis or conjunctivitis existed, it must occur at extremely low frequencies. Several limitations of this study should be noted. First, the investigators recruited volunteers who may have systematically differed from the general populations from which they were

sampled. One of the exposure groups comprised cigarette smokers, who have exposures to many chemicals in addition to their formaldehyde exposures. Although the study focuses on formaldehyde antibodies, which would be unaffected by the other chemicals, respiratory symptoms among smokers would reflect exposures to the other smoke constituents.

Wantke et al. (1996a) measured elevated levels of formaldehyde-specific IgE in 24/62 8-year-old children who were students in three particle board-paneled classrooms with estimated formaldehyde air concentrations of 0.075, 0.069, and 0.043 ppm. In a health survey, the children reported headaches (29/62), fatigue (21/62), dry nasal mucosa (9/62), rhinitis (23/62), cough (15/62), and nosebleeds (14/62). Sums of numbers of children with each of nine symptoms for each classroom decreased with decreasing formaldehyde concentration (49, 47, and 24, respectively, for the 0.075-, 0.069-, and 0.043-ppm classrooms), but the investigators reported that elevated levels of specific IgE did not correlate with the number and severity of symptoms. The children were moved to a new school without particle board paneling and were evaluated again, 3 months after moving. Estimated formaldehyde concentrations in the new classrooms were 0.029, 0.023, and 0.026 ppm. The numbers of children reporting symptoms decreased significantly compared with premoving reporting figures, and mean serum levels of formaldehyde-specific IgE, measured in 20 of the children, declined significantly compared with premoving mean levels.

Formaldehyde-specific IgE was not detected in a group of 45 medical students, before or after the students attended a 4-week anatomy dissecting course (Wantke et al. 1996b). Estimates of laboratory air concentrations of formaldehyde ranged from 0.059 to 0.219 ppm (mean 0.124±0.05 ppm). Surveys revealed frequencies of irritation symptoms consistent with other studies (e.g., itching of the skin in 33/45 students, headache in 15/45, and burning eyes in 13/45).

Thrasher et al. (1987) assessed the effects of formaldehyde exposure on cellular immunity and antibody formation in eight symptomatic and eight unexposed individuals. The exposed group was comprised of three males and five females. Seven of the exposed individuals resided in mobile homes for periods ranging from 2 to 7 years; the eighth exposed subject was a laboratory worker who resided in a newly decorated, energy-efficient apartment. Air monitoring in four of the homes revealed formaldehyde vapor concentrations ranging from 0.07 to 0.55 ppm. Venous blood samples were collected from all subjects and lymphocytes were used for T- and B-cell enumeration and blastogenesis; serum samples were used to determine IgG and IgE antibodies to formaldehyde. IgE antibodies to formaldehyde were not detected in

exposed or control subjects; IgG antibodies in exposed subjects ranged from 1:8 to 1:256, but were undetected (1:4) in 7 of the controls. T- and B-cell numbers were significantly lower ($p<0.05$) in mobile home residents (48 and 12.6%, respectively) compared to control subjects (65.9 and 14.75%, respectively). Phytohemagglutinin-stimulated T- and B-cell blastogenesis was significantly depressed ($p<0.01$) in mobile home residents compared to control subjects (17,882 versus 28,576 counts per minute, respectively).

In a later study, Thrasher et al. (1990) evaluated four groups of patients with varying levels and durations of formaldehyde exposure. The groups consisted of asymptomatic chiropractic students exposed during anatomy classes (controls), mobile home residents, office workers, patients with multiple symptoms who had been removed from the source of formaldehyde for at least a year, and occupationally exposed patients. All groups were assessed for immunologic function via white cell, lymphocyte and T-cell counts, T-helper/suppressor ratios, B cell counts, and production of antibodies against f-HSA. When compared to controls (students), the patient groups had significant elevations in formaldehyde antibody titers and B-cell titers. The level of autoantibodies was also significantly elevated in patients exposed long-term to formaldehyde.

Gorski et al. (1992) investigated the correlation between formaldehyde-induced contact dermatitis and granulocyte chemiluminescence resulting from free-radical release in healthy and formaldehyde-sensitive patients. Thirteen patients with contact dermatitis who were occupationally exposed to formaldehyde and five healthy volunteers participated in the study. All subjects underwent skin-prick tests for common allergens as well as a histamine inhalation provocation test. Subjects were exposed to 0.5 mg/m^3 (0.41 ppm) formaldehyde for 2 hours, and peak expiratory flow was measured immediately before exposure, at 60 and 120 minutes of exposure, and at 6 and 21 hours after completion of exposure. In formaldehyde-sensitive patients, skin-prick tests and total serum IgE were normal; no antiformaldehyde IgE was detected. In formaldehyde-sensitive patients, peripheral blood granulocyte chemiluminescence significantly increased within 30 minutes of exposure commencement, and remained elevated 24 hours later, compared to initial values. Granulocyte chemiluminescence did not increase in healthy patients.

Pross et al. (1987) evaluated the immunologic response of asthmatic subjects exposed to UFFI off-gas products. Subjects consisted of 23 individuals with a history of asthmatic symptoms attributed to UFFI and 4 individuals with asthma unrelated to UFFI byproducts. All subjects were exposed to the following in an environmental chamber: room air (placebo) for 30 minutes; 1 ppm formaldehyde gas for 3 hours;

UFFI particles (4 μm, 0.5 particles/mL) for 3 hours, commencing 48 hours after formaldehyde gas exposure; and UFFI off-gas products for 3 hours, commencing 48 hours after UFFI particle exposure. There was a significant increase in the percentage and absolute number of eosinophils and basophils in the subjects that lived in UFFI-homes. There were no differences between exposure groups with respect to lymphocyte subpopulations either before or after UFFI exposure. However, when T8 suppressor cell count control values for the UFFI-exposed group were compared to T8 (suppressor) cell count values collected after UFFI chamber exposure, a small but statistically significant ($p<0.01$) increase in T8 cell count was observed. The significance of this change in T8 cell count is not known. Phytohemagglutin- and formalin-treated-red-blood-cell-stimulation studies revealed no differences between treatment groups in nonspecific or specific lymphocyte reactivity in response to UFFI exposure. Likewise, UFFI exposure had no effect on humoral immunity. Natural killer function was also unaffected by in-home or chamber exposure to UFFI, as was the interferon-boosted (IFN) natural killer cell response. Approximately half of the subjects from each group were classified as atopic based on skin-prick tests, but there was little correlation with NK function. The authors concluded that short-term exposure to formaldehyde was not immunosuppressive and did not result in systemic immune reactivity.

No histopathological effects on lymphoreticular tissues (e.g., spleen, thymus, lymph nodes) were observed in Rhesus monkeys exposed to 6 ppm, 6 hours/day, 5 days/week for 6 weeks (Monticello et al. 1989); in rats exposed to up to 10 ppm, 6 hours/day, 5 days/week for 13 or 52 weeks (Appelman et al. 1988); in rats exposed to up to 20 ppm, 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987); in mice exposed to 40 ppm, 6 hours/day, 5 days/week for 13 weeks (Maronpot et al. 1986); in rats and mice exposed to up to 14.3 ppm, 6 hours/day, 5 days/week for 24 months (Kerns et al. 1983b); or in rats exposed to up to 15 ppm, 6 hours/day, 5 days/week for 28 months (Kamata et al. 1997).

In a study by Adams et al. (1987), the effects of exposure to formaldehyde on the maturation of the mononuclear phagocyte system in female B6C3F1 mice were investigated. Mice were exposed to a target concentration of 15 ppm formaldehyde 6 hours/day, 5 days/week for 3 weeks. Exposure to formaldehyde for 3 weeks did not affect lymphoid organ weights or the number of resident or activated macrophages. Formaldehyde exposure resulted in lower peritoneal macrophage leucine aminopeptidase concentrations, but did not appear to induce maturation of resident macrophages. Formaldehyde treatment did not alter the ability of induced macrophages to bind and lyse tumor cells. In macrophages elicited by pyran copolymer MVE-2, the ability to release reactive oxygen intermediates (H_2O_2) was increased almost 2-fold as a result of formaldehyde exposure. The authors concluded that formaldehyde

exposure did not disturb the systemic development of tumoricidal macrophages, but did enhance the release of reactive oxygen intermediates.

Dean et al. (1984) studied immune function in female B6C3F1 mice 6–8 weeks of age. Mice were exposed by inhalation to 15 ppm formaldehyde for 6 hours/day, 5 days/week for 3 weeks. Several tests that evaluated immune function were used: (1) tumor challenge procedure consisting of a subcutaneous injection of PYB6 sarcoma cells, (2) tumor resistance assessment consisting of an intravenous injection of B16F10 melanoma cells, and (3) an intravenous challenge using *Listeria monocytogenes* bacteria. Other tests that evaluated immune function were cell-mediated immunity (consisting of monitoring the delayed hypersensitivity response to keyhole limpet hemocyanin); lymphoproliferative responses to T-cell mitogens (phytohemagglutinin) and B-cell mitogens (*Escherichia coli lipopolysaccharide*); spontaneous cytotoxicity (natural killer cell); macrophage function (elicitation, activation, phagocytic); plaque-forming cell activity; and spleen and bone marrow cellularity. Thymus and spleen weights were unaffected by formaldehyde exposure. A significant decrease in the absolute number of monocytes was observed in the formaldehyde-treated mice ($4/mm^3$ versus $43/mm^3$ in controls; $p<0.05$); all other hematological parameters in treated mice were similar to those of controls. Spleen and bone marrow cellularity were similar in treated and control groups. Formaldehyde-treated animals experienced lower mortality (30%) than controls (70%) in response to challenge with *Listeria monocytogenes*. Formaldehyde-treated mice were also less susceptible to tumor transfer or formation compared to controls. No differences were noted in treated and control mice for the following parameters: delayed hypersensitivity reaction; natural killer cell-mediated tumor cytotoxicity; lymphocyte proliferation; lymphocyte surface markers; macrophage function; and plaque-forming cell response. The authors concluded that exposure to 15 ppm formaldehyde for 3 weeks was not immunotoxic; they hypothesized that this was due to the highly reactive nature of the compound which prevents penetration into the deep lung and tissue penetration in general.

Holmstrom et al. (1989b) evaluated the long-term inhalation effects of formaldehyde exposure to immune function in female Sprague-Dawley rats exposed to 12.6 ppm formaldehyde for 6 hours/day, 5 days/week for 22 months. After 22 months of formaldehyde exposure, the rats were inoculated subcutaneously with Pneumovax (Merck Sharpe and Dohme) and antitetanus vaccine (National Bacteriological Laboratory). Animals were sacrificed at 21–25 days after vaccination. Blood samples were collected from each animal before vaccination and just prior to sacrifice. The blood was analyzed for response to Pneumovax and tetanus vaccination using an enzyme-linked immunosorbant assay technique. The results indicated that

there were no differences between exposed and control animals in IgM production in response to Pneumovax. Mean overall IgG production in response to Pneumovax was similar between exposed and control rats; however, a 2-fold increase in IgG production in response to the 19F pneumococcal antigen was seen in 4 of 8 exposed rats compared to 1 of 6 control rats. The IgM response to tetanus immunization was similar in the exposed and control groups; levels increased at least 2-fold in a majority of animals in both groups. Likewise, IgG levels increased significantly in response to tetanus toxoid, but the response did not differ between treatment groups. The authors concluded that there was no evidence of immunosuppression in response to long-term exposure to near-maximal levels of formaldehyde in rats.

Whereas other animal experiments have not found convincing evidence that repeated inhalation exposure to formaldehyde has direct effects on the immune system, there is suggestive evidence that it may have an indirect effect by facilitating sensitization of nasal tissue to high-molecular weight allergens in mice (Tarkowski and Gorski 1995). The ability of intranasal administration of 25 μg of ovalbumin (once a week for 7 weeks) to increase the titer of serum IgE antibodies to ovalbumin (IgE anti-OVA) was examined in groups of 10 Balb/c mice preexposed to 0 or 1.6 ppm formaldehyde 6 hours/day for 10 days, or to 0 or 1.6 ppm, 6 hours/day once a week for 7 weeks. In a second experiment, groups of mice were preexposed to 0 or 1.6 ppm, 6 hours/day for 10 days, injected with up to 4 doses of 1 μg ovalbumin in the peritoneum, and examined for serum IgE antiOVA titers. Serum titers of IgE antiOVA were significantly higher (after four intranasal doses of OVA) in mice preexposed to formaldehyde 6 hours/day for 10 days compared with control titers; mean IgE antiOVA titer at 7 weeks in 10-day preexposed mice was >60 units compared with about 15 units for controls. No significant difference in IgE-OVA was found between controls and the group preexposed to formaldehyde once a week for 7 weeks. With intraperitoneal administration of ovalbumin, preexposure to formaldehyde for 10 consecutive days had no effect on serum IgE-OVA titers compared with controls.

In a similar experiment with guinea pigs, Riedel et al. (1996) observed a greater percentage of allergic responses to inhaled ovalbumin in a group of guinea pigs pre-exposed to 0.25 ppm formaldehyde, 8 hours/day for 5 days than in a control group without preexposure to formaldehyde (10/12 versus 3/12) (Riedel et al. 1996).

The highest NOAEL values and all LOAEL values from each reliable study for immunological/ lymphoreticular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Bach et al. (1990) sought to determine whether humans reacted acutely to formaldehyde exposure, and if previous chronic-duration exposure to formaldehyde altered the responses noted in acute exposure. Thirty-two men with at least 5 years of occupational exposure to formaldehyde and 29 matched controls were exposed to formaldehyde at concentrations of 0, 0.12, 0.32, or 0.98 ppm for 5.5 hours. During the exposure period, subjects underwent a battery of performance tests designed to estimate the subject's distractibility, short-term memory, and capability to understand and perform certain tasks. Controls tended to suffer from headaches, "heavy head", and physical tiredness more than the exposed workers. In both occupationally exposed subjects and nonexposed subjects, decreased performances in several tests were statistically significantly correlated with increasing acute concentration of formaldehyde. Occupationally exposed subjects showed significantly decreased performance, compared with nonexposed subjects, only in a digit span test, but not in variables for a graphic continuous line test, an addition test, or a digit symbol test. The authors noted that the typical dose-related symptoms of respiratory irritation were not seen in this study.

Kilburn and colleagues have presented evidence for neurological impairments in several studies of formaldehyde-exposed histology technicians, but confounding exposure to other neurotoxic solvents prevents drawing definitive conclusions concerning the neurotoxicity of formaldehyde from these studies (Kilburn 1994; Kilburn and Warshaw 1992; Kilburn et al. 1985b, 1987). Kilburn et al. (1985b) reported that a group of 76 female histology technicians reported statistically significantly greater frequencies of neurobehavioral symptoms such as lack of concentration and loss of memory, disturbed sleep, impaired balance, variations in mood, and irritability than did a referent group of 56 non-exposed female clerical workers. The technicians had been employed from 2 to 37 years (mean 12.8 years). Analysis of workplace air samples indicated concentrations for several solvents ranging from 0.2 to 1.9 ppm for formaldehyde, 3.2 to 102 ppm for xylene, 2 to 19.1 ppm for chloroform, and 8.9 to 12.6 ppm for toluene. Subsequently, Kilburn et al. (1987) administered a battery of 10 tests that assessed memory, balance, coordination, dexterity, motor speed, and aspects of cognitive function to 305 female histology technicians and analyzed the results by regression analysis with age, years of smoking, hours per day of exposure to formaldehyde and other solvents as explanatory variables. Increased daily hours of exposure to formaldehyde were significantly correlated with decreased performance in several tests, whereas hours of daily exposure to other solvents were only correlated with decreased perfomance in a single test. However, in a later prospective study of performance by 318-494 histology technicians in a battery of

neurobehavioral tests, no statistically significant cumulative effects due to occupational exposure to formaldehyde (or other solvents) or of aging were found over a 4-year period (Kilburn and Warshaw 1992). Kilburn (1994) further reported that three anatomists and one railroad worker, who were occupationally exposed to airborne formaldehyde for 14-30 years and who were disabled, each showed impaired performance on several neurobehavioral tests (e.g., choice reaction time, abnormal balance, digit symbol, and tests of perceptual motor speed).

In laboratory animals, Morgan et al. (1986a) studied male Fischer 344 rats exposed to 15 ppm formaldehyde for 10, 20, 45, or 90 minutes, or 6 hours. Some additional rats were also exposed to 2 ppm formaldehyde for 90 minutes or 6 hours to establish whether this level was a no-effect concentration. The rats exposed to 15 ppm formaldehyde exhibited restless behavior for the first 10–15 minutes of exposure.

Boja et al. (1985) investigated the effects of low-level formaldehyde exposure on behavior and neurochemistry in male Sprague-Dawley rats. Animals were exposed to either air or formaldehyde at concentrations of 5, 10, or 20 ppm for 3 hours. The following day the rats were exposed to either the same treatment or the opposite treatment (i.e., treatment groups of air-air, air-formaldehyde, formaldehyde-air, or formaldehyde-formaldehyde). Behavioral activity was periodically monitored. After the second day of exposure, rats were sacrificed, their brains were removed, and samples of striatum, nucleus accumbens, frontal cortex, lateral septum, amygdala, hypothalamus, and hippocampus were collected and analyzed for norepinephrine, dopamine, and 5-hydroxytryptamine and their major metabolites. Exposure to 5 ppm formaldehyde resulted in statistically significant decreased motor activity within 15 minutes. At the beginning of day 2, all of the rats exposed to formaldehyde on day 1 displayed lower activity levels. Similar effects on motor activity were seen at the 10 ppm formaldehyde exposure level, whereas effects seen after 20 ppm exposure were reported to be "not readily interpretable" and were not shown. Exposure to 5 ppm formaldehyde statistically significantly increased concentrations of 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenylacetic acid, and dopamine in the hypothalamus, but did not affect the concentrations of norepinephrine or 5-hydroxytryptamine. Data for other brain regions or exposure concentrations were not reported (Boja et al. 1985).

Wood and Coleman (1995) assessed the behavioral response to formaldehyde exposure in male Swiss mice. Eight mice were trained to terminate exposure to noxious gases, using 1,000 ppm ammonia. All animals learned to terminate 100% of the ammonia exposures. After mice consistently terminated

ammonia exposures, they were exposed to a series of formaldehyde exposures at concentrations of 0, 1, 1.8, 3, 5.6, and 10 ppm. Beginning at the lowest formaldehyde concentration (1 ppm), mice terminated significantly more exposures compared to air ($p<0.0005$). The number of terminations increased and the time to termination decreased as the concentration of formaldehyde increased. Exposure durations in the second series were significantly shorter ($p=0.0012$) than those experienced in the first series, indicating an increased sensitivity to formaldehyde. Wood and Coleman (1995) suggested that a conditioned response may have developed in the mice rather than a change in the sensitivity of the sensory epithelium.

In studies of intermediate-duration exposure, Maronpot et al. (1986) studied the effects of formaldehyde exposure in male and female B6C3F1 mice. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for 13 weeks at target concentrations of 0, 2, 4, 10, 20, or 40 ppm. No obvious gross signs of neurotoxicity were seen in mice treated with 2, 4, or 10 ppm formaldehyde, but mice in the 20-ppm group exhibited dyspnea, listlessness, and hunched posture. These symptoms were also noted in the 40-ppm groups with greater severity; in addition, mice in this group exhibited ataxia.

Appelman et al. (1988) examined the effects of preexisting nasal damage and formaldehyde exposure in male SPF Wistar rats. Groups of 40 rats each were exposed to 0, 0.1, 1, and 10 ppm formaldehyde. Within each dose group, half of the animals had their nasal mucosa damaged by electrocoagulation. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for either 13 or 52 weeks ($n=10$ per dose/nasal damage subgroup). Behavior and appearance were not affected by formaldehyde exposure; brain weights and histopathology in all of the formaldehyde-treatment groups were not significantly different from the control animals.

Woutersen et al. (1987) examined the effects of inhalation exposure to formaldehyde in male and female Wistar rats. Groups of 10 animals per sex were exposed to target concentrations of 1, 10, or 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks. Uncoordinated movement and wall-climbing were noted during the first 30 minutes of each exposure period in the 20-ppm group; the rats in the lower-dose groups did not exhibit abnormal behavior. In the 20-ppm males, relative organ weights were higher in 6 of the 11 animals examined (no further data supplied), and in the females of this dose group, only relative brain weights were significantly greater than those of controls. No treatment-related gross or histopathological lesions of the brain were noted in any sex or dose-group at necropsy.

Kerns et al. (1983b) studied the effects of long-term formaldehyde exposure on 120 male and female Fischer 344 rats and B6C3F1 mice exposed to 0, 2, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months. The dosing period was followed by a 6-month observation period. Interim sacrifices were performed at 6, 12, 18, 24, 27, and 30 months. No dose-related neurofunctional effects were noted at any dose or interim sacrifice time-point in either sex or species.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

Ward et al. (1984) investigated whether formaldehyde exposure resulted in altered sperm numbers or morphology in male pathologists. Exposed subjects consisted of 11 men; 10 were employed for 1–11 months (average 4.3 months) and the other was employed for several years. All subjects provided three semen samples collected at 2–3 month intervals. Sperm samples were analyzed for sperm count, morphology, and F-body frequency. Time-weighted average air concentrations in workplaces ranged from 0.61 to 1.32 ppm (midpoint of range 0.97 ppm). The mean sperm count for exposed workers was lower than that of controls (62.9×10^6/mL versus 87.4×10^6/mL); however, the difference was not statistically significant. The frequency of abnormal sperm was not greater in exposed subjects. The frequency of sperm containing 1F- or 2F-bodies was similar between exposed and control subjects. The small number of subjects in this study limited its detection power.

Garry et al. (1980) investigated the health effects associated with formaldehyde exposure in Minnesota residents. A total of 275 cases of possible formaldehyde exposure were investigated between February and June 1979. Medical histories of the patient and all family members were recorded, and 30-minute air samples were collected from the living room and bedroom of each residence. Environmental information (age, type of home, type of insulation, type of heat) was also collected. Formaldehyde levels ranged from 0.1 to 3 ppm. The rate of miscarriages in exposed women in this study (11.6%) did not differ from the rate of miscarriages seen in other studies of non-exposed women. There is no information on the duration of exposure; therefore, chronic-duration exposure is assumed.

The possible teratogenic effects of inhaled formaldehyde were investigated in groups of 25 female rats exposed to airborne formaldehyde at levels of 0, 2, 5, and 10 ppm, 6 hours/day on gestation days 6–15.

No maternal or fetal deaths occurred, and pregnancy parameters (numbers of corpora lutea, implantation sites, pre-implantation losses) were not affected by formaldehyde exposure (Martin 1990).

Although maternal toxicity, expressed as a statistically significant decrease in bodyweight gain, was observed in pregnant Sprague Dawley rats exposed to 40 ppm, but not 20 ppm, 6 hours/day on gestation days 6–20 (Saillenfait et al. 1989), other statistically significant changes in reproductive variables (e.g., number of implantation sites and number of resorptions), however, were not found.

Woutersen et al. (1987) examined the effects of inhalation exposure to formaldehyde in male and female Wistar rats. Groups of 10 animals per sex were exposed to target concentrations of 1, 10, and 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks. No treatment-related gross lesions were noted for the ovaries and testes at necropsy.

Appelman et al. (1988) provided data on the reproductive organs of rats exposed to formaldehyde. Male SPF Wistar rats were exposed to 0, 0.1, 1, and 10 ppm formaldehyde. Within each dose group, half of the animals (n=20) had their nasal mucosa damaged by electrocoagulation. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for either 13 or 52 weeks. No significant changes in testicle weights of treated rats were noted when compared to controls.

Maronpot et al. (1986) examined the effects of formaldehyde exposure on reproductive organs in male and female B6C3F1 mice. Animals were exposed to formaldehyde 6 hours/day, 5 days/week for 13 weeks at concentrations of 2, 4, 10, 20, and 40 ppm. Gross and histopathological examination showed ovarian and uterine hypoplasia characterized by decreased prominence of endometrial glands and stroma and an associated lack of ovarian luteal tissue in 40-ppm females. Ovarian and uterine hypoplasia were not observed in the lower exposure groups. No histopathological effects were noted in male reproductive organs. Maronpot et al. (1986) ascribed to the belief that the ovarian and uterine effects reflected "the general debility and weight loss rather than a direct target organ effect of formaldehyde".

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects for the intermediate duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

Studies regarding the developmental toxicity of airborne formaldehyde in humans are limited to a population-based case-control study of 244 mothers with "low-birth weight" newborns in Lithuania compared with 4,089 control mothers with "normal weight" newborns (Gra ulevi iene et al. 1998). Questionnaire information was collected from cases and controls for risk factors including place of residence. Based on air monitoring data, residential districts were grouped into low (mean concentration 1.6 ppb), moderate (2.8 ppb), or high (3.8 ppb) formaldehyde-exposure districts. After adjustment for other risk factors such as age, occupation, last pregnancy outcome, and smoking habit, the odds ratio (OR) for low-birth weight incidence was elevated in those with formaldehyde exposure >2.8 ppb compared with those with exposure <2.8 ppb, but not to a statistically significant degree (OR=1.37, 95% confidence interval [CI] 0.90–2.09).

Martin (1990) exposed groups of 25 pregnant Sprague-Dawley rats to 0, 2, 5, or 10 ppm in an inhalation chamber, 6 hours/day from gestation days 6 to 15. Another nonexposed group of 25 pregnant rats was housed outside of the inhalation chamber ("room control"). Dams were sacrificed on day 20 and uterine contents were evaluated. Statistically significant decreased food consumption and weight gain occurred in the 10-ppm dams. No statistically significant effects from exposure were found on the following variables: numbers of corpora lutea, implantation sites, live fetuses, dead fetuses and resorptions, fetal weights, fetal sex ratios, and pre- and postimplantation losses. Likewise, no exposure-related effects were reported on the incidences of litters and fetuses with major malformations, minor external and visceral anomalies, and minor skeletal anomalies. The only statistically significant finding reported was for increased incidences of reduced ossification of the pubic and ischial bones in the 5- and 10-ppm groups, compared with the 0-ppm groups but not the "room control" group. Martin (1990) did not consider these findings to be biologically significant, noting that they were considered to be related to the "slightly lower" fetal weights and "slightly larger" litter sizes in the 5- and 10-ppm groups. The published report, however, did not provide more details on the quantitative data collected, making assignment of fetal effect levels in this study uncertain.

Saillenfait et al. (1989) assessed the effects of maternal formaldehyde inhalation on embryonic and fetal development in Sprague-Dawley rats. Groups of 25 mated females were exposed to 0, 5, 10, 20, and 40 ppm formaldehyde on gestation days 6–20. The dams were weighed on gestation days 0, 6, and 21. All dams survived the experiment. On gestation day 21, the dams were sacrificed and their uteri were

exposed and examined. The following parameters were assessed: maternal weight gain, percentage pregnant, litter sex ratio, fetal mortality, fetal weight, cleft palate malformations, and alterations of soft and skeletal tissues. Exposure to 40 ppm formaldehyde resulted in a 51% reduction in weight gain in dams compared to controls ($p<0.01$). There were no significant differences between treatment groups in the incidences of pregnancies; number of implantations or resorptions; numbers of dead or live fetuses; fetal sex ratios; or the incidences of external, visceral, or skeletal abnormalities. Fetal weights were significantly lower in male offspring from dams exposed to 20 ppm formaldehyde ($p<0.05$) and in male and female offspring from dams exposed to 40 ppm formaldehyde ($p<0.01$); the decreases seen in the 20 ppm group were <5% of control values. At 40 ppm, the differences in weights averaged 21%. The authors concluded that maternal exposure to formaldehyde during gestation days 6–20 was not teratogenic at levels 40 ppm, but was slightly fetotoxic at 20 ppm.

The highest NOAEL value and less serious and serious LOAEL values from the Saillenfait (1989) study for developmental effects in rats are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

Several studies were identified that described the genotoxic effects of formaldehyde after inhalation exposure. In one study, peripheral lymphocytes from eight anatomy students exposed to formaldehyde-embalming solution over a 10-week course were examined for sister chromatid exchange (SCE). Results were compared with preexposure values for each student. Breathing-zone monitoring revealed mean exposure of 1.2 ppm (range 0.73–1.95 ppm). A small average increase in the incidence of SCE was observed in the lymphocytes of the students after exposure (7.2/cell) when compared to values obtained before exposure (6.39/cell) (Yager et al. 1986). Conversely, Vasudeva and Anand (1996) examined the effects of formaldehyde exposure on the incidence of chromosomal aberrations in peripheral blood lymphocytes of 30 medical students exposed to formaldehyde vapors at concentrations of <1 ppm for 15 months. Questionnaires established that the participants were healthy and had insignificant medical histories. There was no difference in the incidences of chromosomal aberrations among the exposed and control groups. The mean frequencies of aberrant metaphases in the exposed and control groups were 1.2 and 0.9%, respectively. There was no correlation between reported irritant effects of formaldehyde and the number of aberrant metaphases, and the authors concluded that exposure to formaldehyde at concentrations seen in this study does not lead to chromosomal aberrations.

Fleig et al. (1982) performed chromosome analyses on 15 exposed and 15 non-exposed employees from formaldehyde manufacturing facilities. Exposed workers had an average duration of exposure of 28 years (range 23–35 years). Average exposure concentrations did not exceed 5 ppm prior to 1971 and 1 ppm after 1971. The formaldehyde exposures of individual workers were classified into one of the three following categories: Category 1: exposure 25% of the maximum workplace concentration (MAK); Category 2: exposure up to a maximum of 60% MAK; and Category 3: exposure up to 100% of the MAK. Peripheral blood samples were collected from each worker and lymphocytes were separated and cultured for 70–72 hours at 37 C. Cells were subsequently fixed and examined for chromatid- and chromosome-type aberrations. There were no differences between exposed and control groups in the incidence of chromosomal aberrations. The mean frequency of aberrant metaphases among formaldehyde-exposed persons was 3.07 versus 3.33% in controls. No correlation was found between formaldehyde exposure levels and the number of aberrant metaphases.

Shaham et al. (1996a) measured the formation of DNA-protein cross links in peripheral white blood cells of occupationally exposed workers (n=12) and unexposed controls (n=8). The average length of occupational exposure was 13 years. All subjects completed a questionnaire regarding demographics, occupational and medical background, and smoking and hygiene habits. Venous blood samples were collected from each worker and were processed to isolate DNA-protein cross links. Personal and room concentrations of formaldehyde were collected at various periods during the working day among the exposed subjects, with formaldehyde room concentrations ranging from 1.38 to 1.6 ppm. Personal monitoring devices indicated formaldehyde concentrations of 2.8–3.1 ppm during peak work and an average concentration of 1.46 ppm at times when work was usually completed. Exposure to formaldehyde resulted in a significant increase in the incidence of DNA-protein cross links. Mean (±sd) incidences in exposed and nonexposed workers were 28±6 and 22±6%, respectively. Within the exposed workers group, technicians had significantly greater levels of DNA-protein cross links than physicians (32.3±4.3 and 26.3±4.4%, respectively). A linear relationship between years of exposure and DNA-protein cross links formation was also detected. When the data were analyzed considering worker smoking habits, DNA-protein cross links was consistently elevated among formaldehyde-exposed versus corresponding controls (p=0.03). The authors concluded that DNA-protein cross links can be used as a biomarker of exposure; however, the assay measures DNA-protein cross links in general, not those specific to formaldehyde cross link formation.

Chebotarev et al. (1986) examined the lymphocytes sister chromatic exchanges (SCEs) of 40 wood-working employees and 22 control workers for chromosomal aberrations, SCEs, and unscheduled DNA repair or synthesis. The level of chromosomal aberrations in formaldehyde-exposed workers was 2.76%, which was significantly elevated compared to spontaneous chromosomal aberrations in controls (1.64%, $p<0.05$). The incidence of chromosomal breakage in exposed workers (2.95%) was significantly greater than the frequency of spontaneous breakage (1.64%, $p<0.05$). No differences between exposed and control subjects were seen for SCEs either at baseline (8.01 versus 8.24 exchanges per cell) or after induction with the genotoxin thiotepa (23.32 versus 25.78 exchanges per cell). There were no differences between formaldehyde-exposed and control samples in unscheduled DNA repair rates at baseline (335.2 versus 341.9) or after treatment with hydroxyurea (179.8 versus 194.2). However, when treated with thiotepa, unscheduled DNA repair rates in lymphocytes from formaldehyde-exposed workers were lower than those from control workers (217.2 versus 270.4, $p<0.05$). Using another measure of mutagenicity, Ballarin et al. (1992) evaluated 15 nonsmoking workers (8 males, 7 females) who worked in a plywood factory for cytopathologic changes in nasal mucosal cells, and compared the results to matched controls. Mean levels of exposure to formaldehyde ranged from 0.07 to 0.08 ppm in the sawmill and shearing press departments to 0.32 ppm in the warehouse. The total range of exposure in all areas containing formaldehyde vapors was 0.06–0.49 ppm. Workers were also exposed to wood dust. Nasal mucosal cells from exposed workers exhibited significantly increased incidence of micronuclei (0.9 versus 0.25 for controls), chronic inflammation, and a significantly higher frequency of squamous metaplasia cells (histological score: 2.3 versus 1.6) than cells from control workers. Micronuclei were found mainly in the ciliated cells.

In another study, Connor et al. (1985b) tested urine obtained from hospital autopsy service workers exposed to formaldehyde and from matched control workers for cellular mutagenicity. Exposed workers had worked in the hospital for at least 6 months. Actual exposure to formaldehyde was determined to be from 0.1 to 5.8 ppm, using personal breathing zone monitoring; the TWA exposures to formaldehyde in work areas were estimated to be 0.61–1.32 ppm. Mutagenicity tests using *Salmonella typhimurium (S. typhimurium)* TA 100 and TA 98 were conducted, with or without rat S9 (microsomes containing cytochrome P-450) suspension. No increase was seen in mutagenicity using urine of exposed workers, compared to control urine. Addition of S9 had no significant effect on the genotoxicity of the urine.

Studies in laboratory animals have also demonstrated that formaldehyde can be genotoxic in some cells after inhalation exposure. Dallas et al. (1992) exposed male Sprague-Dawley rats to formaldehyde

concentrations of 0, 0.5, 3, and 15 ppm, by inhalation for 6 hours/day for 5 days. The rats were sacrificed, and their pulmonary macrophages and bone marrow cells were harvested and analyzed by flow cytrometry and cytogenetic analysis. Cell division was arrested using colchicine treatment (1 mg/kg) 2 hours prior to sacrifice. Five days after the beginning of exposure, formaldehyde-exposed groups exhibited no more than 4% chromosomal aberrations in the bone marrow cells, which was not significantly different from control values. There were no differences with respect to dose group. Chromatid breaks, chromosome breaks, and centric fusions were observed in bone marrow cells, but were not considered to be associated with formaldehyde exposure. An increase in chromosomal abnormalities in pulmonary macrophages, predominantly chromatid breaks, was observed in the 15 ppm group (7.5 versus 3.4% for controls) after 5 days of exposure. Small increases were also seen in the 0.5 and 3 ppm groups, but these were not statistically significant. No chromosome breaks or centric fusions were observed in control cells obtained by pulmonary lavage.

Dallas et al. (1992) also extended the exposure treatment time to 1 or 8 weeks. The rats were sacrificed after 1 or 8 weeks of exposure, and pulmonary macrophages and bone marrow cells were harvested and analyzed by flow cytrometry and cytogenetic analysis. Formaldehyde-exposed groups exhibited no more than 4% chromosomal aberrations in the bone marrow cells, which was not significantly different from control values. Chromatid breaks, chromosome breaks, and centric fusions were observed in bone marrow cells, and again, were not associated with formaldehyde exposure. With respect to pulmonary macrophages, an increase in chromosomal abnormalities was observed in the 15 ppm group (9.2 versus 4.8% for controls) after 5 days of exposure. Small increases were also seen in the 0.5 and 3 ppm group, but these were not statistically significant. The predominant cytogenetic damage was chromatid breaks, observed in both control and treated cells. No chromosome breaks or centric fusions were observed in control cells obtained by pulmonary lavage. In formaldehyde-treated animals, chromosome breaks and centric fusions were noted, but were not dose-related.

Lam et al. (1985) studied the effects of inhalational co-exposure to acrolein and formaldehyde in male Fischer 344 rats. Rats were exposed for 6 hours to room air (controls), 2 ppm acrolein, 6 ppm formaldehyde, or a combination of 2 ppm acrolein and 6 ppm formaldehyde. The animals were sacrificed immediately after completion of exposure, and their nasal tissues were harvested. The DNA was isolated and the aqueous and interfacial portions were collected separately. Exposure to formaldehyde significantly increased the percentage of interfacial DNA (12.5%), the specific portion of the DNA which contains the DNA cross linked to proteins, compared to rats exposed to room air only

(8.1%, $p<0.05$). Co-exposure to acrolein resulted in a further increase in the percentage of interfacial DNA (18.6%) which was significantly greater than the effect of formaldehyde alone ($p<0.05$). The authors concluded that simultaneous exposure to acrolein enhanced formaldehyde-induced DNA-protein cross linking.

Other genotoxicity studies are discussed in Section 2.5. More extensive evaluation of the genotoxic potential of formaldehyde is available (IARC 1995; WHO 1989).

2.2.1.8 Cancer

Human Studies Overview. The finding of nasal tumors in rodents exposed to high levels of airborne formaldehyde in the early 1980s (Albert et al. 1982; Kerns et al. 1983b; Swenberg et al. 1980) led to a concern for cancer effects in occupationally exposed workers. There are now more than 40 epidemiology studies examining the potential for occupational formaldehyde exposure to cause cancer in humans. The studies include cohort mortality studies of formaldehyde-exposed industrial workers, cohort mortality studies of formaldehyde-exposed professionals or medical specialists, and case-control studies that looked for associations between occupational exposure to formaldehyde and cancers of the nose, pharynx, or lung. Published reviews and evaluations of the epidemiology studies include early reviews by IARC (1987), Purchase and Paddle (1989), and an *ad hoc* panel convened by Universities Associated for Research and Education in Pathology (1988). More recent reviews have been published by Conaway et al. (1996), ECETOC (1995), IARC (1995), and McLaughlin (1994). In addition, three meta-analyses of the data have been published (Blair et al. 1990a; Collins et al. 1997; Partanen 1993). Although some of the epidemiological studies have found some scattered evidence for extra-respiratory site cancers in groups of formaldehyde-exposed workers, the data are not consistent across studies and adjustment for potential confounding cancer risk factors has not often been possible. Most, if not all reviewers, have agreed that cancer of the respiratory tract, particularly the upper respiratory tract, is more biologically plausible than formaldehyde-induced cancer at distant sites given the reactivity of formaldehyde, the capacity of tissues to metabolize formaldehyde, and the results from chronic rodent inhalation studies showing that formaldehyde-induced nonneoplastic and neoplastic effects are restricted to the upper respiratory tract with exposures to concentrations below 5–10 ppm. Accordingly, the meta-analyses of the human data have focused on the findings for respiratory cancer deaths in occupationally exposed humans.

Six mortality studies of the following cohorts of formaldehyde-exposed industrial workers are included in recent reviews and the meta-analyses: 26,561 U.S. workers involved in formaldehyde production, resin making, and several other activities using formaldehyde (Blair et al. 1986, 1990a); 7,660 workers in six British plants using formaldehyde (Acheson et al. 1984a; Gardner et al. 1993); 11,030 workers in three U.S. garment facilities (Stayner et al. 1988); 1332 Italian workers involved in resin making (Bertazzi et al. 1986, 1989); 3929 foundry workers exposed to formaldehyde (Andjelkovich et al. 1994b, 1995a); and 6,039 workers in a Conneticut chemical plant that included some of the workers from the Blair et al. study (Marsh et al. 1994, 1996). Data from the Blair et al. (1986) study have been independently analyzed by Sterling and Weinkam (1989, 1995).

In the industrial worker cohort studies, the range of standardized mortality ratios (SMR; see Table 2-2 for definitions of selected epidemiological terms) relevant to exposure to airborne formaldehyde were (a zero reflects a finding of no deaths from the subject cancer):

for *lung cancer* - 0.9 to 1.4 (lung cancer deaths were reported in each cohort);

for *nasopharyngeal cancer* - 0 to 3.0 (only the Blair et al. [1986, 1990a] study had nasopharyngeal cancer deaths: 6 observed versus 2 expected);

for *nasal cancer* - 0 to 0.6 (Andjelkovich et al. 1994b, 1995a; Bertazzi et al. 1986, 1989; Marsh et al. 1994, 1996; and Stayner et al. 1988, however, did not report nasal cancer deaths); and

for *buccal cavity and/or pharynx cancer* - 1.1 to 1.69 (only Bertazzi et al. 1986, 1989 did not report buccal cavity and/or pharynx cancer).

Small excess relative risks for buccal cavity and/or pharynx cancer and lung cancer were most consistently observed across these studies. The increases in risk were generally not of statistical significance with the exception of the Blair et al. (1986) report of an SMR of 3.0 (95% CI, 1.3–6.6) for nasopharyngeal cancer.

Nine mortality studies of the following cohorts of formaldehyde-exposed professionals or medical specialists are included in recent reviews and the meta-analyses: 2,079 British pathologists and 12,944 medical specialists (Harrington and Shannon 1975); 1,263 deceased New York embalmers (Walrath and Fraumeni 1983); 1,109 deceased California embalmers (Walrath and Fraumeni 1984); 1,477 Ontario funeral workers (Levine et al. 1984a); 2,317 U.S. anatomists (Stroup et al. 1986); 5,810 U.S. pathologists (Matanoski 1991); 5,585 U.S. pathologists (Logue et al. 1986); 4,046 deceased

Table 2-2. Definitions of Selected Epidemiology Terms

Standardized mortality ratio (SMR)	is the ratio of a cause-specific mortality rate in an exposed cohort during a given period to the mortality rate of an unexposed cohort; mortality rates are often adjusted for age or other confounding variables.
Proportionate mortality ratio (PMR)	is the ratio of a cause-specific mortality proportion in an exposed group to the mortality proportion in an unexposed group; mortality proportions may be adjusted for confounding variables such as age. Cause-specific mortality proportions can be calculated when the cohort (the population at risk) cannot be defined due to inadequate records, but the number of deaths and the causes of deaths are known.
Standardized proportionate incidence ratio (SPIR)	is similar to a PMR in that it is a ratio of a proportion of a specific disease in an exposed group compared with the proportion in an unexposed group.
Odds Ratio(OR) and Relative Risk (RR)	are risks expressed as ratios of the incidence of diseased subjects exposed to a particular risk factor to the incidence of diseased subjects in a nonexposed referent group.

members of U.S. funeral directors' organizations (Hayes et al. 1990); and 4,512 British pathologists (Hall et al. 1991).

In the professional worker cohort studies, the range of SMRs or proportionate mortality ratios (PMRs) for respiratory or buccal cavity sites were:

for *lung cancer* - 0.1 to 1.1 (the group of New York State embalmers [Walreth and Fraumeni 1983] was the only cohort that showed an excess: 72 observed versus 66.8 expected);

for *nasopharyngeal cancer* - 2.1 (the group of deceased U.S. funeral directors was the only professional cohort reporting this type: 4 observed versus 1.85 expected [Hayes et al. 1990]);

nasal cancer deaths were either reported as zero or not reported among the nine professional cohorts;

for *buccal cavity and/or pharynx cancer* - 0.2 to 1.3 (at least one buccal cavity and/or pharyngeal cancer death was noted in each of the professional cohorts).

Case-control studies examining potential associations between occupational exposure to formaldehyde and specific types of cancer include those of:

lung cancer (Bond et al. 1986; Chiazze et al. 1993; Coggon et al. 1984; Gerin et al. 1989; Jensen and Andersen 1982; Partanen et al. 1985, 1990) with relative risks ranging from 0.6 to 1.1;

nasal cancer (Brinton et al. 1984, 1985; Hayes et al. 1986; Hernberg et al. 1983a, 1983b; Luce et al. 1993b; Olsen et al. 1984; Rousch et al. 1987; Vaughan et al. 1986a, 1986b) with relative risks ranging from 0 to 12.6; and

nasopharyngeal cancer (Olsen et al. 1984; Rousch et al. 1987; Vaughan et al. 1986a, 1986b; West et al. 1993) with relative risks ranging from 0.6 to 5.5.

The first two meta-analyses of the epidemiology studies (Blair et al. 1990a; Partanen 1993) took similar approaches to analyzing the same data, except that Partanen included three case-control studies not included in the earlier analysis. Both analyses calculated summary or aggregate relative risks for lung cancer, cancer of the nose and nasal sinuses, and nasopharyngeal cancer, and analyzed data from a subset of the available studies that were classified into "low/medium" or "substantial" exposure categories based on exposure level and/or duration of exposure information. Although different methods to calculate aggregate relative risks across studies were used in the two studies, similar results were obtained and conclusions reached.

In both analyses, aggregate relative risks for lung cancer deaths calculated for formaldehyde-exposed medical and nonmedical professionals were at or below those expected. Aggregate relative risks for lung cancer in industrial worker studies showed a small excess relative risk (1.1) in both analyses, but no evidence for an exposure-related increase in relative risk comparing the "low/medium" relative risks (1.2) with those of the "substantial" exposure class (1.0 or 1.1). Small excess aggregate relative risks for occupationally-exposed workers in all of the studies existed for cancer of the nose and nasal sinuses (1.1 [95% CI, 0.8–1.4] - Blair et al. 1990a; 1.1 [95% CI, 0.8–1.5] - Partanen 1993), and cancer of the nasopharynx (1.2 [95% CI, 0.8–1.7] - Blair et al. 1990a) and 2.0 [95% CI, 1.4–2.90] - Partanen 1993). Relative risks for both types of cancer increased with increasing exposure intensity in Table 2-3.

Both Blair et al. (1990a) and Partanen (1993) concluded that a causal role for formaldehyde in the induction of the observed cancers of the nasopharynx and nasal cavities was supported by their evidence for exposure-response relationships, the portal-of-entry site of these cancers, and the consistency of these findings with results from animal studies.

A third meta-analysis by Collins et al. (1997) arrived at the conflicting conclusion that the available studies do not support a causal relationship between formaldehyde exposure and nasopharyngeal cancer. This study analyzed data from essentially the same case-control studies, but included a few cohort mortality studies that were not available or included in the earlier meta-analyses (e.g., Andjelkovich et al. 1994b, 1995a; Gardner et al. 1993). Collins et al. (1997) noted that nasopharyngeal cancer rates were elevated in a minority of the available studies, that most studies did not find any nasopharyngeal cancers, and that many studies did not report on nasopharyngeal cancer. Unlike the calculational techniques used in the previous meta-analyses, a calculational technique was used to adjust for underreporting of expected mortality rates in the calculation of "weighted meta relative risks". Meta relative risks (with 95% CIs) for nasopharyngeal cancer were 1.0 (0.5–1.8) for the 14 cohort studies included in the analysis, 1.2 (0.4–2.5) for the six industrial worker cohort studies, and 1.3 (0.9–2.1) for the seven case-control studies. Collins et al. (1997) concluded from their review of the available studies that exposure estimates for the case-control studies were both lower and less certain than exposures in the industrial worker cohort studies, and that their analysis does not support an exposure-response relationship between formaldehyde and nasopharyngeal cancer.

Recent reviews of the available epidemiology studies arrive at differing conclusions. NTP (1998) notes that formaldehyde is reasonably anticipated to be a human carcinogen. IARC (1995) concluded, "Taken

Table 2-3. Meta-analysis of Epidemiology Studies of Cancer of the Nose and Nasal Sinuses and Nasopharyngeal Cancer

Cancer site	Level or duration of exposure to formaldehyde							
	Low/medium				Substantial			
	O/E[a]	RR[b]	O/E	RR	O/E	RR	O/E	RR
	Blair et al. 1990a		Partanen 1993		Blair et al. 1990a		Partanen 1993	
Nose and nasal sinuses	38/46	0.8 (0.6–1.1)	33/30	1.1 (0.7–1.8)	30/28	1.1 (0.7–1.5)	36/21	1.7 (1.0–2.8)
Nasopharynx	30/27	1.1 (0.7–1.6)	23/16	1.6 (1.0–2.7)	13/6	2.1 (1.1–3.5)	11/4	2.7 (1.4–5.6)

[a] Observed/Expected cancer deaths
[b] Relative risk (with 95% CI); CIs for the Blair et al. 1990a entries were calculated by Partanen (1993).

together, the epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer, although the conclusion is tempered by the small numbers of observed and expected cases in the cohort studies". IARC's overall evaluation that formaldehyde is probably carcinogenic to humans (Group 2A) was based on specific evaluations that there is limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals. EPA (1991a) classified formaldehyde in Group B1 - probable human carcinogen, based on an evaluation of limited human evidence and sufficient laboratory animal evidence. More recently, in a collaborative review and evaluation of the formaldehyde epidemiology studies, EPA and CIIT (CIIT 1998) concluded, "It appears that a weak association between nasopharyngeal cancer and formaldehyde exposure cannot be completely ruled out." Adopting another view, McLaughlin (1994) concluded, "Clearly, the causal criteria used by epidemiologists to evaluate an association, such as strength of the association, consistency, specificity, dose-response, plausibility, and coherence, are not satisfied by the epidemiologic studies in the formaldehyde-cancer research domain". ECETOC (1995) similarly concluded, "After a careful review of the cytologic, cytogenic and epidemiological studies there is an absence of evidence to support the judgement of an etiologic relationship between formaldehyde and human cancer risk."

Selected Cohort Mortality Studies. Blair et al. (1986) performed a historical cohort study to evaluate the mortality experience of 26,561 workers in 10 formaldehyde-producing or -using workplaces. TWA exposures to formaldehyde were estimated to range from trace amounts to >2 ppm. The mortality experience of workers exposed to workplace air concentrations 0.1 ppm was compared with that of "nonexposed" workers in the cohort exposed to concentrations <0.1 ppm. Using national rates of mortality as reference, greater than expected mortalities for a number of cancer types were noted in the exposed group, but the elevated rates of mortality were not statistically significantly different than national rates. Types of cancers with elevated SMRs included: Hodgkin's disease (SMR=1.42); and cancers of the liver (SMR=1.02); larynx (SMR=1.42); lung (SMR=1.11); bone (SMR=1.23); prostate (SMR=1.15); and kidney (SMR=1.23). The nonexposed group generally showed less than expected deaths from these cancers, (i.e., SMRs<1.00) Mortality from selected cancers were also compared among several subgroups of the cohort with varying exposure-concentration experiences. Among the aforementioned cancers, only deaths due to Hodgkin's disease exhibited a dose response. No individual exposure category SMR, however, was significantly elevated, and comparisons of the SMRs across different exposure categories is inappropriate for this indirectly adjusted measure. No unusual cancer patterns were noted among white women or black men. Among subsites of the buccal cavity, the nasopharynx had a significantly greater than expected incidence (7 cases observed versus 2.2 cases

expected) of cancer. This study demonstrated that there was insufficient evidence to firmly associate occupational formaldehyde exposure with the observed cancers, even when considering that the SMRs for the unexposed workers were small. No consistent correlation was noted between cumulative exposure and the risk of any cancer. This study used a cohort study design with a large study population. Additional strengths of this study included the fact that experienced nosologists assigned the cause of death and in addition to the SMR analysis based on vital statistics data, the study also included analyses using internal comparison groups. Industrial hygienists made estimates of the intensity of formaldehyde exposures using all available sources of information (most similar studies estimated only the duration). Overall, the analysis was very thorough and allowed for different exposure intensity levels and different possible "latency" periods between exposure and death. The investigators attempt to rule out confounding factors from socioeconomic status, and the follow up was good overall (95%), although it was only 83% for women. Weaknesses included the fact that death certificate data can often be inaccurate, so some cancers of interest could have been missed. Also, no information about tobacco use or other nonoccupational exposures was available.

In a later study by Blair et al. (1990b), the risk of lung cancer was assessed among 20,714 white male workers exposed to formaldehyde in 10 production plants. The estimated average levels of exposure were 0.1–1.9 ppm formaldehyde. The overall risk of lung cancer did not appear to be correlated with average formaldehyde levels in each plant. Among the exposed sample, the SMRs did not increase consistently with any measure of exposure. The SMR for those with cumulative exposures of <0.5 ppm-year was 1.3, while the SMR for those with >5.5 ppm-year was 1.7. The risk of lung cancer did not increase with the time from last exposure; however, the risk did increase based upon the year of entry into the industry. Among the >20-year latency group, those beginning employment prior to 1958 had a greater risk of cancer than did those beginning work in 1958 or later (SMR=1.4). Those exposed to formaldehyde at or after the age of 35 were more likely to have lung cancer than those exposed prior to age 35 (SMR=1.3). The interaction of formaldehyde with other noxious substances was investigated and the results suggested that those exposed to formaldehyde were not at risk of cancer unless exposed to another substance. The authors concluded that no clear exposure-response trends could be identified from the data. Strengths and weaknesses of this study were basically the same as those described in the Blair et al. (1986) study.

Data from the Blair et al. (1986) study were reanalyzed by Sterling and Weinkam (1989, 1995) to account for the healthy worker effect. The cohort was composed of all workers employed in 10 selected

plants. For lung cancer mortalities, mortality risk increased with cumulative exposure, approaching statistical significance in all workers with cumulative exposures of >2 ppm-years. The authors concluded that, when comparing workers with high formaldehyde exposures to those with little or no exposure, there is an increased risk of lung cancer associated with exposure to formaldehyde.

Harrington and Shannon (1975) examined a population of 2,079 British pathologists and 12,944 medical laboratory technicians or pathologists between January 1, 1955 and December 31, 1973. During that period, 154 technologists and 156 pathologists died, and copies of all death entries were obtained. The SMR was 60 for pathologists and 67 for medical technologists. Excess deaths from lymphatic and hematopoietic neoplasms were noted in male pathologists (observed 8, expected 3.3, $p<0.01$). No other neoplastic diseases were noted as causing excess mortality in either occupational group. It should be noted that the study group was too small for any firm conclusions to be drawn about the carcinogenicity of formaldehyde exposure in humans. No records were available and no adjustment was made for smoking or other possible confounding factors.

Levine et al. (1984a) studied the mortality patterns of 1,477 male undertakers licensed from 1928 to 1957 (dose not specified). The numbers of deaths due to malignant neoplasms (SMR=0.87) and specific cancers (SMR=0.52–1.24) were not significantly elevated. Mortality due to nonmalignant diseases was slightly elevated, but could not be clearly related to the inhalation of formaldehyde. Strengths of this study include the following: a cohort design with a high rate of success for ascertaining vital status (96%), death certificates obtained for most decedents, and underlying cause of death coded by a trained nosologist. Several apparent weaknesses should be noted, including the sample size, which was small for detecting rare outcomes of disease. Exposure levels to formaldehyde were low, and the undertakers did not necessarily engage in embalming work, so the exposures may have been too low to cause mortality excesses. Death certificate data are often inaccurate, so some cancers of interest could have been missed. Exposure began in the late 1920s, but the 40 deaths that occurred before 1950 (13% of all deaths) were excluded from the analysis. These earlier decedents could have had higher exposure levels than those who were still alive in 1950, so a potentially important source of information was unavailable due to data constraints for the reference population.

Harrington and Oakes (1984) established a population of 2,307 men and 413 women to study the incidence of cancer induction due to formaldehyde exposure in humans. During the study period, 126 of these pathologists died; death certificates were obtained for 121 of them. Observed and expected deaths

from all causes and from certain specific causes were reported as well as the corresponding SMR for observed deaths as a percentage of expected deaths. Excess deaths from brain tumors were found (observed 6, expected <2, p<0.02), but no nasal cancers were found. Strengths of this study included the use of a cohort design and a very low rate of follow up loss (0.6% for pathologists and 1.5% for medical laboratory technicians). The study also achieved some adjustment for possible confounding effects of socioeconomic status for one of the analyses by comparing the study cohort mortality experience with that of other medical groups, although that analysis could only examine broad categories of death. Weaknesses of this study included the fact that specific exposures or their possible levels were not identified for the two cohorts (there is no mention of formaldehyde exposure). The follow up period (19 years maximum for pathologists and only 11 years for the technicians) was somewhat short, but it is unclear whether exposures may have occurred before the beginning of the follow up period. Moreover, the modest number of pathologists (n=2,079) results in low statistical power for detecting any excesses of rare outcomes. It was also noted that for the primary analysis, there presumably were substantial socioeconomic differences between the cohort members and the reference population, so confounding could have occurred. Because the SMR is an indirectly standardized measure (i.e., it uses internal weights), the comparison of SMRs across occupational groups was considered to be inappropriate.

Walrath and Fraumeni (1984) performed a proportionate mortality study of 1,007 white male embalmers in California from 1916 to 1978 who were known to have died between 1925 and 1980. Total cancer mortality was significantly elevated, with PMR of 1.21. Deaths from cancers of the brain and the nervous system (PMR=1.94), colon (PMR=1.87), prostate (PMR=1.75), and leukemia (PMR=1.75) were significantly higher than expected. The reported types of brain cancer were for glioblastoma (2), astrocytoma (3), adenocarcinoma (1), and unspecified cancers (3). No increase in mortality for cancers of the respiratory tract, including the nasal passages was noted in this study. A parallel mortality study of embalmers from New York State (Walrath and Fraumeni 1983) showed similar findings with significant excess of deaths from cancers of the brain and nervous system (PMR=1.56), colon (PMR=1.43), ischemic heart disease (PMR=1.12), and nonsignificant excess of cirrhosis of the liver (PMR=1.33), and leukemia (PMR=1.40). PMRs were significantly elevated for cancers of the skin, kidney, and brain among those who were licensed only as embalmers. Even with these findings, the authors suggested that a more thorough investigation was needed to quantify the risks of cancer and other chronic diseases in relation to formaldehyde exposure. Strengths and weaknesses for both of these studies are similar. Strengths included the fact that formaldehyde was probably the primary chemical exposure for this PMR analysis of embalmers, although embalming fluid does include smaller amounts of other chemicals

(methanol, diethylene glycol, propylene glycol, phenol, benzoic acid, fragrances, etc.). Exposure durations and follow up periods were probably long enough for the study to detect any cancer excesses associated with formaldehyde exposure, although details about individual decedents were unavailable. For the final analysis, death certificates were available for a large percentage (92%) of the identified decedents. A trained nosologist coded the underlying cause of death for all death certificate using the coding rules in effect at the time of each death. Therefore, the assignment of the cause of death should have been comparable to that used for standard (comparison) population. The analysis controlled for potential confounding effects from age, race, sex, and calendar year. Several weaknesses of this study were also noted. In general, PMR studies have a relatively weak design compared to other types of studies. The analysis included only those deaths reported to the Bureau of Funeral Directing and Embalming, and the completeness of this reporting is not known. The authors indicate that deaths at ages >65 years were substantially under reported. Consequently, the causes of death in the analysis could have differed systematically from the causes found in the total population of deceased embalmers (e.g., for chronic conditions that led to death at older ages). The total U.S. population was used as the external comparison population, even though rates from New York state would probably be stable enough to provide expected values. Possible regional differences in cancer incidence (rather than occupational exposures) could have affected the observed pattern of mortality excesses and deficits. Study weaknesses included that cancer deaths are often reported inaccurately on death certificates. Exposure levels for formaldehyde were unknown, no analyses that combine the white and black decedents (with appropriate adjustment) were presented, even though there were similarities in the pattern of excess deaths. A combined analysis presumably would have greater statistical power. Lastly, the expected number of deaths for nasal cancer, an end point of particular interest, was only 0.7, so the study had low statistical power to detect an excess of this cancer.

Stroup et al. (1986) evaluated the risk of death due to cancers and other causes in 2,317 anatomists in a retrospective cohort study. Of the 2,317 in the study population, 33% (n=738) were known to have died. SMRs for deaths due to various cancers in anatomists was variable; the only condition with a significantly elevated SMR (SMR=2.7, $p<2.25$) was brain cancer. All of the anatomists that died of brain cancer were in either gross anatomy, microanatomy, or a combination of the two, indicating relatively high exposures to formaldehyde. The authors concluded that there was a substantial risk of brain cancer among anatomists, but since these anatomists were also exposed to a large number of biological stains and solvents, in addition to formalin and formaldehyde, the etiologic agent responsible for these results was not certain. This study has several strengths and weaknesses. The study of the anatomists used a

classic retrospective cohort design with a well defined denominator; follow up was at least 10 years for all cohort members. Follow up and death certificate acquisition was good and a trained nosologist coded the underlying cause of death for all cohort members. In addition to using national disease rates for the SMR analysis, the authors also used mortality rates from a cohort of psychiatrists, who presumably have similar demographic and socioeconomic characteristics compared with the anatomists. Subgroups of anatomists were studied in an attempt to separate possible effects of formaldehyde from those of other occupational chemical exposures. Among the study weaknesses was the fact that exposure levels for formaldehyde were unknown and occupational exposures to chemicals other than formaldehyde (or to viruses) could have been responsible for the observed cancer excesses. Diagnoses from death certificates are unreliable, but the use of the psychiatrist comparison group helps eliminate the possibility of differential disease misclassification (i.e., detection bias). The low expected number of deaths (0.5) for cancer of the nasal cavity and sinus indicates that the study had low statistical power for detecting an excess of nasal cancer.

Stayner et al. (1985a, 1985b, 1988) evaluated the carcinogenicity of formaldehyde in garment workers by performing a proportionate mortality study of 256 deaths reported from three shirt-manufacturing plants. All three plants had processed formaldehyde-treated fabrics since 1958 and the duration of employment for the study group averaged 9.4 years. Air monitoring in two of the plants revealed that virtually all employees were exposed to 0.1–1 ppm formaldehyde. Statistically significant excesses in mortality were detected for cancers of the buccal cavity (PMR=7.50), biliary passages and liver (PMR=3.13), and other lymphatic and hematopoietic sites (PMR=4.00). The number of deaths in each organ category was low; hence, the degree of confidence in PMRs and in the conclusion that cancers are associated with formaldehyde exposure must also be low. Stayner concluded that, based upon factors such as the long latency period and lack of exposure to other known carcinogens, the excesses in mortality in garment workers due to cancers of the buccal cavity, biliary passages and liver, and other lymphatic and hematopoietic sites were likely associated with formaldehyde exposure. There was no attempt to adjust the cancer rate for smoking or other confounding factors, and no air sampling records were evaluated. Later, Stayner et al. (1988) examined the relationship between formaldehyde exposure and the development of upper respiratory cancers in garment factory workers. A total of 2,008 men and 9,022 women from three garment factories had a formaldehyde concentration exposure geometric mean value of 0.15 ppm (range 0.14–0.17 ppm). Across all workers, mortality from all causes was less than expected, as was mortality from all malignant neoplasms. However, significantly ($p<0.05$) greater than expected mortalities were detected for the buccal cavity (SMR=3.43) and connective tissue (SMR=3.64).

Nonsignificant elevations were also noted for the trachea/bronchus/lung (SMR=1.14), pharynx (SMR=1.13), bladder (SMR=1.12), leukemia and aleukemia (SMR=1.14), and other lymphopoietic neoplasms (SMR=1.70). When stratified by sex and race, white females had significant excesses of buccal cavity cancer (SMR=4.85). When stratified by latency period, cancers of the buccal cavity (SMR=7.05) and leukemia (SMR=3.10) were significantly elevated for workers with latencies of 20 years or more, while cancers of the trachea/bronchus/lung (SMR=1.71) were significantly elevated among workers with latencies of >10 years. When stratified by duration of exposure, mortalities due to cancers of the buccal cavity (SMR=7.57) and other lymphopoietic neoplasms (SMR=3.81) were significantly elevated for workers with exposure durations of 10 years or more, while mortalities due to connective tissue cancers were significantly elevated in workers exposed for 4–9 years (SMR=6.19). Mortalities due to cancer of the trachea/bronchus/lung appeared to be inversely related to duration of exposure. In their discussion, the authors stressed that, while no excesses in nasal cancer were seen, the power of the study was too low to detect an effect for this rare cancer. Also, the authors noted that the patterns seen in trachea/bronchus/lung cancers (most prevalent in short duration/latency groups) were inconsistent with normal dose-response patterns; this was also attributed to a lack of statistical power. A strength of this study is that the cohort study design is more powerful than the PMR design used in the earlier study (Stayner et al. 1985a, 1985b) that included some of the same workers. As in the earlier study, confounding factors from other occupational exposures were unlikely. Vital status was ascertained for a very high proportion of the cohort members (96%). The authors also used various sources to verify the employment histories and vital status of the workers and the analyses of mortality by duration of exposure add credibility to the observed cancer excesses (i.e., the risk was positively associated with duration of exposure). Some of the weaknesses were the same as in the authors' earlier PMR study: exposures that may have been too low to cause a detectable increased risk of mortality and historical exposures that may have been higher, but with unknown levels. Because of the small study population, the study had only modest statistical power to detect possible excesses of rare outcomes. Death certificate data are often inaccurate, so some cancers of interest could have been missed. The authors attempted to rule out possible nonoccupational confounding factors with mixed results. For example, at least two of the four who died from buccal cancer had a history of tobacco use (one had used snuff, a fairly strong risk factor for buccal cancer). The authors concluded that the results of the study should be viewed with caution, due to limited statistical power and latency periods and the possibility of other confounding factors.

Bertazzi et al. (1986) attempted to correlate occupational exposure to formaldehyde with cancer rates in male resin workers using SMR analysis. Based on job descriptions, workers were divided into three groups: "exposed to formaldehyde", "exposed to other chemicals", or "exposure unknown". An analysis of the death rates revealed a significantly ($p<0.05$) elevated rate of deaths from all cancers when compared to the national rates (SMR=1.54); however, significance declined when the cohort was compared to the local population trends (SMR=1.06). Among individual cancer types, significantly elevated SMRs were detected for lung cancer against the national and local trends (SMRs=2.36 and 1.86, respectively). Deaths from hematologic neoplasms were elevated (SMRs=1.54 and 2.01), but not significantly. When the cohort was divided by chemical exposure, the group exposed to formaldehyde tended to have elevated SMR values; however, the trends were not significant. The authors concluded that, in addition to the significantly elevated lung cancer mortality rate among all workers, the mortality rates among formaldehyde-exposed workers for all cancers, and cancers of the alimentary tract, lung and blood system were noteworthy, although nonsignificant. Study strengths included a cohort design with high rate of follow up (98.6%); formaldehyde exposure levels that were apparently high (although not well characterized); and past exposures that were not measured but were presumably higher. It appears that most workers with formaldehyde exposure had not been exposed to other chemicals in the plant (although this point was not made completely clear by the authors). Subanalyses looked at SMRs with regard to duration of employment and by formaldehyde exposure status. Some apparent weaknesses of this study were that the cohort was too small (1,332 persons) to detect increases in rare diseases and that the follow up period after formaldehyde exposure was somewhat short (as noted by the authors), so that exposure-related cancers with long latency periods might not have had time to appear during the course of this study. Environmental measurement data were very sparse and detailed work history records were unavailable for most cohort members, so “reconstructions” were obtained through interviews of past workers and others (few details were provided). No exposure levels were provided for 18% of workers. Data for individuals with regard to potential confounding variables were unavailable, and no information was provided on the assignment of the cause of death codes used in the SMR analyses.

Gardner et al. (1993) assessed the risk of disease and cancers among British male chemical workers exposed to formaldehyde. The cohort for the study consisted of 7,660 men who began employment prior to 1965 and 6,357 men who began employment after 1964. Formaldehyde exposure ranged from <0.1 to >2 ppm. There was one death from nasal cancer and no deaths from nasopharyngeal cancer, nor were any nonfatal cases of nasopharyngeal reported. Among lung cancer cases, there was no association of cancer with formaldehyde exposure. Among men classified as exposed to the higher end of possible

exposure levels of formaldehyde, there was no indication of a relationship between cancer and duration of employment, and no association between cancer and cumulative dose. In those employed prior to 1965, there was a significant excess of lung cancer, with the authors stating that the increase was probably due to smoking and other environmental pollution. This appears to be related to one factory in which more men were exposed to high levels of formaldehyde. The determination of exposure levels in this study was crude and the information on co-exposure to other chemicals was not analyzed. The possibility of dermal exposure cannot be ruled out in many of these workers. Strengths of this study included the cohort design, with careful checks of member eligibility and systematic assignment of estimated exposure levels. SMR analyses use disease rates from local populations to help avoid potential biases due to regional differences in disease rates and the long follow up period allows time for the manifestation of any exposure-related cancers. Weaknesses of this study included the observation that no actual measurements of formaldehyde exposure levels occurred, but the investigators did undertake a detailed estimation procedure for classifying expected exposure levels. There were also potential confounding factors from other occupational exposures. In addition, the procedure for assigning the underlying cause of death for cohort members was not explicitly described, and comparisons of the SMRs across different exposure categories is inappropriate for this indirectly adjusted measure. The authors presumably could have used a regression modeling approach to explore possible dose-response associations without the need for an external referent population. A pronounced "healthy worker effect" is typically expected in this type of cohort study for all-causes mortality, but only one of the six factory populations showed an SMR <0.95, even for workers who were hired relatively recently. The authors may have overlooked this indirect evidence of a health hazard in the factories.

Andjelkovich et al. (1990) examined mortality in a cohort of 8,147 foundry workers who worked in an automobile manufacturing plant for at least 6 months between 1950 and 1979. For the observation period of 1950 through 1984, a significant excess was found for lung cancer mortality, but most of the excess of lung cancer deaths was accounted for by smoking habits. In a subsequent nested case control study of this cohort that examined risk factors for 220 cases of lung cancer mortality that occurred between 1950 and 1989 compared with 2,200 age- and race-matched controls without lung cancer, cigarette smoking was a strong predictor of lung cancer mortality, but exposure to formaldehyde was not significantly associated with lung cancer (Andjelkovich et al. 1994b). In a final phase of these studies, Andjelkovich et al. (1995a) studied the mortality experience (for the period between 1960 and 1989) of a subset of 3,929 members of the cohort who were exposed to formaldehyde in the foundry during the period of January 1960 through 1987, and compared it to the experience of a referent, nonexposed

population of 2,032 men who worked at the foundry, but not in formaldehyde-exposed jobs. The year 1960 was chosen as the starting point of the study because it was the year that formaldehyde was introduced into the operations used in the foundry. Exposure to formaldehyde was assessed via work histories and was ranked as high, medium, low, or none (but exposure concentration ranges were not reported). In the exposed group, elevated SMRs (calculated using national rates for comparison) were found for deaths from several cancer types, but the elevation was not statistically significant for any cancer type. Cancer types with elevated SMRs were (with SMRs noted in parentheses): buccal cavity and pharynx (1.31); stomach (1.64); rectum (1.17); trachea, bronchus, and lung (1.20); and urinary organs (1.13). Similar SMRs were found for the nonexposed control group. Because of the findings from animal studies of formaldehyde-induced nasal tumors, special attention was given to malignant and non-malignant diseases of the respiratory system (cancers of the buccal cavity and pharynx, larynx, or trachea, bronchus, and lung, and emphysema), but comparison of the cause-specific mortality between the exposed and nonexposed groups showed no statistically significant difference, except for a significantly elevated SMR for emphysema in the nonexposed group.

Strengths of the Andjelkovich et al. (1990, 1994b, 1995a) studies included the nested case-control design, which provided a high degree of efficiency while ensuring that the controls were selected from the same population that gave rise to the cases. Incidence density sampling of controls leads to an unbiased estimate of the mortality rate ratio. The use of conditional logistic regression analysis enabled appropriate adjustments for covariates and attempts to control for effects of cigarette smoking appeared to be fairly successful, although the response rate for collecting the smoking information was less than ideal (about 70%). In addition, the follow up duration was long enough for exposure-related lung cancer excesses to appear, and the data analysis allowed for "latency" periods of different duration. Industrial hygienists estimated the exposure levels for formaldehyde as well as for silica, a potential confounder of the formaldehyde-cancer association. There was no opportunity for "recall bias" (except for the smoking information, which was collected from cohort members or their families). Study weaknesses were related to lung cancer information, which came almost exclusively from death certificates, which can be inaccurate. Tumor histology information was unavailable. It seemed apparent that no actual measurements of formaldehyde exposure levels were available, although some silica measurements were available. The study authors point out that a only a modest proportion of the cohort was exposed to formaldehyde, so the statistical power of the study was somewhat low. However, the estimated odds ratios indicate a lack of association that would presumably be unaffected by an increase in the study's sample size.

Selected Case-Control Studies. Luce et al. (1993b) attempted to determine whether occupational exposure to formaldehyde was associated with an increased risk of sinonasal cancer in humans. Case subjects were patients with primary malignancies of the nasal and paranasal sinuses. Odds ratios for squamous cell carcinomas in formaldehyde-exposed workers, when adjusted for wood dust and glue exposure, were not significantly elevated. The odds ratio for adenocarcinomas was confounded by the frequent co-exposure to wood dust, a known carcinogen. However, in those exposed to wood dust, an increased odds ratio was noted in those also exposed to formaldehyde. The authors concluded that the data did not support an increased risk of nasal cancers due to formaldehyde alone.

Partanen et al. (1985), in a case-referent study, attempted to determine whether respiratory cancer was associated with formaldehyde exposure in woodworkers. Anatomic sites classified as "respiratory cancers" included the tongue, mouth, pharynx, nose, sinuses, larynx, epiglottis, lung, trachea, and "other". Fifty-seven male production workers diagnosed with respiratory cancers were selected, with the average level of formaldehyde exposure being 1 ppm and the average duration of exposure being 10 years. The odds ratios for respiratory cancers due to formaldehyde, adjusted for latency periods, peak exposures, or co-exposures, were statistically significant. The authors concluded that a positive relationship between respiratory cancers and formaldehyde exposure could not be substantiated, because 87% of the workers exposed to formaldehyde were also exposed to wood dust, a known nasal carcinogen. The strengths of this study were that cases and controls were sampled from a large cohort, so the population at risk is well defined. Exposure status was determined from a review of work histories (blinded with regard to disease status), so recall bias was avoided. Some air measurements were available for assessing exposure levels. The investigators used a fairly elaborate exposure matrix approach to classify cases and controls with regard to exposure status, and at least some control for potential confounding effects from other occupational exposures and cigarette smoking was possible. Study weaknesses included the notation that the cohort was too small for studying nasal cancer; there were no reported cases, and the expected number of cases in the total cohort was <1. In addition, smoking information was missing for a large proportion of cases and controls, and there was high correlation between formaldehyde and wood dust exposures, so it was difficult to separate their respective effects. The breaking of the matched case-control pairs in the analysis can lead to inflation of the odds ratio even if the analysis stratifies by levels of the matching variables.

In a later study, Partanen et al. (1990) performed a retrospective study that attempted to determine the association of respiratory cancer (136 cases, 408 controls) with formaldehyde exposure; this case control

study was nested in a total cohort of 7,307 woodworkers having had a minimum level of 0.1 ppm and a minimum cumulative exposure of 3 ppm months to formaldehyde. The odds ratio for respiratory cancers in exposed versus unexposed workers, when corrected for vital status, smoking, and a latency period of 10 years, was not statistically significant. The strengths were that the study population was an expansion of that used in the authors' earlier study (Partanen et al. 1985). Additional industries were added and the follow up period was extended, so the number of workers with respiratory cancers was considerably larger. The strengths and weaknesses were essentially the same as those in the earlier study. However, there were improvements over the initial study. First, the study's statistical power was greater due to the larger sample size. Second, the authors conducted a more proper analysis by using conditional logistic regression modeling that preserved the matched sets of cases and controls (the earlier analysis broke the matched sets). Lastly, the authors presented some separate analyses for lung cancer cases and upper respiratory cancer cases, so that more homogeneous groups of respiratory cancers that might have different etiologies were analyzed separately.

In a study by Roush et al. (1987), the potential for mortality from nasopharyngeal cancer and sinonasal cancer associated with occupational exposure to formaldehyde was investigated. Cases of nasopharyngeal and sinonasal cancer were identified through the Connecticut Tumor Registry; the list was restricted to males with these cancers who died in Connecticut during the period 1935–1975. Controls were obtained from men dying in Connecticut during the same time period. Information on the death certificate was used to search for information on the subjects' work history. The work history information was used by an industrial hygienist to classify each subject into formaldehyde exposure categories based on likelihood and level of exposure. For those with probable exposure at some point at least 20 years before death, the odds ratio for nasopharyngeal cancer was 2.3. The odds ratio increased to 4 in the same group when narrowed to those dying at the age of 68. When frequencies of cancers were analyzed by occupation, the odds ratio for developing either cancer in the rubber industry was elevated (2.2), but not significantly. All four printers developed cancer. The authors concluded that there is an increased risk of nasopharyngeal cancer associated with probable exposure to formaldehyde; further, they concluded that the association is latency- and age-dependent. The authors suggest that the cause of sinonasal cancer in printers may be due to the presence of mineral oil mist, which has previously been associated with sinonasal cancer in the metals industry. Strengths of this study included a fairly large number of cases and a clinical review of medical records conducted for 75% of cases to confirm the diagnosis. Weaknesses included the fact that all cases and controls were deceased, and the possibility that risk factors for nasopharyngeal or sinonasal cancer that also increase the risk of death from other

causes (e.g., cigarette smoking) could be over represented in the control groups (a conservative bias would disguise exposure-disease associations for nasal cancer). Occupational information was ascertained from death certificates and city directories, so substantial exposure misclassification was likely. Information about possible occupational or nonoccupational confounders was lacking, as persons with formaldehyde exposures may also have had other carcinogenic exposures. The low prevalence of substantial formaldehyde exposures among study participants leads to low statistical power for detecting exposure-disease associations. This study is also limited because it was dependent on indirect information in creating the exposure index, nonoccupational exposures to formaldehyde were not addressed, and exposure to other potentially causal agents was not addressed.

Hayes et al. (1986) attempted to determine the environmental factors associated with nasal cancers in males from the Netherlands. A total of 91 case and 195 control subjects were included in the study. Patients or, if already deceased, close relatives completed interviews concerning work, smoking, and drinking histories. Based on these interviews, subjects were classified based on probability and level of formaldehyde exposure. The relative risk (measured as the odds ratio) of adenocarcinomas of the nasal cavity and sinuses was elevated (11.3) for those working in the wood and paper industries; the relative risk for all other cancers was not elevated. The relative risk for squamous cell carcinomas associated with formaldehyde exposure was significantly elevated ($p<0.05$) when the data were adjusted for wood dust exposure. Adjustments for smoking did not perceptibly change the relative risk. The authors concluded that formaldehyde may be a human carcinogen, but conceded that the study's limitations (questionable exposure conditions) prevented conclusive statements. Although the authors describe this case-control study as having low statistical power, they included a substantial number of persons with nasal cancer (n=116) given the rarity of this tumor. The study included incident (rather than prevalent) cases. Tumor histology information was available and trained industrial hygienists, who were unaware of each participant's case/control status, estimated the potential for formaldehyde and wood dust exposure for each reported job. The study collected fairly extensive information about exposures and potential confounders. Regarding study weaknesses, no actual exposure measurements were available for cases or controls. The disagreements between the two industrial hygienists demonstrate the inherent inaccuracy of the exposure assessment (the exposure misclassification presumably caused a conservative bias). Because the study relied on interview data for assessing exposures, possible "recall bias" could have led to over reporting of exposures by cases (or their next-of-kin) compared to controls. Although industrial hygienists estimated the potential for formaldehyde exposure based on reported jobs, the cases compared to controls may have been more likely to remember and report jobs that involved chemical

exposure. In addition, next-of-kin interviews were necessary for a substantial number of cases. Response rates were fairly low (64%) for next-of-kin interviews for cases as well as controls, and those who chose to participate (especially among families of deceased cases) compared to nonparticipants may have been those who tended to be aware of jobs held by the decedent that involved chemical exposures.

Hansen and Olsen (1995) investigated the risk of cancer due to occupational exposure to formaldehyde in Danish male workers. A total of 126,347 men born between 1897 and 1964 and diagnosed with cancer during the period of 1970–1984 were identified from the Danish Cancer Registry. The risk of cancer at a specific site was estimated from the standardized proportionate incidence ratio (SPIR), which was the proportion of cases of a specific cancer among workers from formaldehyde-associated industries versus the number of cases of the same cancer among all Danish workers. Of the 91,182 subjects with a full employment history, 2,041 had their longest length of employment at least 10 years prior to their cancer diagnosis. Among these 2,041 subjects, there were significant increases in the relative risk of cancers of the sinonasal cavity (SPIR=2.3), kidney (SPIR=1.3), and colon (SPIR=1.2). When analyzed by intensity of formaldehyde exposure and co-exposure to wood dust, there was a significant elevation in sinonasal cancers among workers exposed to formaldehyde and wood dust (SPIR=5.0) and workers moderately exposed to formaldehyde and probably not exposed to wood dust (SPIR=3.0). Workers with a low exposure to formaldehyde had a SPIR close to unity. The authors concluded that the increased incidences of kidney and colon cancers were biologically irrelevant due to the rapid metabolism of formaldehyde. Strengths of this study included the observation that this population-based proportionate morbidity ratio study used the entire adult white male population of Denmark as the population at risk. The determination of exposure status required at least a 10-year interval between first potential exposure to formaldehyde and the diagnosis of cancer (although a longer interval may have been more appropriate) and, because the study used cancer incidence (rather than mortality) based on cancer registry records, disease misclassification was probably low. Several weaknesses were also noted in this study. First, the exposure classification was crude and was based on having worked in a company that used or manufactured at least one kilogram of formaldehyde per worker (no exposure measurements were available), and it was based solely on the longest job held. Exposure misclassification is therefore likely. In the extreme case, some workers classified as "exposed" could have had shorter exposure durations than some who were classified as unexposed. The study authors point out that the study excludes exposures that occurred before April 1964, so nondifferential exposure misclassification probably occurred. They correctly state that any nondifferential misclassification should cause a conservative bias (i.e., the SPIR would underestimate the true magnitude of the association). In addition, use of the

"longest job held" approach for classifying exposure status could lead to confounding if, for example, the longest job was associated with formaldehyde exposures and other shorter jobs were associated with wood dust exposure. However, there is no reason to believe that such confounding actually occurred. Exposure intensity was based on white collar/blue collar status, which presumably is also a surrogate for socioeconomic status. Confounding by socioeconomic status (e.g., from nutrition differences) could have occurred between the lower and higher exposure categories.

Gerin et al. (1989) investigated the cancer risk involved with occupational exposure to <1 ppm formaldehyde in a study which included 3,726 subjects. From the data collected, the OR between formaldehyde exposure and each type of cancer was estimated. The only cancer with a slightly elevated OR was adenocarcinoma of the lung in the long-duration/high-exposure group (OR=2.3). The 95% CI was 0.9–6 and the authors concluded that this result was compatible with the null hypothesis of no carcinogenic effects of formaldehyde. Cancer diagnoses were pathologically confirmed and extensive information was collected about possible nonoccupational confounders. Because, by definition, this case-control study sampled on disease rather then exposure status, the study population included persons from many different jobs and industries where formaldehyde exposure occurred, and the assessment of such exposures was necessarily limited. Controls were samples from electoral lists; registered voters might differ from the overall population (and the cases) in some respects (e.g., socioeconomic status), although the investigators presumably collected data that would allow control of such differences. The very low prevalence of substantial formaldehyde exposures among study participants leads to low statistical power for detecting exposure-disease associations. The authors also mention that the probable formaldehyde exposure levels in the "high" group was a TWA of >1 ppm. They further state that the small number in this group likely led to imprecise results. The study also analyzed the data after correcting for confounding factors; these factors (listed above) may play a role in the cancer risk.

Animal Cancer Studies. As discussed previously in Section 2.2.1.2 subsection entitled *Chronic Inhalation Animal Studies*, chronic exposure to airborne formaldehyde concentrations ranging from about 6 ppm to 15 ppm induced increased incidences of nasal tumors (squamous cell carcinomas, squamous cell papillomas, or polyploid adenomas) in three bioassays with Fisher 344 rats (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Swenberg et al. 1980). Increased incidences of lower respiratory tract tumors or distant site tumors were not found in these studies, and exposure to concentrations of 2 ppm and lower induced no malignant nasal tumors.

In the earliest chronic inhalation rat bioassay (Kerns et al. 1983b; Swenberg et al. 1980), polyploid adenomas in the nasal cavity were found in 1/232, 8/236, 6/235, and 5/232 Fisher 344 rats (males and females were included) exposed 6 hours/day, 5 days/week for 24 months to 0, 2, 5.6, and 14.3 ppm, respectively. Malignant nasal tumors (predominately squamous cell carcinomas) were found in 0/232 control, 0/236 2-ppm, 2/235 5.6-ppm, and 106/232 14.3-ppm rats (Kerns et al. 1983b).

Monticello et al. (1996) exposed male Fisher 344 rats to 0, 0.7, 2, 6, 10, or 14 ppm, 6 hours/day, 5 days/week for 24 months. Nasal polypoid adenomas, located in or adjacent to the lateral meatus, were found in 10-ppm (5/90) and 15-ppm (14/147) rats. No polypoid adenomas were found in the control group or in the 0.7-, 2-, or 6-ppm groups. Squamous cell carcinomas were found in the nasal cavities of 1/90 6-ppm rats, 20/90 10-ppm rats, and 69/147 15-ppm rats. These tumors also were located predominately in the anterior lateral meatus. Squamous cell carcinomas were not found in the control, 0.7-, or 2-ppm groups. Buccal squamous cell carcinomas were observed in three 15-ppm rats and one 2-ppm rat.

Kamata et al. (1997) exposed groups of 32 male Fisher 344 rats to 0, 0.3, 2, or 15 ppm, 6 hours/day, 5 days/week for up to 28 months, and found nasal squamous cell carcinomas only in the 15-ppm group (13/32 rats). In contrast to the studies by Kerns et al. (1983b) and Monticello et al. (1996), no polyploid adenomas were found, but squamous cell papillomas were found in 3/32 rats in the 15-ppm group.

In experiments with male Sprague-Dawley rats, nasal tumors (predominately squamous cell carcinomas) were observed in 10/100 rats exposed to 14.2 ppm, 6 hours/day, 5 days/week for 588 days, compared with 0/100 in controls (Albert et al. 1982) and in 60/100 rats exposed to 14.8 ppm for up to 128 weeks, compared with 0/99 in controls (Sellakumar et al. 1985). No tumors were found in the trachea or lungs in these studies, and tumors found at extra-respiratory sites were not considered by the investigators to be exposure-related.

Wistar rats appear to be less carcinogenically responsive than Fisher 344 or Sprague-Dawley rats. Woutersen et al. (1989) observed nasal squamous cell carcinomas in only 1/26, 1/28, and 1/26 Wistar rats exposed to 0.1, 1, or 10 ppm, respectively 6 hours/day, 5 days/week for 28 months compared with 0/26 in controls; early physical damage to the nasal mucosa (electrocoagulation) increased the carcinogenic response only with subsequent exposure to 10 ppm (15/58 with 28-month exposure to 10 ppm versus 1/54 in nonexposed Wistar rats with electrocoagulation treatment). In 28 Wistar rats exposed to 10 ppm

for 3 months followed by a 25-month observation period, only one had a nasal squamous cell carcinoma and one had a nasal polypoid adenoma (Woutersen et al. 1989).

In an earlier experiment by the same laboratory, groups of 44–45 male Wistar rats were exposed to 0, 10, or 20 ppm, 6 hours/day, 5 days/week for 4, 8, or 13 weeks followed by observation periods as long as 126 weeks (Feron et al. 1988). Nasal tumors were found in 1/45 (polyploid adenoma), 1/43 (polyploid adenoma), and 4/44 (3 squamous cell carcinomas and 1 polyploid adenoma) 20-ppm rats exposed for 4, 8, or 13 weeks, respectively, compared with 0/45 in a control group. Two other nasal tumors found in the 10-ppm groups were not considered by Feron et al. (1988) to be induced by formaldehyde exposure. These results suggest that if nasal epithelial damage from intermediate exposure is sufficiently severe, then the risk for nasal tumors in later life may be increased.

Nasal tumors, similar to those observed in rats, were observed in two male B6C3F1 mice exposed to 14.3 ppm, 6 hours/day, 5 days/week for 24 months; no nasal tumors were found in control mice or mice exposed similarly to 2 or 5.6 ppm (Kerns et al. 1983b). No other neoplastic responses were found at other sites. In each group in this bioassay, less than 25 of the approximately 120 male mice in each group lived beyond 18 months. Reduced survival among males was attributed to fighting and infections of the genitourinary tract associated with group housing. The exact incidence of occurrence of nasal tumors in the Kerns et al. (1983b) mouse study could not be determined from the published report, but the available data suggest that mice are less carcinogenically responsive to inhaled formaldehyde than rats.

No nasal tumors or tumors at other respiratory tract sites were found in groups of 50 Golden Syrian hamsters exposed to either 10 ppm, 6 hours/day, 5 days/week for life or 30 ppm, 6 hours/day, once a week for life (Dalbey 1982). Hyperplastic and metaplastic areas were seen in the nasal epithelium of 5% of the hamsters exposed to 10 ppm, but were not seen in controls.

NTP (1998) noted that formaldehyde is reasonably anticipated to be a human carcinogen, and IARC (1995) determined that formaldehyde is probably carcinogenic to humans (Group 2A) based on specific evaluations that there is limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals.

EPA (1991a; IRIS 1999) classified formaldehyde in Group B1 - probable human carcinogen, based on an evaluation of limited human evidence and sufficient laboratory animal evidence.
EPA (1991a) used dose-response data for nasal tumors in rats exposed to high concentrations of formaldehyde (from Kerns et al. 1983b) to extrapolate to human cancer risk at low exposure concentrations, using rates of DNA-protein cross links in target tissue as a measure of delivered dose. Relationships between formaldehyde air concentrations and rates of formation of DNA-protein cross links in nasal epithelial tissue of rats (Casanova et al. 1989) or of Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) and adjustments to continuous exposure were used to calculate lifetime human cancer unit risk estimates of 3.3×10^{-4} per ppm formaldehyde based on the monkey data, and 2.8×10^{-3} per ppm formaldehyde based on the rat data (see Section 2.4.3).

Using the monkey-based human cancer unit risk estimate, air concentrations associated with cancer risk levels of 10^{-4} to 10^{-7} from lifetime exposure are 0.3 to 3×10^{-4} ppm, respectively, and are plotted in Figure 2-1. The CEL values from each reliable study for cancer in each animal species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

Most of the available reports of controlled studies of health effects from oral exposure to formaldehyde have not provided information regarding how frequently dosing solutions were analyzed for formaldehyde content. Some studies reported how frequently formaldehyde solutions were prepared (e.g., in drinking water studies, Til et al. [1988b, 1989] and Tobe et al. [1989] prepared solutions weekly and twice weekly, respectively), or how frequently formaldehyde was added to the diet (e.g., Hurni and Ohder [1973] daily sprayed formaldehyde solutions [that were prepared weekly] on food just prior to feeding dogs). Other study reports, however, provide no information regarding solution-preparation frequency, conditions of storage, or analysis of test material for formaldehyde content (e.g., Johannsen et al. 1986; Soffritti et al. 1989; Takahashi et al. 1986a). Because of this reporting deficiency, and because formaldehyde solutions are very unstable (due to formaldehyde's high reactivity and volatility), the reader should be aware that there is uncertainty associated with oral dose levels reported in this profile. Another issue of uncertainty regards the impurity of commercially available aqueous solutions of formaldehyde (often called formalin) which normally contain approximately 10–15% methanol to prevent polymerization. Reports of human poisonings from formalin and animal studies that used formalin (e.g., Marks et al. 1980; Takahashi et al. 1986a) are included in this profile. Attempts have

been made, however, to note when formalin was the source of the ingested formaldehyde, so that the reader will be aware of possible confounding effects from methanol.

Exposure to formaldehyde by the oral route can occur, but exposure is not as common as by the inhalation route because of the instability of formaldehyde in aqueous solution. Much of the information available about the effects of formaldehyde after oral exposure in humans comes from case reports of acute poisoning. Small amounts of formaldehyde can occur in foodstuffs, usually added as a preservative.

2.2.2.1 Death

In humans, death has been associated with acute oral exposure to formaldehyde. Four cases are described in detail here. Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg formaldehyde/kg) in a suicide attempt. The man was found unconscious by a co-worker about 1 hour after his shift began. In the emergency room, the subject regained consciousness but was lethargic. Laboratory results indicated significant acidosis. Approximately 3 hours after ingesting the formalin, the patient complained of abdominal pain and began retching without emesis; he was admitted for observation and treated with ethanol. The patient's abdominal pains became more severe and he had difficulty breathing. At 5.5 hours after ingestion, the patient became obtund, and both his respiratory rate and blood pressure fell significantly; he was intubated and placed on 100% oxygen. Shortly thereafter, the patient began to experience seizures; treatment with diazepam and phenytoin was unproductive, but pancuronium was effective in treating the seizures. Intravenous bicarbonate and ethanol therapies were begun after the seizures started. The patient was transported for dialysis, but on arrival, had clinical signs of intravascular coagulopathy. He subsequently sustained a cardiac arrest from which he could not be revived. At autopsy, the patient's stomach was hard, white, and leathery; the esophagus and intestines appeared to be normal.

A 55-year-old woman and a 34-year-old man ingested, with suicidal intent, an unknown amount of what was reported to have been formalin (Koppel et al. 1990). The female patient was found in a coma and admitted to the hospital with shock (systolic blood pressure 50 mm Hg), respiratory insufficiency, and metabolic acidosis. The male patient, who had a history of alcohol abuse, was also hospitalized with shock (systolic blood pressure 60 mm Hg), respiratory insufficiency, and metabolic acidosis. Both patients underwent hemodialysis and hemofiltration treatment. Analysis of the formaldehyde samples

ingested by both patients showed no evidence that these products contained methanol, although it was expected to have been detected. A chemical-toxicological screening indicated that no drugs other than formaldehyde had been ingested; neither methanol or ethanol were detected in blood samples. Three weeks after ingestion of formaldehyde, the female patient died of cardiac failure refractory to catecholamine therapy. The male patient developed adult respiratory distress syndrome and died 8 weeks after formaldehyde ingestion with signs of cardiac failure.

Eells et al. (1981) describe the case of a 41-year-old woman who swallowed 120 mL formalin (37% formaldehyde solution; 624 mg formaldehyde/kg). The woman was brought to the emergency room within 30 minutes. The patient complained of abdominal pain and subsequently lost consciousness. Upon admission, the patient was cyanotic, apneic, and hypotensive. Laboratory results indicated significant acidosis. The patient was intubated, ventilation was initiated, and gastric lavage was performed. Intravenous fluid therapy consisting of Ringers solution followed by 5% dextrose, epinephrine, and sodium bicarbonate was initiated and the patient was transferred to intensive care. The patient was maintained via endotracheal respiration and dopamine therapy. The patient became anuric approximately 7.5 hours after admission, and her health continued to deteriorate over the next day; she died 28 hours after admission.

Mortality data for acute duration experimental animal studies do not present a consistent picture. Reports of death in animal studies after acute oral exposure were found (Tobe et al. 1989), although other studies showed no mortality. For instance, groups of male and female Wistar rats were given formaldehyde at 0, 10, 50, and 300 mg/kg/day in their drinking water (Tobe et al. 1989). Animals given 300 mg/kg/day were observed to have died as early as 9 days after the start of the treatment. The number and sex of rats that died were not reported. In a group of 34 pregant mice given gavage doses of 185 mg/kg/day on gestation days 6–15, 22 died by gestation day 18 (Marks et al. 1980). Marks et al. (1980) noted that the drinking water contained 0.6–0.75% methanol (60–75 mg/kg/day) which possibly could have contributed to the lethality. However, Johannsen et al. (1986) reported no mortality after acute-duration exposure of Sprague-Dawley rats of both sexes to doses 150 mg/kg/day. Similarly, Takahashi et al. (1986a) observed no mortality after exposure of male Wistar rats to 258 mg/kg/day of formaldehyde (as formalin) for acute duration.

Intermediate-duration exposure of animals to orally administered formaldehyde resulted in a more consistent picture of mortality. Vargova et al. (1993) observed no treatment-related mortality in male

Wistar rats exposed to doses of formaldehyde by gavage of 80 mg/kg/day for 4 weeks. No deaths were reported in weanling SPF-bred rats (Cpb WU, Wistar random) that received up to 125 mg/kg/day formaldehyde in their drinking water for 4 weeks (Til et al. 1988b), in male and female Sprague-Dawley rats given up to 150 mg/kg/day formaldehyde in drinking water for 90 consecutive days (Johannsen et al. 1986), or in male Wistar rats after administration of 258 mg/kg/day formaldehyde (as formalin) in drinking water for periods up to 32 weeks (Takahashi et al. 1986a). Mortality rates were calculated for male and female Wistar rats given 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for 12 months (Tobe et al. 1989). For the high-dose group, mortality at 3, 6, and 9 months was 10, 15, and 20% for male rats, respectively, and 25, 30, and 30% for female rats, respectively. No mortality was reported in the low- and mid-dose groups after exposure for periods 9 months (Tobe et al. 1989).

Four male and 4 female pure-bred Beagle dogs were administered 0, 50, 75, or 100 mg/kg/day formaldehyde in the diet for 90 consecutive days (Johannsen et al. 1986). No deaths or abnormal reactions were observed in the treated dogs.

In chronic-duration animal studies, no dose-related excess mortality was seen in male and female Sprague-Dawley rats after 104 weeks of exposure to doses 300 mg/kg/day (males) or in SPF-bred rats exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) in their drinking water for 2 years (Til et al. 1989). Deaths were significantly higher than control in males at 15 mg/kg/day in the Til study, but not at 82 mg/kg/day.

Mortality rates were calculated for male and female Wistar rats given 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months (Tobe et al. 1989). For the high-dose group, mortality at 12, 15, and 18 months was 45, 67, and 67% for male rats, respectively, and 55, 55, and 70% for female rats respectively (Tobe et al. 1989). All animals in the high-dose group died by 21 (females) or 24 (males) months.

The LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
ACUTE EXPOSURE							
Death							
1	Human	once (IN)				517 M (death)	Burkhart et al. 1990 (formalin)
2	Human	once (IN)				624 F (death)	Eells et al. 1981 (formalin)
3	Rat (Wistar)	9 d (W)				300 (death observed in 9 days)	Tobe et al. 1989
Systemic							
4	Human	once (IN)	Resp			517 M (decreased respiratory rate)	Burkhart et al. 1990 (formalin)
			Cardio			517 M (decreased blood pressure; cardiac arrest)	
			Gastro			517 M (abdominal pain and retching; hard, white & leathery stomach)	
			Hemato			517 M (intravascular coagulopathy)	
			Metab			517 M (acidosis)	
5	Human	once (IN)	Resp			624 F (apneic)	Eells et al. 1981 (formalin)
			Cardio			624 F (hypotensive)	
			Gastro		624 F (abdominal pain)		
			Renal			624 F (anuric)	
			Metab			624 F (acidosis)	

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
6	Human	once (IN)	Resp		234 F (increased cough; tachypnea)		Kochhar et al. 1986
			Cardio		234 F (tachycardia)		
			Gastro			234 F (dysphagia, ulceration and sloughing of soft palate and posterior pharyngeal wall; ulceration of epiglotis; pyriform fossae and arytenoids; edematous and ulcerated esophageal mucosa with black sloughing; areas of stomach hyperemic; and superficial ulceration in the distal body and antrum)	
			Hemato	234 F			
7	Rat (Sprague-Dawley)	2 wk (W)	Bd Wt	225			Johannsen et al. 1986
			Other		75 (decreased water consumption)		
8	Rat (Wistar)	1-2 wk (W)	Bd Wt	15 M	82 M (significantly decreased body weight)		Til et al. 1989
9	Rat (Wistar)	2 wk (W)	Bd Wt	50		300 (lost weight during normal weight-gain period)	Tobe et al. 1989
			Other		300 (reduced food and water intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	Neurological						
10	Human	once (IN)				517 M (lethargy; loss of consciousness; seizure)	Burkhart et al. 1990 (formalin)
11	Human	once (IN)				624 F (loss of consciousness)	Eells et al. 1981 (formalin)
	Reproductive						
12	Rat (Wistar)	once		100 M		200 M (19% increase in total sperm heads and 5% increase in abnormal sperm heads)	Cassidy et al. 1983 (formalin)
	Developmental						
13	Mouse (CD-1)	gd 6-15 (GW)		185			Marks et al. 1980 (formalin)
	INTERMEDIATE EXPOSURE						
	Death						
14	Rat (Wistar)	up to 24 mo (W)				300 M (10% [3 mo], 15% [6 mo], 20% [9 mo] & 45% [12 mo] mortality)	Tobe et al. 1989
						300 F (25% [3 mo], 30% [6 mo], 30% [9 mo] & 55% [12 mo] mortality)	

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	Systemic						
15	Rat (Sprague-Dawley)	90 d ad lib (W)	Resp	150			Johannsen et al. 1986
			Cardio	150			
			Gastro	150			
			Hemato	150			
			Hepatic	150			
			Renal	150			
			Endocr	150			
			Bd Wt	50 M	100 M (10-15% decrease in terminal body weight)		
				100 F	150 F (10-15% decrease in terminal body weight)		
			Other	50 M	100 M (>10 % decreased water intake)		
					50 F (>10 % decreased water intake)		
16	Rat (Wistar)	32 wk (W)	Gastro			258 (erosions and ulcers in limiting ridge of fundic mucosa)	Takahashi et al. 1986a (formalin)
			Bd Wt	258 M			

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
17	Rat (Wistar)	4 wk (W)	Resp	125			Til et al. 1988b
			Gastro	25[b]	125 (thickening of the limiting ridges & hyperkeratosis in the forestomach & focal atrophic inflammation in the glandular stomach; 1/10 females had moderate papillomatous hyperplasia)		
			Hemato	125			
			Hepatic	25 M 125 F	125M (decrease plasma protein and albumin concentrations)		
			Renal	125			
			Bd Wt	125			
			Other	25	125 (25-42 % decreased water intake; decreased food intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
18	Rat (Wistar)	less than or equal to 52 wks	Hemato	82 M 109 F			Til et al. 1989
		(W)	Renal	15 M	82 M (occult blood [wk 27]; increased urine density & decreased urine volume [wks 27 & 52])		
				21 F	109 F (increased urine density & decreased urine volume [wk 27])		
			Bd Wt	15 M	82 M (significantly decreased body weight after 1 week)		
				21 F	109 F (significantly decreased body weight after 24 weeks)		
			Other	15 M	82 M (decreased food and water intake)		
				21 F	109 F (decreased food and water intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
19	Rat (Wistar)	2 wk-12 mo (W)	Resp	300			Tobe et al. 1989
			Gastro	50		300 (forestomach squamous cell hyperplasia, erosions and/or ulcers and glandular stomach glandular hyperplasia at 12 months)	
			Hemato	300			
			Hepatic	50	300 (decreased serum protein, albumin, total cholesterol at 12 months)		
			Renal	50	300 (increased blood urea nitrogen at 12 months)		
			Bd Wt	50		300 (>20% decrease in body weight after 2 weeks)	
			Other		300 (decreased food and water intake)		
20	Rat (Wistar)	4 wk 5 d/wk 1 x/d (GW)	Resp	80 M			Vargova et al. 1993 (formalin)
			Gastro	80 M			
			Hemato	80 M			
			Hepatic	40 M	80 M (increase in the incidence of hepatocellular vacuolation)		
			Renal	80 M			
			Bd Wt	80 M			

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
21	Dog (Beagle)	90 d (F)	Cardio	100			Johannsen et al. 1986
			Gastro	100			
			Hemato	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Bd Wt	75	100 (unspecified significant decrease in body weight)		
			Other	75 M 50 F	100 M (decreased food intake) 75 F (decreased food intake)		
	Immunological/Lymphoreticular						
22	Rat (Wistar)	4 wk (W)		125			Til et al. 1988b
23	Rat (Wistar)	2 wk-12 mo (W)		300			Tobe et al. 1989
24	Rat (Wistar)	4 wk 5 d/wk 1 x/d (GW)			20 M (decrease in combined IgM & IgG titers, increased relative lymph node weight)		Vargova et al. 1993 (formalin)
25	Dog (Beagle)	90 d (F)		100			Johannsen et al. 1986
	Neurological						
26	Rat (Sprague-Dawley)	90 d (W)		150			Johannsen et al. 1986

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
27	Rat (Wistar)	4 wk (W)		125			Til et al. 1988b
28	Rat (Wistar)	12 mo (W)		300			Tobe et al. 1989
29	Dog (Beagle)	90 d ad lib (F)		100			Johannsen et al. 1986
	Reproductive						
30	Rat (Sprague-Dawley)	90 d ad lib (W)		150			Johannsen et al. 1986
31	Rat (Wistar)	4 wk (W)		125			Til et al. 1988b
32	Rat (Wistar)	12 mo (W)		300			Tobe et al. 1989
33	Rat (Wistar)	4 wk 5 d/wk 1 x/d (GW)		80 M			Vargova et al. 1993 (formalin)
34	Dog (Beagle)	52 d gd 4-56 (F)		9.4 F			Hurni and Ohder 1973 (formalin)
35	Dog (Beagle)	90 d (F)		100			Johannsen et al. 1986

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	Developmental						
36	Dog (Beagle)	52 d gd 4-56 (F)		9.4 F			Hurni and Ohder 1973 (formalin)
	CHRONIC EXPOSURE						
	Death						
37	Rat (Wistar)	up to 24 mo (W)				300 (mortality as early as 9 days; 45-55% mortality by 12 months; 100% mortality by 24 months)	Tobe et al. 1989

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
	Systemic						
38	Rat (Wistar)	up to 2 yr (W)	Resp	82 M 109 F			Til et al. 1989
			Cardio	82 M 109 F			
			Gastro	15[c] M 21 F		82 M 109 F (papillomatous hyperplasia with hyperkeratosis, chronic atrophic gastritis, focal ulceration in forestomach, glandular hyperplasia)	
			Hemato	82 M 109 F			
			Musc/skel	82 M 109 F			
			Hepatic	82 M 109 F			
			Renal	15 M 21 F		82 M 109 F (increased incidence of renal papillary necrosis and increased relative kidney weight in females)	
			Endocr	82 M 109 F			
			Dermal	82 M 109 F			
			Ocular	82 M 109 F			
			Bd Wt	15 M 21 F	82 M 109 F (body weights about 10-15% lower than controls)		
			Other	15 M 21 F	82 M 109 F (decreased food/water intake)		

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
39	Rat (Wistar)	up to 24 mo (W)	Resp	300			Tobe et al. 1989
			Cardio	300			
			Gastro	10	50 (forestomach hyperkeratosis)	300 (severe degenerative lesions in epithelium of forestomach and glandular stomach)	
			Hemato	300			
			Hepatic	50	300 (decreased serum protein, albumin, total cholesterol)		
			Renal	300			
			Endocr	300			
			Bd Wt	50		300 (40-45% decrease in terminal body weight)	
			Other	50	300 (25-50% decreased food/water intake)		
	Immunological/Lymphoreticular						
40	Rat (Wistar)	up to 2 yr (W)		82 M 109 F			Til et al. 1989
41	Rat (Wistar)	up to 24 mo (W)		300			Tobe et al. 1989
	Neurological						
42	Rat (Wistar)	up to 2 yr (W)		15 M 21 F	82 M (17% increase in relative brain weight) 109 F (8% increase in relative brain weight)		Til et al. 1989

Table 2-4. Levels of Significant Exposure to Formaldehyde - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form[d]
43	Rat (Wistar)	up to 24 mo (W)		300			Tobe et al. 1989
	Reproductive						
44	Rat (Wistar)	up to 2 yr (W)		82 M 109 F			Til et al. 1989
45	Rat (Wistar)	up to 24 mo (W)		300			Tobe et al. 1989

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.3 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.2 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (F) = food; Endocr = endocrine; F = female; gastro = gastrointestinal; (GW) = gavage in water; gd = gestation day; (IN) = ingestion; Hemato = hematological; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year(s)

[d]Formalin designation herein means that the study either involved direct exposure to formalin (~40% aqueous solution of formaldehyde containing 10-15% methanol as a stabilizing agent) or used such a solution as a stock for the preparation of orally administered material.

Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral

Acute (≤14 days)

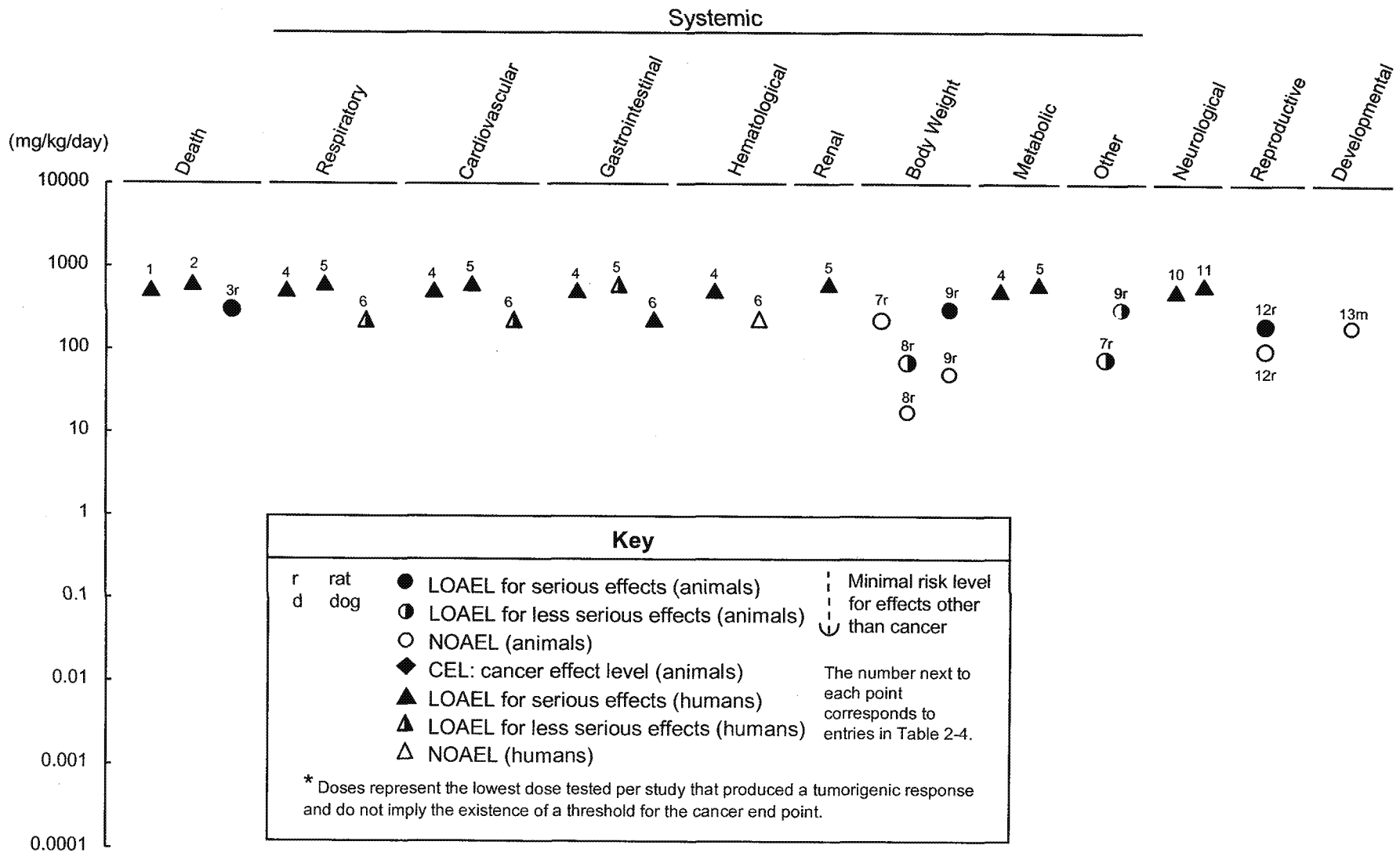


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Intermediate (15-364 days)

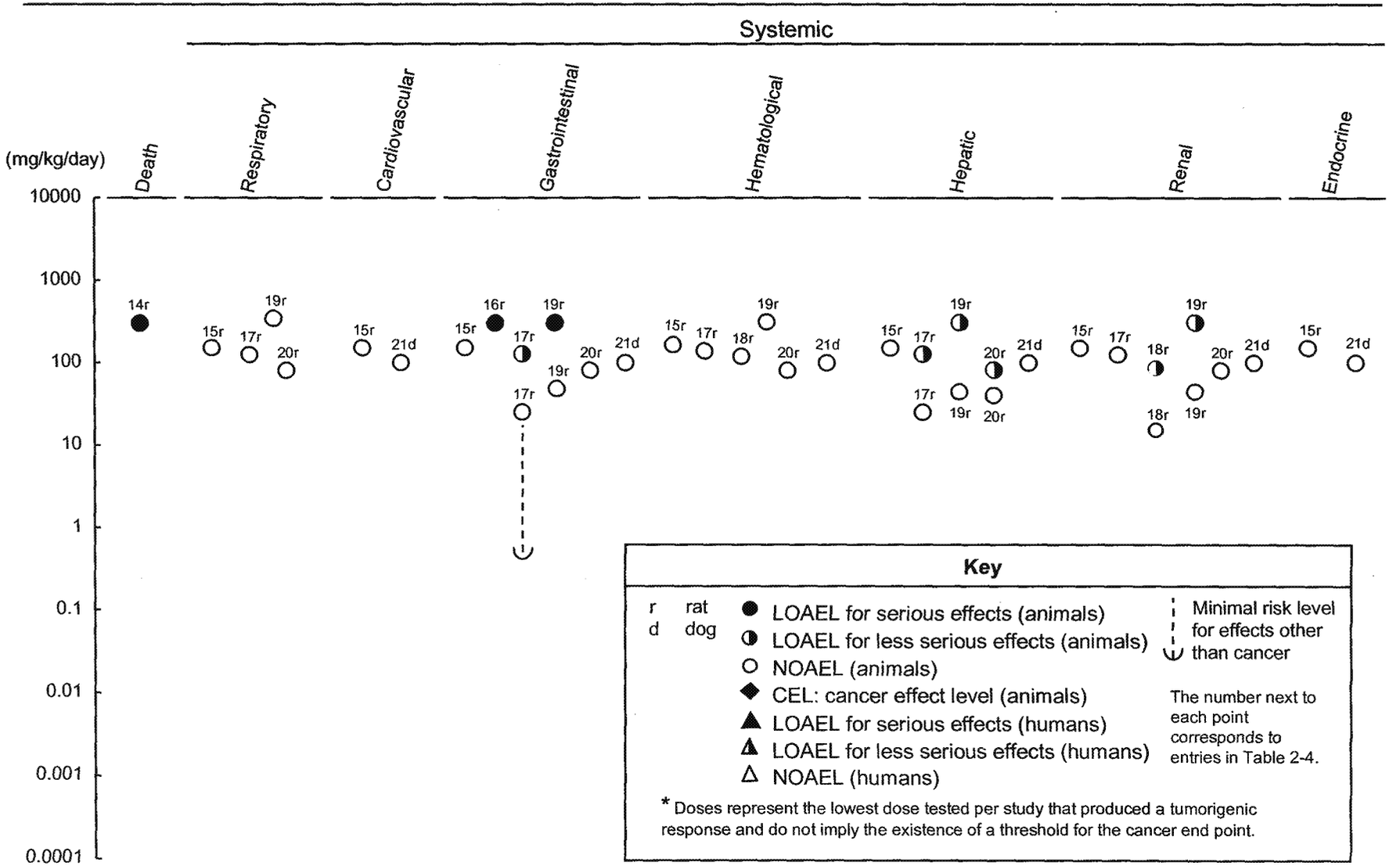


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Intermediate (15-364 days)

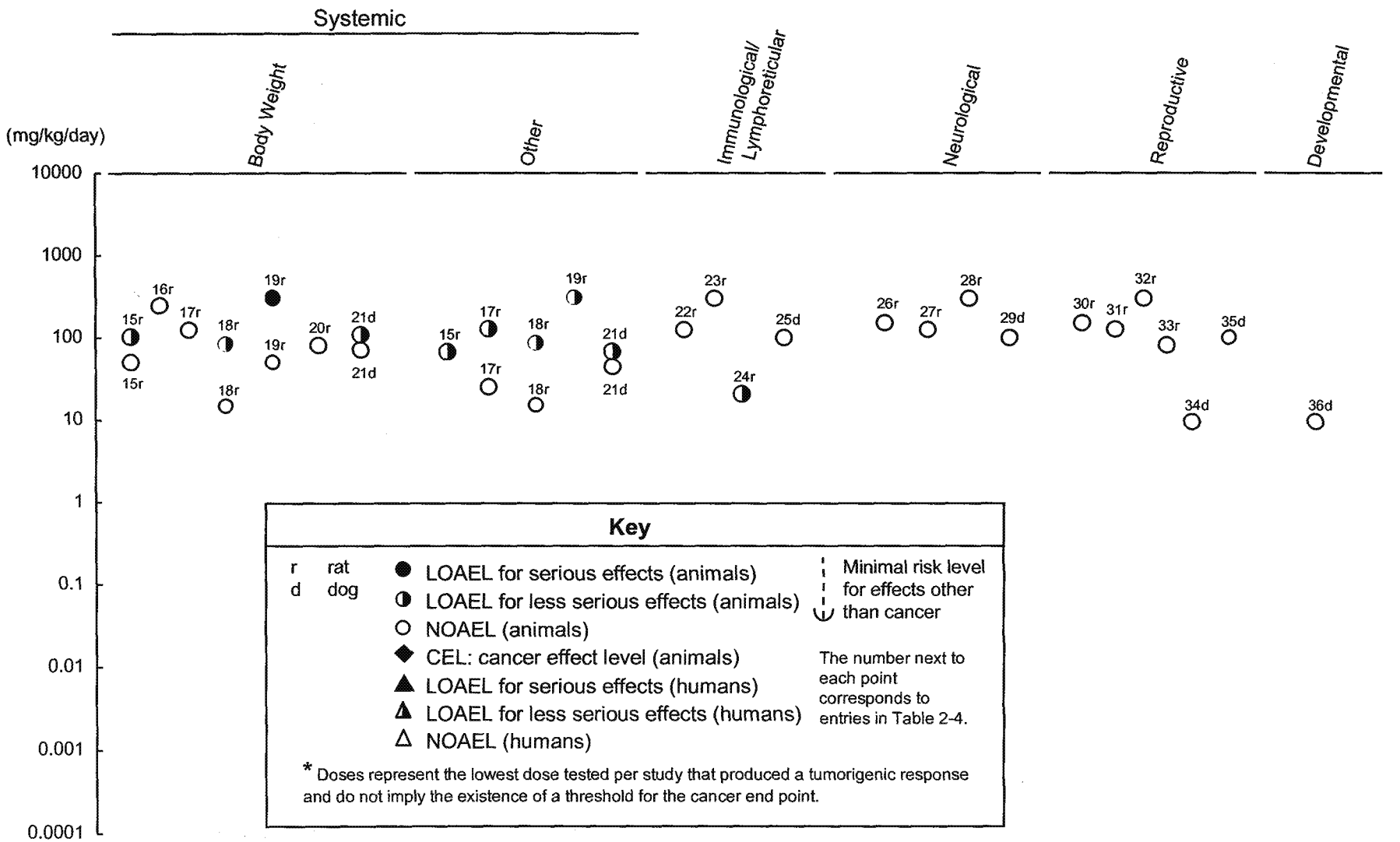


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Chronic (≥365 days)

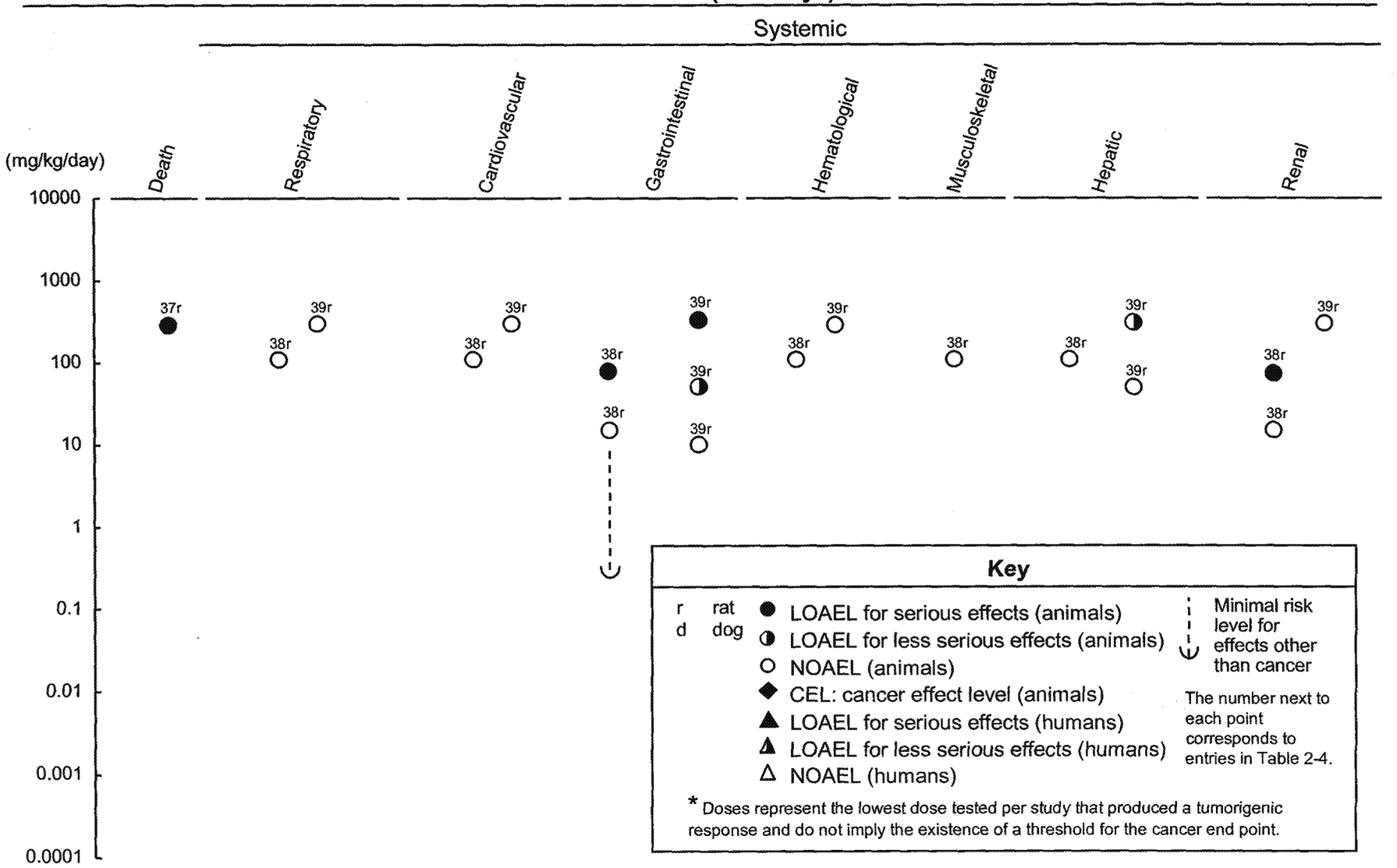
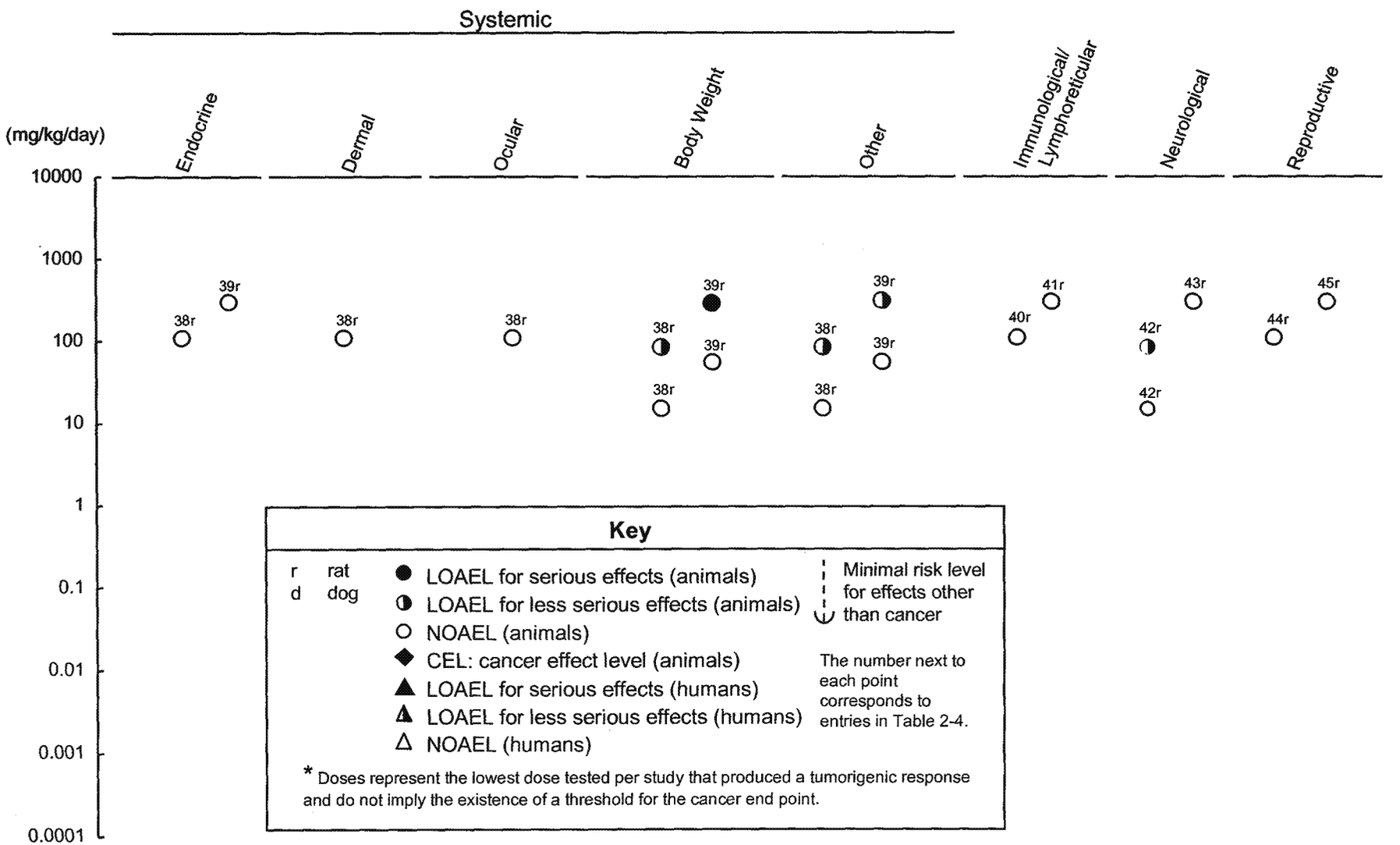


Figure 2-2. Levels of Significant Exposure to Formaldehyde - Oral (cont.)

Chronic (≥365 days)



2.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

Respiratory Effects. Respiratory effects have been observed in humans after ingestion of formaldehyde. A 55-year-old woman and a 34-year-old man ingested an unknown amount of formalin with suicidal intent and were admitted to the hospital (Koppel et al. 1990). Respiratory insufficiency was noted upon admission to the hospital. Both patients died; however, the man developed adult respiratory distress syndrome prior to death.

Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces (517 mg/kg) of a formaldehyde solution in a suicide attempt. The man was found unconscious by a co-worker about 1hour after his shift began. In the emergency room, the subject regained consciousness, but was lethargic. At 5.5 hours after ingestion, the patient became obtund, and his respiratory rate fell significantly; he was intubated and placed on 100% oxygen. He subsequently sustained a cardiac arrest from which he could not be revived.

Eells et al. (1981) described the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting 120 mL of formalin (37% formaldehyde solution; 624 mg/kg). Upon admission, the patient was cyanotic, apneic, and hypotensive. The patient was intubated and ventilation was initiated. The patient was maintained via endotracheal respiration and dopamine therapy; she died 28 hours after admission. Other adverse respiratory effects have been noted in other reports of human ingestion including difficulty breathing and speaking (Freestone and Bentley 1989), increased cough, and tachypnea after 234 mg/kg formaldehyde (Kochhar et al. 1986).

Intermediate-duration oral exposure data on respiratory effects in experimental animals are limited to organ weight and/or histopathological results, and are negative. After 90-day exposure to doses of 150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on lung weight or histopathology (Johannsen et al. 1986). Til et al. (1988b) saw no effect on the histopathology of the nose and pharynx of male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Vargova et al. (1993) saw no adverse effect on the histopathology of lung tissue of male Wistar rats after 4 weeks of gavage exposure to doses of

formaldehyde of 80 mg/kg/day. No adverse effects on lung weight or histopathology were seen in Beagle dogs exposed to 100 mg/kg/day of formaldehyde in the diet for 90 days (Johannsen et al. 1986).

Chronic-duration exposure data are similarly limited in scope. Til et al. (1989) saw no adverse effect on nose and lung tissue or lung weight in male and female Wistar rats exposed to doses 82 mg/kg/day (male) or 109 mg/kg/day (females) in drinking water for up to 2 years. Tobe et al. (1989) also saw no effect on lung weight or histopathology from doses of formaldehyde of 300 mg/kg/day in drinking water administered to male and female Wistar rats for up to 24 months.

Cardiovascular Effects. Shock and cardiac failure have been noted in patients after intentional ingestion of formaldehyde solution (Koppel et al. 1990). Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg/kg formaldehyde) in a suicide attempt. The man was found unconscious by a co-worker about 1hour after his shift began. In the emergency room, the subject regained consciousness, but was lethargic. At 5.5 hours after ingestion, his blood pressure fell significantly. He subsequently sustained a cardiac arrest from which he could not be revived. Other reports of cardiovascular effects in humans after ingestion of formaldehyde include hypotension after 624 mg/kg formaldehyde (as formalin) (Eells et al. 1981), circulatory collapse (Freestone and Bentley 1989), and sinus tachycardia after 234 mg/kg formaldehyde (Kochhar et al. 1986).

Intermediate-duration exposure data on cardiovascular effects in experimental animals are limited to organ weight and/or histopathological results, and are negative. After 90-day exposure to doses of 150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on heart weight or histopathology (Johannsen et al. 1986). No significant effects on the histopathology of the heart were observed in Wistar rats after 12 months of exposure to up to 300 mg/kg/day in drinking water (Tobe et al. 1989). In addition, 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet found no effect on heart weight or histopathology (Johannsen et al. 1986).

Til et al. (1989) saw no adverse effect on heart tissue or organ weight in male and female Wistar rats exposed to doses 82 mg/kg/day (male) or 109 mg/kg/day (females) in drinking water for up to 2 years. Tobe et al. (1989) also saw no effect on heart weight or histopathology of doses of formaldehyde of 300 mg/kg/day in drinking water administered to male and female Wistar rats for up to 24 months.

Gastrointestinal Effects. Formaldehyde is corrosive to mucosal tissues. Intentional ingestion of formaldehyde has been associated with extensive congestion, hemorrhaging, and necrosis of the gastrointestinal mucosa (Koppel et al. 1990). Burkhart et al. (1990) described the case of a 58-year-old man who swallowed 4 ounces (517 mg/kg formaldehyde) of formalin in a suicide attempt. Approximately 3 hours after ingesting the formalin, the patient complained of abdominal pain and began retching without emesis; he was admitted for observation and treated with ethanol. The patient's abdominal pains became more severe, and he subsequently died from cardiac arrest. At autopsy, the patient's stomach was hard, white, and leathery; the esophagus and intestines appeared to be normal.

Eells et al. (1981) described the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting 120 mL formalin (624 mg/kg formaldehyde). The patient complained of abdominal pain and subsequently lost consciousness; she died 28 hours after admission. Freestone and Bentley (1989) describe gastrointestinal effects after presumed gargling with formaldehyde, including dysphagia due to esophageal mucosal damage. The patient was placed on parenteral feeding to allow resting of the gut and to improve nutritional status. After several weeks in intensive care, the patient was taken off of ventilation; after two additional months, the patient was released.

A 26-year-old woman who ingested 234 mg/kg formaldehyde exhibited extensive gastrointestinal damage (Kochhar et al. 1986). Immediately after ingesting formaldehyde, the patient experienced repeated vomiting with occasional streaks of blood. Anti-emetics and antacids were prescribed but did not relieve symptoms. Examination of the oropharynx revealed ulceration and sloughing of the soft palate and posterior pharyngeal wall. Indirect laryngoscopy revealed ulceration of the epiglottis, pyriform fossae, and arytenoids. At 96 hours, an upper gastrointestinal endoscopy revealed that the esophageal mucosa was edematous and ulcerated with patches of black slough along the entire length. Areas of the stomach were hyperemic, and there was superficial ulceration in the distal body and antrum; the duodenal mucosa appeared normal. The patient underwent a feeding jejunostomy and made an uneventful recovery. At 4 weeks, a repeat endoscopy revealed a normal esophagus. The stomach appeared normal with the exception of slight hyperemia and limited distensibility of the antrum. Barium examination revealed scarring of the antrum and distal portion of the gastric body. At 6 weeks, the patient was asymptomatic.

Intermediate-duration exposure data on gastrointestinal effects in experimental animals are limited to organ weight and/or histopathological results, but are sufficient to describe a no-effect level for gastrointestinal effects in rats. After 90-day exposure to doses up to 150 mg/kg/day formaldehyde in

drinking water, male and female Sprague-Dawley rats showed no adverse effects on the histopathology of the gastrointestinal mucosa (Johannsen et al. 1986). In contrast, erosions and/or ulcers, associated with regenerating mucosa, were noted in the limiting ridge of the fundic mucosa in glandular stomach of male Wistar rats exposed to 0.5% formalin (258 mg/kg/day formaldehyde) in drinking water for 32 weeks (Takahashi et al. 1986a). Erosions were described as "diffuse deep gastric pits with clearly increased numbers of mucous neck cells in the fundic mucosa". Benign papillomas in the forestomach also were noted in 8 of the 10 exposed rats in this study, compared with none in 40 controls. Increased incidences of forestomach squamous cell hyperplasia and glandular stomach glandular hyperplasia were observed in Wistar rats exposed for 12 months to 300 mg/kg/day in drinking water, but not in rats exposed to 50 mg/kg/day (Tobe et al. 1989). Til et al. (1988b) saw thickening of the limiting ridges of the stomach and hyperkeratosis in the forestomach of male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. One of the 10 females receiving this dose also exhibited moderate papillomatous hyperplasia, presumably of the glandular stomach. Focal atrophic inflammation was also observed in the glandular stomach. No adverse effects of treatment were observed at 25 mg/kg/day formaldehyde in either sex. An intermediate-duration MRL of 0.3 mg/kg/day was derived from the data of Til et al. (1988b). The MRL of 0.3 mg/kg/day was based on a NOAEL of 25 mg/kg/day for lack of gastrointestinal effects in rats and calculated as described in the footnote to Table 2-4 and in Appendix A of this profile.

Vargova et al. (1993) saw no adverse effect on the histopathology of stomach tissue of male Wistar rats after 4 weeks of gavage exposure to doses of 80 mg/kg/day formaldehyde. In addition, no effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on stomach weight or histopathology (Johannsen et al. 1986).

Til et al. (1989) observed adverse gastrointestinal effects at 82 mg/kg/day formaldehyde in male and 109 mg/kg/day formaldehyde in female Wistar rats exposed in drinking water for up to 2 years. Lesions were first seen after 53 weeks. These adverse effects included papillomatous hyperplasia with hyperkeratosis, chronic atrophic gastritis, focal ulceration in the forestomach, and hyperplasia in the glandular stomach. No adverse gastrointestinal effects were noted in the male rats receiving a dose of 15 mg/kg/day. A chronic-duration oral MRL of 0.2 mg/kg/day was derived from the data of Til et al. (1989). The MRL of 0.2 mg/kg/day was based on a NOAEL of 15 mg/kg/day for lack of gastrointestinal effects in male rats and was calculated as described in the footnote to Table 2-4 and in Appendix A of this profile.

Tobe et al. (1989) also saw forestomach hyperkeratosis at a drinking-water dose of 50 mg/kg/day and severe degenerative lesions in the epithelium of the forestomach and glandular stomach at 300 mg/kg/day in male and female Wistar exposed for up to 24 months.

Hematological Effects. Some hematological effects have been noted in humans after acute ingestion, but do not appear to be primary effects in formaldehyde poisoning. Burkhart et al. (1990) described intravascular coagulopathy in the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg/kg formaldehyde) in a suicide attempt. However, Kochhar et al. (1986) indicated that normal hematology was observed in a 26-year-old female who ingested a formaldehyde dose of 234 mg/kg (Kochhar et al. 1986). Other reports of human ingestion do not indicate adverse effects on the hematological system (Eells et al. 1981; Freestone and Bentley 1989; Koppel et al. 1990).

Intermediate-duration exposure data on hematological effects in experimental animals are limited to routine hematological parameters and are negative. After 90-day exposure to doses of 150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on hematocrit or hemoglobin (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on hemoglobin concentration, packed cell volume, or erythrocyte counts in male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. In a companion study, no effect was seen on hematological variables in male and female rats exposed to doses 82 mg/kg/day (males) or 109 mg/kg/day (females) for 52 weeks (Til et al. 1989). Vargova et al. (1993) saw a statistically significant increase in the hematocrit of male Wistar rats after 4 weeks of gavage exposure to doses of 40–80 mg/kg/day formaldehyde. At 80 mg/kg/day, erythrocyte count and hemoglobin were statistically significantly increased, whereas mean corpuscular hemoglobin was significantly depressed compared to control animals (Vargova et al. 1993). Vargova et al. (1993) reported that the hemotological effects noted, although statistically significant, were within the background range for Wistar rats, and were therefore of questionable clinical significance. No effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on hematological parameters including hematocrit and hemoglobin (Johannsen et al. 1986).

Til et al. (1989) observed no adverse hematological effects in male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years. Similarly, Tobe et al. (1989) observed no exposure-related effects on red blood cell count, hematocrit, or hemoglobin in rats exposed to drinking water doses up to 300 mg/kg/day for up to 24 months.

Musculoskeletal Effects. No reports of musculoskeletal effects in humans after acute-, intermediate-, or chronic-duration oral exposure to formaldehyde were found in the literature.

Til et al. (1989) observed no adverse histopathological effects on the skeletal muscle of male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years.

Hepatic Effects. Intentional ingestion of formaldehyde in a suicide attempt has been associated with hepatomegaly, icterus, and congestion of the hepatic parenchyma (Koppel et al. 1990). Some reports of human ingestion of formaldehyde include hepatotoxicity and increased liver enzymes (Freestone and Bentley 1989), although other reports do not indicate hepatic effects (Eells et al. 1981).

Intermediate-duration exposure data on hepatic effects in experimental animals are limited to measurement of liver weight and histopathology and are mostly negative. After 90-day exposure to doses of 150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on liver weight or histopathology (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on liver weight or histopathology in male and female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water; however, a decrease in plasma protein and albumin concentration was observed. Vargova et al. (1993) saw an increase in the incidence of hepatocellular vacuolization in male Wistar rats after 4 weeks of gavage exposure to doses of 80 mg/kg/day formaldehyde. No effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on liver weight, histopathology, or activities of serum enzymes indicative of liver damage (Johannsen et al. 1986).

Til et al. (1989) observed no adverse effects on organ weight or histopathology of the liver of male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years. Likewise, hepatic weight determinations and histopathology were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months. However, serum protein, albumin, and total cholesterol were all statistically significantly decreased in both sexes at 300 mg/kg/day at 12 months in this study. In exposed rats, serum hepatic enzyme levels (alkaline phosphatase, glutamate-oxaloacetic transaminase, and glutamic-pyruvic transaminase) were either not different from or were significantly lower than control values (Tobe et al. 1989).

Renal Effects. Renal failure has been associated with acute intentional ingestion of formaldehyde (Eells et al. 1981; Freestone and Bentley 1989; Koppel et al. 1990). In the case reported by Eells et al. (1981), the patient, who ingested 624 mg/kg formaldehyde (as formalin), became anuric approximately 7.5 hours after ingestion, and her health continued to deteriorate over the next day; she died 28 hours after admission. Koppel et al. (1990) also describe renal failure prior to death, occurring soon after ingestion of an unknown quantity of formaldehyde. However, in the report by Freestone and Bentley (1989), hypoalbuminemia and renal failure were noted upon admission to the hospital after the patient gargled with formaldehyde. Dopamine was given until renal function improved. After several weeks in intensive care, the patient was taken off of ventilation; after two additional months, the patient was released.

Intermediate-duration exposure data on renal effects in experimental animals are limited to kidney weight measurement and histopathology and are mostly negative. After 90-day exposure to doses of 150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on kidney weight or histopathology (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on kidney histopathology in male Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Vargova et al. (1993) saw no effect on the weight or histopathology of the kidneys in male Wistar rats after 4 weeks of gavage exposure to doses of 80 mg/kg/day formaldehyde. No effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on kidney weight or histopathology (Johannsen et al. 1986). Til et al. (1989) reported, however, that male and female Wistar rats had increased urine density, decreased urine volume, and occult blood (males only) after exposure for 27 to 82 weeks to 109 mg/kg/day formaldehyde in drinking water, respectively.

In a 2-year drinking water study, Til et al. (1989) observed an increase in the incidence of renal papillary necrosis in male rats exposed to 82 mg/kg/day and an increase in renal papillary necrosis accompanied by increased relative kidney weight in female rats exposed to 109 mg/kg/day. Kidney weight determinations and histopathology were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months, but blood urea nitrogen was increased in the 300-mg/kg/day group at 12 months.

Endocrine Effects. No reports describing endocrine effects of acute-, intermediate-, or chronic-duration oral exposure to formaldehyde in humans or acute-duration oral exposure in animals were found.

After 90-day exposure to doses of 150 mg/kg/day formaldehyde in drinking water, male and female Sprague-Dawley rats showed no adverse effects on adrenal or thyroid weight or histopathology (Johannsen et al. 1986). Similarly, Til et al. (1988b) saw no effect on adrenal and thyroid weight in male Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Vargova et al. (1993) saw no effect on the weight of the adrenals or pituitary in male Wistar rats after 4 weeks of gavage exposure to doses of 80 mg/kg/day formaldehyde. No effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on adrenal and thyroid weight or histopathology (Johannsen et al. 1986).

Til et al. (1989) observed no effect on the weight of the adrenal, pituitary, and thyroid, or histopathology of the adrenal, pituitary, thyroid, or pancreas in male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years. Adrenal, pituitary, and thyroid weight determinations and histopathology, in addition to histopathology of the pancreas, were not influenced by exposure in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

Dermal Effects. No reports of dermal effects of acute-, intermediate-, or chronic-duration oral exposure of humans to formaldehyde were found in the literature.

No adverse histopathology was noted in skin samples from male and female Wistar rats receiving 109 mg/kg/day formaldehyde in drinking water after 2 years of exposure (Til et al. 1989)

Ocular Effects. No reports of ocular effects after acute-, intermediate-, or chronic-duration oral exposure of humans, or acute- or intermediate-duration oral exposure of animals to formaldehyde were found in the literature.

Til et al. (1989) observed no effect on the histopathology of the Harderian and exorbital lachrymal glands and eye of male and female rats exposed to 82 and 109 mg/kg/day formaldehyde, respectively, in drinking water for up to 2 years.

Body Weight Effects. No reports of body weight effects in humans after oral exposure to formaldehyde were located.

Groups of Sprague-Dawley rats (sex not specified) were administered formaldehyde at 0, 37.5, 75, 150, or 225 mg/kg/day by gavage for 2 weeks (Johannsen et al. 1986). Mean body weight decreased at concentrations above 75 mg/kg/day. However, another pilot study conducted by Johannsen et al. (1986), Sprague-Dawley rats given formaldehyde at 0, 75, 150, or 225 mg/kg/day in drinking water for 2 weeks showed no significant changes in final body weights. Til et al. (1989) noted a decrease in body weight gain (unspecified) after 1 week of exposure of male Wistar rats to 82 mg/kg/day formaldehyde in drinking water, with statistically significant decreases in food consumption reported at 82 mg/kg/day for males and 109 mg/kg/day for females. No effect on body weight was noted until week 24 in female rats in the same study exposed to a high dose of 109 mg/kg/day. Body weight was not affected in male and female Wistar rats exposed to formaldehyde in drinking water at doses 125 mg/kg/day for 4 weeks (Til et al. 1988b). Likewise, Vargova et al. (1993) saw no effect on body weight in male Wistar rats exposed by gavage 5 days/week for 4 weeks, to doses of 80 mg/kg/day formaldehyde.

Johannsen et al. (1986) noted that significant decreases in body weights occurred in both sexes of Sprague-Dawley rats exposed to 150 mg/kg/day in drinking water for 90 days and in males exposed to 100 mg/kg/day, and that these decreases were associated with decreased water, but not food, consumption. Terminal mean body weights at these dose levels were about 10–15% lower than control values, whereas at 50 mg/kg/day for both sexes, and at 100 mg/kg/day for female rats, they were within 10% of control body weight values. In contrast, no significant effects on body weights were noted in male Wistar rats exposed to 0.5% formalin (258 mg/kg/day formaldehyde) in drinking water for 32 weeks (Takahashi et al. 1986a). Male and female Beagle dogs exposed to 100 mg/kg/day formaldehyde in the diet for 90 days had significantly reduced body weights, compared with controls, but not at lower exposure levels of 50 or 75 mg/kg/day (Johannsen et al. 1986). The magnitude of the decreased body weight was not specified. Significantly reduced food consumption was noted in males, but not in females, in the 100-mg/kg/day group and in females, but not males, in the 75-mg/kg/day group.

Wistar rats exposed for up to 2 years to estimated daily drinking water doses of 300 mg/kg/day lost weight during the first 2 weeks of exposure, whereas control rats and rats exposed to up to 50 mg/kg/day increased their body weights by about 20–30% during the same period (Tobe et al. 1989). Mean body weights and food and water intakes were markedly decreased in the 300-mg/kg/day rats, compared with

controls, throughout the study. After 5–10 weeks of exposure, body weights were about 20–30% lower than controls. Mean terminal body weights were about 40–45% lower than controls. At doses up to 50 mg/kg/day, terminal body weights were within 10% of control body weights throughout the study.

In another chronic drinking water study, mean body weights were significantly decreased, compared with controls, in male Wistar rats after 1 week and in female rats after 24 weeks of exposure to doses of 82 and 109 mg/kg/day, respectively (Til et al. 1989). These decreases were associated with decreases in food and water intake. Terminal body weights were approximately 10–15% lower than controls. Body weights were within 10% of control values in male and female rats exposed to up to 15 and 21 mg/kg/day, respectively.

Metabolic Effects. Metabolic effects have been noted in patients after ingestion of formaldehyde. Metabolic acidosis, high plasma formic acid, and hyperlactatemia were noted in two patients who intentionally ingested formaldehyde in suicide attempts (Koppel et al. 1990). Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of formalin (517 mg/kg formaldehyde) in a suicide attempt. The man was found unconscious by a co-worker about 1 hour after his shift began. Laboratory results at the emergency room indicated significant acidosis. Intravenous bicarbonate and ethanol therapies were begun after the seizures started. Eells et al. (1981) described the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting 120 mL of formalin (624 mg/kg formaldehyde). Laboratory results indicated significant acidosis. Intravenous fluid therapy consisting of Ringers solution followed by 5% dextrose, epinephrine, and sodium bicarbonate was initiated and the patient was transferred to intensive care; she died 28 hours after admission.

No reports were found of metabolic effects in animals orally exposed to formaldehyde.

Other Systemic Effects. Some effects of acute-duration oral exposure to formaldehyde have been seen on food and water consumption in animal studies, and may be related to taste aversion at higher doses in some cases. For example, Johannsen et al. (1986) reported that Sprague-Dawley rats given formaldehyde at 0, 75, 150, or 225 mg/kg/day in drinking water for 2 weeks showed no significant changes in food consumption, but mean water consumption decreased proportionately to dose in all three treated groups. In contrast, food and water consumption were reduced at levels above 75 mg/kg/day in other groups of Sprague-Dawley rats given formaldehyde at 0, 37.5, 75, 150, or 225 mg/kg/day by intubation for 2 weeks (Johannsen et al. 1986).

Intermediate-duration exposure data on food and water consumption are also available from animal studies. In Sprague-Dawley rats exposed to formaldehyde in drinking water for 90 days, decreases in water intakes (>10% of control values) were found in females exposed to 100 or 150 mg/kg/day and in males exposed to 50, 100 or 150 mg/kg/day, but in both sexes, food consumption was not significantly affected (Johannsen et al. 1986). Four-week exposures to 125 mg/kg/day in drinking water were associated with 25–42% decreased water intake and decreased food intake in male and female Wistar rats (Til et al. 1988b). Food consumption was significantly decreased in male Beagle dogs during 90 day dietary exposure to 100 mg/kg/day; food consumption was significantly decreased in females at 75 mg/kg/day(Johannsen et al. 1986).

With chronic drinking water exposure to formaldehyde, statistically significant decreases in food intake (ranging from about 7–14% of control values) and water intake (ranging from about 20–50% of control values) occurred at various intervals throughout a 2-year period of exposure to 82 mg/kg/day in male Wistar rats and to 109 mg/kg/day in female Wistar rats, but not at respective exposure levels 15 and 21 mg/kg/day (Til et al. 1989). In the other 2-year drinking water study by Tobe et al. (1989), significantly decreased food intake (about 10–25% of control values) and water intake (about 40–50% of control values) occurred throughout the exposure period in male and female Wistar rats exposed to 300 mg/kg/day, but not at dose levels of 50 mg/kg/day and lower. In general, the repeated oral exposure animal studies indicate that dosage levels associated with decreased food and/or water consumption were associated with decreased body weights and with the development of gastrointestinal tract lesions.

2.2.2.3 Immunological and Lymphoreticular Effects

Little information is available about immunological and lymphoreticular effects of formaldehyde ingestion in humans. Splenomegaly was observed in one woman who ingested formaldehyde in a suicide attempt (Koppel et al. 1990). However, this effect was most likely secondary to extensive hemorrhaging and necrosis of the gastrointestinal system.

Til et al. (1988b) saw no effect on spleen or thymus weight in male or female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water.

No effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on spleen weight or histopathology (Johannsen et al. 1986).

Vargova et al. (1993) administered 20, 40, or 90 mg/kg/day formaldehyde 5 days/week for 4 weeks to male Wistar rats by gavage. Increased absolute and relative lymph node weights were observed beginning at 40 mg/kg/day. Antibody production was assayed by measurement of total blood IgG and IgM, a hemagglutination assay, a plaque-forming cell assay, and by measurement of IgM production in spleen cells. Only the hemagglutination assay showed a significant effect; the combined IgG and IgM titers were significantly lower than controls at 20 mg/kg/day and above, although individual IgM and IgG titers were only significantly different from controls at 40 and 80 mg/kg/day.

Weanling, SPF-bred rats were exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) formaldehyde in their drinking water for up to 2 years (Til et al. 1989). There was no effect of treatment on spleen weight or histopathology, or the histopathology of the mesenteric and axillary lymph nodes. Spleen weight determinations and histopathology, in addition to histopathology of the lymph nodes, were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

The LOAEL value decreased IgG and IgM titers and increased lymph node weights in rats (Vargova et al. 1993) and the highest NOAEL values from each reliable study for immunological/lymphoreticular effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Little information is available about the neurological effects of formaldehyde ingestion in humans. However, neurological effects appear to be prevalent in reported cases of formaldehyde ingestion. A woman who ingested formaldehyde in a suicide attempt was found in a coma (Koppel et al. 1990). Other neurological effects observed include lethargy, seizure, and loss of consciousness at 517 mg/kg formaldehyde (Burkhart et al. 1990). Loss of consciousness was also observed in another woman (Eells et al. 1981) after ingesting 624 mg/kg formaldehyde.

No effect of 90-day treatment of male and female Sprague-Dawley rats with doses of 150 mg/kg/day formaldehyde in drinking water was found on brain weight or histopathology (Johannsen et al. 1986). Til et al. (1988b) saw no effect on brain weight in male or female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Tobe et al. (1989) saw no effect on the weight or

histopathology of the brain of male and female Wistar rats exposed to doses of 300 mg/kg/day formaldehyde in drinking water for 12 months. No effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on brain weight or histopathology (Johannsen et al. 1986).

Weanling Wistar rats were exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) in their drinking water for up to 2 years (Til et al. 1989). Relative brain weights were statistically significantly increased (by 7–17%) in the high-dose groups of both sexes. However, no effect of treatment on brain histopathology or the histopathology of the spinal cord or sciatic nerve was observed. Brain weight determinations and histopathology were negative in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No reports were found describing reproductive effects in humans after acute-, intermediate-, or chronic-duration oral exposure to formaldehyde.

Male Wistar rats (5 per group) were weighed and fasted for 18 hours overnight (Cassidy et al. 1983). Rats were then administered single dosages of 100 and 200 mg/kg formaldehyde orally. Eleven days after dosing, rats were weighed, sacrificed, and necropsied. There were no significant changes in testes weights observed in animals treated with 100 or 200 mg/kg formaldehyde. At 200 mg/kg formaldehyde, testicular sperm head counts were significantly increased (19%) compared to control values. The percentage of abnormal sperm heads also significantly increased (5%) in the 200 mg/kg dose groups compared to control groups. The toxicological significance of these changes in sperm head number and percentage of abnormal sperm heads is not known since no functional tests of reproductive competence were conducted.

Pregnant CD-1 mice were given formaldehyde at 0, 74, 148, and 185 mg/kg by gavage on gestation days 6–15 (Marks et al. 1980). The formaldehyde solution given to the animals in this study contained

12–15% methanol as a preservative. These animals received formaldehyde solution at 185 mg/kg, which contained 0.6–0.75% methanol, resulting in a concurrent dose of 60–75 mg/kg/day of methanol. On gestation day 18, the mice were sacrificed, implantation sites were counted, and general condition of each conceptus were recorded. Formaldehyde at 74 or 148 mg/kg/day had no consistent and statistically significant effects on indices of reproduction (e.g., the number of resorptions and the number of implantation sites per dam), but only 12 of the 34 dams who were exposed to 185 mg/kg/day survived to gestation days 18. Marks et al. (1980) noted that the methanol could have contributed to the lethality. Among the 12 surviving 185-mg/kg/day dams, only 8 (67%) remained pregnant at gestation day 18; the average percent of resorptions per litter was increased in these dams, compared with controls, but not to a statistically significant extent.

Formaldehyde was evaluated in the Chernoff/Kavlock developmental toxicity screen (Seidenberg and Becker 1987). Based on range-finding studies, timed-pregnant ICR/SIM mice were administered a single minimally toxic dose (not reported) by gavage on gestation days 8–12. Three or four compounds and a vehicle (corn oil or distilled water) were tested concurrently. Dams were allowed to deliver. The litters were counted and weighed on days 1 and 3. Dead pups were examined for external abnormalities. Dams that had not given birth by gestation days 21 or 22 were necropsied, and their uteri were examined for possible implantation sites. Formaldehyde was designated as a nonteratogen or non-embryotoxin based on results of the developmental toxicity screen.

No adverse effects of 90-day treatment of male and female Sprague-Dawley rats with doses of 150 mg/kg/day formaldehyde in drinking water were found on gonad weight or histopathology (Johannsen et al. 1986). Til et al. (1988b) saw no effect on testis weight in male or ovary weight in female Wistar rats after 4 weeks of exposure to 125 mg/kg/day formaldehyde in drinking water. Tobe et al. (1989) saw no effect on the weight or histopathology of the testis of male and ovary of female Wistar rats exposed to doses of 300 mg/kg/day formaldehyde in drinking water for 12 months. Vargova et al. (1993) saw no effect on testis or prostate weight of exposure to 80 mg/kg/day formaldehyde by gavage 5 days/week for 4 weeks in male Wistar rats. No effect of 90-day treatment of male and female Beagle dogs with doses of 100 mg/kg/day formaldehyde in the diet was found on gonad weight or histopathology (Johannsen et al. 1986).

Weanling Wistar rats were exposed to 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) in their drinking water for up to 2 years (Til et al. 1989). There was no effect of

treatment on ovary or testis weight or histopathology, or the histopathology of the mammary gland, epididymides, prostate, or uterus. Testis and ovary weight determinations and histopathology were negative, as was histopathological evaluation of the uterus in the study conducted by Tobe et al. (1989), wherein male and female Wistar rats were exposed to 0, 10, 50, or 300 mg/kg/day formaldehyde in drinking water for up to 24 months.

Hurni and Ohder (1973) investigated the effects of oral administration of formaldehyde on reproductive function in female beagle dogs during gestation. Formaldehyde was sprayed on the pelleted food at dietary levels of 125 and 375 ppm (calculated by authors to be equivalent to 3.1 and 9.4 mg/kg, respectively). Although the feed was not assayed for formaldehyde content, the authors reported that formaldehyde solutions, prepared weekly from a commercial 40% aqueous solution, were sprayed daily on the food just prior to feeding. Ten to 11 mated females were fed the treated feed on gestation days 4–56. Exposure to formaldehyde did not affect pregnancy rates, maternal body weights, or litter size.

The serious LOAEL value for rats (Cassidy et al. 1983) and the highest NOAEL value from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to formaldehyde.

Pregnant CD-1 mice were given formaldehyde at 0, 74, 148, and 185 mg/kg by gavage on gestation days 6–15 (Marks et al. 1980). On gestation day 18, mice were sacrificed, implantation sites were counted, and general condition of each conceptus was recorded. Live fetuses were weighed individually, sexed internally, and examined for external malformations. The viscera of at least one-third of the fetuses of each litter, as well as stunted fetuses and those having external malformations, were examined for abnormalities. The heads of the fetuses which were subjected to visceral examination were cut off at the base and prepared for free-hand sectioning. The formaldehyde solution given to the animals in this study contained 12–15% methanol as a preservative. Formaldehyde solution at 185 mg/kg contained 0.6–0.75% methanol or 60–75 mg/kg/day. No attempt was made to remove the methanol. There were no statistically significant effects on fetal weight, ratio of males to females, or incidences of visceral or

skeletal fetal malformations in any exposed group, compared with the control group, even though at the highest dose group, only 12 of 34 dams survived to gestation day 18.

Formaldehyde was evaluated in the Chernoff/Kavlock developmental toxicity screen (Seidenberg and Becker 1987). Based on range-finding studies, timed-pregnant ICR/SIM mice were administered a single minimally toxic dose (not reported) by gavage on gestation days 8–12. Dams were allowed to deliver. The litters were counted and weighed on days 1 and 3. Dead pups were examined for external abnormalities. Dams that had not given birth by gestation days 21 or 22 were necropsied, and their uteri were examined for possible implantation sites. Formaldehyde was designated as a nonteratogen or nonembryotoxin based on results of the developmental toxicity screen. Neonatal development was not affected by formaldehyde treatment. Formaldehyde had no effect in the number of live neonates per litter or on the average neonatal body weight at birth in this investigation.

No exposure-related effects on pregnancy success, maternal weight gain, gestation length, litter size, pup body weight, number of stillborn pups, or numbers of live pups that survived to weaning were found in a study in which groups of 9–10 pregnant Beagle dogs were fed diets delivering reported doses of 0, 3.1, or 9.4 mg/kg/day on gestation days 4–56 (Hurni and Ohder 1973). In the few stillborn pups that were found, no internal or skeletal malformations were observed. Formaldehyde solutions were prepared weekly from a commercial 40% aqueous solution and sprayed daily on the food just prior to feeding. The study identifies 9.4 mg/kg/day as a NOAEL for maternal and fetal developmental effects.

The highest NOAELs for developmental effects in the Hurni and Ohder (1973) and Marks et al. (1980) studies are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No reports of genotoxic effects in humans or animals were found after oral exposure to formaldehyde.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans orally exposed to formaldehyde.

Takahashi et al. (1986a) administered 0 or 0.5% formalin (about 0.185% formaldehyde=1,850 ppm formaldehyde) in drinking water to groups of 10 male Wistar rats for 32 weeks, and evaluated surviving animals for neoplasms at 40 weeks. An estimated dose of 258 mg/kg/day was calculated using an average reported body weight of 0.280 kg and a water consumption rate of 0.039 L/day calculated with an allometric equation based on body weight (EPA 1988e). No carcinoma-bearing animals were reported; however, 8 of 10 (80%) rats showed benign papillomas of the forestomach in the exposed group compared with none in 40 control rats. No tumors (benign or malignant) were found in the fundus, pylorus, or duodenum of the glandular stomach in exposed rats, but erosions and/or ulcers associated with regenerating mucosa were found along the limiting ridge of the fundic mucosa in exposed rats.

Soffritti et al. (1989) administered formaldehyde in drinking water to Sprague-Dawley rats for life beginning at various ages. Groups of 50 male and 50 female rats were exposed to 0 (methanol:water control), 10, 50, 100, 500, 1000, or 1,500 ppm from 7 weeks of age for life. Another control group consisted of 100 male and 100 female rats exposed to plain drinking water. Two groups of 18–20 male and 18–20 female breeders were exposed to 0 or 2,500 ppm formaldehyde starting at 25 weeks of age for life. Offspring of the breeders, 36–59 males and 37–49 females, received, for life, the same levels of formaldehyde as their parents. Estimated average doses were calculated, using reference values for Sprague-Dawley rats of 0.431 kg body weight and 0.054 L water consumed/day (EPA 1988e), as follows: 0, 1, 6, 13, 63, 125, 188, and 313 mg/kg/day. In rats treated from 7 weeks of age, leukemia was reported in controls and exposed groups at the following incidences: 8/100 (methanol control), 7/200 (plain control), and 3/100, 9/100, 9/100, 12/100, 13/100, and 18/100 for the 10- through 1,500-ppm groups, respectively. Leukemia was described as lymphoblastic leukemias and lymphosarcomas, immunoblastic lymphosarcomas, or hemolymphoreticular neoplasias. Lymphoblastic leukemia-lymphosarcomas were predominant among the leukemias noted. Pair-wise comparisons using the Fisher exact test (performed by Syracuse Research Corporation) indicate that only the high-dose incidence was significantly ($p<0.05$) increased compared with the methanol controls, but comparisons to the combined control incidence indicated significantly increased incidence at the 500-, 1,000- and 1,500-ppm levels. In the breeders exposed from 25 weeks of age, incidences for leukemia were 1/40 for controls and 4/36 for the

2,500-ppm group, and 6/108 for control offspring and 4/73 for 2,500-ppm offspring. Pair-wise comparisons of these incidences indicate no statistical difference between control and exposed groups.

Stomach and intestinal tumors were also reported in the Soffritti et al. (1989) study. In rats treated from 7 weeks of age, a few stomach tumors were found (2/100 at 10 ppm, 1/100 at 1,000 ppm, and 2/100 at 1,500 ppm, but none in the other groups), but no statistically significant association with exposure was found. A few intestinal tumors were also reported (1/100 at 10 ppm, 2/100 at 50 ppm, 1/100 at 1,000 ppm, and 6/100 at 1,500 ppm), but only the incidence at 1,500 ppm was significantly ($p<0.05$) increased compared with the methanol control using the Fisher Exact test (performed by Syracuse Research Corporation). No significant difference was found in incidence of either type of gastrointestinal tract tumor in the control and 2,500-ppm exposed breeders, but offspring displayed significantly ($p<0.05$) increased incidence of stomach tumors (5/73 versus 0/108) and intestinal tumors (8/73 versus 0/108). The neoplasms included benign tumors (papillomas and acanthomas of the forestomach and adenomas) and malignant tumors (including adenocarcinomas and leiomyosarcomas). Leiomyosarcoma was the most frequent malignant tumor. The majority of the malignant tumors of the intestine was found in the duodenum, jejunum, and ileum.

Two other chronic-duration rat drinking water studies showed no evidence for formaldehyde-induced carcinogenicity. Groups of 70 male and 70 female Wistar rats were exposed for 2 years to formaldehyde in drinking water at concentrations that delivered average measured doses of 0, 1.2, 15, or 82 mg/kg/day (males) and 0, 1.8, 21, or 109 mg/kg/day (females) (Til et al. 1989). Average drinking water concentrations were reported to be 0, 20, 260, and 1,900 ppm (mg/L). In high-dose animals, histopathological examination revealed gastric changes (including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach and focal chronic atrophic gastritis), but no increased incidences of nonneoplastic lesions were found in groups exposed to lower concentrations compared with controls. No statistically significant increased incidences of tumors, benign or malignant, were found in exposed groups compared with controls. Til et al. (1989) concluded that exposure to 82–109 mg/kg/day formaldehyde in drinking water produced severe damage to the gastric mucosa, but no tumors. In the other experiment, groups of Wistar rats (20 males, 20 females) were exposed to formaldehyde in their drinking water at concentrations of 0, 200, 1,000 or 5,000 ppm for 24 months (Tobe et al. 1989). Estimated average doses of 0, 10, 50, and 300 mg/kg/day were reported by the authors. All animals in the 5,000-ppm group died before 24 months and showed degenerative lesions in the forestomach (erosions and/or ulcers and hyperplasia of the squamous epithelium with or without

hyperkeratosis) and glandular stomach (erosions and/or ulcers accompanied by submucosal inflammatory cell infiltrates). In animals exposed to 50 mg/kg/day formaldehyde, forestomach hyperkeratosis was observed in 1 of 6 males and in 1 of 8 females. There were no lesions of the forestomach or glandular stomach in the 10-mg/kg/day groups. There were no significant differences in the incidences of any tumors in any exposed group compared with controls.

The evidence for the carcinogenicity of formaldehyde in rats exposed to formaldehyde-containing drinking water is not strong due to inconsistency of findings across studies and inconsistent evidence of a dose-response relationship for either leukemia or gastrointestinal tumors in the Soffritti et al. (1989) study.

Among the four studies that assessed the potential carcinogenicity of formaldehyde in drinking water (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989), only Soffritti et al. (1989) reported increased incidence of leukemia in exposed rats. Feron et al. (1990) have questioned whether the increased leukemias may have been "chance effects unrelated to formaldehyde ingestion", due to reported wide variation in leukemia incidences in groups of untreated Sprague-Dawley rats of the same colony, citing reports of leukemia incidences in controls as high as 19% (the highest incidence in Soffriti et al. exposed groups was 18/100). Another limitation to the strength of the evidence for formaldehyde-induced leukemia is the lack of a consistent dose-response relationship in the Soffritti et al. study. Although IARC (1995) has noted that a statistically significant trend for increasing leukemia incidence with increasing exposure concentration can be demonstrated in the Soffritti et al. data for rats exposed from 7 weeks of age to dose levels ranging from 1 to 188 mg/kg/day; the second part of the Soffriti et al. (1989) study found no statistically increased incidence of leukemia in groups of breeding pairs of rats or their offspring exposed for life to the higher dose level of 313 mg/kg/day. A further limitation is the absence of corroborating evidence for effects at sites distant from portals-of-entry in the other drinking-water rat studies, and in inhalation-exposure animal studies.

Findings for formaldehyde-induced gastrointestinal tract tumors are not consistent across the available drinking-water rat studies. Significantly increased incidences of intestinal tumors were found only in rats exposed to 188 mg/kg/day from 7 weeks of age and in offspring of breeding pairs of rats exposed to 313 mg/kg/day, but were not found in groups exposed to lower concentrations or to the breeding pairs exposed to 313 mg/kg/day (Soffritti et al. 1989). Stomach tumors were found at increased incidence only in the 313-mg/kg/day offspring of the breeding pairs in the Soffriti et al. (1989) study and in 8/10 rats

exposed to 258 mg/kg/day in the Takahashi et al. (1986a) study. Takahashi et al. (1986a) reported only benign forestomach papillomas, whereas Soffritti et al. (1989) reported papillomas, adenocarcinomas, and leiomyosarcomas. In contrast, Til et al. (1989) found no increased incidence of gastrointestinal tract tumors in rats exposed to average dose levels up to 82 or 109 mg/kg/day for life, and Tobe et al. (1989) likewise found no increase in gastrointestinal tumors in rats exposed to up to 300 mg/kg/day for life. Til et al. (1989) noted that the difference between their finding of forestomach papillary epithelial hyperplasia and the finding Takehashi et al. (1986a) of forestomach papillomas might be ascribed to the use of different lesion-classification criteria. Although there are inconsistencies among the available studies with respect to formaldehyde-induced gastrointestinal tract tumors from oral exposure, the studies consistently show that exposure to drinking water dose levels >50 mg/kg/day can damage epithelial tissue of the gastrointestinal tract, especially at dose levels >100-200 mg/kg/day. The possibility of tumor occurrence as a portal-of-entry effect from high-level exposure appears biologically plausible given the reactive nature of formaldehyde, its cytotoxicity at high levels that exceed protective mechanisms, and the findings for upper respiratory tract tumors in rats exposed to high, but not low, levels of airborne formaldehyde.

Given the equivocal nature of the evidence for carcinogenicity from existing studies of rats exposed to formaldehyde in drinking water, no CEL values are recorded in Table 2-4 or plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

Studies regarding death in humans after dermal exposure to formaldehyde were not located. Repeated dermal exposure of mice to solutions containing up to 10% formaldehyde produced no increased mortality. Iversen (1988) applied 4% formaldehyde to the shaved skin of Sencar mice twice weekly for 58 weeks. No increase in mortality was observed. Similarly, applications of 1 or 10% formaldehyde to the backs of hr/hr Oslo mice for 2 days/week for 60 weeks did not affect mortality (Iversen 1986).

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal health effects in humans or animals after dermal exposure to formaldehyde.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-5.

Respiratory Effects. No reports were located regarding respiratory effects in humans after predominantly dermal exposure to formaldehyde or in animals after acute or intermediate-duration dermal exposure to formaldehyde.

Iversen (1988) tested the carcinogenic potential of formaldehyde via classical skin-painting experiments. Formalin (37% formaldehyde volume for volume) was dissolved in distilled water and used at final concentrations of 1 and 10% formaldehyde. Hairless mice (hr/hr Oslo strain, in which spontaneous tumors have not been noted) were used. One group consisting of 16 males and 16 females was dosed with 200 μL of 1% formaldehyde in water on the skin of the back twice per week (Tuesdays and Fridays) for a total of 60 weeks. A second group of identical composition received a 10% formaldehyde solution in an identical manner for 60 weeks. Small, nonspecific granulomas were found in the lungs of two animals from the 10% group. No exposure-related lesions were found in the nasal mucosa.

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious		LOAEL Serious	Reference Chemical Form[a]
ACUTE EXPOSURE							
Systemic							
Human (patients with skin problems)	patch test, 48 hr	Dermal		1% soln	(3.7% of 1619 patients showed positive reactions for formaldehyde)		Kiec-Swierczynska 1996
Human (patients with skin problems)	patch test, 48 hr	Dermal		1% soln	(7.8% of patients showed positive reactions to formaldehyde)		Marks et al. 1995
Human (patients with eczematous dermatitis)	patch test, 48 hr	Dermal		2% soln	(1.6% of 1081 patients showed positive reactions to formaldehyde)		Meding and Swanbeck 1990
Human (patients with eczematous dermatitis)	patch test, 48 hr	Dermal		1% soln	(2.6% of 4713 patients showed positive reactions to formaldehyde)		Menne et al. 1991
Rat (Sprague-Dawley)	single dose to eye	Ocular		1% soln	(eye irritation; increased protein in aqueous humor)		Krootila et al. 1986
Gn Pig (Hartley)	rubbed daily into skin up to 9 d	Dermal		0.1 mL 0.4% soln	(erythema at day 6; increased skin-fold thickness at day 9)		Wahlberg 1993 (formalin)
		Bd Wt	0.1 mL 4% soln				

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form[a]
Hamster (Golden Syrian)	gd 8, 9, 10 or 11 2 hr	Bd Wt	0.5 mL F 37 % soln					Overman 1985 (formalin)
Immunological/Lymphoreticular								
Human (sensitized patients)	patch test, 48 hr			0.1% soln	(positive reaction in 8/35 allergic subjects)			DeGroot et al. 1988
Human (sensitized patients)	patch test, 48 hr			0.015% soln	(positive reaction in 1/25 allergic subjects)			Fischer et al. 1995
Human (formaldehyde sensitized patients)	patch test, 48 hr			0.025% soln	(positive reaction in 1/20 allergic subjects)			Flyvholm et al. 1997
Human formaldehyde sensitized patient	patch test, 48 hr					1% soln	(patient had an anaphylactic response)	Maurice et al. 1986
Mouse (BALB/c)	1 d on shaved flanks; 7 days later on dorsum of each ear		18.5% soln (serum IgE levels)					Hilton et al. 1996 (formalin)

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form[a]
Mouse (BALB/c)	2x in 10 d on shaved flanks; 5 days later on dorsum of each ear			3.7% soln	(increased cell proliferation of draining lymph node cells; increased production of the cytokine, IFN-gamma)			Hilton et al. 1996 (formalin)
Mouse (BALB/c)	1 d on shaved flanks; 7 days later on dorsum of each ear		6.8 mg in 0.05 mL (serum IgE levels)					Potter and Wederbrand 1995 (formalin)
Gn Pig (Hartley)	6 intra-dermal injections followed by 48 hr occluded dermal exposure			0.25% soln	(sensitized skin of 100% of animals to 2% soln)			Hilton et al. 1996 (formalin)
Reproductive								
Hamster (Golden Syrian)	gd 8, 9, 10 or 11 2 hr					0.5 mL 37 % soln	(increased resorptions)	Overman 1985 (formalin)
Developmental								
Hamster (Golden Syrian)	Gd 8, 9, 10 or 11 2 hr		0.5 mL 37 % soln					Overman 1985 (formalin)

Table 2-5. Levels of Significant Exposure to Formaldehyde - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form[a]
INTERMEDIATE EXPOSURE						
Immunological/Lymphoreticular						
Gn Pig (Hartley)	3 weekly 6-hr occluded exposures			5% soln	(sensitized skin of 70% of animals to 1% soln)	Hilton et al. 1996 (formalin)
CHRONIC EXPOSURE						
Systemic						
Mouse (hr/hr Oslo)	60 wk 2 d/wk 1 x/d	Resp	0.2 mL 10% soln	0.2 mL 10% soln	(nonspecific granulomas in the lungs)	Iversen 1986 (formalin)
		Dermal	0.2 mL 10% soln	0.2 mL 10% soln	(slight hyperplasia of epidermis, small skin ulcers)	

[a]Formalin designation herein means that the study either involved direct exposure to formalin (~40% aqueous solution of formaldehyde containing 10-15% methanol as a stabilizing agent) or used such a solution as a stock for the preparation of dermally administered material. Percent in table refers to percent formaldehyde.

Bd Wt = body weight; d = day(s); F= female; Gd - gestational day; Gn Pig = guinea pig; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; wk = week(s); x = times; soln = solution

Dermal Effects. As discussed earlier in Section 2.2.1, occupational exposures to formaldehyde have been associated with dermal irritation and the diagnosis of allergic contact dermatitis by patch tests. Reported historical percentages of subjects with skin problems showing positive allergic responses to formaldehyde in patch tests performed by dermatologists using aqueous solutions with 1 or 2% formaldehyde include 7.8% in North America between 1992 and 1994 (Marks et al. 1995), 1.6% in a 1983–1984 Swedish study (Meding and Swanbeck 1990), 2.6% in a 1988–1989 European study (Menné et al. 1991), and 3.7% in a 1990–1994 Polish study (Kiec-Swierczynska 1996). Fischer et al. (1995) generally concluded that, in more than 30 years of experience with patch test reporting, about 1–4% of tested subjects are sensitive to formaldehyde. With standard patch testing protocols, formaldehyde concentrations of 2% and higher may produce skin irritation in nonsensitized individuals demonstrating that concentrations that evoke a skin irritation response can be similar to those evoking allergic skin responses (Fischer et al. 1995; Maibach 1983). Because of the reactive and irritating properties of formaldehyde, early use of formaldehyde concentrations as high as 5% in patch tests, and inexperience on the part of test administrators, Maibach (1983) speculated that many cases of irritant responses have been incorrectly interpreted as allergic responses. Lack of specific exposure information for many cases precludes determining the degree to which reported cases of dermal sensitization may have been caused by direct dermal contact to formaldehyde in liquids or by contact with formaldehyde gas in air, but the widespread use of formaldehyde or formaldehyde-releasing chemicals in cosmetics and cleaning agents (Flyvholm 1991; Rastogi 1992) suggest that the dermal route of exposure may be the more important sensitizing route. Studies showing that allergic skin responses in sensitized subjects exposed to formaldehyde in aqueous solutions are rare at concentrations below 0.025–0.05% are discussed in Section 2.2.3.3.

A study by Nethercott and Holness (1988) examined the prevalence of cutaneous disease in selected funeral service workers in Toronto, Canada. Eighty-four workers from funeral homes in the Toronto area were evaluated via a questionnaire which focused on past and family medical histories, present symptoms, and work practices. Physical examination of the participants' skin was performed, and all participants underwent skin-patch testing for formaldehyde and glutaraldehyde sensitivity. Embalmers were divided into high- and low-exposure groups for comparative analysis. Cutaneous examinations revealed a greater incidence of contact dermatitis among exposed workers (11%) compared to controls (0%), and the prevalence of positive skin-patch tests for formaldehyde was greater among exposed workers (3%) than among controls (0%). Among exposed workers, there were no differences between

the high- and low-exposure groups with regard to prevalence of contact dermatitis or positive skin-patch results.

Cases of contact dermatitis caused by formaldehyde released from "no-iron" textiles were described frequently in the literature from the late 1950s until the mid-1970s; after this period, the finishing processes for these types of textiles were changed so that only small amounts of formaldehyde are released after finishing (see Peters and Heese 1997 for review). In most cases of clothing-induced contact dermatitis, the dermatitis developed specifically in areas of very close contact between the skin and the clothing (e.g., the underarms, the elbows, the insides of the thighs).

Formaldehyde has also been shown to cause dermal allergic reactions in nurses and doctors (Rudzki et al. 1989). One hundred-sixty-seven doctors, 92 dentists, and 333 nurses were patch-tested with a standard panel of allergens plus allergens common to their work environment. Among nurses, formaldehyde was the disinfectant that most frequently caused allergic reactions (9.6%). Three doctors also had positive skin tests for formaldehyde.

Albino guinea pigs (Hartley strain) were treated with 0.1 mL of various dilutions of formalin (1, 3, and 10% formalin; 0.4, 1.2, and 4% formaldehyde) to demarcated test sites, and the formalin solution was gently rubbed into the skin with a cotton-tipped applicator (Wahlberg 1993). An unexposed control site and a vehicle control were used in each series. The sites were left unoccluded and the treatments were repeated once daily immediately after skin-fold measurements. Each site was examined prior to skin-fold measurements for the presence of erythema, edema, fissuring, and scaling. From a mean of 10 sites, erythema appeared on day 2 (4%), day 5 (1.2%), and day 6 (0.4%). Increased skin-fold thickness was statistically significant on day 3 (4%), day 7 (1.2%), and day 9 (.04%) after daily treatment with various concentrations of formaldehyde.

Iversen (1988) tested the carcinogenic potential of formaldehyde via classical skin-painting experiments. Formalin (37% formaldehyde volume for volume) was dissolved in distilled water and used at final concentrations of 1 and 10% formaldehyde. Hairless mice (hr/hr Oslo strain, in which spontaneous tumors have not been noted) were used. Two groups consisting of 16 males and 16 females were dosed with 0.2 mL of 1 or 10% formaldehyde in water on the skin of the back twice per week (Tuesdays and Fridays) for a total of 60 weeks. Animals dosed with 10% formaldehyde, but not with 1% solutions,

generally had slight epidermal hyperplasia, and a few mice had cutaneous ulcers. These studies indicate that formaldehyde applied dermally is irritating to the skin (hyperplasia and ulcers) and can also induce an inflammatory response.

Ocular Effects. As discussed in Section 2.2.1.2 (in the Respiratory Effects and Ocular Effects sections), health surveys of occupationally-exposed workers and acute controlled exposure studies with volunteers have demonstrated that exposure to formaldehyde air concentrations in the range of 0.4–3.0 ppm and above can cause eye irritation.

To examine the dependence of ocular response to formaldehyde irritation on the trigeminal sensory nerve, Krootila et al. (1986) topically applied a 1% solution of formaldehyde in an aqueous phosphate buffer (pH 7.4) to the right eye of a group of unoperated male Sprague-Dawley rats and two groups of denervated rats. Rats were anesthetized with pentobarbital for the experiments and operations. Sensory denervation of the right eye was accomplished in one group by coagulation of the intracranial, opthalmic branch of the right trigeminal nerve, and, in the other group, unilateral sympathetic denervation was accomplished by removing the right superior cervical ganglion. Application of 1% formaldehyde to the eye of unoperated rats caused a breakdown of the blood-aqueous barrier of the eye indicated by increased protein concentration in the aqueous humor or increased leakage of Evans blue dye from the iris vessels. This response was also observed in rats without the right superior cervical ganglion, but was absent in rats with a coagulated right trigeminal nerve. The authors concluded that the irritative response of the eye to formaldehyde is dependent on the trigeminal sensory nerve, but not the superior cervical ganglion.

Body Weight Effects. No studies were located regarding body weight effects in humans following dermal exposure to formaldehyde.

Exposure-related effects on body weight were not found in pregnant hamsters dermally exposed during gestation to 0.5 mL solutions of 37% formaldehyde (Overman 1985) or in guinea pigs dermally exposed for 9 days to 4% formaldehyde solutions (Wahlberg 1993). In the Overman (1985) experiment, the control and exposed pregnant hamsters were anesthetized during treatment to prevent grooming; exposure was for 2 hours on gestation day 8, 9, 10, or 11.

2.2.3.3 Immunological and Lymphoreticular Effects

As discussed earlier in Section 2.2.1.2, 2.2.1.3, and 2.2.3.2, formaldehyde is a commonly diagnosed contact allergen, accounting for about 1–4% of cases presented at dermatology clinics (Fischer et al. 1995; Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991). Studies of concentration-response relationships for skin allergic reactions induced by occluded dermal exposures to formaldehyde in formaldehyde-sensitive subjects suggest that a dermal allergic response to formaldehyde concentrations below about 0.025–0.05% is rare. In a serial dilution test, the lowest concentration tested, 0.1%, produced allergic reactions in 8/35 formaldehyde-sensitive subjects (DeGroot et al. 1988). Another serial dilution test, examining concentrations of 1, 0.5, 0.25, 0.13, 0.063, 0.032, and 0.015% in 25 formaldehyde-sensitive subjects, found decreasing frequency of response with decreasing exposure concentration; positive reactions were found in 3/25 at 0.063%, 1/25 at 0.032%, and 1/25 at 0.015% (Fischer et al. 1995). Flyvholm et al. (1997) reported that, in an occluded patch test study of 20 sensitized subjects and 20 healthy volunteers, no skin irritation occurred in the controls exposed to 1% formaldehyde. In sensitized subjects, the frequency of response decreased with decreasing formaldehyde concentrations as follows: 9/20 at 0.5%, 3/20 at 0.1%, 2/20 at 0.05%, and 1/20 at 0.025%.

A report by Maurice et al. (1986) describes the case study of 20-year-old woman who experienced anaphylactic shock after exposure to a dialyzer sterilized with formaldehyde. The woman, who required long-term hemodialysis due to renal failure, had previously experienced mild episodes of localized, delayed-type hypersensitivity contact dermatitis from adhesives sterilized with formaldehyde. After experiencing the episode of anaphylaxis, the patient was tested for formaldehyde sensitivity by a skin-prick test using 0.1 and 1% formaldehyde solutions, and a skin-patch test using a 1% solution. The patient developed a strong positive response to skin pricks using both 0.1 and 1% formaldehyde solutions. Twenty-six hours after skin application of formaldehyde, the patient developed anaphylactic symptoms characterized by laryngeal edema and bronchospasm. The patient was treated with subcutaneous epinephrine and all symptoms other than angioedema resolved rapidly.

Potter and Wederbrand (1995) examined the IgE response to dermal exposure to formaldehyde in female BALB/c mice. Ten mice per dose received 0.42–6.8 mg formaldehyde in 50 μL water:acetone (50:50), administered topically to the shaved flank. Seven days later, the animals received 25 μL of a half-strength solution, applied to the dorsal surface of each ear. Serum samples were collected 14 days after

the initial treatment. Dermal exposure to 0.42–6.8 mg formaldehyde in acetone:water did not induce IgE production.

Hilton et al. (1996) assessed the sensitizing properties of topical applications of formaldehyde in guinea pigs using standard tests (guinea pig maximization test and Buehler test) and in mice using a test for IgE production after dermal exposure, a local lymph node assay, and an assay for cytokine secretion by draining lymph node cells. In the guinea pig maximization test, pretreatment with a series of intradermal injections of 0.25% formaldehyde solutions and occluded patch exposure to 10% formaldehyde produced sensitization to 48-hour occluded patch dermal exposures to 2% formaldehyde solutions in 100% of treated animals. In the Buehler test, a series of 6-hour occluded patch dermal exposures to 5% formaldehyde solutions produced sensitization to subsequent exposures to 1% formaldehyde in 70% of treated animals. In mice treated with topical applications of solutions containing up to 50% formalin (approximately 18.5% formaldehyde), no increase in serum IgE concentrations occurred, whereas in mice similarly treated with solutions containing 25% trimellitic anhydride, a well-documented respiratory sensitizing agent, serum concentrations of IgE were markedly increased. Application of 10, 25, or 50% formalin solutions (3.7, 9.25, and 18.5% formaldehyde) to the dorsum of ears of mice stimulated cellular proliferation in lymph node cells cultured from draining auricular lymph nodes excised from the mice. Profiles of cytokines produced by draining lymph node cells from mice topically treated with 10, 25, or 50% formalin solutions were different from those produced by a solution of 10% trimellitic anhydride; formalin solutions stimulated production of IFN-γ, whereas trimellitic anhydride stimulated production of IL-10. The investigators concluded that these data are consistent with studies of occupationally-exposed workers suggesting that formaldehyde is a contact dermal allergen, but an equivocal agent for respiratory sensitization.

The highest NOAEL values and all LOAEL values from each reliable study for immunological/ lymphoreticular effects in each species and duration category are recorded in Table 2-5.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following dermal exposure to formaldehyde.

2.2.3.5 Reproductive Effects

No reports of reproductive effects in humans after dermal exposure were found.

Overman (1985) conducted a study designed to evaluate the embryotoxic effects of topical exposure to formaldehyde in pregnant hamsters. Virgin female hamsters (Lak LVG[SYR] Golden Syrian) were bred and then treated directly on the skin with 0.5 mL formaldehyde solution (37%) on gestation days 8, 9, 10, or 11 for 2 hours. The animals (including controls) were anesthetized during treatment to prevent grooming. After the 2-hour treatment period, the skin of the animals was washed thoroughly with water to remove any remaining formaldehyde. Fetuses were recovered by laparotomy at gestation day 15, fixed in Bouin's fixative or in 95% ethyl alcohol. Fixed fetuses were blotted dry, weighed, measured (crown-rump length), and examined for malformations by free-hand sectioning technique. Fetuses fixed in ethyl alcohol were cleared and stained for skeletal tissue observation. Exposure did not significantly affect maternal weight gain, but a statistically significant increased incidence of resorptions in treated litters was observed (3–8% of sites resorbed versus none in controls). Overman (1985) suggested that this effect may have been caused by the stress of treatment during pregnancy rather than to a direct effect of formaldehyde, noting that exposed animals scratched at treated areas and were "irritable and hard to handle" for 1 to 2 days after treatment.

The LOAEL value of 0.5 mL of a 37% solution for increased resorptions is recorded in Table 2-5.

2.2.3.6 Developmental Effects

No reports of developmental effects in humans after dermal exposure to formaldehyde were found.

In the hamster study by Overman (1985) described in the previous section, formaldehyde treatment did not significantly change fetal crown rump length or fetal body weights. After treatment on day 8, two fetuses from the same litter were significantly smaller than their littermates (>3 sd below mean). After treatment on day 10, one fetus of normal size had a subcutaneous hemorrhage in the dorsal cervical region. There were no skeletal malformations found, and no other malformations were observed during the course of the study.

The NOAEL value of 0.5 mL of 37% solution for no developmental effects is recorded in Table 2-5.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to formaldehyde. Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

Studies on cancer incidence in humans exposed occupationally to formaldehyde are discussed in Section 2.2.1.8.

In one laboratory animal study reported by Iversen (1986), the carcinogenic potential of formaldehyde using classical skin painting experiments was determined. Formalin (37% formaldehyde volume/volume) was dissolved in distilled water at final concentrations of 1 and 10% formaldehyde. Groups of hairless mice (hr/hr Oslo strain) consisting of 16 males and 16 females were dosed with 0.2 mL of 1% formaldehyde in water on the skin of the back twice per week for a total of 60 weeks. A second group of identical composition was dosed with a 10% formaldehyde solution in like manner for 60 weeks. A third group of mice was initially painted with 51.2 μg dimethylbenz(a)anthracene (DMBA) in 0.1 mL acetone and 9 days later, received a twice weekly treatment regimen of paintings with 10% formaldehyde in water. Animals dosed with 10% formaldehyde generally had slight epidermal hyperplasia, and a few animals had cutaneous ulcers and scratches. In animals dosed with DMBA followed by formaldehyde, 3 animals developed lung adenomas, while 11 animals developed a total of 25 skin tumors (3 squamous cell carcinomas and 22 papillomas). There was no evidence of any other tumor type. Skin painting with either 1 or 10% formaldehyde alone had no significant carcinogenic potential; however, dermal exposure to 10% formaldehyde after DMBA dosing significantly reduced the latency period of DMBA-induced tumors.

No statistically significant increased incidence of formaldehyde-induced skin tumors was found in a second study with SENCAR mice, a strain of mouse bred for maximal sensitivity to chemically induced tumors (Iverson 1988). Groups of 16 male and 16 female mice were dosed with 0.1 mL acetone or 0.2 mL 4% formaldehyde (in water) twice weekly for 58 weeks. Two animals with small benign skin papillomas were found in the exposed group and also in the acetone-control group. In this study, twice weekly dermal application of 0.2 mL 4% formaldehyde following application of a single 51.2 μg dose of DMBA did not significantly affect the skin tumor yield compared with DMBA alone, but, like in the

study with hr/hr Oslo mice, decreased the latency period for the appearance of DMBA-induced skin tumors. The report of this study did not mention if non-neoplastic skin lesions were produced by exposure with 4% formaldehyde solutions.

2.3 TOXICOKINETICS

The toxicokinetics of formaldehyde after inhalation, oral, or dermal exposure has been reported in several species by many investigators. The toxicokinetics in all of the animals studied is similar across species lines. Formaldehyde is an essential metabolic intermediate in all cells. It is produced during the normal metabolism of serine, glycine, methionine, and choline and also by the demethylation of *N*-, *S*-, and *O*-methyl compounds. After oxidation of formaldehyde to formate, the carbon atom is further oxidized to carbon dioxide (CO_2) or incorporated into purines, thymidine, and amino acids via tetrahydrofolate-dependent one-carbon biosynthetic pathways. Exogenous formaldehyde appears to be readily absorbed from the respiratory and gastrointestinal tracts, but poorly absorbed following dermal application. Formaldehyde is metabolized to formate by the enzyme formaldehyde dehydrogenase; this appears to take place at the initial site of contact. Being normal components of intermediary metabolism, neither formaldehyde nor formate are stored to any significant extent in any tissue of the body. Formate is either excreted in the urine (primarily as formic acid), incorporated into other cellular molecules, or oxidized to carbon dioxide and exhaled.

In the metabolic labeling studies using ^{14}C-formaldehyde discussed below, it should be noted that the detection of the ^{14}C radiolabel does not imply that it is still in the form of unmetabolized formaldehyde.

2.3.1 Absorption

Formaldehyde vapors are readily absorbed from the respiratory tract. Due to rapid metabolism to formate, little, if any, intact formaldehyde can be found in the blood of humans or animals exposed to formaldehyde. Formaldehyde is also readily absorbed from the gastrointestinal tract and meets with the same metabolic fate as formaldehyde after inhalation exposure. The studies available in the open literature suggest that very little formaldehyde is absorbed via the dermal route. In all cases, absorption appears to be limited to cell layers immediately adjacent to the point of contact. Entry of formaldehyde into the blood (i.e., systemic absorption) occurs to a very limited extent, if at all.

2.3.1.1 Inhalation Exposure

Formaldehyde is absorbed by the tissues of the respiratory tract during inhalation exposure in several species. Heck et al. (1985) determined the fate of inhaled formaldehyde in humans. Four men and two women were exposed to a 1.9 ppm air concentration of formaldehyde in a large walkin chamber for 40 minutes. Shortly before and shortly after the exposure, venous blood samples were taken from each person (each person served as his/her own control) and the blood was analyzed for formaldehyde content. Mean venous blood formaldehyde concentrations in humans prior to exposure showed a blood concentration of 2.61±0.41 μg/g of blood. Individual variability was markedly present. Immediately after a 40-minute exposure, mean blood concentration of formaldehyde was 2.77±0.28 μg/g of blood. There was no significant difference between pre- and postexposure blood concentrations of formaldehyde at the formaldehyde air concentrations tested in this study. This result suggests that formaldehyde was absorbed only into the tissues of the respiratory tract. The absence of increased formaldehyde concentrations in the blood is likely due to its rapid metabolism in these tissues and/or fast reaction with cellular macromolecules.

Heck et al. (1985) also determined the fate of inhaled formaldehyde in the rat. Male Fischer 344 rats were placed in a nose-only inhalation chamber and exposed to a 14.4±2.4 ppm air concentration of formaldehyde for 2 hours, were sacrificed, and a venous blood sample was collected and analyzed for formaldehyde content. Unexposed control rats had a mean formaldehyde blood level of 2.24±0.07 μg/g of blood. Rats exposed to the 14.4 ppm air concentration of formaldehyde had blood concentrations of 2.25±0.07 μg/g. These results indicate that during a nose-only inhalation exposure of rats to this concentration of formaldehyde, no significant quantities of formaldehyde could be detected in the blood. Lack of increase in blood formaldehyde levels indicates that only local absorption took place and absorbed formaldehyde was metabolized before reaching the bloodstream. In a similar study by Heck et al. (1983), Fischer 344 rats were exposed by inhalation to ^{14}C-formaldehyde at 8 ppm for 6 hours. Concentrations of total ^{14}C radioactivity (most likely as ^{14}C-formate) in the whole blood and plasma were monitored for an additional 8 days. Plasma concentrations of ^{14}C increased over the exposure period, reaching a maximum at the termination of exposure. Plasma ^{14}C concentrations then declined slowly over the next few days.

Using dogs as a model, Egle(1972) determined the respiratory fate of formaldehyde and other aldehydes. This study measured the retention of formaldehyde along the entire respiratory tract, both upper and

lower portions, and measured the effects of ventilation rate, tidal volume, and concentration of inhaled formaldehyde. Mongrel dogs of both sexes (at least 4 dogs per experiment) were anesthetized and exposed to 0.15–0.35 μg (122–235 ppm) of formaldehyde vapor produced from formalin. The retention of formaldehyde was measured over the entire respiratory tract, including the upper region only (nose and trachea, down to the bifurcation of the trachea), lower region only (from the bifurcation of the trachea, bronchioles, and below), and over the entire respiratory tract. Retention of formaldehyde (amount of formaldehyde not returning after an exhalation) when the entire upper and lower respiratory tract was exposed to formaldehyde vapors was near 100% and seemed to be independent of the airborne concentration of formaldehyde or variations in the tidal volume. When the upper respiratory tract was isolated from the lungs, the 2-way exposures showed a 100% uptake of formaldehyde. The 1-way exposures of formaldehyde showed that the retention of formaldehyde was slightly lower than in the 2-way exposure, but the uptake of formaldehyde still exceeded 95% at all respiratory rates. When the lower respiratory tract was isolated and examined, the uptake of formaldehyde still exceeded 95%; however, it appeared to decrease slightly as the ventilation rates increased. This study concluded that when formaldehyde is inhaled at the concentrations studied, very little formaldehyde vapor would actually reach the lower respiratory tract.

In another study by Casanova et al. (1988), blood levels of formaldehyde were determined in Rhesus monkeys after exposure to 6 ppm formaldehyde for 6 hours/day, 5 days/week for 4 weeks. Immediately after the last exposure, the monkeys were sedated and blood samples were collected within 7 minutes and at 45 hours after exposure. Blood samples were analyzed for formaldehyde content by gas chromatography/mass spectrometry (GC/MS). Mean blood concentrations at 7 minutes and 45 hours postexposure were 1.84 and 2.04 μg/g, respectively. Blood concentrations of formaldehyde in the three nonexposed monkeys (2.42 μg/g) were not significantly different from those of the exposed group. The authors concluded that exposure to moderately high levels of formaldehyde had no effect on blood concentrations due to rapid local metabolism.

2.3.1.2 Oral Exposure

Formaldehyde is absorbed from the gastrointestinal system after ingestion. Eells et al. (1981) described the case of a 41-year-old woman who swallowed 120 mL (624 mg/kg) of a formaldehyde solution (as formalin). Formic acid accumulated in the blood rapidly after formaldehyde ingestion. Burkhart et al. (1990) describe the case of a 58-year-old man who swallowed 4 ounces of a formaldehyde solution

containing methanol in a suicide attempt. Blood methanol levels continued to climb throughout 12 hours of observation. The apparent half-life for formaldehyde was 3.3 hours.

In a study by Galli et al. (1983), the absorption, fate, and excretion of the complexes between ^{14}C-formaldehyde and milk proteins in mice and rats, and their toxicological significance were examined. Male Sprague-Dawley rats were given a single oral dose of 2.2 g (18 μCi) ^{14}C-labeled grana cheese. Groups of rats were sacrificed 4, 8, 16, 32, and 64 hours after the end of food consumption. Blood, liver, gastrointestinal tract, kidneys, spleen, testes, brain, muscle, and adipose tissues were removed, and urine and feces were collected from metabolic chambers. In all cases, the biological samples were immediately frozen after removal until used for radioactivity measurement. Within 32 hours of administration, 67% of the radioactivity had been excreted in the feces and urine and 28% of the radioactivity had been exhaled as $^{14}CO_2$ in rats, indicating absorption from the ingested cheese. In the companion study, male Swiss albino mice (CD-1) were given a single oral dose of 0.5 g (4 μCi) ^{14}C-labeled grana cheese. The cheese was made by following the usual process but using milk with added ^{14}C-formaldehyde. Rats fed with unlabeled cheese were used as controls. Groups of mice were sacrificed after 2, 4, 8, 16, 32, 64, and 96 hours and 8 and 12 days. Within 32 hours of administration, 64% of the radioactivity had been excreted in the feces and urine and 24% of the radioactivity had been exhaled as $^{14}CO_2$, indicating absorption from the ingested cheese.

A study by Barry and Tome (1991) sought to quantitate the concentration of formaldehyde in the milk of goats given feed containing varying amounts of formaldehyde-treated soybean oil-meal. The goat ration consisted of 750 g medium quality grass hay, 600 g maize-based concentrate, and 600 g soybean oil-meal; the soybean oil-meal was either treated with formaldehyde, untreated, or a 50:50 mixture. Five lactating adult Alpine goats each received 1 of 3 diets (no formaldehyde; 28 mg/kg formaldehyde; a 50:50 mixture of the 2 rations, equal to 14 mg/kg formaldehyde) for 1 week. Milk samples from the last 5 days of each dosing period were collected and analyzed for formaldehyde content by high performance liquid chromatography. Mean milk formaldehyde concentrations were 0.033, 0.083, and 0.153 mg/kg in the 0, 14, and 28 mg/kg/day groups, respectively. These values were significantly different from each other ($p<0.05$), and were highly correlated with formaldehyde intake ($r=0.938$, $p<0.01$), and indicate absorption from the gastrointestinal tract.

Buckley et al. (1988) measured formaldehyde levels in the milk and blood of dairy cows given formalin-treated whey. Twelve Holstein cows in their first trimester of lactation were used in a series of three

feeding trials lasting 35 days and separated from each other by 14 days. Six of the cows received a diet consisting of low-energy pelleted concentrate, liquid acid whey, and grass hay. The whey was fed once a day beginning at 10:00 am, and all whey was consumed by 4:30 pm. In the three trials, the calculated amounts of ingested formalin were 19.9, 39.7, and 59.4 mg/kg/day, respectively. The remaining six cows received untreated whey throughout the three trials. Morning milk was sampled on days 3, 2, 3, 4, 5, 6, 13, 20, 27, and 34 of each 35-day trial. Blood samples were collected on the day before initiation of the third trial, and on days 9 and 33. Formaldehyde levels were below detectable limits prior to and at 46 hours after the completion of each trial. The levels of formaldehyde in milk were positively correlated to dose ($p<0.01$, no other details given). In a companion study (Buckley et al. 1988), formaldehyde levels were measured in the muscle tissues of dairy calves fed formalin-treated whey. Eighteen Holstein bull calves were fed diets containing whey treated with formalin at doses of 0, 0.05, or 0.1% (n=6 per treatment group). Calves were individually fed the formalin-treated whey in two equal feedings daily. Two calves from each treatment group were sacrificed at days 81, 88, and 95. Blood samples were collected on the day before sacrifice. At sacrifice, sections of muscle, kidney, liver, and heart were obtained for formaldehyde determinations. Concentrations of formaldehyde in fresh muscle samples of the high-dose group (0.256 μg/g) were significantly greater than those of controls (0.178 μg/g) ($p<0.05$). Concentrations of formaldehyde in fresh blood and frozen heart, kidney, liver, and muscle samples of treated animals were similar across treatment groups.

2.3.1.3 Dermal Exposure

Jeffcoat et al. (1983) studied the absorption and disposition of ^{14}C-formaldehyde administered topically to Fischer 344 rats, Dunkin-Hartley guinea pigs, and Cynomolgus monkeys. One day prior to formaldehyde exposure, each monkey had a portion of its posterior shaved and had a carotid artery catheter implanted. Monkeys were placed in restraining chairs for drug delivery, and plexiglass hoods were placed around the animals' heads for the collection of expired air. Animals were dosed with 2 mg ^{14}C-formaldehyde in 200 μL of aqueous carrier solution, applied to an 18 cm^2 area. The ^{14}C content in each dose was approximately 590–730 μCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Urine and feces were collected at daily intervals for 3 days. Expired air was passed through two sodium hydroxide (NaOH) traps which were changed each time a blood sample was collected. Rats and guinea pigs were housed individually in glass metabolism cages, which allowed the collection of urine, feces, and the combination of expired air and evaporation products from excreta. One day prior to formaldehyde exposure, each animal had a portion of its back shaved and had a carotid artery catheter

implanted. Animals were dosed with an aqueous solution which was applied to a 2 cm^2 area. The dose applied was either 0.1 mg in 10 μL of solution or 11.2 mg in 40 μL of solution; the ^{14}C content in each dose was approximately 30 μCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Animals were sacrificed 72 hours after exposure began. Data from the monkeys were more variable than the rats and guinea pigs. The sum of ^{14}C recovered in the excreta of monkeys (urine, feces, and expired air) was <1%. The concentration of ^{14}C in the blood was extremely low, averaging approximately 0.015% of the dose over the estimated blood volume. After 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The application site contained approximately 9.5% of the ^{14}C dose. In rats dosed with 0.05 or 5.6 mg/cm^2 ^{14}C-formaldehyde, the total recoveries of ^{14}C for the low and high doses were 73.4 and 60.4%, respectively. Approximately 28% of the low dose and 22% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.12% of the low dose and 0.13% of the high dose over the total estimated blood volume. At 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The application site contained approximately 16% of the low-^{14}C dose and 3% of the high dose. In guinea pigs receiving 0.05 or 5.6 mg/cm^2 ^{14}C-formaldehyde, total recoveries of ^{14}C for the low and high doses were 70 and 63.6%, respectively. Approximately 21% of the low dose and 24% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 6% of the low dose and 8% of the high dose was excreted in the urine and feces combined. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.1% of the low dose and 0.09% of the high dose of the estimated blood volume. After 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The application site contained approximately 16% of the low-^{14}C dose and 4% of the high dose. It appears that the skin of the monkey is much less permeable to formaldehyde than the skin of the rodent. Significant evaporation of formaldehyde from the skin application site also probably occurred in this study.

Bartnik et al. (1985) sought to characterize the absorption and excretion of percutaneously applied formaldehyde in male and female WISW rats. Twenty-four hours prior to dosing, the dorsal skin hair of all rats was carefully clipped to avoid abrasions. Ten male and 4 female rats were dosed with 200 mg of cream containing 0.1% ^{14}C-formaldehyde. The dosing area of each rat was covered with a glass capsule; in all cases except two males, the glass capsules were perforated, resulting in a nonocclusive application. The dose areas of the remaining two males were covered with solid glass capsules, resulting in an

occluded application. The cream remained on the skin for 48 hours, during which time urine, feces, and air samples were collected. Air samples were passed through a series of filters to separate ^{14}C-formaldehyde and $^{14}CO_2$. At the end of the study, rats were sacrificed, the treated area of skin was removed and dissolved, fecal samples and the remaining carcass were homogenized, and air-trap samples were processed for ^{14}C determinations. The amount of ^{14}C remaining in the treated skin was similar in occluded and nonoccluded animals (69.9 versus 70.2%). Total percutaneous absorption in 48 hours was 6.1% of the applied radioactivity. Of this amount, 38% was recovered in urine, 11% in the feces, 21% as respired CO_2, and 30% in the carcass. Absorption was lower in occluded (3.4%) than in nonoccluded animals (6.1%). The authors speculate that the greater formaldehyde absorption seen in the animals with nonoccluded dose sites was due to some of the volatilized formaldehyde being inhaled by the animals prior to being trapped. The authors did not specify the fate of dose in the treated skin (i.e., loose or bound on surface, or actually integrated into skin).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located that described the distribution of formaldehyde or its metabolites in humans after inhalation exposure. Several studies are available that describe the distribution of formaldehyde in laboratory animals. Heck et al. (1983) examined the fate of ^{14}C-formaldehyde in Fischer 344 rats. Rats were exposed by inhalation to ^{14}C-formaldehyde at 8 ppm for 6 hours. Concentrations of total radioactivity in the whole blood and plasma were monitored for 8 days. The terminal half-life of the ^{14}C was approximately 55 hours, which was considerably longer than the known half-life of formaldehyde (about 1.5 minutes in monkeys), indicating both the metabolism of ^{14}C-CH_2O to other molecules (i.e., formate) and incorporation into other molecules. Radioactivity in the packed blood cell fraction was multiphasic; it initially increased during exposure, declined during the first hour postexposure, then began to increase again, reaching a maximum at approximately 35 hours postexposure. The terminal phase of the packed red blood cell fraction had a very slow decline in radioactivity, which would likely continue for several weeks after exposure ended (half-life >55 hours).

Heck et al. (1983) also examined distribution of ^{14}C-formaldehyde in formaldehyde-naive and formaldehyde-pretreated male Fischer 344 rats. Pretreated rats were exposed whole-body to 15 ppm formaldehyde 6 hours/day for 9 days. On the tenth day, these rats and the formaldehyde-naive rats (never

exposed to formaldehyde vapors) were then exposed head-only to ^{14}C-formaldehyde at concentrations of 14.9 ppm for 6 hours. All rats were sacrificed immediately after completion of the ^{14}C-formaldehyde exposure. Immediately after completion of the inhalation exposure, ^{14}C concentrations were greatest in the mucosal tissues. At 15 ppm, ^{14}C concentrations were as follows: nasal mucosa, 2 μmole equivalents/g tissue; trachea, 0.3 μmole equivalents/g tissue; and plasma, 0.1 μmole equivalents/g tissue. Radioactive concentrations were relatively equivalent in all of the mucosal linings monitored. Tissue concentrations of ^{14}C in naive and pretreated rats did not differ from each other. Tissue concentrations of ^{14}C were low, resembling plasma concentrations; the ratio of ^{14}C in internal organs to that in plasma were: esophagus, 4.94±1.23; kidney, 3.12±0.47; liver, 2.77±0.25; intestine, 2.64±0.48; lung, 2.05±0.36; spleen, 1.59±0.50; heart, 1.09±0.09; brain, 0.37±0.06; testes, 0.31±0.05; and erythrocytes, 0.30±0.08.

Distribution studies by Chang et al. (1983) investigated the effects of previous formaldehyde exposure on its distribution after inhalation exposure in male Fischer 344 rats and male B6C3F1 mice. Some rats and mice were exposed to only one dose of ^{14}C-formaldehyde (15 ppm for 6 hours) (naive mice), while another group was exposed to formaldehyde (nose-only) at a concentration of 15 ppm for 6 hours/day for 4 days and then additionally exposed to ^{14}C-formaldehyde (nose-only) at a concentration of 15 ppm for 6 hours (pretreated group). After exposure, the mice were immediately sacrificed and prepared for whole-body radiography. The amounts of radioactivity deposited in the nasal cavities of naive and pretreated rats were similar. Pretreated rats had less visceral radioactivity compared to naive animals. However, more radioactivity was found in the nasal cavity of naive mice than in pretreated mice. The decreased visceral radioactivity seen in the pretreated mice was thought to be due to decreased grooming and mucociliary clearance.

Early studies by Casanova-Schmitz et al. (1984a) examined the mechanisms of labeling of macromolecules (DNA, RNA, and proteins) in the respiratory and olfactory mucosa and bone marrow of male Fischer 344 rats. Rats were exposed nose-only for 6 hours to 0.3, 2, 6, 10, or 15 ppm mixtures of ^{14}C and ^{3}H-formaldehyde 1 day after a 6-hour exposure to the same concentration of unlabeled formaldehyde. The predominant route of macromolecule labeling was metabolic incorporation. There was some evidence of DNA-protein cross linking present in the nasal tissues. It was found that concentrations of ^{14}C DNA in respiratory and olfactory mucosa tissues increased linearly with dose; at any given dose, the concentrations of ^{14}C DNA in respiratory mucosa tissues were approximately two to three times that in olfactory mucosa tissues. Incorporation of ^{14}C into DNA increased with exposure concentrations 6 ppm, but decreased at 10 and 15 ppm, suggesting an inhibition of DNA synthesis.

Studies by Casanova et al. (1991a, 1991b) described the formation of DNA-protein cross links in the respiratory tract measured in male Fischer 344 rats and Rhesus monkeys. Rats were exposed nose-only to a mixture of ^{14}C-labeled and nonradiolabeled formaldehyde at concentrations of 0.3, 0.7, 2, 6, or 10 ppm for 6 hours. Formaldehyde-DNA-protein cross links were detected at all concentrations tested. Male Rhesus monkeys were exposed to 0.7, 2, or 6 ppm formaldehyde ^{14}C-labeled and nonradiolabeled mixture for 6 hours, and it was determined that approximately 90% of all ^{14}C was associated with the thymine, while 10% was associated with the guanine and adenine. Concentrations of formaldehyde-protein cross links were greatest in the middle turbinate tissues and lowest in the nasopharyngeal tissues. Some evidence of cross link formation was seen in the larynx/trachea/carina and major intrapulmonary airway tissues of two monkeys in the high-dose group. No evidence of cross link formation was seen in the sinus or lung tissues at any exposure concentration.

2.3.2.2 Oral Exposure

In a study by Galli et al. (1983), the fate of the complexes between ^{14}C-formaldehyde and milk proteins in mice and rats, and their toxicological significance were examined. Male Sprague-Dawley rats were given a single oral dose of 2.2 g (18 μCi) ^{14}C-labeled grana cheese. The cheese was made by following the usual process but using milk with added ^{14}C-formaldehyde. Animals fed with unlabeled cheese were used as controls. Groups of rats were sacrificed 4, 8, 16, 32, and 64 hours after the end of food consumption. Blood, liver, gastrointestinal tract, kidneys, spleen, testes, brain, muscle, and adipose tissues were removed, and urine and feces were collected from metabolic chambers. In all cases, the biological samples were immediately frozen after removal until used for radioactivity measurement. Peak radioactivity concentrations in the tissues occurred 16 hours after food consumption. The maximum concentrations of ^{14}C-activity equivalent to a value of 0.08% of the dose were present after 8 hours in the rat blood. In the companion study, male Swiss albino mice (CD-1) were given a single oral dose of 0.5 g (4 μCi) ^{14}C-labeled grana cheese. The highest concentrations of radioactivity in the liver, kidney, adipose tissue, spleen, testes, brain, and muscle occurred 4 hours after administration. The maximum concentrations of ^{14}C-activity equivalent to a value of 0.03% of the dose were present after 2 hours in the blood of mice.

Buckley et al. (1988) measured formaldehyde levels in the milk and blood of dairy cows given formalin-treated whey. There was a high degree of variability in milk and blood concentrations, presumably due to the variable amount of time (several minutes to 7 hours) taken to consume the treated feed. In a

companion study, Buckley et al. (1988) measured formaldehyde levels in the muscle tissues of dairy calves fed formalin-treated whey. Eighteen Holstein bull calves were fed diets containing whey treated with formalin at doses of 0, 0.05, or 0.1%. Calves were individually fed the formalin-treated whey in two equal feedings daily. Two calves from each treatment group were sacrificed at days 81, 88, and 95. Blood samples were collected on the day before sacrifice. At sacrifice, sections of muscle, kidney, liver, and heart were obtained for formaldehyde determinations. Concentrations of formaldehyde in fresh muscle samples of the high-dose group (0.256 μg/g) were significantly greater than those of controls (0.178 μg/g). Concentrations of formaldehyde in fresh blood and frozen heart, kidney, liver, and muscle samples were similar across treatment groups.

2.3.2.3 Dermal Exposure

Jeffcoat et al. (1983) studied the disposition of ^{14}C-formaldehyde administered topically to Fischer 344 rats, Dunkin-Hartley guinea pigs, and Cynomolgus monkeys. One day prior to formaldehyde exposure, each monkey had a portion of its posterior shaved and had a carotid artery catheter implanted. Monkeys were placed in restraining chairs for drug delivery, and a plexiglass hood was placed around their heads for the collection of expired air. Animals were dosed with an aqueous solution which was applied to an 18 cm^2 area. A dose of 2 mg in 200 μL of solution was applied to the skin surface; the ^{14}C content in each dose was approximately 590–730 μCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Urine and feces were collected at daily intervals for 3 days. Expired air was passed through two NaOH traps which were changed each time a blood sample was collected. At 72 hours after dosing, the animals were sacrificed and the following tissues were collected and analyzed for ^{14}C content: heart, liver, lung, spleen, kidney, leg, brain, gonads, application site skin, and distant skin; the remaining carcass was also analyzed for ^{14}C content. Rats and guinea pigs were housed individually in glass metabolism cages, which allowed the collection of urine, feces, and the combination of expired air and evaporation products from excreta. One day prior to formaldehyde exposure, each animal had a portion of its back shaved and had a carotid artery catheter implanted. Animals were dosed with an aqueous solution which was applied to a 2 cm^2 area. The dose applied was either 0.1 mg in 10 μL of solution or 11.2 mg in 40 μL of solution; the ^{14}C content in each dose was approximately 30 μCi. Blood samples were collected at 1, 2, 3, 4, 7, and 24 hours after dosing. Urine and feces were collected at daily intervals for 3 days. Air exiting the metabolism cages was passed through two NaOH traps which were changed each time a blood sample was collected and at 48 and 72 hours after dosing. At 72 hours after dosing, the animals were sacrificed and the following tissues were collected and analyzed for ^{14}C content: heart, liver, lung, spleen, kidney, leg, brain, gonads, application site skin, and distant skin; the remaining

carcass was also analyzed for ^{14}C content. Data from the monkeys were more variable than the rats and guinea pigs. The sum of ^{14}C recovered in the excreta (urine, feces, and expired air) was <1%. The concentration of ^{14}C in the blood was also low, averaging approximately 0.015% of the dose over the estimated blood volume. At 72 hours, no large accumulation of formaldehyde occurred in any tissue measured. The total amount of radioactivity recovered in all internal organs combined was <0.05% of the applied dose; the ^{14}C was distributed fairly evenly across all tissues.

In rats, the application site contained approximately 9.5% of the ^{14}C activity, with a total recoveries of ^{14}C for the low and high doses of 73.4 and 60.4%, respectively. Less than 3% of ^{14}C in the air was in the form of CO_2. About 7% of the low dose and 9% of the high dose was excreted in the urine and feces combined. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.12% of the low dose and 0.13% of the high dose over the total estimated blood volume. After 72 hours, no large accumulation of ^{14}C radioactivity occurred in any tissue measured in rats. The application site contained approximately 16% of the low-^{14}C dose and 3% of the high dose.

In guinea pigs, total recoveries of ^{14}C for the low and high doses were 70 and 63.6%, respectively. Approximately 21% of the low dose and 24% of the high dose were collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 6% of the low dose and 8% of the high dose was excreted in the urine and feces combined. The concentration of ^{14}C in the blood remained fairly constant throughout the experiment, averaging approximately 0.1% of the low dose and 0.09% of the high dose over the total estimated blood volume. After 72 hours, no large accumulation of ^{14}C occurred in any tissue measured. The application site contained approximately 16% of the low-^{14}C dose and 4% of the high dose. The authors concluded that topically applied formaldehyde, once absorbed, was primarily excreted by the urinary and fecal routes.

2.3.3 Metabolism

Formaldehyde is rapidly metabolized and storage is not a factor in its toxicity. The metabolism of formaldehyde to formate (via formaldehyde dehydrogenase/class III alcohol dehydrogenase) takes place in all of the tissues of the body as a consequence of endogenous formation of formaldehyde, and the formate is quickly removed by the supporting blood supply (Heck et al. 1982). Formaldehyde

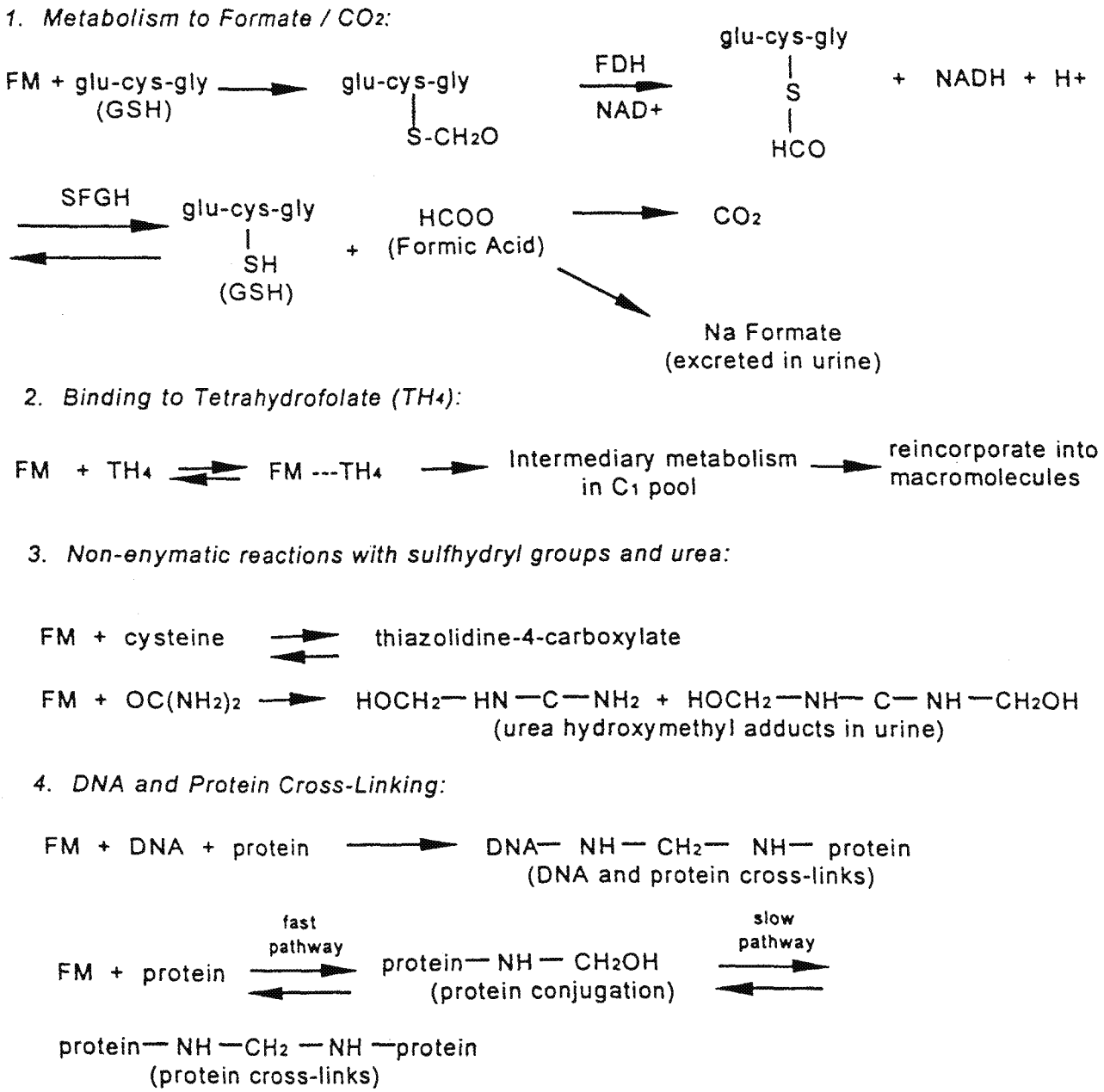
dehydrogenase (FDH) is the major metabolic enzyme involved in the metabolism of formaldehyde in all of the tissues studied; it is widely distributed in animal tissues, particularly in the rat nasal mucosa, and is specific for the glutathione adduct of formaldehyde. If formaldehyde is not metabolized by FDH, then it can form cross linkages between proteins, between protein and single-stranded DNA (see Figure 2-3) or enter the 1 carbon intermediary metabolic pool by initially binding to tetrahydrofolate (Bolt 1987). Several enzymes can catalyze the reaction that oxidizes formaldehyde to formic acid (i.e., nonspecific aldehyde dehydrogenase and catalase); however, FDH is the primary enzyme that performs this function and is specific for formaldehyde; other aldehydes are left intact in the presence of FDH. Endogenous or exogenous formaldehyde enters the FDH metabolic pathway and is eliminated from the body as metabolites, primarily as formate or CO_2. Formaldehyde dehydrogenase activity does not increase (i.e., not inducible) in response to formaldehyde exposure (Casanova-Schmitz et al. 1984b); thus no increase in metabolism occurs.

A summary of the metabolic pathways for formaldehyde metabolism is represented in Figure 2-3.

2.3.3.1 Inhalation Exposure.

Heck et al. (1985) determined the fate of inhaled formaldehyde in the human. Four men and two women were exposed to a 1.9±0.06 ppm air concentration of formaldehyde in a large walk-in chamber for 40 minutes. Shortly before and shortly after the exposure, venous blood samples were taken from each person (each person served as his/her own control) and the blood was analyzed for formaldehyde content. Mean venous blood formaldehyde concentrations in humans prior to exposure showed a blood concentration of 2.61±0.41 μg/g of blood. Individual variability was markedly present. Immediately after a 40-minute exposure, mean blood concentration of formaldehyde was 2.77±0.28 μg/g of blood. There was no significant difference between pre- and postexposure blood concentrations of formaldehyde at the formaldehyde air concentrations tested in this study, most likely indicating rapid metabolism and/or local absorption in the respiratory tract mucosa rather than systemic absorption into the blood. In the same report by Heck et al. (1985), the fate of inhaled formaldehyde was determined in the rat. Male Fischer 344 rats were placed in a nose-only inhalation chamber and exposed to a 14.4±2.4 ppm air concentration of formaldehyde for 2 hours, were sacrificed, and a venous blood sample was collected and analyzed for formaldehyde content. Unexposed control rats had a mean formaldehyde blood level of 2.24±0.07 μg/g of blood while rats exposed to the 14.4 ppm air concentration of formaldehyde had blood concentrations of 2.25±0.07 μg/g. These results indicate that during a nose-only

Figure 2-3. Metabolic Pathways of Formaldehyde Biotransformation



Key to Figure:

FM = Formaldehyde TH4 = Tetra hydrofolate DNA = Deoxyribonucleic Acid GSH = Glutathione
NAD+ = Nicotinomide adenosine dinucleotide SFGH = S-Formyl Glutathione hydrolase
FDH = Formaldehyde Dehydrogenase

Sources: Bolt 1987; Restani & Balli 1991; d'A. Heck et al. 1990;
IARC 1995; WHO 1989; Casanova-Schmitz et al. 1984

inhalation exposure of rats to this concentration of formaldehyde, no significant quantities of formaldehyde can be detected in the blood, most likely indicating fast metabolism and/or local absorption in the respiratory tract mucosa.

Heck et al. (1982) studied the effects of formaldehyde exposure on nasal mucosal tissue in male Fischer 344 rats. Rats were exposed to clean air or air containing 6 ppm formaldehyde for 10 days, 6 hours/day. Immediately after the last exposure, animals were sacrificed and nasal mucosal tissues were isolated. The tissues were homogenized and formaldehyde was extracted and analyzed by GC/MS. The mean concentration of formaldehyde in the nasal mucosal tissues of rats exposed to 6 ppm formaldehyde (0.39 μmol/g tissue) was not significantly different from the mean concentrations found in the tissues of control animals (0.42 μmol/g tissue). The authors attributed this to the rapid metabolism of formaldehyde to formate or the rapid irreversible binding of formaldehyde to macromolecules.

The ability of respiratory and olfactory tissues to oxidize formaldehyde was examined in male Fischer 344 rats. To determine the effects of repeated formaldehyde exposure on enzyme activities, rats were exposed to 15 ppm formaldehyde 6 hours/day for 10 days. At the completion of formaldehyde exposure, rats were sacrificed and respiratory and olfactory mucosal tissues were harvested. The enzymatic capacity of the tissues was determined in the presence and absence of glutathione. Tissue homogenates from both the respiratory and olfactory mucosae demonstrated the ability to oxidize formaldehyde; the oxidation of formaldehyde occurred at similar rates in the respiratory and olfactory mucosal homogenates (Casanova-Schmitz et al. 1984b).

The effects of glutathione depletion on the cross linking of formaldehyde with macromolecules (DNA, RNA, and proteins) in the respiratory and olfactory mucosa and bone marrow of male Fischer 344 rats were examined by Casanova and Heck (1987). Rats were exposed nose-only for 3 hours to 0.9, 2, 4, 6, or 10 ppm mixtures of ^{14}C- and ^{3}H-formaldehyde 1 day after a 3-hour exposure to the same concentration of unlabeled formaldehyde. Two hours prior to the second exposure, five of the rats were injected with phorone in corn oil, and the other three were injected with corn oil alone. Phorone successfully depleted nonprotein sulfhydryls levels to minimal values. The metabolic incorporation of label into macromolecules was significantly decreased by this treatment, whereas the amount of DNA-protein cross linking significantly increased. Since formaldehyde oxidation depends on glutathione, this experiment suggests that when this process is inhibited, formaldehyde levels rise high enough to form DNA-protein cross links.

2.3.3.2 Oral Exposure.

Eells et al. (1981) describe the case of a 41-year-old woman who was brought to the emergency room 30 minutes after ingesting approximately 120 mL of formalin (624 mg/kg formaldehyde). Formic acid accumulated in the blood rapidly after formaldehyde ingestion.

2.3.3.3 Dermal Exposure

No information on metabolism of formaldehyde after dermal exposure was found in the literature.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Heck et al. (1983) examined the fate of ^{14}C-formaldehyde in male Fischer 344 rats. Rats were exposed to 0.63 or 13.1 ppm formaldehyde for 6 hours. Upon completion of the exposure, the rats were placed in metabolic cages which allowed the continuous collection of urine, feces, and expired air; they remained in the cages for 70 hours and were then sacrificed. The average $^{14}CO_2$ excretion was biphasic, with a rapid decline over the first 12 hours followed by a more gradual decline in excretion over the remainder of time. Changing the concentration of formaldehyde did not affect the proportion of dose recovered in each type of excreta. Radioactivity in urine accounted for 17.6 and 17.3% of the total radioactivity detected for low- and high-dose rats, respectively; radioactivity in feces accounted for 4.2 and 5.3% of the total respective amounts of recovered radioactivity. Exhalation was the major route of excretion, accounting for 39.4% of the low dose and 41.9% of the high dose. The amount of ^{14}C remaining in the carcass after 70 hours was roughly equivalent (38.9% of low dose; 35.2% of high dose) to that expired over the same period. At 15 ppm, ^{14}C concentrations exposure were as follows: nasal mucosa, 2 μmole equivalents/g tissue; trachea, 0.3 μmole equivalents/g tissue; and plasma, 0.1 μmole equivalents/g tissue.

2.3.4.2 Oral Exposure

In a study by Galli et al. (1983), the excretion of the complexes between ^{14}C-formaldehyde and milk proteins in mice and rats, and their toxicological significance were examined. Male Sprague-Dawley rats were given a single oral dose of ^{14}C-labeled grana cheese. Rats fed with unlabeled cheese were used as

controls. Groups of rats were sacrificed at 4, 8, 16, 32, and 64 hours after the end of food consumption. Blood, liver, gastrointestinal tract, kidneys, spleen, testes, brain, muscle, and adipose tissues were removed, and urine and feces were collected from metabolic chambers. In all cases, the biological samples were immediately frozen after removal until used for radioactivity measurement. Within 32 hours of administration in rats, 67% of the radioactivity had been excreted in the feces and urine and 28% of the radioactivity had been exhaled as $^{14}CO_2$. The half-life calculated from the regression line of the β phase (where $C_{(t)}=C_0\ [e^{-\alpha t} + e^{-\beta t}]$) in blood was found to be 26.4 hours for the rats. The liver was the only tissue where the radioactivity concentration/g tissue was equivalent to more than 0.1% of the administered dose 64 hours after the ingestion of ^{14}C-labeled cheese. Excretion of radioactivity by all routes from rats was completed within 32 hours. In the companion study, male Swiss albino mice (CD-1) were given a single oral dose of 0.5 g (4 μCi) ^{14}C-labeled grana cheese. Mice were sacrificed 2, 4, 8, 16, 32, 64, and 96 hours and 8 and 12 days. Within 32 hours of administration, 64% of the radioactivity had been excreted in the feces and urine and 24% of the radioactivity had been exhaled as $^{14}CO_2$. The half-life calculated from the regression line of the β phase in blood was found to be 27.8 hours for the mice. After 96 hours in all of the mouse tissues, the radioactivity concentration/g tissue was lower than 0.5% of the administered dose, and no radioactivity was detectable after 8 days. Excretion of radioactivity by all routes from mice was completed within 32 hours.

A study by Barry and Tome (1991) sought to quantitate the concentration of formaldehyde in the milk of goats given feed containing varying amounts of formaldehyde-treated soybean oil-meal. Mean milk formaldehyde concentrations were 0.033, 0.083, and 0.153 mg/kg in the 0, 14, and 28 mg/kg/day groups, respectively. These values were significantly different from each other ($p<0.05$) and were highly correlated with formaldehyde intake ($r=0.938$, $p<0.01$). The authors concluded that dietary formaldehyde is excreted in the milk of goats.

Buckley et al. (1988) measured formaldehyde levels in the milk and blood of dairy cows given formalin-treated whey. Twelve Holstein cows in their first trimester of lactation were used in a series of three feeding trials lasting 35 days and separated from each other by 14 days. Six of the cows received a diet consisting of low-energy pelleted concentrate, liquid acid whey, and grass hay. The whey was fed once a day beginning at 10:00 am, and all whey was consumed by 4:30 pm. In the three trials, the calculated amounts of ingested formalin were 19.9, 39.7, and 59.4 mg/kg/day, respectively. The remaining six cows received untreated whey throughout the three trials. The average total excretion of formaldehyde in milk in each of the three dose groups during each trial was 0.53, 1.41, and 2.80 mg, respectively.

2.3.4.3 Dermal Exposure

Jeffcoat et al. (1983) studied the elimination of ^{14}C-formaldehyde administered topically to Fischer 344 rats, Dunkin-Hartley guinea pigs, and Cynomolgus monkeys. Data from the monkeys were more variable than the rats and guinea pigs. The sum of ^{14}C recovered in the excreta (urine, feces, and expired air) was >1%. In rats, total recoveries of ^{14}C for the low and high doses were 73.4 and 60.4%, respectively. Approximately 28% of the low dose and 22% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 7% of the low dose and 9% of the high dose was excreted in the urine and feces combined. In guinea pigs, total recoveries of ^{14}C for the low and high doses were 70 and 63.6%, respectively. Approximately 21% of the low dose and 24% of the high dose was collected in the air traps, most within the first 2 hours. Less than 3% of ^{14}C in the air was in the form of CO_2. About 6% of the low dose and 8% of the high dose was excreted in the urine and feces combined. The authors concluded that the fate of topically applied formaldehyde differed significantly from that of formaldehyde administered internally.

Bartnik et al. (1985) sought to characterize the absorption and excretion of percutaneously applied formaldehyde in male and female WISW rats using occluded and nonoccluded application. Ten male and four female rats were dosed with 200 mg of cream containing 0.1% ^{14}C-formaldehyde. Excretion of ^{14}C (presumably formate) via feces, urine, and expired air was consistently lower in animals with occluded dose sites (0.2 versus 0.7%; 1.2 versus 2.3%; and 0.9 versus 1.3%, respectively). The authors speculate that the greater formaldehyde absorption seen in the animals with nonoccluded dose sites was due to some of the volatilized formaldehyde being inhaled by the animals prior to being trapped. The authors did not specify the fate of dose in the treated skin (i.e., loose or bound on surface, or actually integrated into skin).

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in

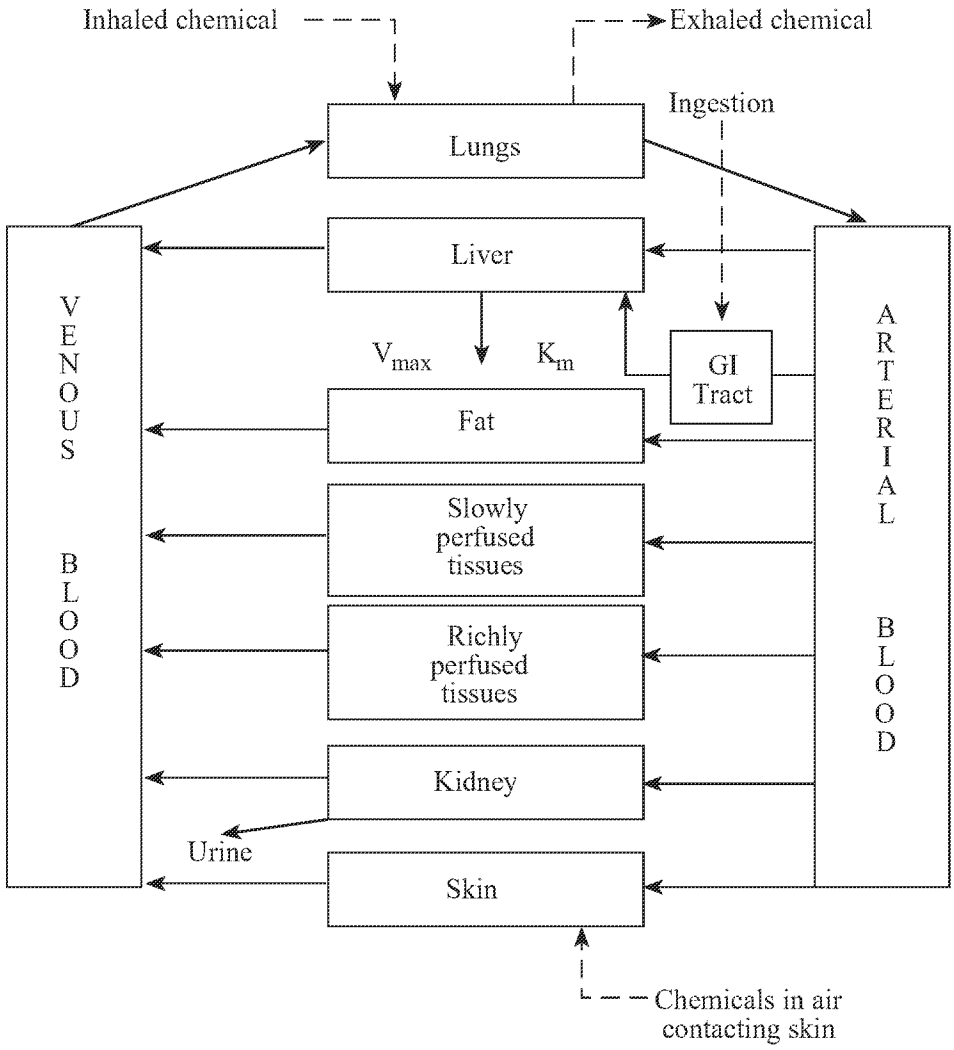
humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

PBPK models for formaldehyde are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Pharmacokinetic models to describe, as a function of formaldehyde air concentration, the rate of formation of formaldehyde-induced DNA-protein cross links in different regions of the nasal cavity have been developed for rats and monkeys (Casanova et al. 1991; Heck and Casanova 1994). Rates of formation of DNA-protein cross links have been used as a dose surrogate for formaldehyde tissue concentrations in extrapolating exposure-response relationships for nasal tumors in rats to estimate cancer risks for humans (EPA 1991a; see Section 2.4.3). The models assume that rates of cross link formation are proportional to tissue concentration of formaldehyde and include saturable and nonsaturable elimination pathways, and that regional and species differences in cross link formation are primarily dependent on anatomical parameters (e.g., minute volume and quantity of nasal mucosa) rather than biochemical parameters. The models were developed with data from studies in which concentrations of DNA-protein cross links were measured in different regions of the nasal cavities of rats (Casanova et al. 1989) and Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) exposed by inhalation to radiolabeled formaldehyde. In agreement with the observed data, the models predict that overall rates of DNA-protein cross link formation in rat respiratory mucosa are higher than rates in Rhesus monkeys, and that there is a nonlinear, convex relationship between this dose surrogate in nasal tissues and increasing air concentrations of formaldehyde (Casanova et al. 1991). Similar nonlinear, convex exposure-response relationships have also been observed in formaldehyde-exposed rats for nasal tumor incidence (Kerns et al. 1983b; Monticello et al. 1996) and cell proliferation indices in regions of the rat nasal epithelium where tumors develop (Monticello et al. 1996).

Computational fluid dynamics (CFD) models of airflow in the nasal passages of rats, monkeys, and humans have been developed to determine the degree to which interspecies and interregional differences in uptake patterns along airway passages may account for differing distributions of formaldehyde-induced upper respiratory tract lesions in rats and primates. These models enable extrapolation of exposures associated with upper respiratory tract tissue damage in rats or monkeys to human exposures

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

(Cohen Hubal et al. 1997; Kepler et al. 1998; Kimbell et al. 1993, 1997a,1997b; Morgan 1997; Morgan et al. 1991; Subramaniam et al. 1998). Airflow pattern is expected to be one of three important determinants of upper respiratory tract tissue uptake, along with interactions at the airway/tissue interface such as off-gassing and tissue properties influencing absorption rates (e.g., mucociliary clearance or rate of metabolism).

Driving forces behind the development of these airflow models include: (1) differences in nasal anatomy and breathing patterns between rats and primates; (2) observations that nonneoplastic respiratory tract lesions in rats exposed to 6 ppm formaldehyde are confined to epithelial tissue in specific anterior regions of the nose posterior to the vestibule (Chang et al. 1983; Morgan et al. 1986b), whereas monkeys exposed to 6 ppm formaldehyde show a wider distribution of similar epithelial lesions in the nose posterior to the vestibule and some extension of the lesions into the tracheal and bronchial regions (Monticello et al. 1989); (3) histochemical localization observations suggesting that regional differences in formaldehyde dehydrogenase, a key enzyme in formaldehyde detoxification, were insufficient to account for localized toxicity in the rat nose (Keller et al. 1990); and (4) observations of correlations between sites of formaldehyde-induced lesions in the nasal epithelium of rats and Rhesus monkeys and site-specific rates of DNA-protein cross link formation (a putative internal dosimeter for formaldehyde as discussed earlier; Casanova et al. 1989, 1991, 1994) or site-specific rates of cellular proliferation (Monticello et al. 1989, 1996).

Using three-dimensional reconstructions of the nasal passages of a F344 rat (Kimbell et al. 1993), a Rhesus monkey (Kepler et al. 1995), and a human (Subramaniam et al. 1998), CFD models were developed to predict patterns of airflow and regional uptake of formaldehyde in the nose of these species. The rat and monkey models were constructed from tracings of embedded tissue specimens, whereas the human model was constructed from tracings of magnetic resonance image scans. The CFD models assume that: (1) rat, monkey, and human nasal epithelial tissues are similar in all characteristics except thickness and location in nasal airways (values for these parameters were estimated from the literature or measured); (2) formaldehyde is absorbed only during inspiration, and that major patterns of inhaled airflow during resting breathing are similar to those at steady-state; (3) air is an incompressible Newtonian fluid; (4) the air-phase diffusivity of formaldehyde is constant throughout the nasal passages; (5) the nasal airway walls are inflexible and have no mucus movement or nasal hairs; and (6) formaldehyde absorption is maximal (i.e., fast and complete) in mucus-covered, nonsquamous epithelium regions of the nose so that concentrations at the surface of these airway walls are taken to be zero.

Simulations of airflow patterns were comparable with descriptions and measurements of flow in nasal molds of each species (Kepler et al. 1998; Kimbell et al. 1997a; Subramaniam et al. 1998).

Regions of high flux predicted by the rat and monkey CFD models correlated with the distribution of formaldehyde-induced squamous metaplasia in nasal passages of rats exposed to 10 or 15 ppm formaldehyde for 6 months (Kimbell et al. 1993, 1997a) and of Rhesus monkeys exposed to 6 ppm formaldehyde for 6 weeks (Kepler et al. 1998). Results from these studies support the hypothesis that airflow patterns are key determinants of the amount of formaldehyde reaching the site of formaldehyde-induced nasal lesions.

The rat CFD model and a modified version of the Casanova et al. (1991) pharmacokinetics model of formaldehyde disposition in the rat nasal lining have been linked to make predictions of DNA-protein cross link formation rates in nasal epithelial regions as a function of formaldehyde concentration in air (Cohen Hubal et al. 1997). The rat nasal lining model assumed a single compartment with three competing disposition processes for formaldehyde: saturable metabolism, nonsaturable metabolism, and DNA-protein cross link formation. The model parameters were kinetic rate constants for formation and loss of DNA-protein cross links, the nasal-lining thickness, rate constants for formaldehyde metabolism by saturable pathways (V_{max} and K_m), and a pseudo-first-order rate constant for nonsaturable formaldehyde metabolism. Saturable and nonsaturable metabolic rate constants were estimated by iterative fitting of the model to whole-nose data for DNA-protein cross links in rats exposed for 6 hours to radiolabeled formaldehyde, collected by Casanova et al. (1989). The combined airflow and pharmacokinetics models were then used to predict DNA-protein concentrations in the rat nasal epithelial region with high tumor incidence; predicted values compared well with measured DNA-protein cross link values in this region of the rat nasal epithelium (Cohen Hubal et al. 1997).

The Chemical Industry Institute of Toxicology and the U.S. EPA (CIIT 1998) are currently exploring options in using the CFD and pharmacokinetic models to extrapolate exposure-response relationships for formaldehyde-induced rat nasal tumors and related end points, such as rates of cellular proliferation in specific regions of the nasal epithelium, to derive estimates of cancer risk in humans exposed to inhaled formaldehyde. One approach being explored makes predictions for nasal and lung tumor risk in humans exposed to inhaled formaldehyde using two-stage clonal-growth cancer models incorporating data on cell division rates, numbers of cell at risk, tumor incidence, and site-specific flux of formaldehyde (see also CIIT 1998; Conolly et al. 1992; Conolly and Andersen 1993; Morgan 1997). A second approach (a

benchmark dose approach) makes predictions of nasal cancer risk in humans using curve fitting of relevant rat exposure-response data (e.g., nasal tumors or precursor lesions such as preneoplastic foci or squamous papillomas, rates of cellular proliferation, or rates of DNA-protein cross link formation) and CFD modeling and/or pharmacokinetic modeling for extrapolation purposes (CIIT 1998).

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Formaldehyde is a small, reactive, water soluble molecule (molecular weight 30.03) which is readily absorbed in the tissues of the respiratory tract (inhalation exposure) and gastrointestinal tract (oral exposure). Absorption from the nasal portion of the respiratory tract is estimated to be at or near 100%. Studies in obligate nose-breathing animals (rats, mice) have demonstrated near 100% absorption in the nasal cavity/mucosa (Casanova-Schmitz et al. 1984a; Casanova et al. 1991; Heck et al. 1982, 1983) primarily in the anterior nasal mucosa in rats (Chang et al. 1983). Absorption from the nasal mucosa, trachea, and bronchi is expected for the oronasal-breathing animals (primates, humans, dogs etc.). Tracheal and bronchial absorption ultimately results from deeper penetration because of the formaldehyde vapors not passing over and coming into contact with the nasal mucosa; however, near 100% absorption of the formaldehyde vapor is still likely, at least in the dog (Egle 1972) and very likely in humans as well. Studies in humans exposed to 1.9 ppm for 40 minutes failed to detect increases in blood formaldehyde levels, which is probably related to formaldehyde's very fast metabolism by one or a combination of metabolic pathways (see Figure 2-3) and not due to lack of local absorption. Similar results were obtained in rats exposed to 14.4 ppm for 2 hours (Heck et al. 1985). Little information is available on the oral absorption characteristics of formaldehyde in humans; however, based on two studies, either the formaldehyde is quickly metabolized to formate in the gastrointestinal tract and the formate is absorbed fairly quickly, the formaldehyde is absorbed quickly and is metabolized to formate in the blood, or a combination of the two mechanisms is responsible for the sharp increases in blood formate levels (Burkhart et al. 1990; Eells et al. 1981). Formaldehyde appears to be rapidly absorbed after oral exposure in rats (Galli et al. 1983) and food-producing animals (Barry and Tome 1991; Buckley et al. 1988). Dermal absorption in monkeys has been shown to be quite low (0.5% of the applied dose); most was either lost to evaporation or bound within the skin (Jeffcoat 1983).

Distribution. Formaldehyde does not appear to be absorbed into the blood stream as an intact molecule, except possibly at very high doses that overwhelm the metabolic capabilities of the tissue with which it comes into contact. Given this rapid metabolic capability of animal tissues, the distribution of the intact formaldehyde molecule to other more distant organs (kidney, fat, spleen, etc.) in the body is not likely and is not considered a major factor in formaldehyde toxicity. Toxicity is generally demonstrated at the point of formaldehyde contact (see Mechanisms of Toxicity, below). Heck et al. (1983) found that in rats, inhaled ^{14}C-formaldehyde (8 ppm for 6 hours) had elevated concentrations of radioactivity in their blood for several days after exposure (terminal half-life 55 hours). Since it is known that blood formaldehyde levels do not increase after inhalation exposure (Heck et al. 1985), the data suggested that there was an incorporation of ^{14}C into the macromolecules of the body. The long plasma half-life may also have been due to formaldehyde's rapid metabolism to formate or CO_2 awaiting excretion into the urine and lung, respectively.

In one study (Casanova et al. 1991), much of the ^{14}C was localized in the nasal mucosa; however, detectable levels of ^{14}C activity were noted in the esophagus, kidney, liver, intestine, lung, spleen, heart, brain, testes, and erythrocytes in some reports (Heck et al. 1983; Swenberg et al. 1983). The geometry of the nasal passages of different species, which results in different airflow patterns through the nose, has a large effect on the local distribution of formaldehyde vapor as well (Schreider 1986). In a study by Casanova-Schmitz et al. (1984a) using male rats exposed to concentrations of 0.3–15 ppm of ^{14}C and ^{3}H labeled formaldehyde for 6 hours, concentrations of ^{14}C-formaldehyde in respiratory and olfactory mucosa tissues increased linearly with dose and at any given dose, the concentrations of ^{14}C-formaldehyde in respiratory mucosa tissues were approximately 2–3 times that in olfactory mucosa tissues. The ^{3}H and ^{14}C radioisotopes were chosen to distinguish between metabolic incorporation of oxidized formaldehyde metabolites (^{14}C) and covalent binding (^{3}H) into macromolecules. At all exposure concentrations, RNA was the most heavily ^{14}C-labeled macromolecule in the respiratory and olfactory mucosa. DNA from the respiratory and olfactory mucosa was ^{14}C-labeled at equivalent or greater levels than proteins. In the bone marrow, DNA was the most heavily ^{14}C-labeled macromolecule. DNA-protein cross links have also been identified in male rats and male Rhesus monkeys exposed to formaldehyde concentrations of 9.87 ppm for 6 hours. Concentrations of formaldehyde-protein cross links were greatest in the middle turbinate tissues and lowest in the nasopharyngeal tissues, with some evidence of cross link formation seen in the larynx, trachea, carina, and major intrapulmonary airway tissues of two of the monkeys tested (Casanova et al. 1989a).

Metabolism. Formaldehyde is a normal metabolic product of animal metabolism, with varying endogenous levels present at all times (Bolt 1987). The major sources of endogenously produced formaldehyde are glycine and serine.

Formaldehyde is rapidly metabolized and storage is not a factor in its toxicity. The metabolism of formaldehyde to formate (via FDH/class III alcohol dehydrogenase) takes place in all of the tissues of the body as a consequence of endogenous formation of formaldehyde and is quickly removed by the supporting blood supply (Heck et al. 1982). FDH is the major metabolic enzyme involved in the metabolism of formaldehyde in all of the tissues studied; is widely distributed in animal tissues, particularly in the rat nasal mucosa; and is specific for the glutathione adduct of formaldehyde. If formaldehyde is not metabolized by FDH, then it can form cross linkages between protein and single-stranded DNA (see Figure 2-3) or enter the 1 carbon intermediary metabolic pool by initially binding to tetrahydrofolate (Bolt 1987). Several enzymes can catalyze the reaction that oxidizes formaldehyde to formic acid (i.e., nonspecific aldehyde dehydrogenase and catalase); however, FDH is the primary enzyme tasked to perform this function and is specific for formaldehyde; other aldehydes are left intact in the presence of FDH. Endogenous or exogenous formaldehyde enters FDH metabolic pathway and is eliminated from the body as metabolites, primarily as formate or CO_2. FDH activity does not increase (i.e., not inducible) in response to formaldehyde exposure (Casanova-Schmitz et al. 1984b). Heck et al. (1985) provided some indirect evidence in both the human and the rat that inhaled formaldehyde (1.9 ppm for 40 minutes for the human, 14.4 ppm for 2 hours in the rat) is quickly metabolized (probably by FDH) and did not raise blood formaldehyde concentrations beyond the measured endogenous levels, although this finding may have also been due to low systemic absorption. Little information about the metabolism of formaldehyde after oral or dermal exposures was available.

Increasing the amounts of formaldehyde in the diet of some lactating ruminants (cows, sheep, goats, etc.) will increase the amount of intact formaldehyde present in their milk (Barry and Tome 1991; Buckley et al. 1988). Neither of these reports offered an explanation for these findings. However, given the marked differences in blood and plasma characteristics and the differences in gastrointestinal anatomy, it is plausible to assume that there are some fundamental differences between formaldehyde metabolism in ruminant animals and in humans (or other monogastrics), which leads to increased milk levels of formaldehyde. There is a close relationship between the amount of formaldehyde ingested and the amount of formaldehyde present in the milk (Barry and Tome 1991). Milk formaldehyde concentrations

are not influenced by the level of milk production, which suggests that the passage of formaldehyde from the blood to the milk is a passive event (Barry and Tome 1991).

Excretion. Given the rapid conversion of formaldehyde to formate and subsequent incorporation into naturally occurring cellular constituents, excretion does not appear to be a factor in the toxicity of formaldehyde. The metabolism of formaldehyde to formate takes place in all of the tissues of the body as a consequence of endogenous formation of formaldehyde. Exogenous formaldehyde enters this pathway and is eliminated from the body as metabolites, primarily CO_2. For example, in rats exposed to ^{14}C-formaldehyde via inhalation, 40% of the radioactivity was recovered as $^{14}CO_2$ (Heck et al. 1983). After oral exposure to formaldehyde in male rats administered 2.2 g (18 μCi) of ^{14}C-formaldehyde, 67% of the radioactivity dose was excreted in the feces and 32% exhaled as CO_2 within 32 hours after dosing. The ^{14}C plasma elimination half-life was calculated to be 26.4 hours (Galli et al. 1983); however, it is unclear what percentage of this activity involves intact formaldehyde and what involves metabolites (i.e., formate). In a similar study in male mice administered 0.5 g (4 μCi) of ^{14}C-formaldehyde, 64% of the total dose of radioactivity was eliminated via the feces and 24% eliminated as exhaled CO_2. The plasma half-life was calculated to be 27.8 hours in this study (Galli et al. 1983). Intact formaldehyde is excreted in the milk in goats (Barry and Tome 1991) and dairy cows (Buckley et al. 1988).

2.4.2 Mechanisms of Toxicity

The exact mechanism by which formaldehyde exerts its irritant, corrosive, and cytotoxic effects is not known. Aldehydes as a group are reactive chemicals with a highly electronegative oxygen atom and less electronegative atoms of carbon(s), and hence have a substantial dipole moment. The carbonyl atom is the electrophilic site of these type of molecules, making it react easily with nucleophilic sites on cell membranes and in body tissues and fluids such as the amino groups in protein and DNA (Feron et al. 1991).

It is also known that formaldehyde can form cross links between protein and DNA *in vivo*. Casanova-Schmitz et al. (1984a) reported that the predominant route of formaldehyde metabolism was metabolic incorporation into macromolecules (DNA, RNA, and proteins) in the respiratory and olfactory mucosa and bone marrow of male Fischer 344 rats. Rats were exposed nose-only for 6 hours to 0.3, 2, 6, 10, or 15 ppm mixtures of ^{14}C and ^{3}H-formaldehyde 1 day after a 6-hour exposure to the same concentration of unlabeled formaldehyde. There was some evidence of DNA-protein cross linking

present in the nasal tissues. Concentrations of ^{14}C DNA in respiratory and olfactory mucosa tissues increased linearly with dose; at all doses, the concentrations of ^{14}C DNA in respiratory mucosa tissues were approximately two to three times that in olfactory mucosa tissues. Later studies by Casanova et al. (1991a, 1991b) described the formation of DNA-protein cross links in the respiratory tract measured in male Fischer 344 rats as well as in Rhesus monkeys. Rats were again exposed nose-only to a mixture of ^{14}C-labeled and nonradiolabeled formaldehyde, using concentrations of 0.3, 0.7, 2, 6, or 10 ppm for 6 hours. Formaldehyde was again observed in the form of formaldehyde-DNA-protein cross links, and was detected at all concentrations tested. Male Rhesus monkeys were exposed to 0.7, 2, or 6 ppm formaldehyde ^{14}C-labeled and nonradiolabeled mixture for 6 hours and it was determined that approximately 90% of all ^{14}C was associated with the thymine, while 10% was associated with the guanine and adenine. Concentrations of DNA-protein cross links were greatest in the middle turbinate tissues and lowest in the nasopharyngeal tissues, with some evidence of cross link formation observed in the larynx/trachea/carina and major intrapulmonary airway tissues of two monkeys in the 6-ppm dose group. No evidence of cross link formation was seen in the sinus or lung tissues at any exposure concentration.

The mechanism by which formaldehyde exerts its toxicological effects is not known; however, it is known that formaldehyde readily combines with free, unprotonated amino groups of amino acids to yield hydroxymethyl amino acid derivatives and a proton (H^+), which is believed to be related to its germicidal properties. Higher concentrations will precipitate protein (Loomis 1979). Either one of these mechanistic properties or perhaps other unknown properties may be responsible for the irritation effects seen with formaldehyde exposure. It is probable that formaldehyde toxicity occurs when intracellular levels saturate formaldehyde dehydrogenase activity, overwhelming the natural protection against formaldehyde, and allowing the unmetabolized intact molecule to exert its effects locally. The primary metabolite of formaldehyde, formate, is not expected to be as reactive as formaldehyde itself and is subject to excretion as a salt in the urine, entrance into the one-carbon metabolic pool for incorporation into other cellular components, or further metabolism to carbon dioxide.

The toxicity of formaldehyde is route-dependent. Irritation at the point of contact is seen by inhalation, oral, and dermal routes. High doses are cytotoxic and result in degeneration and necrosis of mucosal and epithelial cell layers. These observations are consistent with the hypothesis that toxic effects are mediated by formaldehyde itself and not by metabolites. No specific target molecule has been identified, although DNA-protein cross links have been identified (Casanova and Heck 1987). As discussed in

Section 2.2, oral and inhalation toxicity studies with animals generally have found that toxic effects from formaldehyde are restricted to portal-of-entry tissue, but there are scattered reports of toxic effects at sites distant from portals-of-entry. The mechanism whereby distant site toxicity may be expressed is unclear, but given the highly reactive nature of formaldehyde and the ubiquitous metabolic capability of cells to metabolize formaldehyde, it is plausible that distant site effects may occur only when the capacity for local disposition of formaldehyde is exceeded.

An example of a local effect of formaldehyde vapor was demonstrated in the rat nasal epithelium. In rat studies where cell turnover was measured (a measure of formaldehyde cytotoxicity), the no-effect level is approximately 2 ppm (Monticello et al. 1991; Swenberg et al. 1983) for 6 hours/day exposures for 9 days. At higher concentrations (6, 10, or 15 ppm), higher rates of cell turnover were seen (Monticello et al. 1991), and a dose-response was observed. The increase in cell proliferation (as measured by thymidine incorporation) was more sensitive to formaldehyde exposure than histopathological changes. Similar results were seen in a 6-week experiment at these same doses in which the rats were exposed 5 days/week. The relationship between concentration and total dose has been studied in experiments where rats were exposed to a range of concentrations for various lengths of time so that the total inhaled dose was constant (Wilmer et al. 1987, 1989). Studies have shown that formaldehyde concentration in the inspired air may be more important than exposure duration in determining the extent of nasal damage (Wilmer et al. 1987, 1989) (see Section 2.5). Monticello et al. (1996) also determined that the nasal cell target population size, increased cell proliferation of specific target cells (due to differences in regional airflow with the rat nasal cavity), and the nonlinear kinetics of formaldehyde binding to DNA explain why specific regions of the rat nose are more prone to develop formaldehyde-induced nasal squamous cell carcinomas than other sites in the nasal cavity.

Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells has been studied. Monticello et al. (1996) assessed the role of regional increases in nasal epithelial cell proliferation in the formation of formaldehyde-induced nasal cancer in male Fisher 344 rats whole-body exposed to formaldehyde up to 15 ppm for 24 months. The majority of formaldehyde-induced neoplasms consisted of squamous cell carcinomas and polyploid adenomas; however, cell proliferation was not affected by formaldehyde exposures of 6.01 ppm or less. Increases in the cell labeling index were significant at the 10 and 15 ppm exposure levels, and there was a highly significant correlation between formation of tumor cells and proliferating cells within the rat nasal cavity.

Although there is evidence to suggest that exposure concentration is more important than exposure duration in determining the extent of formaldehyde-induced nasal epithelial damage, the development of formaldehyde-induced nasal squamous cell carcinomas is likely to require repeated and prolonged damage to the nasal epithelium. Several key points or events determine the mechanism by which formaldehyde induces cancer in rats. First, a single high dose (40 ppm) for acute durations is not likely sufficient to induce squamous cell carcinoma cancer (Bhalla et al. 1990; Monteiro-Riviere and Popp 1986; Wilmer et al. 1987); repeated exposures for protracted durations are required to induce nasal cancer in rats. Second, the data indicate that a sequence of cellular events must occur in order to induce nasal carcinomas. The induction of nasal cancer in rats by formaldehyde requires repeated exposure for prolonged periods of time to high concentrations that are both irritating and that cause cell damage to a population of the nasal mucosa cells lining the nose. Exposure to high concentrations for prolonged periods during inhalation exposure overwhelms or otherwise exhausts the inherent defense mechanisms to formaldehyde (mucociliary clearance, FDH, DNA repair). This cellular and tissue damage inflicted by unmetabolized formaldehyde is then followed by a regenerative hyperplasia and metaplasia phase (Chang et al. 1983; Feron et al. 1988; Rusch et al. 1983; Wilmer et al. 1987; Woutersen et al. 1987, 1989), which results in increased cell-turnover rates within the mucosa. Formaldehyde has been demonstrated to be genotoxic in some (but not all) cell lines and test systems (Basler et al. 1985; Donovan et al. 1983; Grafstrom et al. 1985, 1993; Rithidech et al. 1987; Snyder and Van Houten 1986; Valencia et al. 1989; Woodruff et al. 1985; Yager et al. 1986). DNA-protein cross links have been demonstrated in experimental animals after inhalation exposure to formaldehyde and can cause mutation or chromosomal aberrations if not repaired prior to cell replication. The DNA damage that occurs in these altered cells is carried into subsequent cell populations and thereby greatly enhances the progression of preneoplastic cells to cancer. In this manner, formaldehyde likely can act as a complete carcinogen (providing initiation, promotion, and progression) with repeated and prolonged duration of exposure at cytotoxic concentrations. Point mutations in the p53 tumor suppressor gene were found in 5 of 11 nasal tumors examined from rats exposed to 15 ppm formaldehyde for 2 years (Recio et al. 1992). The tissues in the Recio et al. (1992) study were reanalyzed using antibodies against p53. One was a monoclonal antibody to mutant p53, and the other a polyclonal antibody directed against epitopes in mutant and wild type p53 (Wolf et al. 1995). Morphologically normal nasal mucosa and metaplastic and hyperplastic tissues were negative for p53 immunoreactivity. In squamous cell carcinomas (the five with previously identified p53 mutations and three of six tumors with no mutations identified), p53 immunoreactivity was focal to diffuse, and the authors stated that their results using these antibodies were solely from reactions with mutant p53.

2.4.3 Animal-to-Human Extrapolations

The target organs for formaldehyde appear to be similar in humans and laboratory animals exposed to airborne, ingested, or dermally-applied formaldehyde. As discussed in Section 2.2.1, airborne formaldehyde is an acute contact irritant in humans and laboratory animals, causing irritation of the eyes and upper respiratory tract during an inhalation exposure. Repeated exposure to airborne formaldehyde has been associated with region-specific damage to the upper respiratory tract epithelium in rats, monkeys, and mice (e.g., Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989, 1996), and evidence for similar lesions has been found in nasal tissue specimens sampled from occupationally-exposed workers (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Lifetime exposure to formaldehyde concentrations between 10 and 15 ppm produced nasal tumors in rats, but no evidence of malignant neoplastic lesions has been found in numerous rat studies at concentrations 2 ppm (e.g., Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Some studies of formaldehyde-exposed workers, typically exposed to average concentrations below 2 ppm, have found evidence for an increase in nasopharyngeal cancer death rate, whereas other studies of other groups of exposed workers have found no cases of nasopharyngeal cancer (see Section 2.2.1.8). Gastric lesions have been induced in rats (e.g., Til et al. 1988b) and in humans (Burkhart et al. 1990; Eells et al. 1981; Kochhar et al. 1986; Koppel et al. 1990) after oral exposure.

Formaldehyde is produced endogenously in all animal species studied. Absorption, distribution, metabolism, and excretion of formaldehyde are similar across species; however, species differences in upper respiratory tract anatomy and physiology likely play a role in determining the location of nonneoplastic (and neoplastic) lesions from inhaled formaldehyde. Formaldehyde-induced epithelial lesions, such as squamous metaplasia, showed a wider distribution of occurrence in the upper respiratory tract of Rhesus (Monticello et al. 1989) and Cynomolgus (Rusch et al. 1983) monkeys than similar lesions which were mostly confined to the anterior portion of the nasal cavity in formaldehyde-exposed rats (Bhalla et al. 1991; Monteiro-Riviere and Popp 1986; Morgan et al. 1986a; Wilmer et al. 1987; Woutersen et al. 1987). The differences in location of these lesions are likely due to differences in airflow pattern through the nasal cavity, resulting in different deposition patterns. The fact that rats are obligate nose-breathers and monkeys have an oronasal breathing pattern likely also has an impact on the location of these lesions. Other species differences have been noted between rats and mice. Mice tend to be more efficient at reducing their minute volumes during formaldehyde exposures than rats, which may

partially account for the differences in the decreased incidences of nonneoplastic lesions (Maronpot et al. 1986) and neoplastic lesions in mice compared rats (Chang et al. 1981, 1983).

Available studies of animals exposed by the oral or inhalation routes clearly show that formaldehyde-induced health effects are restricted to portals-of-entry and that inhaled formaldehyde, at concentrations 6 ppm, produces nasal tumors in rats (as discussed earlier in Section 2.2.1.8). In contrast, epidemiology studies of occupationally-exposed humans have provided only equivocal evidence for respiratory tract cancer. Even so, this does not negate the need to determine human cancer risk estimates, perhaps by employing means other than epidemiological information. The U.S. EPA (1991a) used dose-response data for nasal tumors in rats exposed to high concentrations of formaldehyde to extrapolate to human cancer risk at low exposure concentrations, using the rate of DNA-protein cross links in target tissue as a measure of delivered dose. Estimates of delivered dose and observed rat nasal tumor incidence were modeled with a linearized multistage procedure (i.e., were fit to an exponential polynomial model) to obtain a 95% upper confidence limit on the slope in the low-dose region of the dose-response curve (a rat unit cancer risk estimate of 1.6×10^{-4} per [pmol DNA-protein cross links/mg DNA/day]). Relationships between formaldehyde air concentrations and rates of formation of DNA-protein cross links in nasal epithelial tissue of rats (Casanova et al. 1989) or of Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) and adjustments to continuous exposure were then used to calculate lifetime human cancer unit risk estimates of 3.3×10^{-4} per ppm formaldehyde based on the monkey data, and 2.8×10^{-3} per ppm formaldehyde based on the rat data.

The use of DNA-protein cross link formation as a formaldehyde dosimeter in cancer target tissues is supported by correlative observations of nonlinear (convex) relationships between DNA-protein cross link formation in nasal epithelium of rats and monkeys and formaldehyde air concentrations and similar convex exposure-response relationships for formaldehyde-induced tumors in rats (Casanova et al. 1991; EPA 1991a). The convex nature of these relationships may be explained by a number of mechanisms, including saturation of enzymes involved in metabolism of formaldehyde, a decrease in the functioning of the mucociliary apparatus that may trap and remove formaldehyde before it reaches target tissues, saturation of protein-binding kinetic mechanisms, and saturation of inherent DNA-protein cross link repair mechanisms.

As discussed in Section 2.3.5, The Chemical Industry Institute of Toxicology and the U.S. EPA (CIIT 1998) are currently exploring options in using CFD models of nasal airflow and uptake of formaldehyde,

pharmacokinetic models of nasal disposition of formaldehyde, and two-stage clonal growth cancer models to derive estimates of cancer risk in humans exposed to inhaled formaldehyde based on nasal epithelial responses observed in rats chronically exposed to formaldehyde.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Although formaldehyde is a normal intermediary cellular metabolite involved in the biosynthesis of purines, thymidine, and several amino acids, it is a highly reactive molecule that can be directly irritating to tissues with which it comes into contact. Human and animal studies indicate that formaldehyde, at appropriate exposure levels, can be irritating to the upper respiratory tract and eyes with inhalation exposure, to the skin with dermal exposure, and to the gastrointestinal tract with oral exposure. Reports of allergic dermal sensitization to formaldehyde are widespread and supported by results from animal studies, but the evidence that formaldehyde sensitizes the respiratory tract is less convincing.

Studies of volunteers exposed to airborne formaldehyde for short periods of time (8 hours or less) indicate that eye, nose, and throat irritation occurs at concentrations in the range of 0.4–3 ppm (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Weber-Tschopp et al. 1977; Witek et al. 1986). At the lower end of this range, the irritation is typically described as mild and noted by a lower percentage of exposed subjects than at the upper end of the range. Studies of monkeys, rats, and mice exposed to higher concentrations in the range of 3–9 ppm for acute to intermediate periods of time demonstrate that formaldehyde nonneoplastic toxic effects are restricted to lesions (squamous metaplasia and hyperplasia) in the epithelium of the upper respiratory tract (Chang et al. 1983; Monticello et al. 1989; Morgan et al. 1986a, 1986c; Rusch et al. 1983; Woutersen et al. 1987; Zwart et al. 1988).

Studies of animals exposed for life to formaldehyde in air or drinking water also show that formaldehyde primarily damages tissue at portals-of-entry (i.e., the upper respiratory tract and the gastrointestinal tract); evidence for toxic effects at distant sites is less consistent. Replicated inhalation studies have shown that formaldehyde induced malignant nasal tumors in rats at high exposure concentrations (10–15 ppm) that also induced nasal epithelial necrosis and cellular proliferation, but not at lower concentrations (0.3–2 ppm) that did not markedly damage nasal epithelial tissue (Albert et al. 1982;

Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Exposure-related cancer or noncancer lesions at other sites were not found in these studies. Statistically significant increased incidences of nasal tumors, however, were not found in mice exposed by inhalation for 2 years (Kerns et al. 1983b) or in hamsters exposed for 18 months (Dalbey 1982) at concentrations similar to those producing nasal tumors in rats. Nonneoplastic nasal epithelial damage was found in mice exposed to 14 ppm, but not in mice exposed to 2 ppm (Kerns et al. 1983b). Three lifetime drinking-water exposure studies in rats that found no consistent, exposure-related cancer or noncancer effects at sites distant from the gastrointestinal tract (Soffriti et al. 1989; Til et al. 1989; Tobe et al. 1989) provide support for the expectation that formaldehyde-induced health effects are restricted to portals-of-entry.

More than 40 epidemiology studies (cohort studies of industrial workers, cohort studies of medical specialists and embalmers, and case-control studies) examining the potential for occupational formaldehyde exposure to induce cancer have provided only equivocal evidence of a relationship between formaldehyde and nasopharyngeal cancer in humans, and even less convincing evidence for extra-respiratory cancer.

Occupational and residential exposure to formaldehyde has been associated with reports of symptoms of eye, nose, and throat irritation from exposure to airborne formaldehyde (Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987), and there are numerous reports of skin irritation and contact dermatitis most likely resulting from dermal exposure to formaldehyde in liquids (Fischer et al. 1995; Kiec-Swierczynska 1996; Maibach 1983; Meding and Swanbeck 1990; Menné et al. 1991). Several cross-sectional studies of nasal epithelial tissue specimens from workers exposed to airborne formaldehyde in the approximate average concentration range of 0.2–1 ppm found evidence in some of the workers for mild lesions (stratified squamous epithelium and mild dysplasia) that are indicative of the irritant and reactive properties of formaldehyde (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c).

The apparent restriction of formaldehyde-induced noncancer and cancer effects to portals-of-entry is consistent with the highly reactive nature of formaldehyde and the existence of physiological mechanisms of protection, such as the nasal mucosal barrier and the detoxifying metabolism of formaldehyde in most, if not all, cells. The available weight of evidence indicates that distant site effects from formaldehyde may occur only when the capacity for local disposition of formaldehyde is exceeded.

Issues relevant to children are explicitly discussed in Sections 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Minimal Risk Levels for Formaldehyde.

The details regarding calculations of the MRLs for formaldehyde are described in Appendix A.

Inhalation MRLs

> An MRL of 0.04 ppm has been derived for acute-duration inhalation exposure (14 days or less) to formaldehyde.

The MRL was calculated from a minimal LOAEL of 0.4 ppm for symptoms of increased itching, sneezing, mucosal congestion, and transient burning sensation of the eyes and of the nasal passages, and elevated eosinophil counts and a transient increase in albumin content of nasal lavage fluid in volunteers exposed to formaldehyde for 2 hours (Pazdrak et al. 1993). The LOAEL was divided by an uncertainty factor of nine (three for the use of a minimal LOAEL and three for human variability) as described in Appendix A.

The selection of 0.4 ppm as an acute exposure concentration that produces mild eye, nose, and throat irritation in some human subjects is supported by reports of: nasal irritation, sneezing, and eye irritation in 3/13 subjects with formaldehyde contact dermatitis and eye irritation in 1/5 normal subjects exposed to 0.4 ppm for 2 hours (Gorski et al. 1992); increased eosinophil counts and protein in nasal lavage fluid in other groups of 10 healthy subjects and 10 workers with purported formaldehyde-induced bronchial asthma exposed to 0.4 ppm for 2 hours (Krakowiak et al. 1998); eye and nasal irritation in 3/16 healthy subjects exposed to 0.2 ppm for 4 hours (Andersen and Molhave 1983); and decreased eye irritation response time in 5/12 subjects exposed to 0.35 ppm for 6 minutes (Bender et al. 1983). Several other acute controlled exposure studies with volunteers have noted higher percentages of subjects reporting mild eye, nose, and throat irritation at concentrations between 1 and 2 ppm (Day et al. 1984; Kulle et al. 1987; Weber-Tschopp et al. 1977; Witek et al. 1986). The Anderson and Molhave (1983) study identified an apparent effect level (0.2 ppm) based on subjective reports of irritation that is lower than the effect levels (0.35–0.4 ppm) in the studies by Pazdrak et al. (1993), Krakowiak et al. (1998), and Bender et al. (1983) which used more objective measures of acute irritation. Because of the use of objective measures of toxicity and the general weight of the available data indicating that some people will not

experience eye or upper respiratory tract irritation from formaldehyde even at 1 ppm, the Pazdrak et al. (1993) LOAEL of 0.4 ppm was considered a minimal LOAEL in a group of potentially sensitive individuals (some subjects had dermal hypersensitivity to formaldehyde) and was selected as the basis of the acute MRL.

> An MRL of 0.03 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to formaldehyde.

The MRL is based on a NOAEL of 0.98 ppm for clinical signs of nasopharyngeal irritation (hoarseness and nasal congestion and discharge) and lesions in the nasal epithelium (squamous metaplasia and hyperplasia) observed in Cynomolgus monkeys exposed to formaldehyde for 22 hours/day, 5 days/week for 26 weeks (Rusch et al. 1983). The LOAEL was 2.95 ppm. As described in Appendix A, the NOAEL was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Intermediate-duration inhalation studies with several species of animals clearly identify the upper respiratory tract as the critical target tissue for airborne formaldehyde and suggest that degenerative changes to the upper respiratory tract epithelium may not occur with exposure to concentrations 1 ppm. Formaldehyde-induced epithelial damage in the upper respiratory tract similar to that observed in the Cynomolgus monkeys has been observed in: Rhesus monkeys exposed to 6 ppm for 6 hours/day, 5 days/week for 6 weeks (Monticello et al. 1989); several strains of rats subchronically exposed to concentrations greater than 2 ppm (Appelman et al. 1988; Feron et al. 1988; Monticello et al. 1991; Rusch et al. 1983; Woutersen et al. 1987); and mice exposed to concentrations 4 ppm (Chang et al. 1983; Maronpot et al. 1986). Although there are numerous human studies of acute inhalation toxicity from formaldehyde (controlled-exposure and occupational exposure studies) and numerous investigations of toxic effects from chronic occupational exposures, studies of humans strictly exposed for intermediate durations were not located. In contrast, the database for studies of animals (including primates) exposed by inhalation to formaldehyde is rich, providing data describing exposure-response relationships for formaldehyde-induced effects on the upper respiratory tract system in several species (rats, mice, hamsters, and monkeys). The study by Rusch et al. (1983) examined a number of species and identified the lowest effect level among the available sets of data. Given this observation, the absence of suitable human intermediate-duration data, and the putatively greater relevance of monkeys, compared with

rodents, to humans, the monkey NOAEL of 0.98 ppm and LOAEL of 2.95 ppm for clinical signs of nasopharyngeal irritation were selected as the basis of the intermediate-duration MRL.

> An MRL of 0.008 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to formaldehyde.

The MRL is based on a minimal LOAEL of 0.24 ppm for histological changes (loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium) in nasal tissue specimens from a group of 70 workers employed for an average 10.4 years (range 1–36 years) in a chemical plant that produced formaldehyde and formaldehyde resins for impregnating paper (Holmstrom et al. 1989c). The MRL was derived by dividing the LOAEL by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability) as described in Appendix A.

Several cross-sectional studies of groups of formaldehyde-exposed workers chronically exposed to estimated concentrations ranging from about 0.1 to 0.6 ppm (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c) have found histological evidence for mild damage to nasal epithelial tissue such as the damage described for exposed workers in the Holmstrom et al. (1989c) study. The observed effects were consistently mild, but each study reported a statistically significant, albeit small, increase in average histological score (increasing scores indicating increasing severity of change) for exposed groups compared with nonexposed control groups: 2.8 exposed versus 1.8 on an 8-point scale (Edling et al. 1988); 2.16 versus 1.46 on an 8-point scale (Holmstrom et al. 1989c); 1.9 versus 1.4 on a 5-point scale (Boysen et al. 1990); and 2.3 versus 1.6 on a 6-point scale (Ballarin et al. 1992). The Holmstrom et al. (1989c) study was selected as the basis of the MRL from among these four cross-sectional studies (they each examined equivalent end points and are of similar quality of design) primarily because the statistically significant effects were found in a group exposed to formaldehyde in the absence of potentially confounding exposures to wood dust. A full uncertainty factor of 10 was used to account for human variability because the observed mild effects were seen in groups of chronically exposed workers that were otherwise in apparent good health; a healthy worker effect may have operated causing sensitive individuals to avoid employment in the studied workplaces.

Additional supporting evidence for mild histological changes to the nasal epithelium with chronic exposure to concentrations below 1 ppm comes from rat studies. Although several studies of rats exposed for life (generally with an exposure protocol of 6 hours/day, 5 day/week) found no statistically significant increases in incidences of nonneoplastic lesions in the nasal epithelium of rats exposed to

0.1 to 2 ppm (Kerns et al. 1983b [F344 rats]; Monticello et al. 1996 [F344 rats]; Woutersen et al. 1989 [Wistar rats]), Kamata et al. (1997) reported that some F344 rats, after 28 months of exposure, displayed a mild response at 2 ppm and even at 0.3 ppm. A statistically significantly increased incidence for nasal epithelial squamous metaplasia without hyperplasia was observed in rats exposed to 2 ppm compared with control rats (5/32 versus 0/32); the incidence for nasal epithelial cell hyperplasia with squamous metaplasia was also significantly elevated compared with controls (7/32 versus 0/32). In rats exposed to 0.3 ppm, incidences of the same respective nasal epithelial lesions were also greater than control incidences (1/32 versus 0/32 and 4/32 versus 0/32), but not to a statistically significant degree.

Oral MRLs

Case reports of acute poisoning in humans ingesting doses of formaldehyde greater than 200 mg/kg have reported gastrointestinal effects and symptoms that reflect the chemical reactivity of formaldehyde and have reported other effects (e.g., cardiovascular dysfunction, coma, and renal and hepatic dysfunctions) that are consistent with the exceedance of the capacity of local detoxification mechanisms at these high dose levels (Burkhart et al. 1990; Eells et al. 1981; Kochhar et al. 1986). The acute human poisoning data, coupled with the results from studies of animals orally exposed to formaldehyde for intermediate and chronic durations, suggest that gastrointestinal irritation and damage are the most likely critical effects from acute oral exposure. A no-effect level is not identified by the human data, however, and available studies of animals exposed for acute durations provide no dose-response information for this end point. Available acute-exposure animal data are restricted to 2-week, oral administration studies that only examined body weight in rats (Johannsen et al. 1986) and a 10-day gavage administration study of testicular weight and sperm variables in rats (Cassidy et al. 1983). In the absence of dose-response data for gastrointestinal irritation and damage from acute oral exposure, no acute-duration MRL was derived.

> An MRL of 0.3 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to formaldehyde.

The MRL was based on a NOAEL of 25 mg/kg/day for gastrointestinal effects in rats exposed to formaldehyde in drinking water (Til et al. 1988b). The LOAEL was 125 mg/kg/day. An uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL to derive the MRL. The Til et al. (1988b) study used groups (10 males and 10 females) of weanling Wistar rats that received 0, 5, 25, or 125 mg/kg/day formaldehyde in their drinking water for 4 weeks. Control groups (20 males and 20 females) were given unsupplemented tap water. A water-

restricted group (10 males and 10 females) received the same amount of unsupplemented drinking water as the amount of liquid consumed by the group given the highest dose of formaldehyde. Dosing solutions were prepared fresh every week and fresh drinking water containing a calculated concentration of formaldehyde was provided to the rats every day. The authors did not report if or how often the drinking water was assayed for actual formaldehyde content, so it is not known, due to possible oxidation, polymerization, or evaporation, if the full dose of formaldehyde was received. Histopathology revealed thickening of the limiting ridges, hyperkeratosis in the forestomach, and focal atrophic inflammation in the glandular stomach in animals given a high concentration of formaldehyde. Moderate papillomatous hyperplasia was seen in one female given a high concentration of formaldehyde. Types of lesions in males given 125 mg/kg formaldehyde are as follows: slight-to-moderate focal hyperkeratosis of forestomach, slight-to-moderate focal gastritis, and slight-to-moderate submucosal mononuclear-cell infiltrate. Types of lesions in females given 125 mg/kg formaldehyde are as follows: very slight, slight-to-moderate focal hyperkeratosis of forestomach; very slight, slight-to-moderate focal gastritis; focal papillomatous hyperplasia; and polymorphonuclear leucocytic infiltration. No gastrointestinal effects were noted at the 25 mg/kg/day dose of formaldehyde.

Gastrointestinal irritation and damage have been observed in both humans and animals after ingestion of formaldehyde. In human poisoning studies, effects observed include: ulceration and sloughing of the soft palate and posterior pharyngeal wall; ulceration of the epiglottis, pyriform fossae, and arytenoids; edematous and ulcerated esophageal mucosa with patches of black sloughed tissue along the entire length; hyperemic areas of the stomach; and superficial ulceration in the distal body and antrum after a single dose of 234 mg/kg formaldehyde (Kochhar et al. 1986); abdominal pain and retching; and hard, white, and leathery stomach after a dose of 517 mg/kg (Burkhart et al. 1990); or abdominal pain after a dose of 624 mg/kg (as formalin) (Eells et al. 1981). In human poisoning studies in which the dose of formaldehyde is not known, gastrointestinal symptoms included mucosal damage, ulceration and bleeding of the buccal cavity and tonsils, and dysphagia due to esophageal mucosal damage (Freestone and Bentley 1989); necrosis of the esophagus and stomach, extensive congestion, peptic plaques in esophagus and stomach, colitis, congestion, diffuse necrosis and hemorrhage of gastric and duodenal mucosa, burns in gastrointestinal mucosa, and ileitis (Koppel et al. 1990). In rat studies in which formaldehyde was administered orally for longer periods of time, consistent evidence has been found for gastrointestinal irritation and damage, but the evidence for orally-induced neoplastic lesions is equivocal due to inconsistent findings among the studies (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989).

An MRL of 0.2 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to formaldehyde.

The MRL was based on a NOAEL of 15 mg/kg/day for gastrointestinal effects in male rats exposed to formaldehyde in drinking water (Til et al. 1989). The LOAEL was 82 mg/kg/day. An uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL to derive the MRL. The Til et al. (1989) study used groups of Wistar rats that received formaldehyde in their drinking water for 2 years. Estimated formaldehyde doses in this study were 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females. Dosing solutions were prepared fresh every week and fresh drinking water containing a calculated concentration of formaldehyde was provided to the rats every day. The authors did not report if or how often the drinking water was assayed for actual formaldehyde content, so it is not known, due to possible oxidation, polymerization, or evaporation, if the full dose of formaldehyde was received. Necropsy findings of high-dose rats killed in weeks 53, 79, and 105 revealed a raised and thickened limiting ridge of the forestomach in most male and female rats of the high-dose group and in some males and females of the other groups, including the control group. Also, several rats in the high-dose groups showed irregular mucosal thickenings in the forestomach and/or glandular stomach. These changes were also found in rats of the other groups as well as the control groups. In high-dose animals, histopathological examination revealed gastric changes including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach and focal chronic atrophic gastritis, occasionally accompanied by ulceration and/or glandular hyperplasia, in the glandular stomach. There were no gastric tumors observed apart from two benign papillomas, one in the male of the low-dose group and one in a female control rat.

Death. Cases of death in humans acutely exposed to airborne formaldehyde were not located. Death after the ingestion of formaldehyde (or a formalin solution) in humans has been reported in connection with attempted suicides. Metabolic acidosis has been noted prior to death, along with respiratory, cardiac, and renal failure; autopsy revealed corrosive damage to gastrointestinal mucosa (Burkhart et al. 1990; Eells et al. 1981; Koppel et al. 1990). Increased rates of cancer-related mortality associated with occupational exposure to formaldehyde (predominately by inhalation) have been found in some epidemiological studies, but not in others (see Section 2.2.1.8 and Section 2.5). Animal studies indicate that subchronic inhalation exposure to concentrations below 20 ppm are not lethal (Feron et al. 1988; Maronpot et al. 1986; Martin 1990; Rusch et al. 1983; Saillenfait et al. 1989; Woutersen et al. 1987), but lifetime inhalation exposure to formaldehyde has been associated with early mortalities associated with

nasal tumors in rats exposed to concentrations 10 ppm (Albert et al. 1982; Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Lifetime administration of 5,000 ppm formaldehyde in drinking water (approximate dose of 300 mg/kg/day) to rats resulted in early mortalities associated with degenerative lesions in the epithelium of the forestomach and the glandular stomach (Tobe et al. 1989).

Systemic Effects.

Respiratory Effects. Results from human and animal studies consistently indicate that the upper respiratory tract is a critical target of airborne formaldehyde at concentrations ranging from 0.4 to 20 ppm.

Controlled exposure human studies indicate that short-term exposure to air concentrations ranging from 0.4 to 3 ppm induces eye, nose, and throat irritation that is generally described as mild by most subjects, especially at the lower end of this range, and that is experienced by a greater percentage of subjects at the upper end, compared with the lower end, of the range (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle et al. 1987; Pazdrak et al. 1993; Schachter et al. 1986; Weber-Tschopp et al. 1977; Witek et al. 1986). Changes in nasal lavage fluid contents (elevated eosinophil counts and protein content), consistent with mild irritation of the nasal epithelium, have been found in several studies of groups of subjects exposed to 0.4 ppm for 4 hours (Gorski et al. 1992; Krakowiak et al. 1998; Pazdrak et al. 1993). The studied groups included healthy subjects, as well as groups of subjects with dermal sensitivity to formaldehyde (Pazdrak et al. 1993) and groups with purported formaldehyde-induced bronchial asthma (Krakowiak et al. 1998).

Formaldehyde effects on pulmonary function variables, such as FVC, FEV_1, and forced expiratory flow rates, have not been found in most studies between 0.4 and 3 ppm, even in studies of subjects with bronchial asthma or with dermal sensitivity to formaldehyde (Andersen and Molhave 1983; Day et al. 1984; Gorski et al. 1992; Harving et al. 1986, 1990; Kulle et al. 1987; Schachter et al. 1986; Witek et al. 1986). A few controlled exposure studies have found only subtle or infrequent effects of formaldehyde on lower respiratory tract function in this concentration range, supporting the hypotheses that the upper respiratory tract is a more likely target of formaldehyde toxicity than the lower respiratory tract and that pulmonary hypersensitivity to formaldehyde is rare (Green et al. 1987; Nordman et al. 1985; Sauder et al. 1986).

In groups of humans who experienced repeated exposure to airborne formaldehyde under occupational or residential conditions, symptoms of eye, nose, and throat irritation were frequently reported (Boysen et al. 1990; Edling et al. 1988; Garry et al. 1980; Holmstrom et al. 1989c; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987). Mild lesions in biopsied nasal epithelium tissue (e.g., stratified squamous epithelium and mild dysplasia) that are indicative of the irritant and reactive properties of formaldehyde were consistently found in four cross-sectional studies of groups of workers exposed to estimated average workplace air concentrations ranging from about 0.1 to 1 ppm (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Some studies assessing pulmonary function variables (e.g., FVC, FEV_1, FEFR) in groups of formaldehyde-exposed workers, generally experiencing average workplace air concentrations below 2 ppm, have found no changes that can be attributed to exposure (Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988). Other studies have presented evidence for formaldehyde-induced changes in pulmonary function variables in groups of subjects exposed in their homes or workplaces, but the changes in these studies were generally small or subtle (Alexandersson and Hedenstierna 1988, 1989; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Krzyzanowski et al. 1990; Malaka and Kodama 1990).

Studies in animals confirm that the upper respiratory tract is a critical target for airborne formaldehyde. Studies of monkeys, rats, and mice exposed to concentrations in the range of 0.3–40 ppm for acute to chronic periods of time demonstrate that formaldehyde nonneoplastic effects are restricted to lesions (squamous metaplasia and hyperplasia) in the epithelium of the upper respiratory tract (Chang et al. 1983; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989, 1991, 1996; Morgan et al. 1986a, 1986c; Rusch et al. 1983; Woutersen et al. 1987, 1989; Zwart et al. 1988). In several lifetime rat studies, exposure to 0.1–2 ppm formaldehyde (6 hours/day, 5 days/week) produced no statistically significant increased incidence of rats with nonneoplastic nasal epithelial lesions (Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989). Another 28-month study, however, found significantly increased incidence of nasal epithelial lesions (squamous metaplasia without hyperplasia and epithelial cell hyperplasia with squamous metaplasia) in a group of rats exposed to 2 ppm by the same exposure protocol (Kamata et al. 1997). Incidences of the same lesions in rats exposed to 0.3 ppm also were greater than control incidences, but the difference was not statistically significant.

In rats exposed to the lower concentrations in the 2–20 ppm range, formaldehyde-induced lesions (evidence of which could be found after a few days of exposure) occurred in the anterior regions of the nasal epithelium just posterior to the vestibule and progressed to more posterior regions of the upper

respiratory tract epithelium with higher exposure concentrations (Chang et al. 1983; Monticello et al. 1991; Morgan et al. 1986a, 1986c; Zwart et al. 1988). Results from studies in rats comparing nasal lesion severity following intermittent or continuous exposure protocols at varying concentrations suggest that effects are more concentration-dependent than duration-dependent (Wilmer et al. 1987, 1989). Monkeys exposed to 6 ppm formaldehyde for 6 weeks (Monticello et al. 1989) displayed epithelial lesions similar to those displayed by rats exposed to the same concentration for 6 weeks (Monticello et al. 1991), but the lesions in the monkeys showed a different regional distribution that extended into the trachea. Recent analyses using computational fluid dynamics models to predict airflow and regional uptake of formaldehyde in the upper respiratory tract of monkeys and rats found that predicted regions of high airflow were well correlated with epithelial regions with lesions (Kepler et al. 1998; Kimbell et al. 1993, 1997a). These results support the hypothesis that the rat and monkey may be equally susceptible to formaldehyde-induced tissue damage and that airflow patterns, determined by anatomical features, are key determinants of the amount of formaldehyde reaching sites where lesions develop.

Data on effects on the respiratory tract changes after oral exposure to formaldehyde in rats show no changes attributable to formaldehyde with respect to histopathology and/or lung weights in studies of intermediate (Johannsen et al. 1986; Til et al. 1988b; Vargova et al. 1993) and chronic (Til et al. 1989; Tobe et al. 1989) duration.

Cardiovascular Effects. It is unlikely that formaldehyde is responsible for any significant toxicological effects in organs other than the respiratory tract, particularly after inhalation or dermal exposures that might be encountered in the workplace or home. However, effects on the cardiovascular system, such as decreased blood pressure and hypotension (Burkhart et al. 1990; Eells et al. 1981), circulatory collapse (Freestone and Bentley 1989), and sinus tachycardia (Kochhar et al. 1986) due to the ingestion of high doses of formaldehyde in humans have been reported. It is not clear how formaldehyde induced these symptoms or if other existing conditions contributed in whole or in part to these cardiac responses, but is likely related to the large dose of formaldehyde ingested in a very short period of time.

Rats displayed 5–25% increases in blood pressure, compared with resting values, in response to intravenous administration of formaldehyde doses ranging from 0.5 to 5 mg/kg (Egle and Hudgins 1974). In contrast, an intravenous dose of 20 mg/kg significantly decreased blood pressure by about 30% and induced a transient cardiac arrest. The depressor effect at the high dose level was abolished by vagotomy in the neck region, and only the pressor effect was observed in vagotomized rats exposed to 20 mg/kg.

Egle and Hudgins (1974) suggested that the low-dose pressor effects are caused by formaldehyde-induced release of epinephrine from sympathetic nerve endings and catecholamines from the adrenal medulla, and that the vagal nerve is stimulated at high doses leading to bradycardia and decreased blood pressure. Egle and Hudgins (1974) reported that 1-minute exposures to formaldehyde in inspired air at a concentration of 2 mg/L (1,628 ppm) did not significantly affect blood pressure or heart rate in anesthetized rats. This concentration was reported to be 20-times higher than formaldehyde concentrations in inhaled cigarette smoke. These results indicate that acute cardiovascular effects are not expected at environmentally relevant exposure levels.

Results from repeated exposure animal studies suggest that cardiovascular effects due to formaldehyde toxicity after inhalation are negligible, regardless of the duration of exposure at the concentrations tested (40 ppm). After inhalation exposure, organ weights and/or histopathology remained unchanged from control animals in studies using rats (Appelman et al. 1988; Kerns et al. 1983b; Woutersen et al. 1987, 1989), monkeys (Monticello et al. 1989; Rusch et al. 1983), and mice (Kerns et al. 1983b; Maronpot et al. 1986). Fewer reports were available on cardiovascular toxicity of formaldehyde after oral exposure at doses up to 300 mg/kg/day; however, the findings of no significant effects (weight or histopathology) on this system were consistent in both rats (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989; Vargova et al. 1993) and dogs (Johannsen et al. 1986).

Gastrointestinal Effects. Formaldehyde did not have a detectable effect on the gastrointestinal tract after inhalation exposure of animals (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987) and only nonspecific effects, such as intestinal cramps, and flatus, were reported in four patients that had been exposed occupationally to formalin or phenol-formaldehyde resins (Kilburn 1994). Formaldehyde acts as a contact irritant and corrosive agent after oral exposures of acute, intermediate, and chronic durations. After large doses taken by mouth (acute exposure), lesions can be found in the oropharynx, consisting of ulceration and/or necrosis of the soft palate and phalangeal structures, ulceration of the epiglottis, and esophageal lesions (which may result in dysphagia) (Freestone and Bentley 1989; Kochhar et al. 1986). More vague clinical signs of emesis (with or without hematoemesis) and abdominal pain or cramping were also present in some cases (Burkhart et al. 1990; Eells et al. 1981); these are due, at least in part, to a contact irritant effect, but may also be attributable to corrosive lesions found in the stomach after the ingestion of formaldehyde. In cases which afforded an examination of the duodenum and other portions of the intestinal tract after the stomach, no lesions attributable to formaldehyde intoxication were noted, indicating that the oral cavity

and the stomach share the brunt of the toxicity of formaldehyde after ingestion. Similar findings in the stomachs of Wistar rats noted in one intermediate-duration study (Til et al. 1988b) consisted of hyperkeratosis of the forestomach (indicative of chronic irritation) and focal atrophic inflammation of the glandular stomach at doses of 125 mg/kg/day. Another study by Til and coworkers (1989) found gastric anomalies, consisting of hyperplasia/hyperkeratosis, atrophic gastritis, and ulcerations in Wistar rats at doses ranging from 82 to 109 mg/kg/day in drinking water. Similar effects were also observed in Wistar rats at doses of 50–300 mg/kg/day for up to 2 years (Tobe et al. 1989) and in Wistar rats, exposed to 250 mg/kg/day in drinking water for up to 32 weeks (Takahashi et al. 1986a). Other studies found no significant effect on the gastrointestinal system in both Sprague-Dawley rats (Johannsen et al. 1986; Vargova et al. 1993) and dogs (Johannsen et al. 1986) at doses ranging from 80 to 300 mg/kg/day. The data suggest that formaldehyde has a strong potential to cause damage to the upper gastrointestinal tract (oral cavity, esophagus, and stomach) after oral exposure, and although laboratory animal data are similar to human data, species differences may account for slight differences in the dose required to initiate the damage to the gastrointestinal tract. Evidence for oral exposure to formaldehyde causing tumors of the gastrointestinal tract is discussed below under Cancer Effects.

Hematological Effects. Intravascular coagulopathy was reported in one man who ingested a large dose of formaldehyde (Burkhart et al. 1990); however, the other reports of human ingestion of lower doses suggest no effects on the blood and blood-forming organs (Eells et al. 1981; Freestone and Bentley 1989; Kochhar et al. 1986; Koppel et al. 1990). No consistently significant hematological effects were noted in several studies using the inhalation (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Woustersen et al. 1987) and oral (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989) routes of exposure in laboratory animals. The oral studies with rats used drinking water as the vehicle, with doses ranging from 82 to 150 mg/kg/day, with no hematological effects noted. The lack of toxicity is likely related to rapid metabolism prior to the formaldehyde reaching the blood and blood-forming components (bone marrow). Some evidence suggests, however, that the rapid metabolic capabilities can be overwhelmed to some degree (Vargova et al. 1993), resulting in some minor alterations in blood parameters. In that study, affected male rats received a gavage dose level of 80 mg/kg/day formaldehyde for 4 weeks. This dosing method may have resulted in large doses of formaldehyde being absorbed over a shorter period of time than in the drinking water studies. In this situation, some unmetabolized formaldehyde may have been responsible for the alterations in erythrocyte count and hemoglobin and mean cellular hemoglobin values.

Musculoskeletal Effects. The only reports available that described some manifestations of adverse musculoskeletal effects in humans included vague signs of muscle and joint stiffness after chronic-inhalation exposures to formaldehyde (Holness and Nethercott 1989). It is unlikely that inhalation exposure to formaldehyde is responsible for these complaints, and they may represent an effect from a confounding factor in that study. The lack of human data and the lack of musculoskeletal effects in animal studies (Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Til et al. 1989), coupled with the available toxicokinetic data, suggest that formaldehyde has no adverse effects on the musculoskeletal system.

Hepatic Effects. Hepatic effects (e.g., congestion of hepatic parenchyma and increased serum enzymes associated with liver damage) have been reported for some human cases of acute poisoning from ingestion (e.g., Freestone and Bentley 1989; Koppel et al. 1990), but not reported for other cases (e.g., Burkhart et al. 1990; Eells et al. 1981). Increased incidence of hepatocellular vacuolization was found in rats exposed to gavage dose level of 80 mg/kg/day for 4 weeks (Vargova et al. 1993), but other studies found no exposure-related changes in liver weight or histopathology in rats exposed to drinking-water doses as high as 150 mg/kg/day for 90 days (Johannsen et al. 1986), 125 mg/kg/day for 4 weeks (Til et al. 1988b), 82–109 mg/kg/day for 2 years (Til et al. 1989), and 300 mg/kg/day for 2 years (Tobe et al. 1989). Liver weight and histopathology were likewise unaffected in Beagle dogs exposed to up to 100 mg/kg/day in the diet for 90 days (Johannsen et al. 1986), as were serum enzyme activities indicative of liver damage in rats exposed to up to 300 mg/kg/day for up to 2 years (Tobe et al. 1989). Increased activities of enzymes indicative of liver damage have been reported in rats exposed to air concentrations of 35 ppm for 18 hours (Murphy et al. 1964) or 20 ppm 6 hours/day, 5 days/week for 13 weeks (Woutersen et al. 1987), but accompanying structural changes in the liver were not detected with light microscopy. Other studies with rats have not found evidence for increased serum liver enzymes in rats exposed to air concentrations up to 15 ppm, 5 days/week for up to 28 months (Appelman et al. 1988; Kamata et al. 1997). Several other inhalation studies of intermediate or chronic duration have found no evidence for formaldehyde-induced histological changes in the livers of monkeys exposed to 6 ppm (Monticello et al. 1989), rats exposed to up to 14.3 ppm (Kerns et al. 1983b), or mice exposed to up to 40 ppm (Kerns et al. 1983b; Maronpot et al. 1986).

In general, the information from reports of acute poisoning in humans ingesting formaldehyde and reports of studies of animals exposed to formaldehyde in air, in drinking water, or in the diet indicate that the liver is not a prime target of formaldehyde toxicity, and that hepatic effects from exposure to

formaldehyde are expected to occur only when the capacity of dispositional processes for formaldehyde are exceeded at portals-of-entry.

Renal Effects. The available data suggest that the renal system is not a major target organ of toxicity for formaldehyde. Renal failure/anuria was noted in three case reports involving people ingesting various large or unknown amounts formaldehyde (Eells et al. 1981; Freestone and Bentley 1989; Koppel et al. 1990); however, the mechanism of action for the induction of renal failure is not known. Data for laboratory animals exposed by inhalation for intermediate- and chronic-duration to formaldehyde concentrations ranging from 0.19 to 40 ppm are fairly consistent in the failure of formaldehyde to elicit gross or histological lesions, alterations in renal weight, or to produce significant changes in urine composition (Appelman et al. 1988; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987). Appelman et al. (1988) did report oliguria in rats exposed to 10 ppm for 52 weeks, but Kerns et al. (1983b) did not report a similar finding in rats and mice exposed to up to 14.3 ppm for 2 years. Similarly, lack of renal effects was also reported after intermediate- and chronic-duration oral exposure in most studies (Johannsen et al. 1986; Til et al. 1988b; Tobe et al. 1989; Vargova et al. 1993), but renal papillary necrosis was reported for rats that received 82–109 mg/kg/day in drinking water for 2 years (Til et al. 1989), and increased blood urea nitrogen was reported in rats that received 300 mg/kg/day in drinking water for up to 12 months (Tobe et al. 1989).

Endocrine Effects. No information was available that reported the effects of formaldehyde on the endocrine system of humans after inhalation, oral, or dermal exposure. Formaldehyde has been reported not to exert adverse effects on organs of the endocrine system in laboratory animals and, hence, is not a major target organ for formaldehyde toxicity after inhalation (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987) or oral (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989; Vargova et al. 1993) exposure. No data regarding endocrine effects in animals after dermal exposure were located.

Dermal Effects. Formaldehyde is a widely recognized skin irritant and dermal sensitization agent in humans (see also Immunological and Lymphoreticular Effects section). Patch testing for dermal sensitization to formaldehyde has been carried out with either 1 or 2% solutions because, for most individuals, acute exposure to such concentrations does not produce signs of nonimmune irritation (e.g., erythema [redness], induration, flaking, and/or blistering). Some earlier patch testing procedures utilized concentrations as high as 5%, a practice that has been largely discontinued, presumably because of the

difficulty in discerning between irritant and immune responses at this exposure level (Maibach 1983). Increased incidences of contact dermatitis or allergic contact dermatitis associated with dermal exposure to formaldehyde solutions have been observed in funeral service workers (Nethercott and Holness 1988) and among medical workers (Rudzki et al. 1989). Allergic contact dermatitis from formaldehyde released from "no-iron" textiles was frequently reported until textile finishing processes were changed (in the mid 1970s) so that only small amounts of formaldehyde were released from clothing made from such textiles (Peters and Hesse 1997). Experiments with guinea pigs (Wahlberg 1993) and mice (Iversen 1986) indicated that repeated exposure of skin to concentrations for acute periods as low as 0.4% can be damaging (i.e., produce erythema, epidermal hyperplasia, or increased skin-fold thickness).

Animal studies with repeated exposure to airborne formaldehyde concentrations between 1 and 40 ppm (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Woutersen et al. 1987) and oral doses as high as 109 mg/kg/day (Til et al. 1989) indicate that clinically significant dermal effects are not a concern by these routes of exposure, although mice exposed to the highest air concentration (40 ppm) in these studies showed a "loss of skin elasticity" (Maronpot et al. 1986). Eberlein-Konig et al. (1998) reported that a 4-hour exposure of dermally sensitized human subjects to airborne formaldehyde concentrations as low as 0.08 ppm increased transepidermal water loss compared with nonsensitized subjects, but the clinical significance of this effect is uncertain.

Ocular Effects. Eye irritation is one of the most common complaints among people exposed to airborne formaldehyde. In acute, controlled exposure studies with volunteers, mild to moderate eye irritation has been reported at low-level concentrations in the range of 0.4–4 ppm; at the upper end of this range, greater percentages of subjects experienced eye irritation (Akbar-Khanzadeh and Mlynek 1997; Akbar-Khanzadeh et al. 1994; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Kulle 1993; Kulle et al. 1987; Schachter et al. 1986; Weber-Tschopp et al. 1977; Witek et al. 1986, 1987). Other results indicating formaldehyde's eye-irritation potential include reports that average rates of eye-blinking were significantly increased during exposure to 2.1 ppm, but not to 1.2 ppm (Weber-Tschopp et al. 1977), and that percentages of subjects with shortened response times (i.e., the time taken for the subjects to note eye irritation) were significantly increased with exposure to 1 ppm, but not to lower concentrations (Bender et al. 1983). In addition, survey studies have reported increased rates of eye irritation in groups of persons who have been repeatedly exposed to formaldehyde in residences or workplaces, compared with groups of nonexposed persons (Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987).

Histological examinations of eyes from animals repeatedly exposed to airborne formaldehyde concentrations as high as 6–40 ppm have not found formaldehyde-induced changes (Appelman et al. 1988; Kerns et al. 1983b; Maronpot et al. 1986; Monticello et al. 1989; Swenberg et al. 1980; Woutersen et al. 1987). Ophthalmoscopic examinations likewise revealed no exposure-related changes in rats or mice examined at several intervals during 2-year exposures to concentrations as high as 14.3 ppm (Kerns et al. 1983b), but clinical signs of eye irritation during exposure to 2–15 ppm have been noted in several animal studies (Dinsdale et al. 1993; Monticello et al. 1989; Morgan et al. 1986c). Chronic exposure of rats to drinking water doses as high as 89–102 mg/kg/day produced no histological changes in eyes or Harderian and exorbital lachrymal glands (Til et al. 1989). Direct application of formaldehyde solutions into eyes is expected to be irritating. Krootila et al. (1986) provided evidence that application of a 1% solution of formaldehyde to the eyes of rats caused a breakdown of the blood-aqueous barrier and that the irritative response of the eye is dependent on the trigeminal sensory nerve.

Body Weight Effects. Whereas no reports of body weight effects in formaldehyde-exposed humans were located, numerous reports are available of biologically significant body weight decreases in animals repeatedly exposed to formaldehyde by the inhalation route (Appelman et al. 1988; Kamata et al. 1997; Kerns et al. 1983b; Maronpot et al. 1986; Rusch et al. 1983; Woutersen et al. 1987, 1989) and by the oral route via drinking water or diet (Johannsen et al. 1986; Til et al. 1989; Tobe et al. 1989). Exposure-related effects on body weight were not found in pregnant hamsters dermally exposed during gestation to 37% formaldehyde solutions (Overman 1985) or in guinea pigs dermally exposed for 9 days to 4% formaldehyde solutions (Wahlberg 1993). Air concentrations associated with decreased body weights in repeatedly exposed animals were mostly at or above exposure levels (10 ppm) that produced severe upper respiratory tract lesions. Oral dosage levels associated with decreased body weights in repeatedly exposed animals were generally 80–100 mg/kg/day and also associated with the development of gastrointestinal tract lesions and decreases in food and water intake.

Metabolic Effects. Metabolic acidosis has been observed in patients who ingested large (>500 mg/kg) single doses of formaldehyde (Burkhart et al. 1990; Eells et al. 1981; Koppel et al. 1990). The rapid metabolic production of formate at these high dose levels was likely involved in the observed acidosis.

Other Systemic Effects. Decreased food and water consumption have been observed in animals exposed to oral doses generally greater than 100 mg/kg/day (Johannsen et al. 1986; Til et al. 1989; Tobe et al.

1989). The decreased consumption was generally associated with decreases in body weight and with development of gastrointestinal lesions with intermediate or chronic exposure.

Immunological and Lymphoreticular Effects. Allergic contact dermatitis from formaldehyde is commonly reported at dermatological clinics throughout the world. Patch test reporting from clinics indicates that about 1–4% of tested patients with skin problems are dermally sensitive to formaldehyde (Fischer et al. 1995; see also: Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991). Given the widespread use of formaldehyde in cleaning solutions and cosmetics (Flyvhom 1991; Rastogi 1992), it is likely that most patients presenting with formaldehyde contact dermatitis experienced sensitization through dermal contact, but dermal sensitization through contact with airborne formaldehyde cannot be ruled out. Severe allergic responses to formaldehyde appear to be rare, but one case report was located of a severe response to a patch test with a 1% formaldehyde solution in a woman who was sensitized after exposure to a dialyzer sterilized with formaldehyde (Maurice et al. 1986). Twenty-six hours after the application of the patch, the patient developed anaphylactic symptoms of laryngeal edema and bronchospasm that resolved on administration of subcutaneous epinephrine.

Although formaldehyde is widely recognized as a dermal irritant that can sensitize the skin in humans, the evidence for immunologically-mediated sensitization of the respiratory tract is weak. Despite the widespread use of formaldehyde in several occupational exposure scenarios (and the widespread occurrence of formaldehyde in tobacco smoke), there are only a few available case reports of formaldehyde-exposed workers who display marked changes in pulmonary function variables (e.g., FEV_1 and FEFR) in response to acute challenges with inhaled formaldehyde that are consistent with an immunologically-mediated mechanism of response (Burge et al. 1985; Hendrick et al. 1982; Lemiere et al. 1995; Nordman et al. 1985). Other studies found no marked response to challenges of inhaled formaldehyde in previously-exposed subjects who complained of asthma-like symptoms (Day et al. 1984; Krakowiak et al. 1998; Reed and Frigas 1984). Several studies have found no consistent evidence for increased serum levels of formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed subjects including groups with complaints of respiratory symptoms (Dykewicz et al. 1991; Gorski et al. 1992; Grammar et al. 1990; Krakowiak et al. 1998; Kramps et al. 1989; Thrasher et al. 1987, 1990).

The only other suggestive evidence of IgE-mediated sensitization to formaldehyde comes from a study of schoolchildren who were exposed to particleboard-paneled classrooms with estimated formaldehyde air

concentrations of 0.075, 0.069, and 0.043 ppm and reported respiratory tract symptoms consistent with the irritant properties of formaldehyde (Wantke et al. 1996a). Elevated serum levels of formaldehyde-specific IgE antibodies were detected in these children. The investigators noted that the elevated levels were not correlated with the number and severity of symptoms, but decreased serum levels were measured in a subgroup of the children 3 months after they were moved to another school with lower air concentration of formaldehyde (0.023–0.029 ppm). The significance of these findings is uncertain, as the reported symptoms were more typical of an irritant response than of asthma-like symptoms that are expected to be mediated through IgE antibodies.

Animal studies examining the sensitizing properties of formaldehyde present evidence consistent with the hypothesis that, although formaldehyde can sensitize skin, it apparently lacks a potential to sensitize the respiratory tract (Hilton et al. 1996). Strong positive responses to formaldehyde were found in three animal assays indicative of skin-sensitization potential (guinea pig maximization test, Buehler occluded patch test and the murine local lymph node assay). However, in a mouse IgE test and an assessment of cytokine secretion patterns by lymph node cells, formaldehyde was negative, producing responses that were not like those produced by trimellitic anhydride, a well-established respiratory tract allergen in animals and humans (Hilton et al. 1996). Although these results suggest a lack of ability to sensitize the respiratory tract, another animal experiment suggests that exposure to formaldehyde may enhance allergic responses of the respiratory tract to other respiratory allergens (Tarkowski and Gorski 1995). This study found that that the production of ovalbumin-specific IgE antibodies in response to intranasal administration of ovalbumin was four-fold greater in mice preexposed to 1.6 ppm formaldehyde for 10 consecutive days, compared to the response in mice without formaldehyde preexposure. In similar experiments, groups of guinea pigs preexposed to a formaldehyde concentration of 0.25 ppm, 8 hours/day for 5 days followed by inhalation exposure to 0.5% ovalbumin were found to have a higher percentage of ovalbumin-sensitized animals than control groups with no preexposure (10/12 versus 3/12) (Riedel et al. 1996). Further research is necessary to confirm the hypothesis of formaldehyde facilitation of other respiratory allergens and to determine if this is relevant to humans exposed to formaldehyde.

Other animal studies indicate that repeated inhalation exposure to formaldehyde at high concentrations, between 10 and 15 ppm, did not produce significant effects in several assays of immune function including resistance to intravenous or subcutaneous injection of neoplastic cells in mice (Dean et al. 1984), resistance to intravenous injection of bacterial cells in mice (Dean et al. 1984), and IgM response to tetanus immunization and IgG response to tetanus toxoid in rats (Holmstrom et al. 1989b).

Neurological Effects. Few studies have reported neurological effects after exposure to formaldehyde in humans; however, these studies tend to report vague symptoms. For example, men exposed to formaldehyde vapors at concentrations 0.98 ppm for 5.5 hours reported such symptoms as fatigue, headaches, and "heavy head" (Bach et al. 1990). Reaction times also decreased as formaldehyde concentrations increased. After the ingestion of formaldehyde in humans, coma (Koppel et al. 1990), lethargy, seizures (Burkhart et al. 1990), and loss of consciousness (Burkhart et al. 1990; Eells et al. 1981) have been reported. Kilburn and colleagues have reported evidence for neurological symptoms and impaired performance in neurobehavioral tests in groups of formaldehyde-exposed histology technicians, but confounding exposure to other neurotoxic solvents prevents drawing definitive conclusions regarding the neurotoxicity of formaldehyde from this source (Kilburn 1985b; Kilburn et al. 1987; Kilburn and Warshaw 1992; Kilburn 1994).

Male rats exposed to 15 ppm formaldehyde showed restless behavior within the first 10 minutes of exposure (Morgan et al. 1986a). Exposure to 5 ppm formaldehyde for 3 hours in male rats resulted in decreased motor activity within 15 minutes from the beginning of exposure; increased concentrations of 5-hydroxyindoleacetic acid (a 5-hydroxytryptamine metabolite), 3,4-dihydroxyphenylacetic acid (a dopamine metabolite), and dopamine were present in the hypothalamus at the end of the 3-hour exposure (Boja et al. 1985). With repeated exposure, mice developed an increased sensitivity to the acute sensory irritant properties of formaldehyde; the increased sensitivity attributed, at least in part, to a conditioning (i.e., learning) process (Wood and Coleman 1995). No abnormal clinical signs were noted in mice treated with doses 10 ppm formaldehyde for 6 hours/day, 5 days/week for 13 weeks; however, listlessness and hunched posture were observed in the mice exposed to 20 ppm formaldehyde, and these symptoms plus ataxia were observed in the 40-ppm dose group (Maronpot et al. 1986). No obvious signs of neurological effects were noted in rats (Appelman et al. 1988; Kerns et al. 1983b; Woutersen et al. 1987) or mice (Kerns et al. 1983b) in chronic-duration inhalation studies. No obvious neurological effects were observed in rats receiving 150 mg/kg/day for 90 days in drinking water (Johannsen et al. 1986), in rats receiving 125 mg/kg/day for 4 weeks in drinking water (Til et al. 1988b), or in rats exposed to 300 mg/kg/day for 12 months in drinking water (Tobe et al. 1989). Beagle dogs exposed to formaldehyde in drinking water at concentrations 100 mg/kg/day experienced no effect on brain weight or histopathology. Similar negative findings were noted in studies of chronic duration at doses 300 mg/kg/day in drinking water in rats (Til et al. 1989; Tobe et al. 1989). It appears that formaldehyde has major effects on the nervous system only after large doses are ingested; such as low-level and vague symptoms after chronic, low-level exposure.

Reproductive Effects. Studies regarding possible reproductive effects in humans exposed to formaldehyde are restricted to a study that found no evidence for effects on sperm numbers or morphology in a small number of pathologists (Ward et al. 1984) and a study that found no evidence for increased rates of miscarriage among a group of 275 persons with presumed residential exposure to formaldehyde (Garry et al. 1980).

Studies of animals exposed to formaldehyde in air, in drinking water or diet, or applied to the skin indicate that the reproductive organs are not a critical target for formaldehyde toxicity, but comprehensive assessments of reproductive performance (e.g., 2-generation studies) in formaldehyde-exposed animals were not located.

No effects on histology or weight of reproductive organs were found in rats or mice exposed repeatedly to air concentrations as high as 20 ppm (Appelman et al. 1988; Maronpot et al. 1986, Woutersen et al. 1987), in dogs repeatedly exposed to formaldehyde in the diet at doses up to 100 mg/kg/day (Johannsen et al. 1986), or in rats exposed to oral doses up to 300 mg/kg/day (Johannsen et al. 1986; Til et al. 1989; Tobe et al. 1989; Vargova et al. 1993). Ovarian and uterine hypoplasia were observed in female mice exposed to air concentrations of 40 ppm for 13 weeks, but was attributed to the general weight loss and poor health of these animals rather than to a direct effect of formaldehyde (Maronpot et al. 1986). Maternal toxicity, expressed as a marked decrease in weight gain, occurred in pregnant rats exposed during gestation by inhalation to 40 ppm, but reproductive variables (e.g., numbers of implantations or resorptions) were not affected (Saillenfait et al. 1989). At lower air concentrations, no signs of maternal toxicity were observed in this and another rat study of gestational exposure (Martin 1990). Exposure during pregnancy to gavage dose levels of 185 mg/kg/day, but not 145 mg/kg/day, produced severe maternal toxicity in pregnant mice (22/34 dams died), but did not affect reproductive variables such as numbers of implantation sites or resorptions (Marks et al. 1980). No effects on reproductive variables were found in pregnant dogs exposed to 9.4 mg/kg/day in the diet on gestation days 4–56 (Hurni and Ohder 1973). Dermal exposure of pregnant hamsters to 37% solutions of formaldehyde produced a small increase in resorption rate without affecting maternal weight gain, but the authors of this study proposed that the effect may have been caused by stress associated with the applied treatment protocol (Overman 1985). Single gavage dose levels of 200 mg/kg, but not 100 mg/kg/day, produced changes in sperm morphology in rats (Cassidy et al. 1983), but with no tests of reproductive performance, the toxicological significance of this finding is uncertain. In a review of available reproductive and developmental toxicity data, WHO (1989) concluded, "There is no convincing evidence that formaldehyde is a teratogen in either

animals or human beings. Formaldehyde has not produced any adverse effects on reproduction in test animals or human beings." IARC (1995) reached a similar conclusion in a more recent review.

Developmental Effects. Studies of possible developmental effects in humans exposed to formaldehyde are restricted to a study that found no statistically significant difference in incidence of low birth weights among groups of mothers who lived in residential districts with differing ambient air levels (up to 38 ppb) of formaldehyde (Gra ulevi iene et al. 1998). Exposure of pregnant rats to air concentrations up to 10 ppm during gestation days 6–15 produced no distinct effects on fetal development (Martin 1990). In another study with several exposure levels, pregnant rats exposed during gestation days 6–20 to the highest concentration, 40 ppm, showed a 51% reduction in weight gain (Saillenfait et al. 1989). Fetal weights were decreased in male offspring from dams exposed to 20 ppm and in female offspring from dams exposed to 40 ppm, but no effects attributable to formaldehyde were noted in the incidences of pregnancies, number of implantations or resorptions, number of dead or live fetuses, fetal sex ratios, or incidences of skeletal or visceral anomalies (Saillenfait et al. 1989). Similarly, no effects on fetal development were found in studies of pregnant rats exposed during gestation days 6–15 to gavage dose levels as high as 185 mg/kg/day (Marks et al. 1980), pregnant dogs exposed to up to 9.4 mg/kg/day in the diet during gestation days 4–56 (Hurni and Ohder 1973), and pregnant hamsters dermally exposed to a 37% aqueous solution of formaldehyde on gestation day 8, 9, 10, or 11 (Overman 1985).

Genotoxic Effects. Formaldehyde has been demonstrated to have genotoxic properties in human and laboratory animal studies. Peripheral lymphocytes in anatomy students exposed to 0.73–1.95 ppm formaldehyde for 8 weeks showed a small increase in SCE (Yager et al. 1986). Lymphocytes from wood workers chronically exposed to formaldehyde also showed increased levels of chromosomal aberrations; however, there were no significant changes in the rates of SCE (Chebotarev et al. 1986). Increases in micronuclei formation, primarily in nasal passage ciliated cells, were found in wood workers chronically exposed to 0.07–0.08 ppm formaldehyde (Ballarin et al. 1992). An increased incidence in chromosomal abnormalities in pulmonary macrophages was noted in male rats exposed to 15 ppm formaldehyde for 5 days (Dallas et al. 1992). No reports of genotoxicity strictly related to the oral or dermal exposure routes were found in the available literature.

Conversely, a number of studies have failed to demonstrate the genotoxic potential of formaldehyde. Fleig et al. (1982) performed chromosome analyses on 15 exposed and 15 non-exposed employees from

formaldehyde-manufacturing facilities with average exposure concentrations not exceeding 5 ppm prior to 1971 and 1 ppm after 1971. There were no differences between exposed and control groups in the incidence of chromosomal aberrations. Connor et al. (1985b) tested urine obtained from hospital autopsy service workers exposed to formaldehyde who had actual exposures to formaldehyde of 0.1–5.8 ppm, with the TWA exposures to formaldehyde in work areas were estimated to be 0.61–1.32 ppm. Mutagenicity tests using *S. typhimurium* TA 100 and TA 98 were conducted, with or without rat S9 suspension. Increases in mutation rates were not produced by the urine of workers exposed to formaldehyde, compared to control urine, in the presence or absence of S9.

Formaldehyde has been found to be genotoxic in a number of *in vivo* and *in vitro* test systems. Tables 2-6 and 2-7 present a cross-section of some of the genotoxicity data that are available for formaldehyde examined in *in vivo* and *in vitro* test systems. With *in vivo* test systems, the data are mixed. Formaldehyde has been found to induce chromosomal aberrations (Chebotarev et al. 1986; Dallas et al. 1992; Rithidech et al. 1987) and to cause increases in micronucleus formation (Ballarin et al. 1992), SCE (Yager et al. 1986), DNA-protein cross links (Casavova et al. 1989, 1991b, 1992; Lam et al. 1985; Shaham et al. 1996a), sperm head abnormalities (Topham 1980), and p53 suppressor gene mutations (Recio et al. 1992). Other reports present negative genotoxic findings (Kligerman et al. 1984; Natarajan et al. 1983; Thomson et al. 1984).

Formaldehyde has also been found to be genotoxic in *S. typhimurium* in most cases (Connor et al. 1983, 1985a; Donovan et al. 1983; Glass et al. 1986; Haworth et al. 1983; Schmid et al. 1986; Takahashi et al. 1985) and not mutagenic in others (DeFlora 1981; DeFlora et al. 1984). A number of human cell lines have been tested with formaldehyde giving positive results without activation, resulting in mutations, DNA damage, chromosomal aberrations, and SCEs (Dresp and Bauchinger 1988; Garry et al. 1981; Goldmacher and Thilly 1983; Grafstrom et al. 1983, 1984, 1985; Krieger and Garry 1983; Liber et al. 1989; Schmid et al. 1986; Snyder and Van Houten 1986). Laboratory animal models, such as the Chinese hamster cell lines (Basler et al. 1985; Galloway et al. 1985; Grafstrom et al. 1993; Miller and Costa 1989; Natarajan et al. 1983), Golden Syrian hamsters (Hatch et al. 1983), and rodent cell lines (Basler et al. 1985; Blackburn et al. 1991; Cosma and Marchok 1988; Cosma et al. 1988a; Frazelle et al. 1983; Heck and Casanova 1987; Ragan and Boreiko 1981, 1983; Ross and Shipley 1980) have demonstrated similar results.

Table 2-6. Genotoxicity of Formaldehyde *In Vivo*

Species (test system)	End point	Result	Reference
Mammals:			
Mouse (spleen lymphocytes)	Chromosomal aberrations	+	Rithidech et al. 1987
Human (occupational exposure)	Chromosomal aberrations	–	Vasudeva and Anand 1996
Human (occupational exposure/nasal mucosa)	Micronucleus increase	+	Ballarin et al. 1992
Human (occupational exposure/urine)	Mutagenicity	–	Connor et al. 1985b
Human (occupational exposure/lymphocytes)	DNA-protein cross links, not formaldehyde specific	+	Shaham et al. 1996a
Human (occupational exposure/white blood cells)	Chromosome aberrations and sister chromatid exchange	–	Thomson et al. 1984
Human (occupational exposure/lymphocytes)	Sister chromatid exchange	+	Yager et al. 1986
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Cherbaterev et al. 1986
Rat (pulmonary lavage)	Chromosomal aberrations	+	Dallas et al. 1992
Rat (nasal mucosal cells)	DNA-protein cross links	+	Casanova et al. 1989
Rat (nasal mucosal cells)	DNA-protein cross links	+	Lam et al. 1985
Rat (bone marrow)	Chromosomal aberrations	–	Dallas et al. 1992
Rat (lymphocytes)	Mitotic activity, sister chromatid exchange, chromosomal aberration	–	Kligerman et al. 1984
Monkey (respiratory tract)	DNA-protein cross links	+	Casanova et al. 1991b
Non-mammals:			
D. Melanogaster	Mortality and sterility	+	Valencia et al. 1989
D. Melanogaster	Lethal mutation	+	Woodruff et al. 1985

+ = Positive result; – = negative result; (+) = weakly positive result; DNA = deoxyribonucleic acid

Table 2-7. Genotoxicity of Formaldehyde *In Vitro*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, UTH8414, UTH 8413 (Ames test)	Gene mutation	(+)	(+)	Glass et al. 1986
S. typhimurium TA 98, TA 100 (Ames test)	Gene mutation	No data	+	Takahashi et al. 1985
S. typhimurium TA 100 (Ames test)	Gene mutation	+	+	Schmid et al. 1986
Escherichia coli	Gene mutation	No data	+	Takahashi et al. 1985
S. typhimurium TA97, TA98, TA100 (Ames test)	Gene mutation	No data	+	Donovan et al. 1983
S. typhimurium TM677, TA100 (Ames test)	Gene mutation	+	+	Donovan et al. 1983
S. typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538 (Ames test)	Gene mutation	–	–	DeFlora et al. 1984
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 (Ames test)	Gene mutation	–[a]	–[a]	DeFlora 1981
S. typhimurium TA98, TA100, UTH8413, UTH8414 (Ames test)	Gene mutation	(+)	(+)	Connor et al. 1985b
S. typhimurium TA98, TA100, UTH8413, UTH8414 (Ames test)	Gene mutation	(+)[a]	(+)[a]	Connor et al. 1983
S. typhimurium TA1535, TA1537, TA98, and TA100	Gene mutation	No data	+	Haworth et al. 1983
Eukaryotic organisms:				
Mammalian cells: Human (bronchial fibroblast culture)	Mutations	No data	+	Grafstrom et al. 1985
Human (foreskin fibroblast culture)	DNA damage	No data	+	Snyder and Van Houten 1986
Human (lymphocyte cell culture)	Chromosomal aberrations	No data	+	Dresp and Bauchinger 1988
Human (lymphocyte cell culture)	DNA damage	No data	+	Liber et al. 1989

Table 2-7. Genotoxicity of Formaldehyde *In Vitro* (continued)

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Human (lymphocyte cell culture)	Sister chromatid exchange and chromatid-type aberrations	+	+	Schmid et al. 1986
Rat (tracheal epithelium culture)	DNA damage	No data	+	Cosma et al. 1988a
Rat (tracheal epithelium culture)	DNA damage	No data	+	Cosma and Marchok 1988
Rat (nasal mucosa)	DNA binding	No data	+	Heck and Casanova 1987
Mouse (lymphoma L5178Y TK ±)	Mutagenicitiy	+	+	Blackburn et al. 1991
Chinese hamster (V79 cell culture)	Sister chromatid exchange	–	+	Basler et al. 1985
Chinese hamster (V79 cell culture)	Mutations	No data	+	Grafstrom et al. 1993
Chinese hamster (ovary cell culture)	DNA damage	No data	+	Miller and Costa 1989
Chinese hamster (ovary cell culture)	Chromosomal aberrations; sister chromatid exchange	+	+	Natarajan et al. 1983
Chinese hamster (ovary cell culture)	Chromosomal aberrations; sister chromatid exchange	(+)	(+)	Galloway et al. 1985
Golden Syrian hamster (embryo cell culture)	Viral transformation	No data	+	Hatch et al. 1983
C3H/10T½ mouse embryo fibroblasts	Focus transformations	(+)	–	Frazelle et al. 1983
Rodent (Yoshida sarcoma cells)	DNA cross links	No data	(+)	Bedford and Fox 1981
Calf (thymus chromatin)	Histone redistribution	No data	+	Polacow et al. 1976
C3H/10T½ mouse embryo fibroblasts	Focus transformations	+	–	Ragan and Boreiko 1981
C3H/10T½ mouse embryo fibroblasts	Focus transformations	+	–	Boreiko and Ragan 1983
C3H/10T½ mouse embryo fibroblasts	Focus transformations	+	No data	Frazelle et al. 1983
Mouse leukemia L1210 cells	DNA single strand breaks	No data	(+)	Ross and Shipley 1980
Mouse leukemia L1210 cells	DNA protein cross links	No data	+	Ross and Shipley 1980
Human (lymphocyte cultures)	Sister chromatid exchange	No data	+	Kreiger and Garry 1983

Table 2-7. Genotoxicity of Formaldehyde *In Vitro* (continued)

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Human (bronchoial fibroblast cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1984
Human (bronchoial epithelial cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1984
Human (skin fibroblast cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1984
Human (bronchoial epihtelial cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1983
Human (bronchoial fibroblast cells)	DNA cross links and single-strand breaks	No data	+	Grafstrom et al. 1983
Human (lymphoblastoid TK6 cells)	DNA mutation	No data	+	Goldmacher and Thilly 1983
Human (cultured lymphocytes)	Sister chromatid exchange	No data	+	Garry et al. 1981

[a]test compound was formalin

– = negative results; + = positive results; (+) = weakly positive result; DNA = deoxyribonucleic acid

In summary, no reports of genetic effects in humans were located, but formaldehyde has displayed genotoxic activity in the majority of studies in a variety of *in vivo* tests with organisms ranging from bacteria to rodents and a variety of *in vitro* tests including tests with cultured human cells. The weight of evidence indicates that formaldehyde itself is capable of directly reacting with DNA, and producing genotoxic effects, especially when metabolic capacities are exceeded.

Cancer. As discussed in Section 2.2.1.8, there are more than 40 epidemiology studies (cohort mortality studies of industrial workers, cohort mortality studies of medical specialists and embalmers, and case-control studies) examining the potential for occupational formaldehyde exposure to induce cancer. Two meta analyses of these studies calculated aggregate relative risks (with 95% CIs noted in parentheses) for nasopharyngeal cancer deaths in occupationally exposed workers of 1.2 (0.8–1.7) and 2.0 (1.4–2.90), and noted that an exposure-response relationship for nasopharyngeal cancer could be demonstrated by grouping the studies in exposure categories of "low/medium" and "substantial" (Blair et al. 1990a; Partanen 1993). A third meta analysis (Collins et al. 1997), using the same studies plus additional cohort mortality data not available for the earlier analyses, reported meta relative risks of 1.0 (0.5–1.8) for nasopharyngeal cancer across 14 available cohort studies, 1.2 (0.4–2.5) for six available cohort studies of industrial workers, and 1.3 (0.9–2.1) for seven case-control studies. Collins et al. (1997) concluded that their analysis of the data did not support an exposure-response relationship for formaldehyde exposure and nasopharyngeal cancer.

Other reviewers also have arrived at differing conclusions regarding the evidence from the epidemiological studies. On one side, IARC (1995) and EPA (1991a) judged that there was limited evidence in humans and NTP (1998) judged that formaldehyde was reasonably anticipated to be a human carcinogen; whereas McLaughlin (1994) and ECETOC (1995), on the other side, concluded that a causal relationship was not established by the available data. A more recent collaborative review of the data by EPA and CIIT (1998) appears to take a middle stand concluding that "it appears that a weak association between nasopharyngeal cancer and formaldehyde exposure cannot be completely ruled out".

In contrast to the equivocal, limited, or weak nature of the evidence in humans, replicated inhalation studies have consistently shown that formaldehyde induces nasal tumors in rats exposed to high concentrations (10–15 ppm) that also induce nasal epithelial necrosis and cellular proliferation, but not when exposed to lower concentrations (0.3–2 ppm) that do not markedly damage nasal epithelial tissue (Albert et al. 1982; Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Sellakumar et al.

1985; Woutersen et al. 1989). Exposure-related cancer or noncancer lesions at sites distant from the portal-of-entry were not found in these studies, consistent with the water solubility and reactivity of formaldehyde and the ubiquity of rapid cellular metabolism of formaldehyde.

No information is available as to whether oral exposure to formaldehyde increases the risk of cancer in humans. The evidence for formaldehyde-induced carcinogenicity from four available rat drinking water studies is equivocal due to inconsistent findings (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989). Two studies reported no increased incidence of gastrointestinal tract tumors in rats exposed for life to formaldehyde in drinking water at doses up to 109 mg/kg/day (Til et al. 1989) or 300 mg/kg/day (Tobe et al. 1989). Another study reported increased incidences of gastrointestinal tumors (papillomas, adenocarcinomas, and leiomyosarcomas) in some groups of rats exposed for life to drinking water doses of 188 mg/kg/day, but not in groups exposed to 313 mg/kg/day (Soffritti et al. 1989). The fourth study reported that benign papillomas were found in the forestomach of 8/10 rats exposed for 32 weeks to drinking water doses of 258 mg/kg/day (Takahashi et al. 1986a), but others (Til et al. 1989) have questioned whether a different histologist would have classified the observed lesions as papillary hyperplasia. The weight of the animal evidence suggests that gastrointestinal tract tumors may occur as portal-of-entry effects in rats chronically exposed to formaldehyde in drinking water only at high doses, and that tumors are not likely to occur at dose levels that do not damage the gastric mucosa. The animal studies suggest that there is little likelihood that chronic exposure to non-irritating levels of formaldehyde in drinking water will increase cancer risks in humans.

No studies were located regarding cancer rates in humans predominantly exposed to formaldehyde via the dermal route. Animal cancer studies of dermal exposure are restricted to two studies that found no statistically significant increased incidences of skin tumors in mice exposed twice weekly for 58–60 weeks to solutions containing up to 4% (Iverson 1988) or 10% formaldehyde (Iverson 1986).

NTP (1998) has determined that formaldehyde may reasonably be anticipated to be a human carcinogen, and IARC (1995) made the overall evaluation that formaldehyde is probably carcinogenic to humans (Group 2A) based on specific evaluations that there is limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals.

EPA (1991a; IRIS 1999) classified formaldehyde in Group B1 - probable human carcinogen based on an evaluation of limited human evidence and sufficient laboratory animal evidence. EPA (1991a) used dose-

response data for nasal tumors in rats exposed to high concentrations of formaldehyde to extrapolate to human cancer risk at low exposure concentrations, using rates of DNA-protein cross links in target tissue as a measure of delivered dose. Relationships between formaldehyde air concentrations and rates of formation of DNA-protein cross links in nasal epithelial tissue of rats (Casanova et al. 1989) or of Rhesus monkeys (Casanova et al. 1991; Heck et al. 1989) and adjustments to continuous exposure were used to calculate lifetime human cancer unit risk estimates of 3.3×10^{-4} per ppm formaldehyde based on the monkey data, and 2.8×10^{-3} per ppm formaldehyde based on the rat data. EPA (1987d, 1991a; IRIS 1999) did not derive a cancer risk estimate for oral exposure to formaldehyde. EPA and CIIT (CIIT 1998) are currently working on options to derive new estimates of cancer risk in humans exposed by inhalation using CFD models of nasal airflow and uptake of formaldehyde in rats, monkeys, and humans; pharmacokinetic models of nasal tissue disposition of formaldehyde; and two-stage clonal growth cancer models incorporating data on cellular proliferation rates.

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates

because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Whereas there are numerous studies of adults occupationally exposed to formaldehyde and exposed under acute controlled conditions, data regarding the toxicological properties of formaldehyde in children are limited. Nevertheless, the same type of effects that occur in adults are expected to occur in children (e.g., damage in portal-of-entry tissues at exposure levels that exceed tissue detoxification mechanisms). Symptoms expected to occur in children include eye, nose, and throat irritation from exposure to airborne concentrations between 0.4 and 3 ppm, and dermal irritation from exposure to dermal contact with liquids containing more than 2% formaldehyde. Given the water-soluble and reactive nature of formaldehyde and the apparent ubiquity of rapid cellular metabolism of formaldehyde, it is expected that the irritant effects of formaldehyde would be restricted in children, as in adults, to portals-of-entry, although no

information was located comparing rates of formaldehyde metabolism in children's tissues with rates in adult tissues, either in humans or animals. However, studies of adult humans or rats exposed for short periods to air concentrations of 1.9 ppm or 14.4 ppm, respectively (Heck et al. 1985), and monkeys exposed to 6 ppm for up to 4 weeks (Casanova et al. 1988) found no appreciable changes in circulating blood levels of formaldehyde; these results are consistent with the protective action of rapid metabolism of formaldehyde in portal-of-entry tissues. The developing fetus or nursing infant would be expected to be protected from exposure to formaldehyde (via inhalation, oral, and dermal contact) by the pregnant or breast-feeding mother. Studies of animals exposed during pregnancy to formaldehyde in air (Martin 1990; Saillenfait et al. 1989), in the diet or by gavage (Hurni and Ohder 1973; Marks et al. 1980), or on the skin (Overman 1985) have found no distinct or consistent effects on fetal development, even at exposure levels that produced severe maternal toxicity (e.g., Marks et al. 1980).

Two studies were available providing suggestive evidence that children may be more sensitive than adults to the irritant properties of airborne formaldehyde (Krzyzanowski et al. 1990; Wantke et al. 1996a). Krzyzanowski et al. (1990) questioned a group of 298 children (aged 6–15 years) and 613 adults concerning respiratory symptoms, measured PEFR during evenings and mornings for up to 14 days, and made measurements of household air concentrations of formaldehyde in several rooms of 202 houses. Preliminary reports of this study were published in an earlier report (Quackenboss et al. 1989). Bedroom air concentrations were 0.040 ppm for more than 80% of the subjects, between 0.04 and 0.06 ppm for about 8–10% of the subjects, and greater than 0.06 ppm in about 3% of children and 6% of adults in the study. A few cases were measured with air concentrations exceeding 0.09 ppm, with a maximum value of 0.14 ppm. Regression analysis found no significant relationship between exposure category of children and prevalence rates of subjectively reported respiratory symptoms, but physician-diagnosed chronic bronchitis or asthma prevalence rates were elevated in children with household air concentrations greater than 0.06 ppm, especially in households with environmental tobacco smoke. In adults, neither respiratory symptoms or physician-diagnosed chronic bronchitis or asthma were significantly related to formaldehyde air concentrations. In children, a statistically significant trend for decreasing PEFR values with increasing formaldehyde exposure concentrations was found; the estimated decrease in PEFR associated with 0.06 ppm was 22% compared with mean values for low-level children. In adults, PEFR values (mornings only) were also related to formaldehyde concentrations, but the effect was relatively small; the estimated decrement in adults associated with 0.10 ppm was about 1%.

School children who attended particleboard-paneled classrooms with estimated formaldehyde air concentrations of 0.075, 0.069, and 0.043 ppm reported respiratory tract symptoms consistent with the irritant properties of formaldehyde including rhinitis, cough, nosebleed, and headache (Wantke et al. 1996a). These concentrations are low compared to workplace air concentrations or exposure chamber concentrations associated with irritant symptoms in adults (0.4–3 ppm). Formaldehyde-specific IgE antibodies were detected in serum of 40% of the children. The investigators noted that the elevated levels were not correlated with the number and severity of symptoms, but serum levels and incidence of symptoms decreased in a subgroup of the children 3 months after they were moved to another school with lower air concentration of formaldehyde (0.023–0.029 ppm). As stated earlier when discussing this study, the significance of these findings is uncertain as the reported symptoms were more typical of an irritant response than of asthma-like symptoms that are expected to be mediated through IgE antibodies.

Additional research is necessary to confirm or discard the hypothesis that children may be more susceptible than adults to the irritant effects of formaldehyde and to understand the mechanistic basis of this possible difference.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the

body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to formaldehyde are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by formaldehyde are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Formaldehyde

Formaldehyde is a simple one-carbon molecule and is rapidly absorbed and metabolized by animals, including humans. A thorough review of the available literature failed to produce any reliable biomarkers of exposure to formaldehyde.

As discussed in Section 2.3, formaldehyde is rapidly absorbed by the inhalation and oral routes of exposure. Once absorbed, there are four major metabolic pathways associated with formaldehyde metabolism, with the metabolism to formate and CO_2 the most heavily used (see Figure 2-3 in Section 2.3.3).

Attempts have been made to determine if either blood or urinary levels of formaldehyde or formate could be used as potential biomarkers of exposure, but with disappointing results. Heck et al. (1985) exposed

four men and two women to a 1.9±0.06 ppm air concentration of formaldehyde in a large walk-in chamber for 40 minutes. Shortly before and shortly after the exposure, venous blood samples were taken from each person (each person served as his/her own control) and the blood was analyzed for formaldehyde content. No significant differences were found between pre- and postexposure blood concentrations of formaldehyde at the concentration tested. In the same study, male Fischer 344 rats were placed in a nose-only inhalation chamber and exposed to a 14.4±2.4 ppm air concentration of formaldehyde for 2 hours; rats were sacrificed, and venous blood samples were collected and analyzed for formaldehyde content. Even by using the higher exposure concentration of formaldehyde, no significant differences in blood formaldehyde concentrations were found between the pre- and postexposure blood samples. In addition, the rapid intravenous injection of formaldehyde in monkeys showed a plasma half-life of only 1.5 minutes, with a corresponding increase in blood formate levels.

Einbrodt et al. (1976) exposed students to 0.26–0.92 ppm formaldehyde vapors for 3 hours, with urine samples collected immediately after exposure and 21 hours after exposure. Urine formaldehyde and urine formic acid (formate) concentrations were found to be higher immediately after exposure compared to 21 hours later; however, no baseline sample was obtained prior to exposure. If historic formaldehyde and formic acid baseline levels were assumed, then a closer examination of these data indicates that more formaldehyde (and metabolite) was excreted in the urine than could have possibly been absorbed by inhalation, indicating another route of exposure (perhaps dermal), or co-exposure to another chemical that also has formate as a metabolite (e.g., methanol), or higher personal exposures than were actually measured. There was also no indication that the urine formate levels were adjusted to compensate for urine specific gravity using urine creatinine levels, which may have markedly influenced the test results.

Gottschling et al. (1984) monitored 35 anatomy laboratory students exposed for 2 hours, once a week for 3 weeks, with exposures ranging from 0.036 to 0.111 ppm. Urine was obtained prior to exposure and during the exposure. Wide variations were noted in the urine formate levels prior to exposure, with large intrapersonal and interpersonal variations; mean postexposure urine formate concentrations were elevated after exposure to formaldehyde vapors, but not significantly. In the study by Einbrodt et al. (1976), urine formate levels were significantly elevated in both anatomy laboratory students and in four factory workers exposed to 1 ppm formaldehyde; however, the mass-balance equations for both groups indicated other factors may have influenced the amount of formate found in the urine. Formate production is not specific to formaldehyde because other chemicals such as methanol, halomethanes (e.g., dichloromethane), and acetone have formate in their metabolic pathways (Ferry et al. 1980;

Kornbrust and Bus 1983; Liesivuori and Savolainen 1987). This indicates that even if blood or urine formate levels were elevated, it may be due to individual variation, formaldehyde exposure, or other chemical exposures that result in formate formation. Thus formate blood and urine levels appear to be equally unreliable as definitive biomarkers for formaldehyde exposure.

Formaldehyde that is not rapidly metabolized to formate can react with a variety of cellular components including nucleotides, proteins, and glutathione, forming adducts, such as N6-hydroxymethyl-deoxyadenosine and N2- hydroxymethyldeoxyguanosine, and DNA-protein cross links. Several of these formaldehyde-induced products have been examined as potential biomarkers of exposure for repeated exposure to formaldehyde. A method for detecting biomarkers such as N^6-hydroxymethyldeoxy-adenosine and N^2-hydroxymethyldeoxyguanosine (the major adducts formed by formaldehyde *in vitro*) had experimental complications and does not appear to provide useful biomarkers of formaldehyde exposures (Fennel 1994). Many studies (Casanova-Schmitz et al. 1984a; Casanova and Heck 1987; Casanova et al. 1989a, 1989b, 1991, 1994) utilized radiolabeled compounds tagged with ^{14}C and/or ^{3}H to facilitate detection of DNA-protein cross links; however, this approach would not work to detect past exposures in humans. The formation of DNA-protein cross links in isolated rat nasal epithelial cells (respiratory and olfactory epithelial cells) incubated with formaldehyde has also been reported (Kuykendall et al. 1995). Utilizing a sensitive technique to detect total DNA-protein cross links, Shaham et al. (1996a) reported that cultured human white blood cells showed increasing quantities of DNA-protein cross links when cultured in media with increasing formaldehyde concentrations and that a small group of formaldehyde-exposed persons had a significantly greater mean amount of DNA-protein cross links in their white blood cells than did a group of nonexposed persons. Although DNA-protein cross links are known to be formed by other agents such as ionizing radiation and alkylating agents, Shaham et al. (1996a) concluded that their results suggested that levels of DNA-protein cross links in white blood cells may provide an indicator of formaldehyde-induced tissue damage and a biomarker of occupational exposure to formaldehyde. Shaham et al. (1996b) noted that a larger study of the potential of DNA-protein cross links in white blood cells as a biomarker of effect and exposure was in progress.

Immunological biomarkers of effect (IgG and IgE antibodies against formaldehyde conjugated to human serum albumin) have been examined as potential biomarkers of exposure to airborne formaldehyde. Some studies have reported that increased serum levels of antibodies against formaldehyde-human serum albumin in groups of human subjects correlated with exposure to airborne formaldehyde and symptoms of respiratory distress (Thrasher et al. 1987, 1988b, 1989, 1990), whereas other studies of human subjects

have not found similar correlations (Dykewicz et al. 1991; Grammer et al. 1990; Patterson et al. 1989; Wantke et al. 1996a, 1996b). The hypothesis, put forth by Nordman et al. (1985), concluded that immunological hypersensitivity of the respiratory tract to airborne formaldehyde is rare, and casts doubt that immunological biomarkers for formaldehyde would have been useful biomarkers to indicate exposure. However, Carraro et al. (1997) recently reported that the presence of IgG antibodies against formaldehyde-human serum albumin was significantly associated with smoking habits, but not with self-reported occupational exposure to formaldehyde, in a group of 219 healthy subjects. When only non-smokers were included in the analysis, a statistically significant association was found between the presence of formaldehyde-specific antibodies and occupational exposure to formaldehyde. An indirect competitive immunoenzyme assay for anti-formaldehyde-human serum albumin antibodies was developed for this study. These results suggest that smoking produces a detectable immunological response to formaldehyde and that the technique employed may be useful to indicate occupational or residential exposure to formaldehyde especially in the absence of exposure to tobacco smoke.

Development of biomarkers for exposure is complicated by the fact that the metabolism of many xenobiotics can result in formaldehyde production *in vivo*. Carbon tetrachloride, endrin, paraquat, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Shara et al. 1992), and dichloromethane (Dekant and Vamvakas 1993) are all known to generate formaldehyde during their metabolism.

2.7.2 Biomarkers Used to Characterize Effects Caused by Formaldehyde

Increased eosinophil concentration and increased levels of albumin and total protein have been found in nasal lavage fluid taken from subjects exposed to 0.4 ppm formaldehyde for 2 hours (Krakowiak et al. 1998; Pazdrak et al. 1993). Although these variables are not expected to be only influenced by formaldehyde, they appear to be promising biomarkers of acute respiratory irritation from airborne formaldehyde.

As discussed in the previous section, DNA-protein cross links in white blood cells (Shaham et al. 1996a) and anti-formaldehyde-human serum albumin IgG antibodies in serum (Carraro et al. 1997) are potential biomarkers of both exposure and effect associated with intermediate- or chronic-exposure to formaldehyde.

Li et al. (1995) evaluated the validity of the modified lymphocyte transformation assay for detecting contact hypersensitivity of formaldehyde. Female Hartley guinea pigs were sensitized to formaldehyde

by receiving subcutaneous injections of 1.85% formaldehyde (6 sites, 0.1 mL per site) followed 7 days later by epicutaneous exposure to 0.5 mL of a 1.85% formaldehyde solution. Cells were collected from lymph nodes tissue. Exposure to increasing concentrations of formaldehyde resulted in significant increases in T-lymphocyte blastogenesis ($p<0.05$). Although further refinement of this assay would be required (i.e., use of peripheral blood lymphocytes in lieu of lymph node samples), it does have potential for providing nonspecific biomarker of effect for formaldehyde sensitization.

Another potentially useful biomarker of effect for repeated inhalation exposure to formaldehyde involves the histological examination of nasal biopsy samples. Histological changes in nasal biopsy tissue samples (e.g., loss of ciliated cells, squamous dysplasia and hyperplasia) have been associated with formaldehyde exposure in several cross-sectional studies of formaldehyde-exposed and nonexposed workers (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Each of these studies used a morphological grading method that assigned an increasing point value for histological changes ranging in severity from loss of ciliated cells to the presence of malignant cells. Prevalence of different types of changes and mean histological scores were compared between exposed and nonexposed groups. The findings from rat studies indicating that the development of formaldehyde-induced nasal cancer is preceded by repeated damage to the upper respiratory tract epithelium suggests that monitoring of formaldehyde-exposed workers for cytological abnormalities in nasal biopsy samples may be useful to prevent the development of upper respiratory tract tissue damage or cancer. Similar findings of epithelial squamous dysplasia and hyperplastic nasal mucosa have been found in chronic occupational exposures to formaldehyde (Boysen et al. 1990; Edling et al. 1988); however, as discussed in Section 2.5, these human studies do not conclusively prove that formaldehyde was the primary toxicant responsible for the observed nasal lesions. The squamous metaplasia and mucosal hyperplastic lesions may be useful indicators of more severe formaldehyde-induced effects; however, its usefulness in human exposures is likely to be limited.

2.8 INTERACTIONS WITH OTHER CHEMICALS

The study by Albert et al. (1982) reported the carcinogenic responses to the combined and separate exposures to formaldehyde and hydrochloric acid in male inbred Sprague-Dawley rats. Rats were exposed for 588 days to formaldehyde alone (14.2 ppm); formaldehyde (14.1 ppm) and hydrogen chloride (HCl) (9.5 ppm) combined but not premixed; formaldehyde (14.3 ppm) and HCl (10.0 ppm) combined and premixed; HCl alone (10.2 ppm); or room air. The data did not indicate a synergistic effect on mortality from combined formaldehyde and HCl exposure; no synergism was noted between combined HCl and formaldehyde exposure and the induction of nasal cancers. Rats exposed to formaldehyde alone experienced about a 9% depression in body weights compared to controls; those exposed to HCl alone experienced no noticeable weight loss; exposure to formaldehyde and HCl combined resulted in a 14% depression in body weight, indicating a synergistic adverse effect on body weight from combined HCl and formaldehyde exposure. Lam et al. (1985) studied the effects of inhalation co-exposure to acrolein and formaldehyde in male Fischer 344 rats. Rats were exposed for 6 hours to room air (controls), 2 ppm acrolein, 6 ppm formaldehyde, or a combination of 2 ppm acrolein and 6 ppm formaldehyde. The animals were sacrificed immediately after completion of exposure and their nasal tissues were harvested. Exposure to formaldehyde significantly increased the percentage of interfacial DNA (a measure of DNA-protein cross linking) compared to rats exposed to room air only (12.5 versus 8.1%, $p<0.05$). Co-exposure to acrolein resulted in further increases in the percentage of interfacial DNA (18.6%) which were significantly greater than the effect of formaldehyde alone ($p<0.05$). The authors concluded that simultaneous exposure to acrolein enhanced formaldehyde-induced DNA-protein cross linking and that depletion of glutathione by acrolein inhibited the metabolism of formaldehyde, thereby increasing formaldehyde-induced DNA-protein cross link formation.

To investigate the possibility of additive or potentiating interactions between inhaled aldehydes, Cassee et al. (1996b) compared responses in nasal epithelial histopathology and cell proliferation in groups of male Wistar rats exposed for 3 days (6 hours/day) to 1.0, 3.2, or 6.4 ppm formaldehyde alone; to 0.25, 0.67, or 1.40 ppm acrolein alone; to 750 or 1,500 ppm acetaldehyde alone; or to several mixtures of these aldehydes. At the concentrations tested, the histological and cell proliferation responses measured in the nasal epithelium of rats exposed to the mixture which produced effects (3.2 ppm formaldehyde; 1,500 ppm acetaldehyde; 0.67 ppm acrolein) were attributed by the investigators to the acrolein alone with no additional effects from the formaldehyde or acetaldehyde. The investigators concluded that

combined exposures to these aldehydes at exposure levels in the vicinity of individual no-effect-levels was not associated with a greater hazard than that associated with exposure to the individual chemicals.

As discussed previously in Sections 2.2 and 2.5, experiments with mice (Tarkowski and Gorski 1995) and guinea pigs (Riedel et al. 1996) indicate that exposure to low levels of formaldehyde enhances allergic responses to intranasal administration of ovalbumin and suggest the possibility of formaldehyde facilitation of allergic responses to other respiratory allergens. Mice pre-exposed to 1.6 ppm, 6 hours/day for 10 consecutive days produced four-fold greater ovalbumin-specific IgE antibodies in response to intranasal administration of ovalbumin mice that were not pre-exposed (Tarkowsi and Gorski 1995). A group of guinea pigs exposed to 0.25 ppm formaldehyde, 8 hours/day for 5 days showed a greater percentage of bronchial, presumably allergic, responses to inhaled ovalbumin than a control group without preexposure to formaldehyde (10/12 versus 3/12) (Riedel et al. 1996).

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to formaldehyde than will most persons exposed to the same level of formaldehyde in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of formaldehyde, or compromised function of target organs affected by formaldehyde. Populations who are at greater risk due to their unusually high exposure to formaldehyde are discussed in Section 5.6.

Two populations of humans have received considerable attention in the literature as being particularly sensitive to formaldehyde exposure following inhalation and/or dermal exposure. The first population is asthmatics, and concern focuses on the changes in lung function parameters that formaldehyde may produce (Harving et al. 1990; Kulle et al. 1987; Pazdrak et al. 1993; Reed and Frigas 1984; Sauder et al. 1986; Schachter et al. 1986; Witek et al. 1986). Most of these studies concluded that there is no evidence of increased airway reactivity as a result of formaldehyde exposure in either normal or asthmatic individuals. Formaldehyde exposures at the concentrations tested (usually >3 ppm) did not exacerbate existing asthmatic conditions, either at rest or after exercise. However, Nordman et al. (1985), in a human population of 230 persons suffering asthmatic symptoms and exposed to formaldehyde, found that when exposed to 2.04 ppm formaldehyde for 30 minutes, eight subjects demonstrated an immediate bronchial reaction, four subjects demonstrated a delayed reaction, and two subjects demonstrated both an

immediate and a delayed reaction. Peak expiratory flow rates dropped 19–49% in the immediate-reaction group and 21–47% in the delayed-reaction group. In a study of seven subjects with a history of occupational exposure to glutaraldehyde and asthma, peak expiratory flow rates were decreased in 3/7 subjects by 27–33% in response to a bronchial challenge with 1% formaldehyde (Gannon et al. 1995). Gannon et al. (1995) suggested that respiratory sensitivity produced by exposure to glutaraldehyde may have cross-reactivity to formaldehyde in some subjects.

The second population of potential concern is people with dermal sensitization. Several cases have been reported. Formaldehyde liquid, but neither the gaseous phase nor formalin, is considered to be a dermal sensitizer (Hilton et al. 1996). Anaphylactic reactions have been reported in the literature (Maurice et al. 1986), in a description of a case in which anaphylaxis occurred in a patient due to skin contact with adhesives sterilized with formaldehyde prior to her hemodialysis therapy. Dermal allergic reactions have also been reported in doctors and nurses exposed to formaldehyde (Rudzki et al. 1989) as well as in fiberglass workers (Kilburn et al. 1985a).

Data from acute controlled-exposure studies, supported by data from animal studies, generally indicate that formaldehyde does not induce airway hyper-reactivity at concentrations 3 ppm, but further studies with asthmatics may be required because of somewhat conflicting data in this potentially sensitive population. Other persons with dermal sensitization to formaldehyde are not likely to develop signs of respiratory insufficiency. Persons with multiple chemical sensitivities may represent a third potentially sensitive population, but studies linking this syndrome with exposure to formaldehyde were not located.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to formaldehyde. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to formaldehyde. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to formaldehyde:

Aaron, CK and Howland, MA (eds.) (1994). Goldfrank's Toxicologic Emergencies. Appleton and Lange, Norwalk, CT.

Dreisbach, RH and Robertson, WO, (eds.) (1987). Handbook of Poisoning. Appleton and Lange, Norwalk, CT.

Ellenhorn, MJ and Barceloux, DG, (eds.) (1988). Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Publishing, New York, NY.

Gossel, TA and Bricker JD (1994). Principles of Clinical Toxicology. 3rd edition, Raven Press, New York, NY.

Haddad, LM and Winchester, JF, (eds.) (1990). Clinical Management of Poisoning and Drug Overdose (2nd edition). WB Saunders, Philadelphia, PA.

The primary concern after oral intoxication with formaldehyde is correcting the severe acidosis and decreased blood pressure that this chemical induces. Treatment should aimed at increasing the blood pressure to a somewhat normal state (sympathomimetic drugs may be used) as well as treating the acidosis with bicarbonate (Aaron and Howland 1994; Gossel and Bricker 1994). Dialysis may also be used to remove excess formate (as formic acid) in the blood in order to correct the acidosis (Burkhart et al. 1990; Eells et al. 1981).

2.10.1 Reducing Peak Absorption Following Exposure

Human exposure to formaldehyde may occur by inhalation, ingestion, or dermal contact. There are no known antidotes to formaldehyde poisoning in humans, particularly after oral exposure. General recommendations for reducing absorption of formaldehyde include removing the exposed individual from the contaminated area and removing contaminated clothing, if applicable. If the eyes and skin were exposed, they should be flushed with copious amounts of water. Since formaldehyde is highly corrosive, vomiting after oral ingestion should not be induced. The stomach contents can be diluted with milk or water by mouth if the patient is alert and responsive, otherwise gastric lavage may be indicated. A bolus of charcoal and isotonic saline cathartic may also be useful (Aaron and Howland 1994).

2.10.2 Reducing Body Burden

Formaldehyde is not stored to any appreciable extent in the human body and is mostly metabolized to formate and carbon dioxide (see Section 2.3). The half-life of formaldehyde in monkeys has been observed to be about 1.5 minutes following an intravenous injection. Furthermore, an inhalation exposure study found that no formaldehyde was present in the blood after a 1.9 ppm exposure for

40 minutes, indicating formaldehyde is metabolized very quickly either in the respiratory tract tissues or in the blood.

Despite a relatively fast clearance of formaldehyde from the body, toxic effects may develop in exposed individuals, particularly in cases of acute oral poisonings which quickly overwhelm the body's natural mechanisms to metabolize formaldehyde (particularly via formaldehyde dehydrogenase; see Figure 2-3). There is no standard method or practice to enhance the elimination of the absorbed dose of formaldehyde (Aaron and Howland 1994; Ellenhorn and Barceloux 1988).

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

Target organs of formaldehyde toxicity while in the gaseous phase are the respiratory tract and eyes. After oral exposure, the tissues that formaldehyde comes into contact with on its way to the stomach and intestines (i.e., lips, oral pharynx, esophagus) are the target tissues; after dermal exposure, the adverse effects of formaldehyde are usually localized to the contact area, although other systemic reactions have been reported (Maurice et al. 1986) (see Section 2.2). Formaldehyde readily combines with free, unprotonated amino groups to yield hydroxymethyl adduct derivatives resulting in proton liberation (Loomis 1979). In higher concentrations (5–10%), formaldehyde will precipitate protein, which is the reason for its use in current histological techniques. The mechanism that causes the primary irritant effects is not presently known, but may involve one of the two mechanisms mentioned above. Currently, there are no procedures or therapies that specifically focus on interfering with the mechanism of action of formaldehyde. Supportive care by trained medical personnel is highly recommended.

2.11 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of formaldehyde is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of formaldehyde.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.11.1 Existing Information on Health Effects of Formaldehyde

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to formaldehyde are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of formaldehyde. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figure 2-5, information is available regarding death, acute and chronic systemic effects, immunological, neurologic, reproductive, developmental, genotoxic, and cancer effects in humans after inhalation exposure to formaldehyde. Lesser amounts of information are available for humans exposed to formaldehyde after oral and dermal exposure. The oral and dermal health effects data are primarily limited to death and acute systemic toxicity data, immunological data (skin sensitization) after dermal exposure, and neurological data after acute oral poisonings.

As also seen in Figure 2-5, significantly more information is available on the inhalation, oral, and dermal effects of formaldehyde in laboratory animals. The information on health effects in animals exposed orally or by inhalation is particularly rich but data regarding dose-response relationships for gastrointestinal effects from acute oral exposure and reproductive effects in multiple generations represent the most notable information gaps (see Section 2.11.2 for further discussion). Information was not located regarding death, systemic effects from intermediate-duration exposure, neurologic effects, and genotoxic effects in animals dermally exposed to formaldehyde.

Figure 2-5. Existing Information of Health Effects of Formaldehyde

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●		●	●	●	●	●	●	●
Oral	●	●				●				
Dermal		●			●					

Human

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●	●	●	●	●	●	●	●
Oral	●	●	●	●	●	●	●	●		●
Dermal		●		●	●		●	●		●

Animal

● Existing Studies

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Results from human and animal studies indicate that portal-of-entry tissues are the critical targets of acute-duration exposures to formaldehyde: the nose and eyes with inhalation exposure; the gastrointestinal tract with oral exposure; and the skin with dermal exposure.

Studies of humans under controlled conditions clearly indicate that acute exposures to air concentrations ranging from 0.4 to 3 ppm:

induce reversible eye, nose, and throat irritation (Andersen and Molhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle 1993; Kulle et al. 1987; Pazdrak et al. 1993; Schachter et al. 1986; Weber-Tschopp et al. 1977; Witek et al. 1986);

produce changes in nasal lavage fluid contents, indicative of irritation of the nasal epithelium (Gorski et al. 1992; Krakowiak et al. 1998; Pazdrak et al. 1993); and

do not consistently or markedly affect pulmonary function variables in most individuals (Andersen and Molhave 1983; Day et al. 1984; Gorski et al. 1992; Green et al. 1987; Harving et al. 1986, 1990; Kulle et al. 1987; Nordman et al. 1985; Sauder et al. 1986; Schachter et al. 1986; Witek et al. 1986).

Acute inhalation animal studies confirm that air concentrations below 10–20 ppm produce damage only in specific regions of the epithelium of the upper respiratory tract in rats, mice, and monkeys and not at distant sites (Bhalla et al. 1991; Cassee and Feron 1994; Chang et al. 1983; Dinsdale et al. 1993; Kamata et al. 1996b; Monticello et al. 1989, 1991; Monteiro-Riviere and Popp 1986; Morgan et al. 1986a, 1986c; Wilmer et al. 1987). An acute inhalation MRL of 0.04 ppm was derived based on the LOAEL of 0.4 ppm for transient symptoms of eye and nose irritation and increased albumin content of nasal lavage fluid in volunteers exposed to formaldehyde for 2 hours (Pazdrak et al. 1993). Confidence is high that this MRL will protect the general public health due to the wealth of data, but confidence may increase with additional information about exposure-response relationships for formaldehyde-induced respiratory effects in potentially susceptible populations of individuals, such as asthmatics.

An acute oral MRL for formaldehyde was not derived because data describing dose-response relationships for gastrointestinal tract irritation in humans or animals after acute oral exposure are lacking. The reports of gastrointestinal effects and symptoms in humans who ingested single large doses (>200 mg/kg) of formaldehyde (Burkhart et al. 1990; Eells et al. 1981; Kochhar et al. 1986), coupled with

data from studies of animals exposed orally for intermediate- and chronic-durations (Til et al. 1988b, 1989; Tobe et al. 1989), indicate that gastrointestinal irritation and damage are the most likely critical effects from acute oral exposure. However, as discussed in Section 2.5, the human data do not identify a no-effect level, and the available animal studies of acute oral exposure (Cassidy et al. 1983; Johannsen et al. 1986) did not examine this end point. At least one comprehensive acute oral toxicity study of at least one animal species exposed to several dosage levels may be needed to generate appropriate data for deriving an acute oral MRL for formaldehyde.

Formaldehyde is a well-known skin irritant and dermal sensitization agent, but systemic distant-site effects from acute dermal exposure are not expected given the reactive nature of formaldehyde, the ability of most cells to rapidly metabolize formaldehyde, and the low rates of formaldehyde absorption through the skin (Jeffcoat et al. 1983). This expectation is additionally supported by the observation that no effects on fetal development were found in pregnant hamsters dermally exposed during pregnancy to a 37% formaldehyde solution (Overman 1985). Exposure-response relationships for dermal effects from acute dermal exposure are well characterized in humans and animals. Experience with various types of formaldehyde solutions in the workplace and results from widespread patch testing in skin clinics indicate that acute dermal exposure to formaldehyde concentrations of 2–5% can evoke a mild to moderate non-allergic skin irritation response in some individuals; concentrations greater than 5% are expected to be irritating to most individuals (Fischer et al. 1995; Maibach 1983). In studies of dermally sensitized individuals, allergic skin reactions to concentrations as low as 0.025–0.05% have been reported (DeGroot et al. 1988; Fischer et al. 1995; Flyvholm et al. 1997). The cases of clothing-induced contact dermatitis that were frequently cited in the literature from the late 1950s until the mid-1970's when newly developed "no-iron' textiles that released formaldehyde were used (Peters and Heese 1997) further demonstrate the skin irritation potential of formaldehyde. Experiments with guinea pigs given daily non-occluded dermal doses of solutions of formaldehyde indicate that concentrations as low as 0.4% can produce erythema and increased skin thickness within a 10-day period (Wahlberg 1993).

Intermediate-Duration Intermediate-duration exposure to formaldehyde is expected to affect the same critical targets as acute exposure: the upper respiratory tract with inhalation exposure; the gastrointestinal tract with oral exposure; and the skin with dermal exposure.

Studies of health effects in humans after intermediate-duration inhalation exposure were not located. Studies of humans with predominately chronic inhalation exposure to formaldehyde under occupational

or residential conditions, however, consistently have reported increased incidences of symptoms of upper respiratory tract and/or eye irritation among exposed groups of people (Edling et al. 1988; Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987). Several studies have found nasal epithelial lesions, consistent with the irritant and reactive properties of formaldehyde, in biopsy specimens from workers repeatedly exposed to average concentrations ranging from about 0.2 to 0.5 ppm (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Other studies of similarly exposed groups of workers have either found no, or only small and subtle, exposure-related changes in pulmonary function variables, thus supporting the identification of the upper respiratory tract as the critical target of repeatedly inhaled formaldehyde (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990). Although the persons in these studies are considered to have been exposed for chronic durations, the results, together with the results from the acute controlled inhalation human studies, provide strong evidence that the critical target from intermediate-duration inhalation exposure to formaldehyde will be the upper respiratory tract.

Results from studies of animals exposed by inhalation for intermediate durations provide supporting evidence for the upper respiratory tract as the critical target and describe concentration-response relationships sufficiently well for describing an intermediate-duration inhalation MRL. Data describing intermediate-duration exposure-response relationships for upper respiratory tract lesions and concentrations ranging from 0.2 ppm to as high as 40 ppm are available for rats (Appelman et al. 1988; Casanova et al. 1994; Monticello et al. 1991; Rusch et al. 1983; Woutersen et al. 1987; Zwart et al. 1988), Cynomolgus monkeys (Rusch et al. 1983), hamsters (Rusch et al. 1983), and mice (Maronpot et al. 1986). Comprehensive histological examination of tissues and organs (including the lungs and eyes) in three of these studies (Appelman et al. 1988; Maronpot et al. 1986; Woutersen et al. 1987) and in another study of Rhesus monkeys that included only one exposure concentration (Monticello et al. 1989) found no consistent evidence for lesions outside of the upper respiratory tract. These results confirm the identification of the upper respiratory tract as the target of concern. Other intermediate-duration inhalation exposure studies in rats (Wilmer et al. 1987, 1989) provide evidence that the extent and severity of formaldehyde-induced epithelial lesions in the upper respiratory tract may be more strongly influenced by exposure concentration than duration of exposure.

The intermediate-duration inhalation MRL of 0.03 ppm is based on a NOAEL of 0.98 ppm and a LOAEL of 2.95 ppm for clinical signs of nasopharyngeal irritation and nasal epithelium lesions observed in

Cynomolgus monkeys (Rusch et al. 1983) and an uncertainty factor of 30. Computational fluid dynamic models of airflow and formaldehyde uptake in nasal passages and pharmacokinetic models of tissue disposition of formaldehyde in rats and humans are currently under development (Kimbell et al. 1993, 1997a, 1997b; Subramaniam et al. 1998). The application of these models to the rat intermediate-duration exposure-response data is likely to decrease uncertainty in deriving an intermediate-duration inhalation MRL from animal data. Such models are being developed for Rhesus monkeys (Kepler et al. 1998; Kimbell et al. 1997b), not Cynomolgus monkeys, but the available intermediate-duration data for Rhesus monkeys do not adequately describe concentration-response relationships; therefore a no-effect level cannot presently be estimated. Application of the monkey and human dosimetric models, when they are developed, to data from another Rhesus monkey study that would include multiple exposure levels represents another approach to decreasing uncertainty in the intermediate-duration inhalation MRL.

There is some uncertainty regarding whether or not inhaled formaldehyde can affect the lower respiratory tract by inducing bronchoconstriction or exacerbating asthma in humans, and whether or not repeated exposure may influence these possible, but incompletely understood, effects. As discussed earlier, several acute controlled exposure studies with humans (Andersen and Molhave 1983; Day et al. 1984; Gorski et al. 1992; Green et al. 1987; Harving et al. 1986, 1990; Kulle et al. 1987; Nordman et al. 1985; Sauder et al. 1986; Schachter et al. 1986; Witek et al. 1986) and studies of chronically exposed persons in workplaces or residences (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990) have found only mild or no changes in pulmonary function variables, except in a few rare cases (see Nordman et al. 1985). However, Amdur (1960) and Swiecichowski et al. (1993) reported that acute inhalation exposure to fairly low levels of formaldehyde (0.3 to 9 ppm) induced bronchoconstriction (i.e., increased pulmonary airway resistance) in guinea pigs. Swiecichowski et al. (1993) further reported that airway reactivity to infused acetylcholine increased after acute exposure to formaldehyde and that when the duration of exposure to formaldehyde was increased from 2 to 8 hours, lower concentrations of formaldehyde were effective in increasing airway reactivity to infused acetylcholine. The mechanism underlying these pulmonary effects is not understood, but Swiecichowski et al. (1993) have hypothesized that formaldehyde may change airway epithelial biochemistry leading to release of mediators of bronchoconstriction. Studies to test this hypothesis were not located. The relevance of the guinea pig findings to the report that a group of children living in homes with 0.06–0.12 ppm formaldehyde showed a greater prevalence of bronchitis and asthma than children living in homes

with less than 0.06 ppm (Krzyzanowski et al. 1990) has been questioned (Swiecichowski et al. 1993), but remains unknown.

Studies of health effects in humans after intermediate-duration oral exposure to formaldehyde were not located. Intermediate-duration oral-exposure toxicity studies in animals that examined a range of tissues and organs are extensive and include a 90-day drinking water rat study that found only weight gain decreases at dosage levels of 100–150 mg/kg/day (Johannsen et al. 1986), a 4-week drinking water rat study that identified a NOAEL of 25 mg/kg/day and a LOAEL of 125 mg/kg/day for forestomach and glandular stomach lesions indicative of irritation (Til et al. 1988b), a 4-week gavage rat study that identified a NOAEL of 40 mg/kg/day and a LOAEL of 80 mg/mg/day for hepatocellular vacuolation and a LOAEL of 20 mg/kg/day for a decrease in IgM and IgG titers and increased relative lymph node weight (Vargova et al. 1993), a 90-day dietary exposure dog study that reported a NOAEL and LOAEL of 75 and 100 mg/kg/day for body weight decreases and no other effects (Johannsen et al. 1986), and a 52-day dietary exposure pregnant dog study that found no evidence of maternal toxicity and no effects on fetal development at doses up to 9.4 mg/kg/day (Hurni and Ohder 1973). In addition, a 32-week drinking water study that focused on the gastrointestinal tract found papillomas in the forestomach and erosions and/or ulcers in the limiting ridge of the fundic mucosa of the glandular stomach in rats exposed to 258 mg/kg/day (Takahashi et al. 1986a).

The findings from the intermediate-duration oral exposure studies by themselves do not consistently identify gastrointestinal tract irritation as the critical effect. However, the weight of evidence from chronic oral administration animal studies (Til et al. 1989; Tobe et al. 1989) and the numerous intermediate inhalation toxicity studies (as previously cited), together with mechanistic understanding of formaldehyde's mode of toxic action, supports the selection of it as the critical effect from intermediate duration. Thus the selection of forestomach and glandular stomach lesions in rats (Til et al. 1988b) as the basis of the intermediate-duration oral MRL of 0.3 mg/kg/day is well-supported. As mentioned in the introduction to Section 2.2.2, there is uncertainty regarding the actual doses that were experienced by animals in the published oral exposure studies because of the lack of reporting regarding how frequently dosing solutions were analyzed for formaldehyde and the well-known instability of aqueous solutions of formaldehyde. Given this uncertainty and the lack of consistency in the findings from the available intermediate-duration oral studies, confidence in the MRL may be improved with additional intermediate-duration dose-response data from another comprehensive dietary or drinking water study of rats that includes frequent monitoring of dosing solutions. Dose-response data for gastrointestinal tract

effects in a primate species may provide an additional means of decreasing uncertainty in the intermediate oral MRL.

Formaldehyde is a well-known skin irritant and skin sensitizer in humans that accounts for about 1–8% of all cases of allergic dermatitis presented at skin clinics (Fischer et al. 1995; Kiec-Swierczynska 1996; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991). Studies of embalmers (Nethercott and Holness 1988) and medical workers (Rudzki et al. 1989) with expected repeated dermal exposure to formaldehyde presented evidence for increased prevalence of formaldehyde-induced skin irritation and dermal allergic reactions. Exposure-response relationships for skin irritation and dermal allergic responses from acute exposure are well characterized (under patch testing conditions) in both normal and sensitized individuals, indicating that 1% solutions are not expected to be irritating to most people, and that allergic dermal reactions in sensitized individuals can occur with concentrations as low as 0.015% (DeGroot et al. 1988; Fischer et al. 1995; Flyvholm et al. 1997; Maibach 1983). No published dose-response data were located for dermal irritation or the development of dermal sensitization in humans for intermediate- or chronic-duration exposure. Given the high reactivity, volatility, and aqueous solubility of formaldehyde and its rapid metabolism by cells, it is likely that dose-response relationships for dermal irritation from acute exposure may not be widely different from relationships for intermediate- and chronic-duration exposures. This hypothesis is supported by the results from inhalation exposure studies in rats indicating that exposure concentration is more important than exposure duration in determining the extent and severity of formaldehyde-induced epithelial lesions in the upper respiratory tract (Wilmer et al. 1987, 1989). Nevertheless, additional animal studies comparing dose-response relationships for skin irritation for acute, intermediate, and chronic exposure durations may be useful in estimating concentrations that will not damage the skin with repeated exposures.

The potency of formaldehyde as a contact allergen is demonstrated by the observation that occluded dermal exposure of guinea pigs to 5% formaldehyde for 3 weeks sensitized 70% of the animals to later dermal challenges with 1% formaldehyde (Hilton et al. 1996). However, published studies that describe dose-response relationship or no-effect levels for the development of dermal sensitization in animals with intermediate- or chronic-duration exposure were not located. Such studies are likely to be useful in estimating concentrations of formaldehyde that would minimize the development of dermal sensitization to formaldehyde in humans.

Chronic-Duration Exposure and Cancer. As with the shorter durations of exposure, the critical targets of chronic inhalation, oral, or dermal exposure to formaldehyde are expected to be portal-of-entry tissues. For the inhalation route, the data are abundant, of good quality, and include both human and animal data. Less health effects data are available for chronic oral and chronic dermal exposure, but the weight of the available data is consistent with this expectation.

Studies of humans chronically exposed to airborne formaldehyde concentrations in the approximate range of 0.1–1 ppm have consistently reported increased incidences of upper respiratory tract and eye irritation (Edling et al. 1988; Garry et al. 1980; Holness and Nethercott 1989; Horvath et al. 1988; Ritchie and Lehnen 1987), evidence for mild histological changes in the nasal epithelium (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c), and either no or only mild changes in pulmonary function variables (Alexandersson and Hedenstierna 1988, 1989; Bracken et al. 1985; Holness and Nethercott 1989; Horvath et al. 1988; Khamgaonkar and Fulare 1991; Kriebel et al. 1993; Malaka and Kodama 1990). Several chronic inhalation studies in rats (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Swenberg et al. 1980; Woutersen et al. 1989) and one study in mice (Kerns et al. 1983b) adequately describe concentration-response relationships for formaldehyde effects on the nasal epithelium and have identified no-effect levels ranging from 0.1 to 2 ppm. No consistent evidence for formaldehyde-induced effects at extra-respiratory sites was found in rats (Kamata et al. 1997; Kerns et al. 1983b) or mice (Kerns et al. 1983b) exposed to concentrations as high as 15 ppm. A chronic inhalation MRL of 0.008 ppm has been derived based on a minimal LOAEL of 0.24 ppm for histological changes in nasal epithelial specimens from a group of workers involved in the production of formaldehyde and formaldehyde resins (Holmstrom et al. 1989c) and an uncertainty factor of 30. Although confidence in this MRL is high due to the wealth of available data, increased confidence may result from additional prospective longitudinal studies of nasal tissue specimens from groups of workers experiencing varying formaldehyde exposure levels to investigate if nasal epithelial damage progresses in incidence or severity with longer duration or higher levels of exposure. Computational fluid dynamics models of airflow and formaldehyde uptake in nasal passages and pharmacokinetic models of tissue disposition of formaldehyde in rats and humans are currently under development (Kimbell et al. 1993, 1997a, 1997b; Subramaniam et al. 1998). Application of these models to chronic rat concentration-response data for nasal lesions represents another research approach to decreasing uncertainty in the chronic inhalation MRL.

No studies were located regarding health effects in humans with chronic oral exposure to formaldehyde. Two chronic drinking water studies with rats (Til et al. 1989; Tobe et al. 1989) provide enough reliable data to identify gastrointestinal tract mucosal damage as the critical target for chronic oral exposure and to describe dose-response relationships and estimates of no-effect levels. Results from the chronic oral studies are supported by results from the intermediate-duration rat studies showing gastrointestinal tract effects and associated no-effect levels (Johannsen et al. 1986; Takahashi et al. 1986a; Til et al. 1988b). The chronic MRL of 0.2 mg/kg/day was based on a NOAEL of 15 mg/kg/day and a LOAEL of 82 mg/kg/day for tissue damage in the forestomach (papillomatous hyperplasia, atrophic gastritis, and ulceration) and glandular stomach (hyperplasia) in male rats (Til et al. 1989) and an uncertainty factor of 100. As with the intermediate-duration data, some uncertainty is associated with the described chronic dose-response relationships due to a lack of reporting of the frequency of analysis of the drinking water for formaldehyde content in the available studies. Results from another intermediate-duration drinking water rat study, rather than a chronic-duration study, that includes frequent monitoring of the drinking water for formaldehyde, may decrease this source of uncertainty in the both the intermediate and chronic oral MRLs, given that the weight of evidence that concentration of formaldehyde at the site of toxic action is likely to be more important in determining cytotoxicity than duration of exposure.

As discussed in the Identification of Data Needs section for intermediate-duration exposure, additional animal studies comparing exposure-response relationships for skin irritation for acute- intermediate- and chronic-exposure durations would be useful in estimating concentrations of formaldehyde solutions that will not damage the skin with repeated exposures. Although no comprehensive toxicity studies in animals were located regarding chronic dermal exposure, understanding of formaldehyde toxicokinetics and mechanism of action suggests that distant-site toxicity is not a concern at environmentally or occupationally relevant dermal exposure levels.

The potential for occupational exposure to formaldehyde to cause cancer in humans has been examined in more than 40 epidemiology studies (cohort mortality and case-control studies). In general, these studies have provided inconsistent evidence for carcinogenicity in humans chronically exposed to low levels of formaldehyde in workplace air. In most studies finding statistically significant associations between occupational formaldehyde and human cancer, the associations have not been strong. The epidemiological studies each have shortcomings, such as limited follow-up, limited exposure information, possible misclassification of disease, presence of confounding risk factors, or small numbers of subjects, that make the establishment of a causal relationship between occupational exposure to

formaldehyde and human cancer difficult. Some of the epidemiological studies have found some scattered evidence for extra-respiratory site cancers in groups of formaldehyde-exposed workers, but the data are not consistent across studies and adjustment for potential confounding factors often has not been possible.

Three meta-analyses of the epidemiologic data are available (Blair et al. 1990a; Collins et al. 1997; Partanen 1993). Each meta-analysis has focused on findings for respiratory cancer deaths based on the premise that the respiratory tract is the most biologically plausible site for cancer from exposure to airborne formaldehyde. Strong support for this premise comes from animal studies showing that chronic inhalation exposure to formaldehyde concentrations between approximately 6 and 15 ppm, but not lower concentrations, induces carcinogenic responses in rats that are restricted to the nasal cavity (Albert et al. 1982; Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Sellakumar et al. 1985; Swenberg et al. 1980; Woutersen et al. 1989). Similar tumors were found in chronically exposed mice (Kerns et al. 1983b), but were not found in chronically exposed hamsters (Dalbey 1982). The two earlier meta-analyses showed weak overall associations between formaldehyde exposure and nasopharyngeal cancer. Relative risks and associated 95% CIs of 1.2 (0.8–1.7) and 2.0 (1.4–2.9) were reported by Blair et al. (1990a) and Partanen (1993), respectively. The associations were somewhat stronger in studies classified with "substantial" (as opposed to "low/medium") exposure. Relative risks for substantial exposures in the two analyses were 2.1 (1.1–3.5) and 2.7 (1.4–5.6). The meta-analysis by Collins et al. (1997) also showed a weak association across all available studies for relative risks of nasopharyngeal cancer (RR=1.3 [1.2–1.5]), but after adjusting the cohort studies for underreporting of nasopharyngeal cancer (RR=1.0 [0.5–1.8]) and analyzing the case-control studies separately (RR=1.3 [0.9–2.1]), no statistically significant associations were found.

Given that exposure information in case-control studies is generally poor, it seems that additional case-control studies are unlikely to clarify the potential relationship between occupational formaldehyde exposure and human cancer. Future research approaches that may be helpful include establishing prospective cohort mortality studies or updating existing cohort studies focusing on nasal cancer in groups of workers who have experienced high levels of exposure to formaldehyde or who will experience varying levels of formaldehyde exposure and in groups of appropriately matched nonexposed workers. It may be useful to conduct such a prospective study in a country in which occupational exposure levels to formaldehyde are expected to be higher than those in the United States.

Mechanistic studies indicate that the carcinogenic response to inhaled formaldehyde in rats originates in regions of the nasal cavity epithelium that initially show non-neoplastic damage and provide support for the hypothesis that formaldehyde-induced cancer will occur only at exposure levels that extensively damage epithelium tissue (e.g., Monticello et al. 1996). Comparison of the non-neoplastic upper respiratory tract response in rats and monkeys to intermediate-duration formaldehyde exposure has indicated that both monkeys and rats are similarly susceptible to formaldehyde cytotoxicity but display some regional differences in sites of tissue damage within the upper respiratory tract (Casanova et al. 1989, 1991; Heck et al. 1989; Monticello et al. 1989). These observations support the use of data from rodent studies to extrapolatively estimate risks for nasal tissue damage and nasal cancer with human exposure scenarios.

The application of dosimetric models (e.g., CFD models of airflow and uptake in nasal passages and PBPK models of nasal disposition of formaldehyde) currently under development (Cohen Hubal et al. 1997; Kepler et al. 1998; Kimbell et al. 1993, 1997a, 1997b; Morgan et al. 1991; Subramaniam et al. 1998) holds promise of reducing uncertainties in estimating human cancer risks from the available rodent data (Morgan 1997). Ongoing efforts (see CIIT 1998; Conolly et al. 1992; Conolly and Andersen 1993) to develop two-stage clonal-growth cancer models (i.e., pharmacodynamic models) incorporating data on formaldehyde-induced cell proliferation rates, numbers of cells at risk, tumor incidence, and site-specific flux of inhaled formaldehyde are also likely to reduce uncertainties in estimating the risks for neoplastic damage to the upper respiratory tract in humans exposed to low levels of airborne formaldehyde.

Results from four drinking water rat studies provide some inconsistent evidence for formaldehyde-induced gastrointestinal tract tumors (Soffritti et al. 1989; Takahashi et al. 1986a; Til et al. 1989; Tobe et al. 1989). As discussed in Section 2.5, the weight of evidence from the rat studies suggests that gastrointestinal tract tumors may occur as late-developing portal-of-entry effects only from repeated exposure to high oral doses that damage the gastric mucosa, and that tumors are not likely to develop at dose levels that do not damage the gastric mucosa. It is unlikely that a human population with high oral exposures to formaldehyde can be identified to study possible relationships to cancer, but better characterization of no-effect levels for gastric mucosal damage in animal species exposed repeatedly to formaldehyde in drinking water may provide additional information to support the hypothesis that low levels of formaldehyde in water samples associated with hazardous waste sites do not present considerable risks for cancer.

No studies were located examining potential relationships between skin cancer in humans and dermal exposure to formaldehyde, but two mouse-skin cancer bioassays found no evidence for increased incidence of skin tumors after 58–60 weeks of twice-weekly exposure to formaldehyde solutions at concentrations of 4% (Iverson 1988) and 10% (Iverson 1986). Additional animal bioassays employing lifetime dermal exposure scenarios would provide more complete assessments of the possible dermal carcinogenicity of formaldehyde.

Genotoxicity. Formaldehyde has been demonstrated to have genotoxic properties in human and laboratory animal studies. Peripheral lymphocytes in anatomy students exposed to 0.73–1.95 ppm formaldehyde for 10 weeks showed a small average increase in SCEs (Yager et al. 1986). Lymphocytes from wood workers chronically exposed to formaldehyde also showed increased levels of chromosomal aberrations; however, there were no significant changes in the rates of SCE (Chebotarev et al. 1986). Other positive findings for genotoxicity include increases in micronuclei formation in wood workers (Ballarin et al. 1992) and an increased incidence in chromosomal abnormalities in pulmonary macrophages in rats (Dallas et al. 1992).

Formaldehyde has been found to be genotoxic in a number of cells and genetic end points. Formaldehyde has been found to induce chromosomal aberrations (Dresp and Bauchinger 1988; Natarajan et al. 1983), increases in micronucleus formation (Ballarin et al. 1992), and SCEs (Yager et al. 1986), as well as numerous other genotoxic end points (Recio et al. 1992; Topham 1980). Formaldehyde has also been found to have genotoxic properties in *S. typhimurium* (Donovan et al. 1983) and in human cell lines (Grafstrom et al. 1985; Snyder and Van Houten 1986). The weight of evidence indicates that formaldehyde is capable of directly reacting with DNA. No reports of genotoxicity strictly related to the oral or dermal exposure routes were found in the available literature. Further cytogenetic analysis of cells from formaldehyde-exposed individuals would possibly provide useful information about the ability and mechanisms by which formaldehyde induces its genotoxic end points.

Reproductive Toxicity. Results from human and animal studies indicate that formaldehyde is not a likely reproductive toxicant at low levels of exposure. No effects on sperm numbers or sperm morphology were found in a group of formaldehyde-exposed pathologists (Ward et al. 1984), and increased rates of miscarriage were not found among persons with presumed residential exposure to formaldehyde (Garry et al. 1980). Studies of reproductive outcomes in groups of formaldehyde-exposed workers may be useful to confirm that the potential for reproductive effects from formaldehyde is low.

Results from such a study will have a better chance of being conclusive if a population is identified that is exposed only to formaldehyde.

Animal studies of inhalation exposure found no direct effects of formaldehyde on reproductive organ histopathology or weight (Appelman et al. 1988; Maronpot et al. 1986; Woutersen et al. 1987) and, with exposure during gestation, no effects on maternal reproductive variables other than decreased body weight gains at high exposure levels (Martin 1990; Saillenfait et al. 1989). Similarly, oral exposure of animals has not been associated with histopathologic or weight changes in reproductive organs (Johannsen et al. 1986; Til et al. 1989; Tobe et al. 1989; Vargova et al. 1993) or with maternal reproductive variables such as numbers of resorptions at non-lethal exposure levels in pregnant animals (Hurni and Ohder 1973; Marks et al. 1980). Changes in sperm morphology were noted in rats given single gavage doses of 200 mg/kg/day, but not 100 mg/kg/day (Cassidy et al. 1983). Overman (1985) reported a small increase in resorption rate in pregnant hamsters dermally exposed to 37% formaldehyde solutions, but attributed this effect to treatment stress rather than to a direct effect of formaldehyde. Assays of reproductive performance in formaldehyde-exposed animals were not located, but may be useful to confirm that formaldehyde is not a reproductive toxicant.

Developmental Toxicity. Results from a human study and several animal studies indicate that formaldehyde is not a likely developmental toxicant at low levels of exposure. No associations were found between incidence of low birth weights and ambient air levels of formaldehyde among groups of mothers living in different residential districts (Gra ulevi iene et al. 1998). No embryolethal or teratogenic effects of formaldehyde were found in gestational-exposure studies of rats exposed to air concentrations up to 40 ppm (Martin 1990; Saillenfait et al. 1989), rats exposed to gavage dose levels up to 185 mg/kg/day (Marks et al. 1980), dogs exposed to dietary doses up to 9.4 mg/kg/day (Hurni and Ohder 1973), and hamsters dermally exposed to 37% formaldehyde solutions (Overman 1985). Formaldehyde was designated as a nonteratogen and nonembryotoxin in the Chernoff/Kavlock developmental toxicity screening test in mice (Seidenberg and Becker 1987). The need for additional developmental toxicity studies may not have a high priority, given the evidence from other repeated-exposure animal toxicity and pharmacokinetic studies indicating that health effects from formaldehyde are likely to be restricted to portals-of-entry.

Immunotoxicity. Dermal sensitization to formaldehyde in humans is well recognized from results of patch testing at dermatological clinics throughout the world (Fischer et al. 1995; Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991) and a few studies of formaldehyde-exposed workers (Nethercott and Holness 1988; Rudzki et al. 1989). Severe allergic responses to dermally applied formaldehyde, however, appear to be rare; only one case of a severe anaphylactic response to formaldehyde was located (Maurice et al. 1986). The potency of formaldehyde as a contact allergen is demonstrated by the observation that occluded dermal exposure of guinea pigs to 5% formaldehyde for 3 weeks sensitized 70% of the animals to later dermal challenges with 1% formaldehyde (Hilton et al. 1996). However, published studies that describe dose-response relationships or no-effect levels for the development of dermal sensitization in animals with intermediate- or chronic-duration dermal exposure were not located. Such studies are likely to be useful in estimating concentrations of formaldehyde that would minimize the development of dermal sensitization to formaldehyde in humans.

Although formaldehyde is widely recognized as a dermal irritant that can sensitize the skin in humans, the evidence for immunologically-mediated sensitization of the respiratory tract from exposure to airborne formaldehyde is weak. There are only a few available case reports of formaldehyde-exposed workers who display marked changes in pulmonary function variables in response to acute challenges with inhaled formaldehyde that are consistent with an immunologically-mediated mechanism of response (Burge et al. 1985; Hendrick et al. 1982; Lemiere et al. 1995). Nordman et al. (1985) reported that, among 230 patients with formaldehyde exposure who reported asthma-like symptoms, only 12 showed marked pulmonary responses to acute formaldehyde challenges. Other studies found no marked response to challenges of inhaled formaldehyde in other groups of previously-exposed subjects who complained of asthma-like symptoms (Day et al. 1984; Krakowiak et al. 1998; Reed and Frigas 1984). Several studies have found no consistent evidence for increased serum levels of formaldehyde-specific IgE antibodies in groups of formaldehyde-exposed subjects including groups with complaints of respiratory symptoms (Dykewicz et al. 1991; Gorski et al. 1992; Grammar et al. 1990; Krakowiak et al. 1998; Kramps et al. 1989; Thrasher et al. 1987, 1990). Elevated serum levels of IgE antibodies and respiratory tract symptoms were found in groups of children exposed to classroom air concentrations of 0.075, 0.069, and 0.043 ppm formaldehyde (Wantke et al. 1996a). However, the relevance of these findings to the possibility of respiratory tract sensitization to formaldehyde is uncertain because the elevated levels of IgE were not correlated with the number and severity of symptoms, and the symptoms were more

indicative of irritant responses than asthma-type responses expected to be mediated through IgE antibodies.

Results from studies with guinea pigs confirm that formaldehyde is a potent skin sensitizer, but does not elicit IgE responses and lymph node cytokine secretion patterns that are typically induced by other potent respiratory tract allergens such as trimellitic anhydride (Hilton et al. 1996). Other animal studies indicate that repeated exposure to formaldehyde at air concentrations between 10 and 15 ppm did not produce significant effects in several assays of immune function including resistance to intravenous or subcutaneous injection of neoplastic cells in mice (Dean et al. 1984), resistance to intravenous injection of bacterial cells in mice (Dean et al. 1984), and IgM response to tetanus immunization and IgG response to tetanus toxoid in rats (Holmstrom et al. 1989b). However, two other studies indicate that exposure to airborne formaldehyde may enhance allergic responses of the respiratory tract to other respiratory allergens (Riedel et al. 1996; Tarkowski and Gorski 1995). Further research is necessary to confirm the hypothesis that exposure to airborne formaldehyde may facilitate immunological responses to other respiratory allergens and to determine if this is relevant to humans exposed to formaldehyde.

Information about immunological and lymphoreticular effects in humans orally exposed to formaldehyde is restricted to a report of splenomegaly in a case of acute poisoning (Koppel et al. 1990). In animal studies, decreased IgM and IgG titers in a hemagluttination assay and increased lymph node weights were found in rats exposed to gavage doses of 20 mg/kg/day and higher, but other measures of IgG and IgM production were not affected by exposure (Vargova et al. 1993). No effects on weights or histopathology of spleen and lymph nodes were found in other studies of orally exposed animals (Til et al. 1988b, 1989; Tobe et al. 1989). The data do not clearly identify immunological effects from oral exposure to formaldehyde as effects of concern. Further research on the possible immunotoxicity of ingested formaldehyde may not be warranted given the likelihood that oral exposures to formaldehyde may be low in most groups of people, due to the instability of formaldehyde in aqueous solutions.

Neurotoxicity. The nervous system does not appear to be a major target organ for formaldehyde toxicity; however, some vague neurological symptoms may occur after inhalation exposure in humans. These may include headaches, "heavy head," fatigue, and increased reaction time (Bach et al. 1990). Kilburn and colleagues have reported evidence for neurological symptoms and impaired performance in neurobehavioral tests in groups of formaldehyde-exposed histology technicians, but confounding exposure to other neurotoxic solvents prevents drawing definitive conclusions regarding the

neurotoxicity of formaldehyde from this source (Kilburn 1985b; Kilburn et al. 1987; Kilburn and Warshaw 1992; Kilburn 1994). Restless behavior (Morgan et al. 1986a), increased levels of 5-hydroxy-indoleacetic acid, 3,4-dihydroxyphenylacetic acid, and dopamine in the hypothalamus (Boja et al. 1985), and evidence for the development of a conditioned avoidance behavior (Wood and Coleman 1995) have been reported in rats. The restless behavior may be attributable to the respiratory irritant effects of the formaldehyde vapor; however, the significance of the increased chemical content in the hypothalamus of rats is unclear. Other studies have found no perceptible effects of formaldehyde on the nervous system of rats and mice at 15 ppm (Appelman et al. 1988; Kerns et al. 1983b), although obvious clinical signs of neurological impairment were observed in mice (Maronpot et al. 1986) and rats (Woutersen et al. 1987) exposed to high concentrations (20 ppm) of airborne formaldehyde.

Reports of neurotoxicity in humans after an oral exposure to formaldehyde are limited to case reports. Coma, lethargy, seizures, and loss of consciousness have been reported in humans after drinking formaldehyde (Burkhart et al. 1990; Eells et al. 1981; Koppel et al. 1990). No consistent effects on the nervous system after oral exposure to formaldehyde were found in several toxicity reports using laboratory animal models (Johannsen et al. 1986; Til et al. 1988b, 1989; Tobe et al. 1989). Increased relative brain weights were observed in one group of rats chronically exposed to drinking water doses of 82–109 mg/kg/day (Til et al. 1989), but not in another group exposed to 300 mg/kg/day (Tobe et al. 1989). The data suggest that the nervous system may be affected by formaldehyde exposure, especially if it is ingested in large quantities or if chronically inhaled in low doses in an occupational setting. Additional prospective evaluations of performance on neurobehavioral tests in groups of formaldehyde-exposed workers may be useful in ascertaining if there are subtle neurological effects from chronic inhalation exposure to formaldehyde. Results from such studies would be most useful if the studied workers were not exposed to other neurotoxic airborne agents; this is a condition which may be difficult to find in occupational settings.

Epidemiological and Human Dosimetry Studies. Results from many acute controlled-exposure human studies and cross-sectional studies of groups of persons repeatedly exposed to airborne formaldehyde provide strong evidence that the upper respiratory tract is the critical target of airborne formaldehyde for any duration of exposure, allow reasonable estimates to be made of minimal risk levels for acute and chronic durations of exposure, and provide strong support for deriving intermediate-duration minimal risk levels from animal exposure-response data. There is considerable confidence that adherence to these values will protect persons living near formaldehyde-contaminated hazardous waste

sites from developing upper respiratory tract health problems. Longitudinal studies that examine nasal specimens from groups of workers with varying air exposure levels will provide information that may further increase confidence in the estimated minimal risk levels.

There does not appear to be a pressing need for epidemiology studies of people exposed orally to formaldehyde given the instability of formaldehyde in environmental sources of water and the implausibility of identifying groups of people exposed to oral doses of formaldehyde that are sufficiently high to damage gastrointestinal tract tissue.

The relatively frequent reporting of dermal sensitization to formaldehyde at dermatological clinics (Fischer et al. 1995; see also: Kiec-Swierczynska 1996; Maibach 1983; Marks et al. 1995; Meding and Swanbeck 1990; Menné et al. 1991) suggests that cross-sectional and longitudinal studies of dermal exposure levels and prevalence of skin problems in groups of workers with expected dermal exposure to cleaning and disinfectant solutions (e.g., janitorial and/or medical personnel) may be useful to better describe exposure-response relationships for the development of formaldehyde-induced skin irritation and contact dermatitis from intermediate- or chronic-duration exposure to formaldehyde.

Epidemiological studies of occupationally exposed groups of persons have not found consistent or strong evidence for an association between occupational exposure to airborne formaldehyde and cancer, although animal studies have found consistent evidence for formaldehyde-induced nasal tumors with chronic exposure to air concentrations in the range of 6–15 ppm. The available epidemiological studies have shortcomings such as limited exposure information or follow-up, presence of confounding risk factors, or small numbers of subjects, but one plausible explanation for the lack of a consistent response across the studies is that workplace air levels often may be below values necessary for formaldehyde to induce upper respiratory tract cancer. Studies in animals have shown that no increased incidences of nasal tumors were found in rats with lifetime exposure to low (0.3–2 ppm) air concentrations (Kamata et al. 1997; Kerns et al. 1983b; Monticello et al. 1996; Woutersen et al. 1989), that damaged regions of the nasal epithelium after short-term exposure are correlated with regions that eventually develop tumors with chronic exposure (Monticello et al. 1996), and that regions of the nasal epithelium with epithelial damage correlate with regions of predicted high airflow and uptake of formaldehyde (Cohen Hubal et al. 1997; Kepler et al. 1998; Kimbell et al. 1993, 1997a). Further development is needed of human nasal airflow and formaldehyde uptake models, human pharmacokinetic models for formaldehyde disposition, and human pharmacodynamic models for preneoplastic events in upper respiratory tract tissue.

Application of such models, with associated rat dosimetric models, to the available rat exposure-response data for tumors and preneoplastic events will allow better estimations of air levels presenting minimal risks for cancer in humans.

Biomarkers of Exposure and Effect.

Exposure. Attempts have been made to determine if formaldehyde could be used as a potential biomarker of short-term exposure (Heck et al. 1985); however, no significant difference between pre- and postexposure blood concentrations of formaldehyde could be demonstrated at the concentration tested. In the same study, similar findings were noted in male Fischer 344 rats placed in a nose-only inhalation chamber and exposed to 14.4 ppm formaldehyde for 2 hours. Monitoring blood or urine formate levels has also been considered. Rapid intravenous injection of formaldehyde in monkeys showed a plasma half-life of only 1.5 minutes, with a corresponding increase in blood formate levels; however, formate production is not specific to formaldehyde metabolism (Ferry et al. 1980; Kornbrust and Bus 1983; Liesivuori and Savolainen 1987). Urine formate levels were examined by Einbrodt et al. (1976) and urine formaldehyde and urine formic acid (formate) concentrations were found to be higher immediately after exposure; however, study design posed interpretation concerns. Gottschling et al. (1984) monitored anatomy students exposed to low levels of formaldehyde vapor; wide variations were noted in the urine formate levels prior to exposure, with large intrapersonal and interpersonal variations. Mean postexposure urine formate concentrations were not significantly elevated after exposure. Based on the available data, it appears that the detection of the intact formaldehyde molecule in the blood and tissues, as well as blood and urine formate, are unreliable and poor indicators of formaldehyde exposure in humans and laboratory animals.

Studies of animals have used radiolabeling techniques to measure DNA-protein cross links in nasal epithelium tissue (Casanova-Schmitz et al. 1984a; Casanova and Heck 1987; Casanova et al. 1989a, 1989b, 1991, 1994) and described relationships between exposure levels and the amounts of DNA-protein cross links in regions of the nasal epithelium. Such a technique is impractical for monitoring humans exposed to formaldehyde, but Shaham et al. (1996a) proposed that measurement of total DNA-protein cross links by a different technique in white blood cells may be useful as a biomarker of repeated exposure to formaldehyde. In support of this proposal, it was reported that white blood cells from 12 formaldehyde-exposed anatomists and pathologists had significantly higher average levels of DNA-protein cross links than those from eight subjects without known occupational exposure to formaldehyde

(Shaham et al. 1996a). Additional research to apply these methods to larger groups of occupationally exposed and nonexposed persons may help to determine the reliability of this variable as a biomarker of exposure and to determine the extent to which individuals vary in this response to formaldehyde. Additional research to apply the DNA-protein cross link methods to nasal biopsy specimens may lead to an increased sensitivity of this potential biomarker of exposure and effect. Shaham et al. (1996b) reported that a larger scale study was in progress, but results are not available.

Antibodies (IgG and IgE) against formaldehyde conjugated to human serum albumin have been found to be elevated in some people, but not in others, exposed to formaldehyde (Dykewicz et al. 1991; Grammer et al. 1990; Patterson et al. 1986; Thrasher et al. 1988b, 1989, 1990; Wantke et al. 1996a). The apparently rare frequency of IgE-mediated allergy responses to airborne formaldehyde (Grammer et al. 1990; Kramps et al. 1989; Nordman et al. 1985) suggests that elevation of antibodies against formaldehyde may be too rare to be useful as a generic biomarker of exposure. However, the findings of significant associations between (1) the presence of IgG antibodies against formaldehyde-human serum albumin and smoking habit in a group of healthy subjects, and (2) the presence of such antibodies in non-smokers and occupational exposure to formaldehyde suggest that this biomarker of immunological response may serve as a qualititative biomarker of exposure (Carraro et al. 1997). Additional studies of formaldehyde-specific IgG antibodies in non-smoking groups of formaldehyde-exposed and nonexposed persons may be useful to determine the reliability of this qualitative biomarker of intermediate or chronic exposure to formaldehyde. Additional research may help to further develop the Carraro et al. (1997) assay so that it might be useful for quantifying exposure levels or exposure durations.

Effect. Increased eosinophil concentration and increased albumin and total protein levels have been found in nasal lavage fluid taken from subjects exposed to 0.4 ppm formaldehyde for 2 hours (Krakowiak et al. 1998; Pazdrak et al. 1993). Although these variables are not expected to be specifically influenced by formaldehyde, they appear to provide biomarkers of acute respiratory irritation from airborne formaldehyde or other upper respiratory irritants. Further research on relationships between concentrations of these variables in nasal lavage fluid and prevalence or severity of respiratory symptoms in humans exposed acutely to varying concentrations of formaldehyde may help to confirm their use as biomarkers of effect.

As discussed in the previous section, DNA-protein cross links and anti-formaldehyde-human serum albumin IgG antibodies are potential biomarkers of effect and exposure from intermediate- or chronic-

duration of exposure. Another potentially useful biomarker of effect for repeated inhalation exposure to formaldehyde involves the histological examination of nasal biopsy samples (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Whereas detection of these biomarkers can represent biological responses to repeated exposure to formaldehyde, it is uncertain to what degree their detection indicates that adverse health effects will occur. Prospective studies of these end points in formaldehyde-exposed and nonexposed workers may decrease this uncertainty and describe temporal relationships between formaldehyde-induced upper respiratory tract tissue damage and/or dysfunction and exposure-related intensity changes in these variables.

Absorption, Distribution, Metabolism, and Excretion. Results from studies of rats exposed for short periods (6 hours) to airborne radiolabeled formaldehyde concentrations between 0.63 and 13.1 ppm indicate that inhaled formaldehyde is rapidly absorbed and metabolized, primarily in the upper respiratory tract, and that, at these exposure concentrations, very little formaldehyde reaches the blood or is transported to distant-site tissues and organs (Heck et al. 1983). In these studies, radioactivity recovered within 70 hours after exposure was found in the expired air (39-42%), the urine (17%), feces (4-5%), and in tissues and the carcass (35-39%). These results are consistent with rapid oxidative metabolism to formate and CO_2 and rapid incorporation of the carbon from formaldehyde into cellular constituents. Consistent with these studies, another experiment showed that 2-hour exposures to formaldehyde of rats (to 14.4 ppm) and humans (to 1.9 ppm) did not significantly increase formaldehyde concentrations in blood when measured immediately after exposure (Heck et al. 1985). Casanova et al. (1988) also showed that blood concentrations of formaldehyde were not elevated, immediately after exposure, in rhesus monkeys exposed to 6 ppm (6 hours/day, 5 days/week) for 4 weeks. These toxicokinetic results, together with the weight of evidence from inhalation toxicological studies of animals showing effects only in the upper respiratory tract, provide high confidence that the disposition of inhaled formaldehyde by the upper respiratory tract in this concentration range and below is nearly complete. Additional animal studies designed to compare formaldehyde-specific metabolic capacities in nasal mucosal tissues from adult and immature animals may be useful in determining a possible mechanistic basis for possible age-related differences in susceptibility to irritation from airborne formaldehyde (see Children's Susceptibility data needs section below).

Ingested formaldehyde is also expected to be rapidly absorbed, rapidly metabolized to formate and CO_2, and rapidly incorporated into cellular consituents, but descriptive toxicokinetic studies of orally administered formaldehyde in animals were not located. Observations of elevated formate levels and

metabolic acidosis in cases of acute formaldehyde poisoning (Eells et al. 1981; Burkhart et al. 1990) are consistent with rapid absorption and metabolism of ingested formaldehyde. A study is available of the dispositional kinetics of radioactivity in rats and mice after ingestion of a cheese made from milk with added radiolabeled formaldehyde (Galli et al. 1983), but the radioactivity in the material fed to the animals was largely (80%) linked to proteins. Given that the levels of formaldehyde in sources of food and water for humans are expected to be very low due to formaldehyde's high reactivity, additional animal studies to more completely describe the absorption, distribution, metabolism, and elimination of orally administered formaldehyde do not seem to warrant a high priority.

Results from a study of rats, guinea pigs, and monkeys under nonoccluded dermal exposure conditions indicated that evaporation from the skin was a major disposition route (Jeffcoat et al. 1983). Additional animal studies of absorption, distribution, and metabolism under occluded conditions of dermal exposure would provide information regarding maximal rates of dermal absorption and local tissue metabolism, and may help to confirm that distant-site effects from dermal exposure are unlikely.

Comparative Toxicokinetics. Experiments with humans, rats, and monkeys indicate that inhaled formaldehyde is absorbed and metabolized so rapidly that blood concentrations do not vary during short-term exposures (Casanova et al. 1988; Heck et al. 1985). These results are consistent with the upper respiratory tract being the critical target of inhaled formaldehyde in each of these species as indicated by the available health effects data. The marked differences between rodents and primates in breathing habits (i.e., rodents are obligate nose breathers) and nasal anatomy led to some early questions about the human relevance of the well-characterized nonneoplastic and neoplastic responses of nasal epithelium in rats to chronic exposure to airborne formaldehyde. However, observations of similar non-neoplastic changes in upper respiratory tract epithelium in Rhesus and Cynomolgus monkeys exposed for intermediate durations (Monticello et al. 1989; Rusch et al. 1983) and observations of histological changes in nasal tissue from occupationally exposed subjects (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c) have provided support for the relevance of the rat data. These results have led to the ongoing development of, for each of these species, anatomical models of nasal airflow and uptake, pharmacokinetic models for nasal tissue metabolism, and pharmacodynamic models of development of tumors and preneoplastic tissue changes to be applied to the rodent data to better estimate air levels that will present minimal risks for upper respiratory tract damage in humans (CIIT 1998; Cohen Hubal et al. 1997; Conolly et al. 1992; Conolly and Andersen 1993; Kepler et al. 1998; Kimbell et al. 1993, 1997a, 1997b; Morgan 1997; Morgan et al. 1991; Subramaniam et al. 1998).

In contrast, mice and hamsters appear to be less susceptible to upper respiratory tract damage from inhaled formaldehyde. The basis for this apparent species difference in susceptibility is unknown, but may involve, at least partially for the case of the mouse, the greater efficiency of mice, compared with rats, to reduce minute volumes during exposure to formaldehyde (Chang et al. 1981, 1983).

As with exposure to airborne formaldehyde, portal-of-entry tissues are expected to be the critical targets of orally or dermally administered formaldehyde in humans and animals. Gastrointestinal effects from high oral doses are expected based on reports of gastrointestinal tract irritation and symptoms in humans who ingested large doses of formaldehyde, together with results from studies of rats exposed orally to formaldehyde for intermediate- and chronic-durations (e.g., Til et al. 1988b, Til et al. 1989; Tobe et al. 1989). Skin irritation in humans with dermal occupational exposure to formaldehyde concentrations in the range of 2-5% and greater is expected based on occupational experience and clinical experience in patch-testing (Fischer et al. 1995; Maibach 1983); additionally, the development of dermal sensitization to formaldehyde is frequently found among patients presenting skin problems at dermatology clinics. The expectation of skin irritation and dermal sensitization, without systemic distant-site effects, from exposure to formaldehyde is supported by results from dermal-exposure toxicity studies in animals (e.g., Overman 1985; Wahlberg 1993) and toxicokinetic studies with rats, guinea pigs and Cynomolgus monkeys (Jeffcoat et al. 1983); although results from the latter studies indicated that monkey skin may be more permeable to formaldehyde than rat skin. In contrast to inhalation exposure, however, there is no information indicating that species differ in susceptibility to formaldehyde toxicity by these routes of exposure. Thus, additional studies comparing species differences in toxicokinetic variables with oral or dermal exposure to formaldehyde do not appear to have a high priority at this time.

Methods of Reducing Toxic Effects. Due to formaldehyde's high water solubility and reactivity and the rapidity of cellular metabolism of formaldehyde to formate and CO_2, toxic effects from formaldehyde are expected to be principally caused by formaldehyde itself (not metabolites) and to be restricted to portal-of-entry tissues, except at high exposure levels that exceed metabolic capacities of these tissues. Thus, following acute exposures to formaldehyde, treatments that dilute or remove non-absorbed or non-reacted formaldehyde from the site of exposure or that present alternative substrates for reaction (e.g., washing of the skin or eyes or dilution of ingested formaldehyde with milk or water) may prevent the occurrence of toxic effects if applied in a timely manner. Methods that may enhance the capacity of portal-of-entry tissues to metabolize formaldehyde may be expected to act against the toxic action of formaldehyde, but no such methods have been established. There are no established treatment

protocols to repair tissue damage that may have been caused by formaldehyde at portals-of-entry or to enhance natural repair mechanisms.

Children's Susceptibility. Suggestive evidence from two studies is available indicating that children may be more susceptible to the locally-acting irritant properties of formaldehyde (Krzyzanowski et al. 1990; Wantke et al. 1996a). Additional health survey studies of groups of children known to experience indoor air concentrations exceeding 0.05–0.1 ppm may be helpful in confirming or discarding this hypothesis.

Studies of laboratory animals, as well as studies of adult humans under acute controlled exposure or occupational exposure conditions, indicate that the irritant effects of formaldehyde are restricted to tissues at portals-of-entry due to the water-solubility and reactivity of formaldehyde and the ability of cells to rapidly metabolize (and detoxify) formaldehyde. Studies designed to compare formaldehyde-specific metabolic capacities and efficiencies in portal-of-entry tissues (e.g., nasal mucosa, gastrointestinal mucosa) from adult and immature animals of varying ages may be useful in determining a possible mechanistic basis for possible age-related differences in susceptibility to formaldehyde.

2.11.3 Ongoing Studies

Ongoing studies pertaining to formaldehyde have been identified and are shown in Table 2-8.

Table 2-8. Ongoing Studies on Formaldehyde

Investigator	Affiliation	Research description	Sponsor
B.K. Andrews, B. Morrell and N.M. Morris	Southern Regional Res Center, New Orleans, LA	Durable Press Fabrics from No- and De-minimus Level-Formaldehyde Finishes	US Dept. of Agriculture
A.E. Blair	NCI, NIH	Studies of Occupational Cancer	Division of Cancer Etiology
T.P. Brown and G.E. Rottinghaus	University of Georgia College of Vet Medicine, Athens, GA	Poultry Toxicosis: Evaluation and Amelioration	US Dept. of Agriculture
A. Cederbaum	VA Medical Center, New York, NY	Interaction of Pyrazole and Glycerol with Human Microsomes and P-450IIEI	National Institute of Alcohol Abuse and Alcoholism
B.J. Collier	Louisiana State University School of Human Ecology, Baton Rouge, LA	Measurement of Formaldehyde Release from Durable Press Cotton Fabrics & Other Products	US Dept. of Agriculture
J.T. Coyle	Massachusetts General Hospital, Boston, MA	Psychosis and Brain Glutamate	National Institute of Mental Health
J. Cwi	Survey Research Associates, Baltimore, MD	Support Services for Occupational Studies	Division of Cancer Etiology
L.M. Ferrari and F. Catell	State Pollution Control Commission, Sydney, NSW	Indoor Air Quality and Energy Conservation	NERDDP
J.B. Guttenplan	NYU Dental Center, New York, NY	Smokeless Tobacco Carcinogenesis and Oral Tissue	National Institute of Dental Research
G. Hager	NCI, NIH	Chromatin Structure and Gene Expression	Division of Cancer Etiology
A.T. Hastie	Thomas Jefferson University, Philadelphia, PA	Pollutant Interactive Effects on Ciliary Defense	NIEHS
G.A. Jamieson	American Red Cross, Rockville, MD	Characterization and Isolation of Platelet ADP Receptors	National Heart, Lung, and Blood Institute
K. Knapp, D. Pahl and F. Black	Atmospheric Research and Assessment Laboratory, Research Triangle Park, NC	Hazardous Air Pollutant Regulatory Activities	Office of Research and Development
J. Merchant	University of Iowa, Iowa City, IA	Core--Occupational Health Research	NIEHS
S.S. Mirvish	University of Nebraska Medical Center, Omaha, NE	Nitrosamine Metabolism and Esophageal Cancer	National Cancer Institute
R. Monson	Harvard University, Boston, MA	Occupational Health	NIEHS

Table 2-8. Ongoing Studies on Formaldehyde (continued)

Investigator	Affiliation	Research description	Sponsor
T.N. Pappas	Dept. of Veterans Affairs Medical Center, Durham, NC	Animals Models of Inflammatory Bowel Disease: Relationship to Substance P Receptor Up Regulation	Dept. of Veterans Affairs
T. Shibamoto	University of California Environmental Toxicology, Davis, CA	Isolation and Identification of Mutagens and Carcinogens in Foods	US Dept. of Agriculture
G.M. Thiele	Omaha VA Medical Center, Omaha, NE	Alcohol and Liver Endothelial Cells in Immune Responses	National Institute on Alcohol Abuse and Alcoholism
J-P. Von Sattel	Massachusetts General Hospital, Boston, MA	Core--Neuropathology	National Institute of Neurological Disorders and Stroke

NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health; NIH = National Institutes of Health; NERDDP = National Energy Research, Development and Demonstration Program

3. CHEMICAL AND PHYSICAL INFORMATION

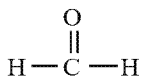
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of formaldehyde is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of formaldehyde is located in Table 3-2.

Table 3-1. Chemical Identity of Formaldehyde

Characteristic	Information	Reference
Chemical name	Formaldehyde	Lide and Frederikse 1996
Synonym(s)	Formic aldehyde, methanal, methyl aldehyde, methylene oxide	Budavari et al. 1989
Registered trade name(s)		
For 37% aqueous solution[a]	Formalin, Formol, Morbicid, Veracur	Budavari et al. 1989
For polymeric form[b]	Paraformaldehyde, Polyoxymethylene, Paraform, Formagene	Budavari et al. 1989
Chemical formula	CH_2O	Aster 1995
Chemical structure		Lide and Frederikse 1996
Identification numbers:		
CAS Registry	50-00-0	Aster 1995
NIOSH RTECS	LP8925000	HSDB 1995
EPA Hazardous Waste	U122	HSDB 1995
OHM/TADS	7216732	HSDB 1995
DOT/UN/NA/IMCO	CLASS 3/UN1198/IMCO 3.2	NFPA 1994
HSDB	164	HSDB 1999
NCI	No data	HSDB 1999

[a] Aqueous solutions of formaldehyde available commercially often contain 10-15% methanol to inhibit polymerization.

[b] Paraformaldehyde is a polymer of formaldehyde and has the formula $(CH_2O)_n$.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Formaldehyde

Property	Information	Reference
Molecular weight	30.03	Lide and Frederikse 1996
Color	Colorless	Budavari et al. 1989
Physical state	Gas	Budavari et al. 1989
Melting point	-92 C	Budavari et al. 1989
Boiling point	-21 C	ASTER 1996
Density at -20 C	0.815 g/mL	Lide and Frederikse 1996
Odor	Pungent, suffocating odor; highly irritating odor	Budavari et al. 1989; NFPA 1994
Odor threshold:		
Water	50 ppm	HSDB 1999
Air	0.5–1.0 ppm	Klaassen 1996
Taste	50 ppm	HSDB 1999
Solubility:		
Freshwater at 20 C	Very soluble; up to 55%	Budavari et al. 1989
Saltwater at 25 C	No data	
Organic solvent(s)	Ether, alcohol, acetone, benzene	Lide and Frederikse 1996; Budavari et al. 1989
Partition coefficients:		
Log K_{ow}	0.350	SRC 1995b
Log K_{oc}	1.567	Calculated from Lyman 1982
	No data, negligible	HSDB 1999
Vapor pressure at 25 C	Gas: vapor pressure>bp; 3,883 mm Hg	HSDB 1999; Howard 1989
Polymerization	Polymerizes; polymerizes readily in water	Budavari et al. 1989
Photolysis	Half-life (in sunlight) 1.6–19 hours producing H_2 and CO or H^+ and HCO^-	Lewis 1993
Henry's law constant at 25 C	3.27×10^{-7} atm-m^3/mol	Howard 1989
Autoignition temperature	300 C	NFPA 1994
Flashpoint	60 C	Budavari et al. 1989
Flammability limits at 25 C	7–73%	NFPA 1994
Incompatibilities	Reacts with alkalies, acids, and oxidizers	NFPA 1994
Conversion factors (25 C)	1 ppb (v/v) = 1.23 μg/m^3 1 μg/m^3 = 0.813 ppb (v/v)	Calculated
Explosive limits	7–73%	Lewis 1993

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Because of its low cost and high purity, formaldehyde has become one of the most important industrial and research chemicals in the world. Between 1958 and 1968, the annual growth rate for formaldehyde production averaged 11.7% (Gerberich et al. 1980). During the late 1960s, production averaged 71% of capacity. The recession of the mid-1970s, however, caused production to drop as low as 54% of capacity (Gerberich et al. 1980). From 1988 to 1997, formaldehyde production averaged an annual growth rate of 2.7% per year (Anonymous 1998). In 1992, formaldehyde ranked 22nd (8.28 billion pounds produced) among the top 50 chemicals produced in the United States (Anonymous 1994). Total annual capacities for the 15–17 U.S. companies listed as the top formaldehyde manufacturers or processors for 1988, 1990, and 1992 were 8.94, 9.70, and 10.08 billion pounds, respectively (SRI 1988, 1990, 1992). The estimated total annual formaldehyde capacity in 1998 was 11.3 billion pounds (Anonymous 1998). With production volumes varying between 6.43 billion pounds and 8.11 billion pounds for 1990, 1991, and the period 1993–1995, formaldehyde ranked either 24th or 25th among the top 50 chemicals produced (Anonymous 1992, 1994, 1995a; Kirschner 1996).

As of 1998, three manufacturers of formaldehyde were responsible for 50% of the annual capacity for the United States: Georgia-Pacific Resins, Inc. (Albany, Oregon; Columbus, Ohio; Conway, North Carolina; Crossett, Arkansas; Grayling, Michigan; Hampton, South Carolina; Healing Springs, North Carolina; Houston, Texas; Lufkin, Texas; Russellville, South Carolina; Taylorsville, Mississippi; Vienna, Georgia; White City, Oregon), Hoechst Celanese Corporation (Bishop, Texas; Rock Hill, South Carolina), and Borden, Inc. (Baytown, Texas; Demopolis, Alabama; Diboll, Texas; Fayetteville, North Carolina; Fremont, California; Hope, Arkansas; Kent, Washington; La Grande, Oregon; Missoula, Montana; Sheboygan, Wisconsin; Springfield, Oregon; Vicksburg, Mississippi) (Anonymous 1998; SRI 1997). In addition to the above facilities, the following companies also contributed to the overall U.S. capacity: Capital Resin (Columbus, Ohio); D.B. Western (Las Vegas, New Mexico; Virginia, Minnesota); Degussa (Theodore, Alabama); DuPont (LaPorte, Texas; Parkersburg, West Virginia); Hercules-Aqualon (Louisiana, Montana); ISP (Calvert City, Kentucky; Texas City, Texas); Monsanto (Alvin, Texas); Neste Resins (five sites); Perstorp (Toledo, Ohio); Praxair (Geismar, Louisiana); Solutia (Alvin, Texas); Spurlock (Malvern, Arkansas; Waverly, Virginia); Trimet Technical Products (Mallinckrodt);

(Allentown, Pennsylvania); and Wright Chemical (Acme, North Carolina) (Anonymous 1998; SRI 1997). Formaldehyde production is predicted to increase 2–3% per year through 2002 (Anonymous 1998).

Table 4-1 lists the facilities in each state that manufacture or process formaldehyde, the intended use, and the range of maximum amounts of formaldehyde that are stored on site. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI96 1998). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. Table 4-2 shows capacity and production volumes for selected years between 1960 and 1978.

Formaldehyde has been manufactured primarily from methanol since the beginning of the century (Gerberich et al. 1980). Because methanol is manufactured from synthesis gas, usually produced from methane, there have been extensive efforts to develop a one-step process that partially oxidizes methane to formaldehyde. Although a successful commercial process has not been developed, a wide range of catalysts and oxidation conditions have been studied (Gerberich et al. 1980). During the decades following World War II, approximately 20% of the production volume in the United States was manufactured by vapor phase, non-catalytic oxidation of propane and butane (Gerberich et al. 1980).

Two primary methods of manufacturing formaldehyde from methanol are used today. The first uses silver as a metal catalyst in its reactions. In earlier years, facilities used a copper catalyst in this process. The simultaneous reactions involved in the metal catalyst process occur at essentially atmospheric pressure and 600–650 C (Gerberich et al. 1980). Approximately 50–60% of the formaldehyde produced using the metal catalyst process is formed during an exothermic reaction; the remainder is formed from an endothermic reaction. The overall yield for this process is 86–90% formaldehyde. The domestic licensors for this process include Borden Chemical Company and Davy Powergas, Inc. (Gerberich et al. 1980).

The second method uses a metal oxide catalyst. All of the formaldehyde is produced from an exothermic reaction occurring at atmospheric pressure and 300–400 C. The patent for formaldehyde production using a vanadium pentoxide catalyst was issued in 1921. Although the patent for an iron oxide-molybdenum oxide catalyst was issued in 1933, the first commercial facility did not begin operating until 1952 (Gerberich et al. 1980).

Gaseous formaldehyde can be regenerated from paraformaldehyde by heating (Gerberich et al. 1980).

Table 4-1. Facilities That Manufacture or Process Formaldehyde

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
AK	1	100,000 - 999,999	8
AL	30	0 - 499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,
AR	15	0 - 9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 12
AZ	3	100 - 9,999	1, 5, 7, 9, 12, 13
CA	26	100 - 9,999,999	1, 3, 4, 5, 7, 8, 9, 11, 12
CO	2	0 - 9,999	12
CT	8	100 - 9,999,999	2, 3, 7, 8, 12
DE	1	10,000 - 99,999	8
FL	6	0 - 99,999	1, 6, 7, 9, 11, 13
GA	35	0 - 999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
IA	5	1,000 - 999,999	7 ,8 ,9 ,10
IL	27	0 - 999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
IN	15	100 - 999,999	1, 5, 7, 8, 9, 11, 12,13
KS	8	100 - 999,999	1, 2, 5, 7, 8, 11, 13
KY	8	1,000 - 9,999,999	1, 3, 4, 7, 8, 10, 11, 12, 13
LA	31	0 - 9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 13
MA	10	1,000 - 9,999,999	1, 3, 4, 7, 8, 9, 11, 13
MD	2	1,000 - 9,999	7, 8, 9
ME	3	1,000 - 999,999	1, 5, 6, 7, 12
MI	33	0 - 9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
MN	15	0 - 999,999	1, 5, 6, 7, 8, 9, 10, 11, 12
MO	12	0 - 9,999,999	1, 3, 4, 6, 7, 8, 11, 12, 13
MS	16	0 - 9,999,999	1, 3, 4, 5, 6, 7, 8, 9
MT	4	0 - 9,999,999	1, 3, 4, 6, 7, 8, 9
NC	39	0 - 9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
NH	4	100 - 999,999	7, 11, 12
NJ	18	100 - 999,999	1, 3, 5, 7, 8, 9, 10, 12, 13
NM	1	100 - 999	9
NV	1	1,000 - 9,999	7
NY	25	100 - 999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
OH	50	0 - 9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
OK	4	100 - 999,999	1, 6, 7, 8
OR	25	100 - 9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 13
PA	21	0 - 9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
PR	4	1,000 - 99,999	2, 3, 7, 11, 12, 13
RI	4	100 - 99,999	1, 3, 5, 7, 8, 9, 10, 11
SC	40	0 - 9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
SD	1	100 - 999	8
TN	8	0 - 9,999,999	1, 5, 7, 8, 11, 12, 13
TX	55	0 - 9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13
UT	4	1,000 - 9,999	1, 5, 7, 11

Table 4-1. Facilities That Manufacture or Process Formaldehyde (continued)

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
VA	26	0 - 9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
VT	1	100 - 999	2, 3, 9, 11
WA	8	0 - 9,999,999	1, 3, 4, 5, 6, 7, 8, 11
WI	24	0 - 9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 13
WV	10	100 - 9,999,999	1, 3, 5, 7, 8, 10, 11

Source: TRI96 1998

[a] Post office state abbreviations used

[b] Range represents maximum amounts on site reported by facilities in each state

[c] Activities/uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation component
9. Article component
10. Repackaging
11. Chemical processing aid
12. Manufacturing aid
13. Ancillary/other uses

Table 4-2. U.S. Formaldehyde Capacity and Production

Year	Capacity (10^3 tons/year)	Production volume (10^3 tons/year)
1960	1,111	848
1965	1,613	1,409
1970	Not available	2,008
1975	3,803	2,067
1977	4,005	2,742
1978	4,086	2,948
1982	Not available	2,185
1986	Not available	2,517
1990	Not available	3,048

Source: Gerberich et al. 1980; data for 1982, 1986, and 1990 are from IARC 1995.

4.2 IMPORT/EXPORT

The Chemical Marketing Reporter (CMR) reported that 140 million pounds of formaldehyde were imported into the United States in 1997. In 1994, import and export volumes were 87 and 25 million pounds, respectively (Anonymous 1995b). The export volume for the same year was reported as 25 million pounds (Anonymous 1998).

4.3 USE

Formaldehyde has been used for many years in consumer goods to deter spoilage caused by microbial contamination (WHO 1989). It has been used as a preservative in household cleaning agents, dish-washing liquids, fabric softeners, shoe-care agents, car shampoos and waxes, and carpet-cleaning agents (WHO 1989). Generally, the formaldehyde content in these products is less than 1% (WHO 1989).

Formaldehyde is used as a chemical intermediate in the manufacture of a large variety of organic compounds, ranging from amino and phenolic resins to slow release fertilizers (Gerberich et al. 1980). Table 4-3 shows the distribution of formaldehyde use for select periods between 1963 and 1977. The demand for formaldehyde in North America was 11.6 billion pounds in 1995, a slight increase from the 11.3 billion pounds reported for 1994 (Anonymous 1995b). These figures include the import and export volumes discussed in Section 4.2. The demand for formaldehyde will continue to track the demand in the housing industry and the various board products used in residential construction and furniture (Anonymous 1998). The most prominent use of formaldehyde in the United States is manufacturing urea-formaldehyde resins; 23% of the annual capacity is used in this market (Anonymous 1998). In 1993, the urea-formaldehyde resins market was described as being mature. Approximately 95% of the particle board products manufactured are based on urea-formaldehyde resins; the remainder are based on phenolic-resins (Gerberich et al. 1980). The market's average annual growth rate of 1–1.5% is projected to continue through 1997 (Anonymous 1993). Urea formaldehyde resins are also used as urea formaldehyde foam insulation or as reinforcing foams in the insulation of buildings and in mining, where hollow areas are filled with the foam (WHO 1989). Anonymous (1993) also reports that the fastest growing formaldehyde market in the United States is in the production of acetylenic chemicals and methylene diisocyanate (MDI). The most recent breakdown found for formaldehyde use is the following: urea-formaldehyde, 23%; phenolic resins, 19%; acetylenic chemicals, 12%; polyacetal resins, 11%; MDI, 6%; pentaerythritol, 5%; urea-formaldehyde concentrates, 4%; hexamethylenetetramine

Table 4-3. Distribution of Formaldehyde Production According to Uses in the United States

	Percentage of consumption				
	1963	1969	1972	1975	1977
Phenol-formaldehyde resins	22	22	26	22	25
Urea-formaldehyde resins	21	25	26	25	25
Acetal resins	4	6	7	7	9
Acetylenics	Not available	2	4	7	6
Melamine resins	6	7	6	3	5
Pentaerythritol	9	7	7	7	5
Hexamethylenetetramine	6	9	6	5	5
Fertilizer	3	3	4	4	Not available
Trimethylolpropane	Not available	1.1	1.5	1.5	Not available
Ethylene glycol	12	4	0	0	0
Miscellaneous	17	14	12	18	20

Source: Gerberich et al. 1980

(HMTA), 4%; melamine resins, 4%; and miscellaneous (including chelating agents, trimethylolpropane, pyridine chemicals, nitroparaffin derivatives, textiles treating, and trimethylolethane), 12% (Anonymous 1998).

The use of formaldehyde in the manufacture of chelating agents represents a modest but important market for formaldehyde. Approximately 75% of the formaldehyde used in the synthesis of chelating agents is consumed in the manufacture of ethylenediaminetetraacetic acid (EDTA). The remaining 25% is used to produce nitrilotriacetic acid (NTA), primarily for export (Gerberich et al. 1980).

Products manufactured using organic compounds, where formaldehyde is used as a chemical intermediate in their production, include: plywood adhesives, abrasive materials, insulation, foundry binders, and brake linings made from phenolic resins; surface coatings, molding compounds, laminates, and wood adhesives made from melamine resins; phenolic thermosetting, resins curing agents, and explosives made from hexamethylenetetramine; urethanes, lubricants, alkyd resins, and multifunctional acrylates made from trimethylolpropane; plumbing components from polyacetal resins; and controlled- release fertilizers made from urea formaldehyde concentrates (WHO 1989). Polyacetal plastics produced by polymerization of formaldehyde are incorporated into automobiles to reduce weight and fuel consumption. They are also used in the manufacture of functional components of audio and video electronics equipment (IARC 1995).

Formaldehyde solutions have also been used for disinfecting dwellings, ships, storage houses, utensils, and clothing (Windholz et al. 1983). Solutions containing 2–8% formaldehyde have been used as germicides to disinfect inanimate objects (HSDB 1999). Formaldehyde is used as a tissue preservative and disinfectant in embalming fluids.

In the agricultural industry, formaldehyde has been used as a fumigant, as a preventative for mildew and spelt in wheat, and for rot in oats (HSDB 1999). It has been used as a preplanting soil sterilant in mushroom houses (HSDB 1999). Formaldehyde has been used as a germicide and fungicide for plants and vegetables; as an insecticide for destroying flies and other insects; and in the manufacture of slow-release fertilizers. Approximately 80% of the slow-release fertilizer market is based on urea-formaldehyde-containing products (HSDB 1999). During the early 1980s, seed treatments, starch formulations, and paper production were included among the minor uses for formaldehyde (IARC 1982). Formaldehyde continues to be used in the manufacture of glass mirrors, explosives, artificial silk, and

dyes; for waterproofing fabrics; for preserving and coagulating rubber latex; and for tanning and preserving animal hides (Windholz et al. 1983). In the photography industry, formaldehyde has been used for hardening gelatin plates and papers, toning gelatin-chloride papers, and for chrome printing and developing (Windholz et al. 1983).

Formaldehyde is used as an antimicrobial agent in many cosmetics products, including soaps, shampoos, hair preparations, deodorants, lotions, make-up, mouthwashes, and nail products (IARC 1995). Formaldehyde is incompatible with ammonia; alkalies; tannin; iron preparations; and salts of copper, iron, silver, potassium permanganate, iodine, and peroxide (Windholz et al. 1983). When it is used as a preservative in shampoos, formaldehyde may interact unfavorably with both fragrance components and color additives (HSDB 1999). Some cosmetics have reportedly contained 0.6% formaldehyde, while concentrations as high as 4.5% have been detected in nail hardeners. Formaldehyde concentrations in dry-skin lotions, creme rinses, and bubble bath oils have reportedly ranged from 0.4 to 0.5% (WHO 1989). Formaldehyde has also been found in sun-tan lotion and hand cream (Bartnik et al. 1985), bath products, mascara and eye make-up, cuticle softeners, nail creams, vaginal deodorants, and shaving creams. Trace amounts of formaldehyde found in cosmetic products could also result from its use as a disinfectant of the manufacturing equipment (WHO 1989).

Compared to its use in product manufacturing, the use of formaldehyde in the medical fields is relatively small. Consumption in this area averages approximately 1.5% of the total production volume (WHO 1989). Some of the earlier, minor, medicinal applications for formaldehyde included its use during vasectomies, as a foot antiperspirant or as a preservative in such products, as a treatment for athlete's foot, and as a sterilant for *echinococcus* cysts prior to their surgical removal (IARC 1982). In veterinary medicine, formaldehyde has been used therapeutically as an antiseptic and as a fumigant. It has also been used to treat tympany, diarrhea, mastitis, pneumonia, and internal bleeding in animals (Windholz et al. 1983). In animal nutrition, formaldehyde is used to protect dietary protein in ruminants. It is used as a food additive to improve the handling characteristics of animal fat and oilseed cattle food mixtures (WHO 1989).

Other industries using formaldehyde in their processes include the sugar industry where formaldehyde is used as an infection inhibitor in producing juices; the rubber industry where it is used as a biocide for latex, an adhesive additive, and an anti-oxidizer additive for synthetic rubber; and the food industry where it is used for preserving dried foods, disinfecting containers, preserving fish and certain oils and

fats, and modifying starch for cold swelling (WHO 1989). It has been use as a bacteriostatic agent in some foods, such as cheese (IARC 1995). In the petroleum industry, formaldehyde is used as a biocide in oil well-drilling fluids and as an auxiliary agent in refining. Formaldehyde has been used as an anti-corrosive agent for metals. In the plastics industry, for the preparations of phenol, urea, and melamine resins, where the presence of water could interfere with the production process, paraformaldehyde may be used in place of aqueous formaldehyde solutions (IARC 1995). In addition to its use in selected pesticide applications, paraformaldehyde has also been used in making varnish resins, thermosets, and foundry resins, the synthesis of chemical and pharmaceutical products, the preparation of disinfectants and deodorants, and the production of textile products (IARC 1995). Formaldehyde was used in the textile industry as early as the 1950s when formaldehyde-based resins were initially used to produce crease-resistant fabrics. Postproduction analysis indicated that these early resins contained a substantial amount of extractable formaldehyde (more than 0.4% by weight of the fabric) (IARC 1995). With the introduction of new resins and other process modifications in the 1970s, the level of extractable formaldehyde in crease-resistant fabrics gradually decreased to 0.01–0.02% (IARC 1995).

4.4 DISPOSAL

The regulations governing the treatment and disposal of formaldehyde-containing wastes are detailed in Chapter 7. Formaldehyde manufacturing is listed among the regulations for commodity organic chemicals for which process waste water discharges are regulated by the Clean Water Effluent Guidelines given in Title 40, Section 414, of the Code of Federal Regulations (CFR) (EPA 1987a).

The Resource Conservation and Recovery Act (RCRA) identifies formaldehyde as a toxic waste if it is discarded as a commercial product, manufacturing intermediate, or off-specification commercial chemical product (EPA 1980). Formaldehyde is identified as the hazardous constituent in waste assigned the hazardous waste number U122 under RCRA (EPA 1988b). Formaldehyde is also among the chemicals that are on the listed hazardous waste identified by the #K010 (EPA 1981). The technology-based standards given in 40 CFR 268.42 identify wet air oxidation, chemical, or electrolytic oxidation followed by carbon adsorption, or incineration as the treatment process for waste waters containing formaldehyde (EPA 1986b). For nonwaste waters, the regulations suggest that the materials be used as fuel substitutes in hazardous waste disposal units (EPA 1986b). When formaldehyde is disposed of in a rotary kiln incinerator, the unit should be operated at a temperature range of 820–1,600 C (HSDB 1999). Disposal of formaldehyde in a fluidized bed incinerator requires an operating temperature range

of 450–980 C (HSDB 1999). The residence time identified for incineration is a matter of seconds. Evaporation and alkaline hydrolysis are not recommended for the disposal of formaldehyde or formaldehyde-containing wastes (IRPTC 1985).

5. POTENTIAL FOR HUMAN EXPOSURE

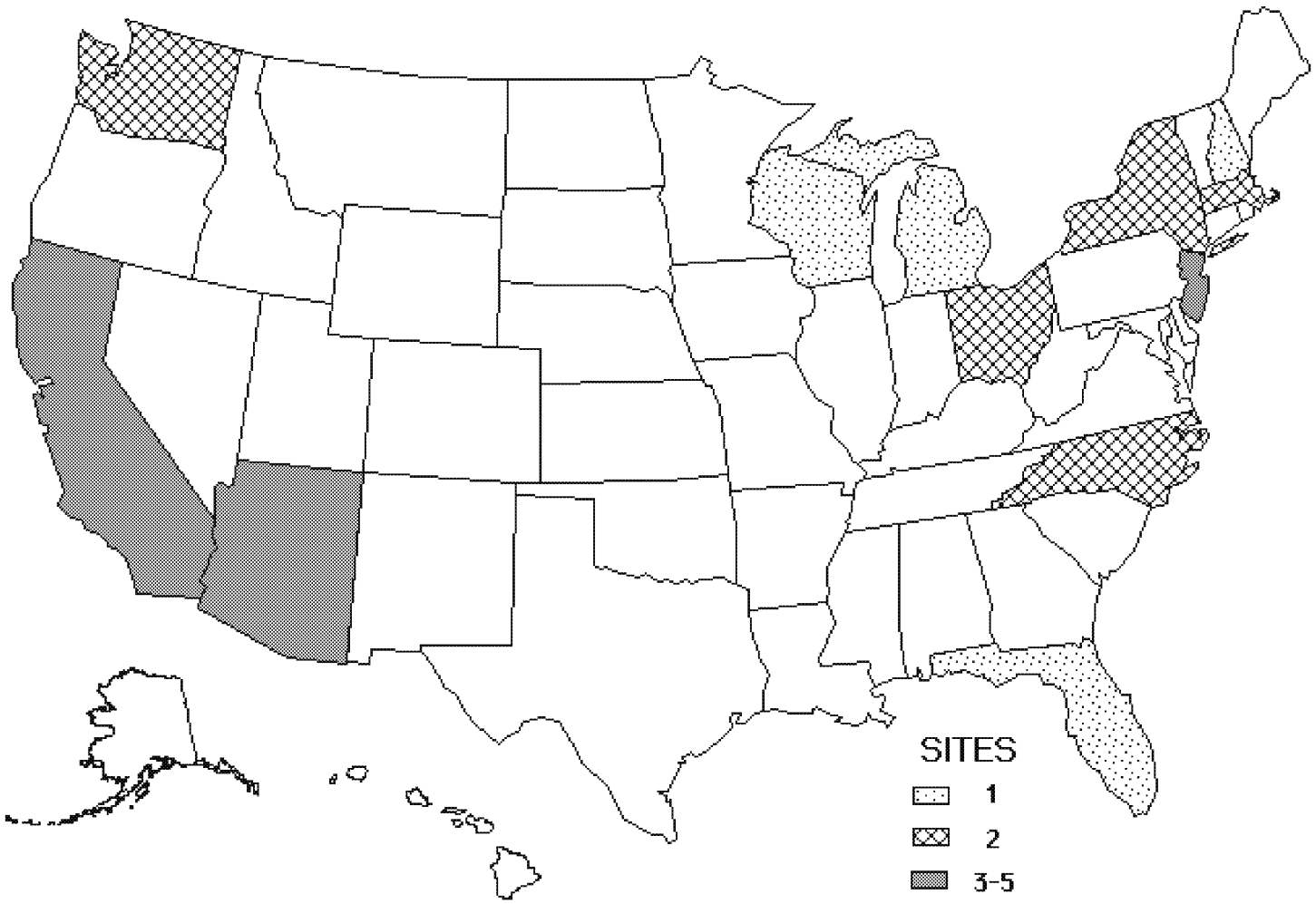
5.1 OVERVIEW

Formaldehyde is produced by both anthropogenic and natural sources. Combustion processes account directly or indirectly for most of the formaldehyde entering the environment. Direct combustion sources include power plants, incinerators, refineries, wood stoves, kerosene heaters, and cigarettes. Formaldehyde is produced indirectly by photochemical oxidation of hydrocarbons or other formaldehyde precursors that are released from combustion processes (NRC 1981). During smog episodes, indirect production of formaldehyde may be greater than direct emissions (Fishbein 1992). Oxidation of methane is the dominant source of formaldehyde in regions remote from hydrocarbon emissions (Staffelbach et al. 1991). Other anthropogenic sources of formaldehyde in the environment include vent gas from formaldehyde production; exhaust from diesel and gasoline-powered motor vehicles; emissions from the use of formaldehyde as a fumigant, soil disinfectant, embalming fluid, and leather tanning agent; emissions from resins in particle board, and plywood; emissions from resin-treated fabrics and paper; waste water from the production and use of formaldehyde in the manufacture of various resins and as a chemical intermediate; and waste water from the use of formaldehyde-containing resins (EPA 1976a; Kleindienst et al. 1986; NRC 1981; Verschueren 1983). Natural sources of formaldehyde include forest fires, animal wastes, microbial products of biological systems, and plant volatiles.

Formaldehyde has been identified in at least 26 of the 1,428 current or former EPA National Priorities List (NPL) hazardous wastes sites (HazDat 1996). However, the number of sites evaluated for formaldehyde is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

Although formaldehyde is found in remote areas, it probably is not transported there but is generated from longer-lived precursors that have been transported there (NRC 1981). Formaldehyde is soluble and will transfer into rain and surface water. Based upon the Henry's law constant for formaldehyde, volatilization from water is not expected to be significant. No experimental data were found concerning the adsorption of formaldehyde to soil, but because of the low octanol/water partition coefficient (log K_{ow}=0.35) (SRC 1995b), little adsorption to soil or sediment is expected to occur. No evidence of bioaccumulation has been found.

Figure 5-1. Frequency of NPL Sites with Formaldehyde Contamination



Derived from HazDat 1996

The input of formaldehyde into the environment is counterbalanced by its removal by several pathways. Formaldehyde is removed from the air by direct photolysis and oxidation by photochemically produced hydroxyl and nitrate radicals. Measured or estimated half-lives for formaldehyde in the atmosphere range from 1.6 to 19 hours, depending upon estimates of radiant energy, the presence and concentrations of other pollutants, and other factors (Atkinson and Pitts 1978; DOT 1980; EPA 1982; Lowe et al. 1980; Su et al. 1979). When released to water, formaldehyde will biodegrade to low levels in a few days (Kamata 1966). In water, formaldehyde is hydrated; it does not have a chromophore that is capable of absorbing sunlight and photochemically decomposing (Chameides and Davis 1983).

Levels of formaldehyde in the atmosphere and in indoor air are well documented. In a survey of ambient measurements of hazardous air pollutants, a median formaldehyde concentration of 2.5 ppb was found for a total of 1,358 samples collected at 58 different locations (Kelly et al. 1994). In several separate studies involving rural and urban areas in the United States, atmospheric concentrations ranged from 1 to 68 ppb (Grosjean 1982; Salas and Singh 1986; Schulam et al. 1985; Singh et al. 1982). Generally, indoor residential formaldehyde concentrations are significantly higher than outdoor concentrations. Formaldehyde concentrations measured in complaint homes (homes where people have complained of adverse symptoms), mobile homes, and homes containing large quantities of particle board or urea-formaldehyde foam insulation (UFFI) have been measured at 0.02 ppm to 0.8 ppm, with levels as high as 4 ppm, sufficient to cause irritating symptoms, observed in some instances (Gold et al. 1993). Since the time many of the above monitoring studies were performed, plywood and particle board manufacturing methods have been changed to reduce the formaldehyde emission levels in the finished product (EPA 1996). Similarly, home construction methods have changed and the use of UFFI has been greatly reduced since the mid-eighties (CPSC 1997). A recent pilot study on a newly constructed home reported localized formaldehyde concentrations of 0.076 ppm (Hare et al. 1996). Approximately 30 days after the installation of pressed wood products, the average indoor concentration attained a level of 0.035–0.45 ppm. Older conventional homes tend to have the lowest indoor concentrations of formaldehyde, with values typically less than 0.05 ppm (Gold et al. 1993), and mobile homes the highest due to their low rate of air exchange (Wolff 1991).

Although pressed wood products may be a source of formaldehyde in indoor air, there are numerous others. These include permanent press fabrics, fiberglass products, decorative laminates, paper goods, paints, wallpaper, and cosmetics (Kelly et al. 1996). Its presence in indoor air also results from combustion sources, such as stoves, heaters, or burning cigarettes (Matthews et al. 1985; NRC 1981).

Formaldehyde may also arise from the degradation of volatile organic chemicals commonly found in indoor air (Weschler and Shields 1996; Zhang et al. 1994b).

Formaldehyde is unstable in water; however, it has been detected in municipal and industrial aqueous effluents, rainwater, lake water, and some waterways (EPA 1976b; Hushon et al. 1980). Formaldehyde levels in rainwater collected in California are low, ranging from not detectable to 0.06 μg/mL (Grosjean and Wright 1983). Measured concentrations of formaldehyde range from 0.12 to 6.8 mg/L in fogwater (Igawa et al. 1989; Muir 1991); from 1.4 to 1.8 mg/L in cloudwater (Igawa et al. 1989); and from 0.25 to 0.56 mg/L in mist samples (Grosjean and Wright 1983). No data on formaldehyde levels in soil could be found in the literature.

Formaldehyde was found in three types of chewing tobacco (Chou and Que Hee 1994) and in cigarette smoke (Mansfield et al. 1977). Formaldehyde has also been found at levels ranging from 1 to 3,517 ppm in fabric samples (Schorr et al. 1974).

A major route of formaldehyde exposure for the general population is inhalation of indoor air; releases of formaldehyde from new or recently installed building materials and furnishings may account for most of the exposure. Environmental tobacco smoke may contribute 10–25% of the exposure. Since formaldehyde in food is not available in free form, it is not included in estimated exposures (Fishbein 1992). Consumers can be exposed to formaldehyde gas through its use in construction materials, wood products, textiles, home furnishings, paper, cosmetics, and pharmaceuticals. Dermal contact with formaldehyde containing materials, including some paper products, fabrics, and cosmetics, may also lead to consumer exposure. Commuters may be exposed to formaldehyde while riding in automobiles or subways, walking, and biking (Chan et al. 1991).

Occupational exposure to formaldehyde can occur during its production and during its use in the production of end products, in the garment industry, in the building materials industry, and in laboratories. Health care professionals may be exposed to formaldehyde vapors during preparation, administration, and/or cleanup of various medicines. Pathologists, histology technicians, morticians, and teachers and students who handle preserved specimens may also be exposed. The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983 indicated that 1,329,332 workers in various professions were exposed to formaldehyde in the United States (NIOSH 1995b).

A subpopulation with potentially high exposures to formaldehyde are residents of mobile homes due to the frequent use of pressed wood products and their low rate of air exchange (Wolff 1991). Members of the general population who come in contact with a large amount of unwashed permanent press fabrics treated with formaldehyde-releasing resins may also be exposed to high levels.

5.2 RELEASES TO THE ENVIRONMENT

According to the Toxics Release Inventory (TRI), in 1996, 21 million pounds (9.6 million kg) of formaldehyde were released to the environment from 674 domestic manufacturing and processing facilities (TRI96 1998). This number represents the sum of all releases of formaldehyde to air, water, soil, and underground injection wells. An additional 1.8 million pounds (0.8 million kg) were transferred to publicly owned treatment works (POTWs), and 1.3 million pounds (0.6 million kg) were transferred off-site (TRI96 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995). This is not an exhaustive list.

5.2.1 Air

Formaldehyde is released to outdoor air from both natural and industrial sources. Combustion processes account directly or indirectly for most of the formaldehyde entering the atmosphere. One important source of formaldehyde is automotive exhaust from engines not equipped with catalytic converters (WHO 1989). Automobiles were found to emit about 610 million pounds (277 million kg) of formaldehyde each year (EPA 1976a). Emissions were reduced with the introduction of the catalytic converter in 1975 (Zweidinger et al. 1988); although they have been found to rise again with the introduction of oxygenated fuels (Kirchstetter et al. 1996). Gaffney and coworkers found that in urban areas the introduction of oxygenated fuels led to increased anthropogenic emissions of formaldehyde during the winter, the season these fuels are used (Gaffney et al. 1997). Formaldehyde in vehicle emissions in 1994 were found to increase by 13% within 2 months after the average oxygen content of fuels sold in the San Francisco Bay area increased from 0.3 to 2.0% by weight (Kirchstetter et al. 1996).

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Formaldehyde

		Total of reported amounts released in pounds per year [a]						
State[b]	Number of Facilities	Air[c]	Water	Land	Underground Injection	Total Environment[d]	POTW[e] Transfer	Off-site Waste Transfer
AK	1	375	0	0	0	375	0	0
AL	31	477,346	1,312	361	0	479,019	2,854	23,887
AR	15	204,464	735	5	0	205,204	1,015	5,229
AZ	3	12,873	0	0	0	12,873	13,000	13,140
CA	25	417,661	250	769	0	418,680	68,609	3,658
CO	2	2,062	0	0	0	2,062	170	0
CT	6	27,833	4,581	0	0	32,414	29,641	16,967
DE	1	1,965	0	0	0	1,965	0	0
FL	6	95,126	1,522	37	0	96,685	0	1,000
GA	36	702,021	714	500	0	703,235	4,600	12,600
IA	4	30,736	400	0	0	31,136	580	1,605
IL	24	37,944	2,084	204	0	40,232	22,900	67,527
IN	15	76,532	0	0	0	76,532	47,761	5,171
KS	8	278,316	0	0	27,000	305,316	10,320	1,198
KY	8	65,275	21,902	0	0	87,177	1,510	27,180
LA	31	330,423	15,674	382	8,601,956	8,948,435	0	76,529
MA	10	60,059	10	1,500	0	61,569	809,791	17,273
MD	2	5,517	0	0	0	5,517	0	6,175
ME	3	121,198	0	0	0	121,198	5,229	58
MI	30	205,766	2,396	12,553	250	220,965	493,193	227,079
MN	15	536,241	0	0	0	536,241	17,250	3,945
MO	12	441,774	1,127	5	0	442,906	19,343	67,062
MS	16	477,785	1,102	2	0	478,889	0	4,671
MT	4	100,214	0	0	0	100,214	0	250
NC	39	1,048,939	6,689	1,201	0	1,056,829	15,905	38,161
NH	4	5,582	9,419	4,100	0	19,101	6,372	512
NJ	18	52,595	3,977	250	0	56,822	42,613	2,509
NM	1	4,570	0	0	0	4,570	0	0

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Formaldehyde (continued)

		Total of reported amounts released in pounds per year [a]						
State[b]	Number of Facilities	Air[c]	Water	Land	Underground Injection	Total Environment[d]	POTW[e] Transfer	Off-site Waste Transfer
NV	1	4,001	0	0	0	4,001	0	802
NY	23	280,861	8,409	40	0	289,310	8,103	56,005
OH	49	1,031,374	87,225	87,335	13,000	1,218,934	126,617	173,090
OK	4	64,911	4	0	0	64,915	0	13,642
OR	25	1,070,119	3,600	20	0	1,073,739	24,928	15,676
PA	21	274,854	1,331	0	0	276,185	0	16,703
PR	4	2,766	0	0	0	2,766	20,827	530
RI	4	4,753	0	0	0	4,753	2,042	0
SC	39	752,317	57,542	3,800	0	813,659	16,718	217,365
SD	1	55,731	0	0	0	55,731	0	0
TN	8	295,461	1,170	397	0	297,028	8,329	5,493
TX	55	996,970	31,770	500	761,069	1,790,309	4,557	60,341
UT	4	18,313	0	0	0	18,313	23,568	285
VA	25	369,447	956	232	0	370,635	15,059	31,235
VT	1	333	0	0	0	333	0	0
WA	8	109,080	45,720	0	0	154,800	3,028	760
WI	22	138,117	7,422	213	0	145,752	17,204	53,649
WV	10	128,600	960	0	0	129,560	5,136	14,154
	Totals	11,419,200	320,003	114,406	9,403,275	21,256,884		

Source: TRI96 1998

[a] Data in TRI are maximum amounts released by each facility
[b] Post office state abbreviations used
[c] The sum of fugitive and stack releases are included in releases to air by a given facility
[d] The sum of all releases of the chemical to air, land, water, and underground injection wells; and transfers off-site by a given facility
[e] POTW = publicly-owned treatment works

Formaldehyde concentrations in jet engine exhaust have been found to range from 0.761 to 1.14 ppm (Miyamoto 1986). Formaldehyde is formed in large quantities in the troposphere by the oxidation of hydrocarbons (Calvert et al. 1972; WHO 1989) leading to elevated formaldehyde levels shortly after periods of high vehicular traffic (Grosjean et al. 1996).

Statistical analyses of formaldehyde data from four sites in New Jersey have been used to evaluate the effects of automobile traffic and photochemical formation on formaldehyde concentrations (Cleveland et al. 1977). Integrated formaldehyde concentrations during the hours 5:00 a.m. to 8:00 p.m. decreased from workdays to Saturdays to Sundays, corresponding to a decrease in motor vehicle traffic. On workdays, formaldehyde concentrations were higher on days with more photochemical activity.

Altshuller (1993) investigated the sources of aldehydes in the atmosphere during the night and early morning hours (between 9:00 p.m. and 9:00 a.m.). At night, the predominant sources of aldehydes should be the reaction of alkenes with O_3 and NO_3; during the early daylight hours, OH radical reactions with alkenes and alkanes will also contribute to aldehyde production. Altshuller (1993) found that, although the emissions of formaldehyde from vehicular exhaust are substantial relative to emissions of alkenes from vehicular exhaust, the secondary atmospheric production of aldehydes from the alkenes emitted from all vehicular sources during the period 9:00 p.m. to 9:00 a.m. can exceed the primary emissions of formaldehyde. However, if there is a large shift in the future to vehicles fueled with methanol and/or natural gas, formaldehyde emissions from the exhaust could predominate over the secondary emissions of formaldehyde during the 9:00 p.m. to 9:00 a.m. period. It should be noted that the rate of secondary production of aldehydes during the period 9:00 p.m. to 9:00 a.m. is much less than during the late morning and afternoon hours (Altshuller 1993).

Grosjean et al. (1983) estimated the relative contributions of direct emissions and atmospheric photochemistry to levels of formaldehyde and other carbonyls in Los Angeles using measurements made simultaneously at a near-source site and at a site where the air quality was dominated by transport of polluted air masses from the downtown area (downwind smog receptor site). They found that the formaldehyde/carbon monoxide ratios were substantially higher at the downwind locations (average values, 3.2–11.7) than at the near-source site (average value, 1.8), indicating that photochemical production predominates over direct emissions in controlling formaldehyde levels in Los Angeles air. Using two models, their data were translated into formaldehyde photochemical production rates of 12–161 tons per day.

The amount of formaldehyde released to the atmosphere in 1996 by U.S. industrial facilities sorted by state is given in Table 5-1 (TRI96 1998). According to TRI96 (1998), an estimated total of 11.4 million pounds (5.2 million kg) of formaldehyde, amounting to approximately 54% of the total environmental release, was discharged to the air from 674 manufacturing and processing facilities in the United States in 1996. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Dempsey (1993) estimated the masses of selected organic emissions from hazardous waste incinerators (HWIs) on a nationwide scale using "reasonable worst-case" assumptions. Formaldehyde emissions formed during combustion of hazardous wastes were estimated to be 892 ng/L, which would result in a release of 7.8 tons of formaldehyde to the air per year. When compared to the 1990 TRI air release data from U.S. manufacturing operations, formaldehyde emissions from HWIs were found to be very small (0.12%).

There is a potential for release of formaldehyde to air from hazardous waste sites. Formaldehyde has been detected in air samples collected at 5 of the 26 hazardous waste sites where formaldehyde has been detected in some environmental medium (HazDat 1996).

Pressed wood products contribute to indoor formaldehyde levels. Combustion sources and phenol-formaldehyde resin bonded products generally are weak emitters to indoor air. Common indoor combustion sources include gas burners and ovens, kerosene heaters, and cigarettes (Matthews et al. 1985).

Formaldehyde also arises in the atmosphere from natural sources. In monitoring studies performed in New Mexico, 1993–94, Gaffney and coworkers looked at total (average) formaldehyde concentrations and formaldehyde:acetaldehyde ratios (Gaffney et al. 1997). These researchers reported that if formaldehyde and acetaldehyde were being formed solely from the atmospheric oxidation of naturally occurring alkenes, the ratio of the two chemicals would be expected to be about 10. In this study, the formaldehyde:acetaldehyde ratio was lowest during the winter months and highest in the summer months. Gaffney et al. (1997) concluded that atmospheric formaldehyde in urban areas resulted from both anthropogenic emissions and natural sources in the summer and primarily from anthropogenic sources during the winter.

In a study conducted at the Inhalation Toxicology Research Institute, formaldehyde release rate coefficients were measured for six types of consumer products (Pickrell et al. 1983). Release rates calculated per unit surface area (μg/m^2/day) were used to rank the products in the following order: pressed wood products > >clothes insulation products paper products > fabric > carpet. Release rates from pressed wood products ranged from below the limit of detection for an exterior plywood to 36,000 μg/m^2/day for some paneling. Other release rates were: for articles of new clothing not previously washed, 15–550 μg/m^2/day; for insulation products, 52–620 μg/m^2/day; for paper plates and cups, 75–1,000 μg/m^2/day; for fabrics, from below the limit of detection to 350 μg/m^2/day; and for carpets, from below the limit of detection to 65 μg/m^2/day. In a follow-up to Pickrell's study (Pickrell et al. 1984), performed as a result of changes to product manufacturing processes, many of these release rates were reinvestigated. Formaldehyde release rates for a variety of bare urea-formaldehyde wood products (1/4 to 3/4") were reported to range from 8.6 to 1,578 μg/m^2/hr, coated urea-formaldehyde wood products from 1 to 461 μg/m^2/hr, permanent press fabrics from 42 to 214 μg/m^2/hr, decorative laminates from 4 to 50 μg/m^2/hr, fiberglass products from 16 to 32 μg/m^2/hr, and bare phenol-formaldehyde wood products from 4 to 9 μg/m^2/hr (Kelly et al. 1996). Paper grocery bags and towels had emission rates of 0.4 and <0.3 μg/m^2/hr, respectively. For wet products, the emission rates were: latex paint 591 μg/m^2/hr; more expensive latex paint 326 μg/m^2/hr; fingernail hardener 215,500 μg/m^2/hr; nail polish 20,700 μg/m^2/hr; and commercially applied urea-formaldehyde floor finish 421 and 1,050,000 μg/m^2/hr for base and topcoats, respectively (Kelly et al. 1996).

Formaldehyde may also arise in indoor air through the degradation of other organic compounds. Naturally occurring unsaturated hydrocarbons, such as limonene and pinene (which may also be released from consumer products), and anthropogenic compounds, such as 4-vinylcyclohexene (an emission from carpet padding), and other alkenes commonly found in indoor air have been found to produce formaldehyde via their initial reaction with ozone (Weschler and Shields 1996; Zhang et al. 1994b). Reiss and coworkers estimated that the amount of formaldehyde released by this process is 0.87 μg/sec in winter months and 2.43 μg/sec in the summer (Reiss et al. 1995).

In another study on indoor formaldehyde emissions, quasi steady-state emission rates of formaldehyde from new carpets were measured in a large-scale environmental chamber (Hodgson et al. 1993). The emission rates were 57.2 and 18.2 μg/m^2/hour at 24 and 168 hours, respectively, after the start of each experiment. Similar results were observed in a Swedish study where indoor formaldehyde levels were found to be higher in homes having wall to wall carpeting (Norback et al. 1995). Another recent

Swedish study on indoor emissions reported that oil-based skin care products known to contain formaldehyde precursors (donors) released formaldehyde to the air even if the material had been in storage for one year (Karlberg et al. 1998).

Formaldehyde release from pressed wood products is due to latent formaldehyde. During the pressing process, hot steam from moist wood particles transfers heat, formaldehyde, and other volatiles from the surface of the mat to the core of the board where unreacted urea-formaldehyde resin components accumulate. The resulting formaldehyde concentration in the core is approximately twice that of the surface. Release of formaldehyde is diffusion-controlled and gradually decreases over time (Meyer and Hermanns 1985). Formaldehyde can also be produced by hydrolytic cleavage of unreacted hydroxy-methyl groups in the formaldehyde resins. Melamine formaldehyde resins generally are more stable, and the amounts of formaldehyde emitted from them are much lower (WHO 1989).

A formaldehyde emission rate of 0.48 μg/kilojoule has been determined for normal operation of unvented gas ranges; however, this emission rate leads to relatively low indoor formaldehyde concentrations (Moschandreas et al. 1986). Formaldehyde emission rates ranging from 0.43 to 4.2 μg/kilojoule were measured from eight well tuned, unvented gas-fired space heaters operated at full fuel input in an environmental chamber with low ventilation (Traynor et al. 1985). In another study, formaldehyde emissions factors from unvented kerosene heaters ranged from 0.18 to 0.47 μg/kilojoule (Woodring et al. 1985).

Using an average cigarette consumption rate of approximately 10 cigarettes per indoor compartment per day with a measured formaldehyde emission rate of 0.97±0.06 mg/hour, Matthews et al. (1985) calculated an average formaldehyde emission rate of 0.4±0.03 mg/hour over 24 hours. Triebig and Zober (1984) report that the level of formaldehyde in side stream cigarette smoke is fifty times higher than main stream smoke, while the National Research Council (NRC 1986) put the value at five to eight times more formaldehyde in side stream smoke. Levels of formaldehyde in nonsmoking office buildings ranged from not detected to 0.22 ppm, while they ranged from not detected to 0.6 ppm where smoking was permitted (Sterling et al. 1987).

Formaldehyde can also be emitted into indoor air from fish during cooking. Amounts of formaldehyde that formed in a headspace when various kinds of fish flesh were heated at 200 C ranged from 0.48 μg/g of mackerel to 5.31 μg/g of sardine (Yasuhara and Shibamoto 1995).

The general population may also participate in activities that release formaldehyde to outdoor air. The concentration of formaldehyde in mosquito-coil smoke was found to be 10.9–21.3 ppm/g (Chang and Lin 1998). Composting household waste was also found to emit formaldehyde to air (Eitzer et al. 1997).

5.2.2 Water

Formaldehyde is released to water from the discharges of both treated and untreated industrial waste water from its production and from its use in the manufacture of formaldehyde-containing resins. Formaldehyde can also be formed in seawater by photochemical processes (Mopper and Stahovec 1986). Calculations of sea-air exchange have indicated that this process is probably a minor source of formaldehyde in the sea (Mopper and Stahovec 1986).

The amount of formaldehyde released to surface water and POTWs in 1996 by U.S. industrial facilities sorted by state is shown in Table 5-1 (TRI96 1998). According to TRI96 (1998), an estimated total of 320,003 pounds (145,153 kg) of formaldehyde, amounting to 2% of the total environmental release, was discharged to surface water in 1996. An additional 1.9 million pounds (0.8 million kg) of formaldehyde were discharged to POTWs (TRI96 1998). The TRI data should be used with caution since only certain facilities are required to report (EPA 1995). This is not an exhaustive list. As a result of secondary treatment processes in POTWs, only a fraction of the formaldehyde that enters POTWs is expected to be released subsequently to surface water; however, this percentage is not known for formaldehyde. Experiments conducted at three full-scale drinking water treatment plants and a pilot plant provided evidence that ozone treatment resulted in the production of measurable levels of formaldehyde in all of the plants studied (Glaze et al. 1989).

There is a potential for release of formaldehyde to water from hazardous waste sites. Formaldehyde has been detected in surface water samples collected at 5 of the 26 hazardous waste sites and in groundwater samples collected at 4 of the 26 hazardous waste sites where formaldehyde has been detected in some environmental medium (HazDat 1996).

5.2.3 Soil

Formaldehyde is released to soils through industrial discharges and through land disposal of formaldehyde-containing wastes. The amount of formaldehyde released to land in 1996 by U.S. industrial facilities sorted by state is shown in Table 5-1 (TRI96 1998). According to TRI96 (1998), an estimated total of 114,406 pounds (51,894 kg) of formaldehyde, amounting to 0.54% of the total environmental release, was discharged to land from U.S. manufacturing or processing facilities in 1996. An additional 9.4 million pounds (4.3 million kg), constituting about 44% of total environmental emissions, were released via underground injection (TRI96 1998). Also, some of the estimated 1.3 million pounds of formaldehyde wastes transferred off-site (see Table 5-1) may be ultimately disposed of in land. The TRI data should be used with caution since only certain facilities are required to report (EPA 1995). This is not an exhaustive list.

There is a potential for the release of formaldehyde to soil from hazardous waste sites. Formaldehyde has been detected in soil samples collected at 1 of the 26 hazardous waste sites and in sediment samples collected at 1 of the 26 hazardous waste sites where formaldehyde has been detected in some environmental medium (HazDat 1996).

5.3 ENVIRONMENTAL FATE

In reviewing the fate of formaldehyde in the environment, it should be noted that the environmental factors that influence the bioavailability to humans of formaldehyde from contaminated air, water, or plant material have not been studied.

5.3.1 Transport and Partitioning

Formaldehyde is released to the atmosphere in large amounts and is formed in the atmosphere by the oxidation of hydrocarbons. However, the input is counterbalanced by several removal paths (Howard 1989). Because of its high solubility, there will be efficient transfer into rain and surface water, which may be important sinks (NRC 1981). One model has predicted dry deposition and wet removal half-lives of 19 and 50 hours, respectively (Lowe et al. 1980). Although formaldehyde is found in remote areas, it probably is not transported there, but is generated from longer-lived precursors that have been transported (NRC 1981).

No information concerning the fate of formaldehyde in groundwater could be found in the literature. Based upon the Henry's law constant for formaldehyde (3.27×10^{-7} atm-m^3/mol) (Dong and Dasgupta 1986), volatilization from water should not be significant (Lyman 1982). Also, little adsorption to sediment would be expected to occur.

No information could be found concerning the adsorption of formaldehyde to soil. However, its low octanol/water partition coefficient (log K_{ow} = 0.35) (SRC 1995b) suggests that adsorption to soil is low. Using the log K_{ow} of 0.35, a log K_{oc} of 1.57 can be calculated (Lyman 1982). This value of log K_{oc} suggests a very high mobility and leaching potential of formaldehyde in soil (Swann et al. 1983). At high concentrations, formaldehyde gas adsorbs somewhat to clay mineral, which is important to its use as a soil fumigant (De and Chandra 1979).

Plants, such as kidney beans and barley, can absorb gaseous formaldehyde through their leaves (EPA 1976a). Experiments performed on a variety of fish and shrimp showed no evidence of the bioaccumulation of formaldehyde (Hose and Lightner 1980; Sills and Allen 1979). Because formaldehyde is rapidly metabolized (Casanova et al. 1988), bioaccumulation is not expected to be important.

5.3.2 Transformation and Degradation

Formaldehyde undergoes a number of different transformation and degradation reactions in the environment as discussed in the following sections. The resulting environmental transformation products within different media are shown in Table 5-2.

5.3.2.1 Air

Formaldehyde is removed from the atmosphere by direct photolysis and oxidation by photochemically produced hydroxyl radicals. Formaldehyde absorbs ultraviolet (UV) radiation at wavelengths of 360 nm and longer (DOT 1980); therefore, it is capable of photolyzing in sunlight. A half-life of 6 hours has been measured for photolysis in simulated sunlight (Su et al. 1979). There are two photolytic pathways, one producing H_2 and CO, and the other producing H and HCO radicals (Calvert et al. 1972; Lowe et al. 1980). When the rates of these reactions are combined with estimates of actinic irradiance, the predicted half-life of formaldehyde due to photolysis in the lower atmosphere is 1.6 hours at a solar zenith angle of

Table 5-2. Environmental Transformation Products of Formaldehyde by Medium

Reaction	Comments	Reference
Air		
$CH_2O + h\nu \quad HCO + H$	Photolysis, pathway 1	Calvert et al. 1972
$CH_2O + h\nu \quad H_2 + CO$	Photolysis, pathway 2	Calvert et al. 1972
$CH_2O + NO_3 \quad HCO + HNO_3$	H-atom abstraction by NO_3 radical	Kao 1994
$CH_2O + HO \quad H_2O + HCO$	H-atom abstraction by HO radical	NRC 1981
Dilute Aqueous Solution		
$CH_2O + H_2O \quad CH_2(OH)_2$	Formation of *gem*-diol methylene glycol; k_{298} = $7.0x10^3$ M atm^{-1}	Kumar 1986
Concentrated Solution		
$CH_2O \quad H(CH_2O)_nOH + C_3H_6O_3$	Formation of paraformaldehyde and trioxane	EPA 1991c
Cloudwater		
$CH_2(OH)_2 + OH \quad CH(OH)_2 + H_2O$ (1) $CH(OH)_2 + O_2 \quad HO_2 + (HCOOH)_{aq}$ (2)	Formation of formic acid; $k_1 = 2x10^9\ M^{-1}\ s^{-1}$ $k_2 = 4.5x10^9\ M^{-1}\ s^{-1}$	Chameides and Davis 1983

40 degrees (Calvert et al. 1972). Based on its rate of reaction with photochemically produced hydroxyl radicals, formaldehyde has a predicted half-life of approximately 19 hours in clean air and about half that time in polluted air (Atkinson and Pitts 1978; DOT 1980; EPA 1982). Lowe et al. (1980) report the lifetime of formaldehyde in the sunlit atmosphere, due to photolysis and reaction with hydroxyl radicals, is 4 hours. Singh et al. (1982) report an estimated daily loss rate of formaldehyde of 88.2% on the basis of hydroxyl radical activity and photolysis. The hydroxyl-radical-initiated oxidation of formaldehyde also occurs in cloud droplets to form formic acid, a component of acid rain (Chameides 1986; Chameides and Davis 1983). Calculations by Benner and Bizjak (1988) suggest that removal of formaldehyde by H_2O_2 is probably negligible in atmospheric droplets. When formaldehyde is irradiated in a reactor, the half-life is 50 minutes in the absence of NO_2 and 35 minutes in the presence of NO_2 (Bufalini et al. 1979; EPA 1976a). The primary products formed are formic acid and CO (Su et al. 1979). The reaction of formaldehyde with nitrate radicals, insignificant in the daytime, may be an important removal mechanism at night (NRC 1981). Formaldehyde reacts with the NO_3 radical by H-atom extraction with a half-life of 12 days, assuming an average nighttime NO_3 radical concentration of $2x10^9$ molecules per cm^3 (Atkinson et al. 1984).

5.3.2.2 Water

When released to water, formaldehyde will biodegrade to low levels in a few days (Howard 1989). In nutrient-enriched seawater, there is a long lag period (40 hours) prior to measurable loss of formaldehyde by presumably biological processes (Mopper and Stahovec 1986). Formaldehyde in aqueous effluent is degraded by activated sludge and sewage in 48–72 hours (EPA 1976a; Hatfield 1957; Heukelekian and Rand 1955; Verschueren 1983). In a die-away test, using water from a stagnant lake, degradation was complete in 30 hours under aerobic conditions and 48 hours under anaerobic conditions (EPA 1976a). Bhattacharya and Parkin (1988) used anaerobic chemostats to study fate and kinetic effects of sludge and continuous additions of formaldehyde to acetate and propionate enrichment systems. The high reduction of formaldehyde with continuous addition is indicative of biodegradation, since the combination of volatilization, adsorption, and chemical transformation should account for less than 25% of the removal. Up to 80% of the formaldehyde was removed, with biodegradation accounting for 55–60%.

Chameides and Davis (1983) postulated that formaldehyde dissolved in cloudwater should not photolytically decompose because $CH_2(OH)_2$ is not a chromophore, and that the more probable fate of

dissolved formaldehyde is oxidation by OH with the ultimate formation of formic acid. Experiments performed by Mopper and Stahovec (1986) suggest that formaldehyde is formed and consumed in seawater as a result of a number of interacting photochemical, biological, and physical processes. Diurnal fluctuations of formaldehyde ranging from 15 to 50 nM were measured in humic-rich waters off the west coast of Florida over a 3-day sampling period.

Concentrated solutions containing formaldehyde are unstable, both oxidizing slowly to form formic acid and polymerizing (Gerberich et al. 1980). In the presence of air and moisture, polymerization takes place readily in concentrated solutions at room temperature to form paraformaldehyde, a solid mixture of linear polyoxymethylene glycols containing 90–99% formaldehyde (EPA 1984).

5.3.2.3 Sediment and Soil

The fate of formaldehyde in soil has not been determined (Howard 1989).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation for human exposure to formaldehyde depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on formaldehyde levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

A recent survey of emission data from stationary and mobile sources was used as input for an atmospheric dispersion model to estimate outdoor toxic air contaminant concentrations for 1990 for each of the 60,803 census tracts in the contiguous United States (Woodruff et al. 1998). The average long term background concentration estimated for formaldehyde was 0.2 ppb (Woodruff et al. 1998).

In a survey of ambient measurements of hazardous air pollutants, a median formaldehyde concentration of 2.5 ppb was found for a total of 1,358 samples collected at 58 different locations (Kelly et al. 1994). Air samples collected daily in Schenectady, New York, during the months of June through August 1983 had formaldehyde concentrations ranging from 1 to 31 ppb. There was a significant daily variation that

appeared to correlate with traffic conditions (Schulam et al. 1985). In the same study, formaldehyde levels measured on the summit of Whiteface Mountain in Wilmington, New York, ranged from 0.8 to 2.6 ppb. Ambient formaldehyde concentrations at the California State University Los Angeles campus ranged from 2 to 40 ppb during the period from May to June 1980; concentrations in Claremont, California, ranged from 3 to 48 ppb from September 19 to October 8, 1980 (Grosjean 1982). Formaldehyde was measured in urban ambient air in 8 cities for 2- to 3-day periods from June 1980 to April 1984. The average concentrations were 11.3 ppb in St. Louis, Missouri (June 5–7, 1980); 12.3 ppb in Denver, Colorado (June 23–24, 1980); 2.3 ppb in Denver, Colorado (April 1–2, 1984); 19 ppb in Riverside, California (July 8–10, 1980); 14.3 ppb in Staten Island, New York (April 3–4, 1981); 18.5 ppb in Pittsburgh, Pennsylvania (April 15–16, 1981); 11.3 ppb in Chicago, Illinois (April 27–28, 1981); 15.5 ppb in Downey, California (February 28–March 1, 1984); and 3.8 ppb in Houston, Texas (March 18–19, 1984). The maximum concentration in each city ranged from 5.5 ppb in Denver in April to 67.7 ppb in Downey (Salas and Singh 1986; Singh et al. 1982).

Formaldehyde was detected in 99% of 48 ambient air samples obtained in Ohio urban centers, June-July 1989, at a mean and maximum concentration of 3.0 and 15.5 ppb, respectively (Spicer et al. 1996). The diurnal changes in concentration were found to be consistent with initial direct emissions from vehicles followed by secondary photochemical production and, ultimately, atmospheric removal. These data indicate that formaldehyde concentrations in urban atmospheres are expected to be the highest during, or shortly after rush hour, or other periods of high vehicular traffic. Similar results were obtained when temporal formaldehyde concentrations were measured during a smog event in California, September 1993 (Grosjean et al. 1996). In central Los Angeles, higher formaldehyde concentrations were found to correlate with vehicular traffic while at a downwind location, the concentration was found to spike later in the day. The average atmospheric formaldehyde concentration for all sites was 5.3 ppbv (parts per billion by volume) in this study, while the background concentration from San Nicolas island (off the Southern California coast) was 0.8 ppmv (parts per million by volume). Average annual formaldehyde concentrations in California have been reported to vary from a minimum of 3.2 ppbv in the San Francisco Bay area to 4.9 ppbv in the South Coast Air Basin (Seiber 1996).

Several monitoring studies have been conducted in the United States to measure the concentration of formaldehyde in indoor environments (EPA 1987d; Gammage and Hawthorne 1985; Hawthorne et al. 1985, 1986b; Stock 1987). The results for a variety of housing types and ages have been compiled by Gold et al. (1993) and are presented in Table 5-3. Much of the data was collected in older homes, in

Table 5-3. Indoor Concentrations of Formaldehyde in U.S. Homes

Building type	Number	Concentration (ppm) Range	Concentration (ppm) Mean	References
With UFFI	>1,200	0.01–3.4	0.05–0.12	EPA 1987d; Gammage and Hawthorne 1985
Without UFFI	131	0.01–0.17	0.025–0.07	Gammage and Hawthorne 1985
Complaint				
Mobile homes	>500	0.00–4.2	0.1–0.9	Gammage and Hawthorne 1985
Non-complaint				
Conventional, randomly selected	560	<0.005–0.48	0.027–0.091	EPA 1987d; Stock 1987
Mobile homes, randomly selected	1,200	<0.01–2.9	0.091–0.62	EPA 1987d
By age				
Mobile homes				
new	260		0.86	Gammage and Hawthorne 1985
older, occupied	—		0.25	Gammage and Hawthorne 1985
Conventional homes				
0–5 years	18		0.08	Hawthorne et al. 1985, 1986b
5–15 years	11		0.04	Hawthorne et al. 1985, 1986b
>15	11		0.03	Hawthorne et al. 1985, 1986b
Overall	40	<0.02–0.4	0.06	Hawthorne et al. 1985, 1986b

UFFI = Urea formaldehyde foam insulation

homes that had UFFI, or in homes in which occupants had filed complaints of formaldehyde irritant symptoms. Since the time many of these monitoring studies were performed, plywood and particle board manufacturing methods have been changed to reduce the formaldehyde emission levels in the finished product (EPA 1996). Similarly, home construction methods have changed, and the use of UFFI has been greatly reduced since the mid-eighties (CPSC 1997). A recent pilot study on a newly constructed and unoccupied house set up to measure formaldehyde emissions from construction materials had a maximum localized formaldehyde concentration of 0.076 ppm, which occurred shortly after a high loading of pressed wood materials, such as kitchen cabinets (Hare et al. 1996). The average indoor concentrations measured in this study were 0.035–0.45 ppm, which was attained approximately 30 days after either high or low loadings of formaldehyde releasing materials were installed.

Earlier studies evaluating randomly selected, non-complaint homes have appeared in the literature. Despite the wide variety of conditions under which these residential formaldehyde studies were conducted, results for given types of housing were consistent within certain broad ranges. In general, indoor residential formaldehyde concentrations were significantly higher than outdoor concentrations which ranged from 0.002 to 0.006 ppm in remote, unpopulated regions from 0.01 to 0.02 ppm (and sometimes 0.05 ppm) in highly populated areas and industrial urban air (Gold et al. 1993). The range of formaldehyde concentrations measured in complaint homes, mobile homes, and homes containing large quantities of particle board or UFFI were 0.02–0.8 ppm, with levels as high as 4 ppm, sufficient to cause irritating symptoms, observed in some instances. Formaldehyde levels in more recently built (<1 year old) conventional homes generally were within the range of 0.05–0.2 ppm, with few measurements exceeding 0.3 ppm. Older conventional homes had the lowest indoor concentrations of formaldehyde with values typically less than 0.05 ppm (Gold et al. 1993), consistent with the expected decrease in latent formaldehyde release from wood-based building materials as they age (EPA 1996; Zinn et al. 1990).

The Texas Department of Health measured formaldehyde in 443 mobile homes between April 1979 and May 1982 at the request of the occupants. Concentrations ranged from below detectable limits (<0.5 ppm) to 8 ppm (Norsted et al. 1985). Of the homes 1 year old, 27% had mean concentrations 2 ppm, while 11.5% of older homes has concentrations 2 ppm. The concentration of formaldehyde in mobile homes would be expected to be higher than that found in conventional homes due to their lower rate of air exchange (Wolff 1991).

Sexton et al. (1989) selected an age-stratified random sample of 470 mobile homes, from the more than 500,000 in California, for measurement of 1-week, average indoor formaldehyde concentrations during the periods July–August 1984 and February–March 1985. They observed relatively little variation in formaldehyde concentrations between summer and winter, with average 1-week formaldehyde values of 0.07–0.09 ppm. Of the homes, 31% exceeded the maximum concentration of 0.1 ppm formaldehyde recommended at the time of the study by AIHA, EPA, and the American Society of Heating, Refrigerating and Air Conditioning Engineers. The investigators noted that formaldehyde levels appeared to have been decreasing in mobile homes manufactured since about 1980, probably as a result of increased use of low-formaldehyde-emitting building materials.

The Indiana State Board of Health measured formaldehyde in four specific office and commercial establishments that had poor ventilation. The concentrations ranged from 0.01 to 1.01 ppm. In one case, the source of formaldehyde was urea-formaldehyde foam. In the others, it was particle board, plywood subflooring, and furniture (Konopinski 1983).

Shah and Singh (1988) collected indoor and outdoor data for volatile organic chemicals from both residential and commercial environments. The average daily outdoor concentration of formaldehyde for all outdoor site types (remote, rural, suburban, urban, and source-dominated) was 8.3 ppbv; the average daily indoor concentration of formaldehyde was 49.4 ppbv.

Zhang et al. (1994b) made simultaneous indoor and outdoor measurements of aldehydes at six residential houses in suburban New Jersey during the summer of 1992. Formaldehyde was the most abundant aldehyde, with a mean outdoor concentration of 12.53 ppb (60% of the total outdoor aldehyde concentration) and a mean indoor concentration of 54.56 ppb (87% of the total indoor aldehyde concentration).

Krzyzanowski et al. (1990) measured formaldehyde concentrations in 202 households in Pima County, Arizona, and found an average value of 26 ppb. Concentrations varied slightly with locations in the house, with the highest levels generally found in the kitchens. Only a few concentrations exceeded 90 ppb, with a maximum value of 140 ppb. The average indoor formaldehyde concentrations measured in homes in Pullman, Washington, ranged from approximately 5–72 ppb (Lamb et al. 1985).

Formaldehyde concentrations measured on two different days inside a tavern during normal smoking conditions were 85–72 ppb (Lofroth et al. 1989). In the same study, the average airborne formaldehyde yield of a cigarette was found to be 2 mg. Levels of formaldehyde in nonsmoking office buildings ranged from not detected to 0.22 ppm, while it ranged from not detected to 0.6 ppm where smoking was permitted (Sterling et al. 1987).

5.4.2 Water

Formaldehyde is unstable in water; however, it has been detected in municipal and industrial aqueous effluents, including those resulting from chemical, oil, and coal processing (EPA 1976b; Hushon et al. 1980). Formaldehyde was not detected in the National Organics Reconnaissance Survey of Suspected Carcinogens in Drinking Water (EPA 1975).

Formaldehyde levels in rainwater collected in California were low, ranging from not detectable to 0.06 μg/mL (Grosjean and Wright 1983). Concentrations of free formaldehyde measured in fogwater in Corvallis, Oregon, ranged from 0.4 to 3 mg/L with a volume-weighted mean of 1.8 mg/L (Muir 1991). Free formaldehyde concentrations in fogwater in Riverside, California, ranged from 4.1 to 228 μM (0.12–6.8 mg/L), with approximately half of the samples measuring less than 90 μM (3 mg/L) (Igawa et al. 1989). Stratus cloudwater at Henninger Flats, California, which typically is highly acidic and concentrated in inorganic pollutants, had concentrations of free formaldehyde ranging from 45.9 to 61.5 μM (1.4–1.8 mg/L), comparable to the mid-range of Corvallis fogwater concentrations (Igawa et al. 1989). Formaldehyde concentrations ranging from 11 to 142 μM were found in cloudwater samples collected in the Los Angeles Basin (Richards et al. 1983). Formaldehyde concentrations in mist samples in Long Beach and Marina del Ray, California, were 0.25–0.56 μg/mL, respectively (Grosjean and Wright 1983).

5.4.3 Sediment and Soil

No data on formaldehyde levels in sediment and soil could be found in the literature.

5.4.4 Other Environmental Media

Fresh shrimp from four local commercial markets in Atlanta, Georgia were found to have formaldehyde levels ranging from 0.39 to 1.44 mg/kg (Radford and Dalsis 1982). In the same study, shrimp kept live in the laboratory were found to contain 0.99 mg/kg immediately after sacrifice, and the level rose to 2.15 mg/kg after refrigeration for 6 days.

Chou and Que Hee (1994) measured the concentrations of carbonyl compounds in artificial saliva leachates of three chewing tobaccos. They found formaldehyde concentrations of 110, 670, and 530 ng/mL (0.11, 0.67, and 0.53 μg/mL, respectively) in three different commercial brands. Mansfield et al. (1977) used liquid chromatography to measure formaldehyde as a combustion product in tobacco smoke from six different brands of American filter tip cigarettes. The average amount of formaldehyde by brand ranged from 45.2 to 73.1 μg/cigarette and from 5.1 to 8.9 μg/puff. Triebig and Zober report that the level of formaldehyde in side stream cigarette smoke is fifty times higher than main stream smoke (Triebig and Zober 1984) while the National Research Council put the value at five to eight times more formaldehyde in side stream smoke (NRC 1986).

Formaldehyde has also been found at levels ranging from 1 to 3,517 ppm in 112 fabric samples, with 18 of the samples having a free formaldehyde concentration greater than 750 ppm (mg/kg) (Schorr et al. 1974).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The contribution of various atmospheric environments to the average exposure to formaldehyde is given below (Fishbein 1992):

Source	mg/day
Air	
Outdoor air (10% of time)	0.02
Indoor air	
Home (65% of time)	
Conventional	0.5–2.0
Prefabricated (chipboard)	1.0–10.0
Workplace (25% of time)	
Without occupational exposure	0.2–0.8
With 1 mg/m^3 occupational exposure	5
Environmental tobacco smoke	0.1–1
Smoking (20 cigarettes/day)	1

The major route of exposure is inhalation of indoor air, with releases of formaldehyde from chipboard and other building and furnishing materials composing the bulk of the exposure. Environmental tobacco smoke contributes 10–25% of the total indoor exposure. Since formaldehyde in food is not available in free form, the intake of formaldehyde from the ingestion of food (1–10 mg/day) has not been included (Fishbein 1992).

Consumers can be exposed to formaldehyde gas through its emission from construction materials, wood products, textiles, home furnishings, paper, cosmetics, and pharmaceuticals (Bartnik et al. 1985; Pickrell et al. 1983; WHO 1989). Members of the general population may also be exposed to formaldehyde by dermal contact with many of these products. Based on a study of dermal absorption of formaldehyde in rats from cosmetic products, Bartnik et al. (1985) made rough estimates of the formaldehyde that could be absorbed through the use of products such as hand cream or sun-tan lotion. In the case of hand cream, approximately 2 g is used per application, containing 2 mg formaldehyde. Assuming 5% absorption, 0.1 mg of formaldehyde would be absorbed. For a whole-body product such as sun-tan lotion, approximately 17 g of the product (containing 17 mg of formaldehyde) would be used, resulting in an absorption of 0.85 mg of formaldehyde.

A study was conducted in Boston to examine the commuter's exposure to six gasoline-related volatile emissions, including formaldehyde, in four different commuting modes (Chan et al. 1991). The mean formaldehyde concentrations (in $\mu g/m^3$) measured while driving private cars, riding in subways, walking, and biking were 5.1 (n=40), 4.5 (n=38), 5.5 (n=31), and 6.3 (n=11), respectively. The maximum concentrations in all commuting modes were usually three to five times higher than the mean

concentrations. A similar study in the New York/New Jersey area found that the mean in-vehicle concentration of formaldehyde during commutes was 0.3 $\mu g/m^3$ (Lawryk et al. 1995; Lawryk and Weisel 1996).

Occupational exposure can occur during the production of end products in which formaldehyde is used, in the garment industry, during various preservation processes, and in laboratories. Health care professionals (pharmacists, physicians, veterinarians, dentists, nurses, etc.) may be exposed to vapors during the preparation, administration, and/or cleanup of various medicines. Pathologists and histology technicians, morticians, and teachers and students who handle preserved specimens may also be exposed (Fleisher 1987; Holness and Nethercott 1989; Korky et al. 1987; Perkins and Kimbrough 1985; Skisak 1983). The laser cutting of felt, woven fabrics, formica, plexiglass, and acrylic materials has been found to release formaldehyde (Kiefer and Moss 1997). Formaldehyde exposure for workers at a fiberglass insulation manufacturing plant were found to range from 49 to 516 $\mu g/m^3$ (Milton et al. 1996a). Mid-range photocopiers (30–135 copies per minute) have also been found to emit formaldehyde (Leovic et al. 1996).

The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, indicated that 1,329,332 workers employed in various professions were potentially exposed to formaldehyde in the United States (NIOSH 1995b). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to the chemical in the workplace. OSHA has estimated that in the late 1980s over 2 million workers in over 112,000 firms were exposed to formaldehyde; about 45% of these workers are estimated to be in the garment industry. About 1.9 million were exposed to levels of formaldehyde between 0.1 ppm and 0.5 ppm (mainly in apparel, furniture, paper mills, and plastic molding); approximately 123,000 were exposed to levels of formaldehyde between 0.5 and 0.75 ppm (mainly in apparel, textile finishing, furniture, laboratories, and foundries); and about 84,000 were exposed to between 0.75 and 1 ppm (mainly in apparel, furniture, and foundries) (OSHA 1996).

OSHA has estimated that in the United States approximately 107,000 employees are exposed to formaldehyde concentrations greater than 1 ppm, and approximately 430,000 employees are exposed to concentrations ranging from 0.5 to 1 ppm (Fishbein 1992). An initial evaluation of formaldehyde exposures in a sewing plant using fabrics with a postcure resin found time-weighted average (TWA)

exposure levels 1.2 ppm, with a mean of 0.9 ppm (Luker and Van Houten 1990). A modification that decreased the amount of residual formaldehyde in the fabric reduced worker exposure by 80–85%. Area concentrations of formaldehyde in a plywood company ranged from 0.28 to 3.48 ppm; the average personal exposure was 1.13 ppm formaldehyde (Malaka and Kodama 1990). Airborne formaldehyde concentrations ranging from 0.187 to 0.783 ppm have been measured during particle-board-sanding operations (Stumpf et al. 1986). Formaldehyde concentrations of 0.5–7 ppm have been measured in leather tanning facilities (Stern et al. 1987). An average airborne formaldehyde level of 0.36±0.19 ppm was measured during 22 embalming procedures (Holness and Nethercott 1989). Fire fighters are exposed to formaldehyde concentrations as high as 8 ppm during knockdown (bringing the main body of fire under control) and 0.4 ppm during overhaul (searching for and extinguishing hidden fire) (Jankovic et al. 1991). Formaldehyde levels 0.3 ppm have been measured inside a fire fighter's self-contained breathing apparatus (Jankovic et al. 1991).

The current OSHA permissible exposure limit (PEL) for all workplaces covered by OSHA is 0.75 ppm for an 8-hour TWA, and the short-term exposure limit (STEL) is 2 ppm over a 15-minute period. The "action level" is 0.5 ppm measured over 8 hours (OSHA 1996). NIOSH has recommended a 0.1 ppm ceiling exposure concentration over a 15-minute period in the workplace (NIOSH 1992).

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Children are exposed to formaldehyde mainly from its presence in air. Formaldehyde levels are typically higher indoors (Gold et al. 1993) where younger children may spend a significant amount of time. Exposure for children outdoors will be similar to adults. It is likely to be greatest during rush hour commutes (Spicer et al. 1996) or near known sources of formaldehyde release, such as factories using formaldehyde or during the use of products (Shah and Singh 1988) that emit formaldehyde. Children may also be dermally exposed to formaldehyde as a result of its release from permanent press fabrics or its presence in cosmetic products. Only a limited number of studies that address formaldehyde exposure to children or body burden measurements have been identified (Krzyzanowski et al. 1990; Wantke et al. 1996a).

In the home, formaldehyde sources include household chemicals, pressed wood products (especially when new) (EPA 1996), combustion sources (NRC 1986), and some new fabrics (Schorr et al. 1974) and garments. A number of common household products may release formaldehyde to indoor air, including antiseptics, medicines, dish-washing liquids, fabric softeners, shoe-care agents, carpet cleaners, glues, adhesives, and lacquers (Kelly et al. 1996). If children use or play with some of these products, or are present when they are used, additional exposure to formaldehyde may occur. Many cosmetic products contain formaldehyde and some, such as nail polish and nail hardeners, contain high levels (Kelly et al. 1996). If children place these products in their mouth or on their skin, or sniff them, they will be exposed to elevated levels of formaldehyde.

New carpets have been found to release formaldehyde (Hodgson et al. 1993). Older carpets, especially wall-to-wall carpets, have been found to be a sink for formaldehyde if there are other indoor sources (Norback et al. 1995). In addition, some carpet cleaners may contain formaldehyde. Infants may be exposed to formaldehyde while crawling on carpets or on newly cleaned carpets (IARC 1982; WHO 1989). Similarly, young children may be exposed while sitting or playing on indoor carpeting.

Formaldehyde is typically not found in water or soil, and children are not expected to be exposed by these routes. Because it is a gas, formaldehyde is not brought home on a parent's work clothes or tools. Occupants of newly constructed homes, including children, may be exposed to formaldehyde due to its release from pressed wood construction materials (see Section 5.7), a process that slowly decreases with time. As discussed above, formaldehyde is released to indoor air from many sources. Children that live in mobile homes may be exposed to higher levels of formaldehyde compared to those that live in conventional homes because mobile homes have lower air exchange rates. Children that live in

households that have a cigarette, cigar, or pipe smoker will also be exposed to higher levels of formaldehyde due to its presence in side stream smoke (Triebig and Zober 1984).

Formaldehyde is released from many pressed wood products used in the construction of furniture (Konopinski 1983). When placed in a new crib manufactured from these materials, infants may be exposed because of their proximity to the furniture's structural components. Also, small rooms that have new furniture manufactured from pressed wood products installed may have localized, elevated concentrations of formaldehyde because of their low total volume.

Formaldehyde is highly water soluble, very reactive, and is rapidly metabolized by tissues at portals of entry. Thus, parental exposure at typical indoor, outdoor, or occupational levels is not expected to result in exposure to parental germ cells or the developing fetus (See Section 2.6 for additional information).

Since formaldehyde is typically found in the air, and since its concentration in indoor air is typically higher than that found outdoors, formaldehyde exposure to children can be reduced by bringing fresh air into the home. This can be accomplished by opening windows or using ventilation fans. It has been established that coated or laminated pressed wood products release less formaldehyde than those that are uncoated (Kelly et al. 1996; Pickrell et al. 1983), so sealing these surfaces would be expected to reduce formaldehyde levels in the home. Since formaldehyde is also formed in indoor air by the degradation of other volatile organic chemicals, such as solvents (Weschler and Shields 1996), commonly found in the home, removing the source of these materials or using them with adequate ventilation will reduce indoor levels of formaldehyde.

Material that acts as a sink for formaldehyde, such as carpets (Norback et al. 1995), can also be removed from the home to lower levels. Securing cosmetic products and other materials that have higher formaldehyde concentrations away from children's reach and not allowing individuals to smoke in the house will also lower levels of exposure.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries where formaldehyde is used or released may receive potentially high exposures. Members of the general population who live in newly constructed homes or homes where pressed wood products have recently been installed may be exposed to high levels of formaldehyde by inhalation for short periods of time until the latent formaldehyde has been released. Exposures in mobile homes are expected to be higher than conventional homes due to their lower rate of air exchange (Wolff 1991). Members of the general population that handle large amounts of permanent press fabrics treated with formaldehyde-releasing resins may also receive potentially high exposures. The use of some cosmetics, such as nail hardeners, may result in high short-term exposure.

Smokers and persons who live in a home with a cigarette smoker also may be exposed to higher levels of formaldehyde. Environmental tobacco smoke, which is a combination of diluted sidestream smoke released from a cigarette's burning end and mainstream smoke exhaled by an active smoker, can contribute 10–25% (0.1–1 mg/day) of the total average indoor exposure to formaldehyde (Fishbein 1992).

5.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of formaldehyde is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of formaldehyde.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of formaldehyde are well characterized and allow prediction of the transport and transformation of the compound in the environment.

Production, Import/Export, Use, Release, and Disposal. Knowledge of a chemical's production volume is important because it may indicate the magnitude of environmental contamination and human exposure. Data regarding the production, trend, use pattern, and disposal of formaldehyde are available.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, became available in May of 1998. According to the Toxics Release Inventory (TRI), in 1996, 21 million pounds (9.6 million kg) of formaldehyde were released to the environment. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The environmental fate of formaldehyde in air has been well studied (Bufalini et al. 1979; Calvert et al. 1972; Chameides and Davis 1983; DOT 1980; EPA 1976a; Kao 1994; Kelly et al. 1994; Lowe et al. 1980; Su et al. 1979). Formaldehyde is removed from the atmosphere by direct photolysis and oxidation by photochemically produced hydroxyl and nitrate radicals. Solutions of formaldehyde are unstable, both oxidizing slowly to form formic acid and polymerizing. When released to water, formaldehyde will biodegrade to low levels in a few days, with little adsorption to sediment (Howard 1989; Lyman 1982). No significant volatilization from water is expected to occur (Lyman 1982). No experimental or estimated values for the half-life of formaldehyde in ambient water were found in the literature. Aqueous solutions of formaldehyde that are released to soil may leach through the soil (Lyman 1982; SRC 1995b; Swann et al. 1983). Although formaldehyde is known to biodegrade under both aerobic and anaerobic conditions, the fate of formaldehyde in soil is still unknown (Howard 1989). There is a need for data on the fate and transport of formaldehyde in soil, including half-life values. The environmental fate of formaldehyde's predominant degradation product, formic acid, is well documented. In air, formic acid is expected to rapidly degrade (half-life approximately 1 month) through

its reaction with hydroxyl radicals or it is expected to undergo wet deposition to the earth's surface (HSDB 1999). In water or soil, formic acid is expected to rapidly biodegrade.

Bioavailability from Environmental Media. Inhalation is the major pathway for exposure to formaldehyde (Fishbein 1992). The environmental factors that may influence the bioavailability of formaldehyde from contaminated air, water, or plant material have not been studied. The role of sorption may not be significant in determining the bioavailability of formaldehyde from soil since formaldehyde is not expected to adsorb to soils and sediments (Lyman 1982). The factors affecting the bioavailability of formaldehyde from soil and other environmental media need further investigation. The bioavailability of formaldehyde from the ingestion of food is not known although it is not expected to be significant.

Food Chain Bioaccumulation. Experiments performed on a variety of fish and shrimp showed no evidence of the bioaccumulation of formaldehyde (Hose and Lightner 1980; Sills and Allen 1979). Because formaldehyde is rapidly metabolized (Casanova et al. 1988), bioaccumulation is not expected to be important. No further information is needed.

Exposure Levels in Environmental Media. The levels of formaldehyde in air are well documented (EPA 1987d; Gammage and Hawthorne 1985; Gold et al. 1993; Grosjean 1982; Hawthorne et al. 1985, 1986a; Kelly et al. 1994; Krzyzanowski et al. 1990; Lamb et al. 1985; Lofroth et al. 1989; Norsted et al. 1985; Salas and Singh 1986; Schulam et al. 1985; Sexton et al. 1989; Shah and Singh 1988; Singh et al. 1982; Stock 1987; Zhang et al. 1994a). Some data on the concentrations of formaldehyde in rainwater, fogwater, and mist have been reported (Grosjean and Wright 1983; Igawa et al. 1989; Muir 1991), but more recent data on the levels of formaldehyde in water would be useful in assessing exposures. No data on levels of formaldehyde in soil were found in the literature. Soil concentrations also are needed to assess exposures.

Reliable monitoring data for the levels of formaldehyde in contaminated media at hazardous waste sites are needed so that the information obtained on levels of formaldehyde in the environment can be used to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Data are available concerning exposure levels in occupational settings (Anonymous 1984a; Fishbein 1992; OSHA 1996). Results of the National Occupational Exposure Survey (NIOSH 1995b) are indicative of the number of workers potentially exposed to formaldehyde in various occupations; however, the database does not contain information on the frequency, concentration, or duration of exposure. Available data indicate that the general population may be exposed to formaldehyde through inhalation and dermal contact; however, because of the wide variety of exposure sources (conventional homes versus mobile homes, smoking versus nonsmoking environment, usage patterns for consumer products, etc.), it is difficult to estimate average daily intakes by these routes. Up-to-date comprehensive monitoring data would be useful in determining the typical amount of formaldehyde to which the general population is exposed. This information is necessary for assessing the need to conduct health studies on these populations and persons residing near hazardous waste sites.

Exposures of Children. Because formaldehyde is found predominately in the air, the main exposure pathway for children is the same as adults. Formaldehyde concentrations in indoor air have been reported, although many of the studies were obtained before manufacturing methods for formaldehyde-releasing building materials were changed to reduce emissions. Current, comprehensive studies that account for all formaldehyde release sources to indoor air would aid in determining the body burden to children. Studies that take into account the different lifestyles of children would be also helpful. For example, formaldehyde emissions to indoor air may be source dominated (e.g., emission from pressed wood furniture). For a given emission level, the resulting formaldehyde concentration would be expected to be greater in children's rooms compared to those of adults because the volume is smaller. Information to address child specific formaldehyde exposure issues is not available.

Exposure Registries. No exposure registries for formaldehyde were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance. Workers in industries where formaldehyde is used or produced should be considered for inclusion in an exposure registry. Given that formaldehyde is routinely found in indoor air samples, members of the general population should also be considered for inclusion in the exposure registry.

5.8.2 Ongoing Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human blood samples for formaldehyde and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

The Federal Research in Progress (FEDRIP 1996) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 5.8.1. These studies are summarized in Table 5-4.

Table 5-4. Ongoing Studies on the Potential for Human Exposure to Formaldehyde

Investigator	Affiliation	Research description	Sponsor
K. Knapp, D. Pahl, and F. Black	EPA-AREAL Research Triangle Park, NC	Characterization of emissions, including formaldehyde, from motor vehicles using both traditional and alternative fuels.	EPA
B.J. Collier	Louisiana State University Baton Rouge, LA	Development of textile materials for environmental compatibility and human health and safety.	USDA
D.V. Sandberg and R.D. Ottmar	Pacific Northwest Forest and Range Experiment Station Portland, OR	Assessment of firefighter exposures to potential health hazards, including formaldehyde.	USDA
T. Shibamoto	University of California Davis, CA	Isolation and identification of mutagens and carcinogens in foods.	USDA
J.S. Gaffney	Argonne National Laboratory Argonne, IL	Atmospheric chemistry of organic oxidants and aldehydes.	USDOE
P. Davidovits	Boston College Chestnut Hill, MA	Laboratory studies of heterogeneous gas-liquid interaction of atmospheric trace gases, including formaldehyde.	NSF
R.C. Bales and M. Conklin	University of Arizona Tucson, AZ	Determination of the atmosphere-to-snow transfer function for peroxide and formaldehyde, whose deposition is reversible.	NSF
R.C. Bales and M. Conklin	University of Arizona Tucson, AZ	Distribution of reactive chemical species, including formaldehyde, in ice and snow.	NSF
V.A. Mohnen	State University of New York Albany, NY	Examination of the involvement of natural hydrocarbons for the formation of peroxide and formaldehyde in air.	NSF
B.G. Heikes	University of Rhode Island Kingston, RI	Background atmospheric measurements of hydrogen peroxide, organic hydro-peroxides, and formaldehyde.	NSF
S.S. Que Hee	UCLA School of Public Health Los Angeles , CA	Carbonyl compounds air sampling method.	NIOSH
R.R. Fall	University of Colorado at Boulder Boulder, CO	Biogenic sources of oxygenated hydrocarbons in the troposphere.	NSF

EPA = Environmental Protection Agency; NSF = National Science Foundation; USDA = United States Department of Agriculture; USDOE = United States Department of Energy; NIOSH = National Institute for Occupational Safety and Health

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring formaldehyde, its metabolites, and other biomarkers of exposure and effect to formaldehyde. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Methods for the determination of formaldehyde in biological samples are given in Table 6-1. Formaldehyde has been measured in blood by gas chromatography (GC) in conjunction with mass spectrometry (MS) after derivatization of the formaldehyde to the pentafluorophenylhydrazone (Heck et al. 1985) and in rat urine by high-performance liquid chromatography (HPLC) with ultraviolet (UV) absorbance detection following formation of the 2,4-dinitrophenylhydrazone derivative (Shara et al. 1992). Although the method was used for rat urine, it would be expected that human urine could also be utilized. The determination of formaldehyde in breath has been demonstrated by Lin et al. (1995) following the formation of 2,4-dinitrophenylhydrazone using 2,4-dinitrophenylhydrazine-impregnated silica cartridges. Formaldehyde has been determined in "biologicals" (vaccines) at concentrations as low as 100 ppb following the formation of the formaldehyde phenylhydrazone (Shrivastaw and Singh 1995). It was noted by the authors that this method was free from interferences from proteins and bacterial cells so it might have applicability to biological fluids such as blood or urine. Formic acid or formate is produced from formaldehyde arising from both exogenous and endogenous sources and can be measured as reported by Baumann and Angerer (1979). Although no literature citations were found, it would seem that formate in urine and blood could be determined by a method based on ion chromatography (IC). The measurement of formaldehyde conjugates of IgE and IgG in people exposed to formaldehyde has been shown (Thrasher et al. 1989), but has not resulted in a routine method.

Table 6-1. Analytical Methods for Determining Formaldehyde and Metabolites in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Venous blood	Addition of water and pentafluorophenyl-hydrazine in dilute phosphoric acid; addition of a known amount of labeled formaldehyde as internal standard; equilibration for 2 hours at 50 C; extraction with hexane/methylene chloride.	GC/MS (SIM)	No data	No data	Heck et al. 1985
Breath	Collection of expired air into Douglas bag, then Tedlar bag; drawing of breath through DNPH-coated silica; elution with acetonitrile and addition of internal standard; evaporation of solvent and redissolution.	HPLC/UV	No data	95.6 (SD= 3.6)	Lin et al. 1995
Urine (rat)	Dilution of urine with water, addition of DNPH in 2 N HCl and pentane followed by intermittent shaking for 30 minutes; extraction with additional aliquot of pentane followed by solvent evaporation; redissolution in acetonitrile.	HPLC/UV	10 pmole/mL (0.3 µg/L, 0.3 ppb)	No data	Shara et al. 1992
Biologicals (vaccines)	Addition of 1 mL of sample to 3 mL of water, addition of phenyl hydrazine, concentrated HCl, methanol, and chloroform followed by shaking for 10–30 seconds; isolation of chloroform layer for spectrophotometric analysis.	Absorbance at 529 nm	100 ng/mL (100 ppb)	No data	Shrivastaw and Singh 1995
Blood, urine (formic acid)	Formic acid transformed by concentrated sulfuric acid into water and carbon monoxide; carbon monoxide converted to methane in chromatographic system.	GC/FID	No data	No data	Baumann and Angerer 1979

Table 6-1. Analytical Methods for Determining Formaldehyde and Metabolites in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (human serum albumin-formaldehyde conjugate; IgE, IgG)	Addition of diluted sample to coated microtiter test plates; ELISA using orthophenyldiamine as substrate.	Absorbance at 490 nm	No data	No data	Thrasher et al. 1989

DNPH = 2,4-dinitrophenylhydrazine; ELISA = enzyme-linked immunosorbent assay; FID = flame ionization detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; IgE = immunoglobulin E; IgG = immunoglobulin G; MS = mass spectrometry; SD = standard deviation; SIM = selected ion monitoring; UV = ultraviolet absorbance detection

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of formaldehyde in environmental samples are given in Table 6-2.

Formaldehyde in air can be trapped using impingers filled with water (Fan and Dasgupta 1994; Hoogenboom et al. 1987; Petreas et al. 1986); an aqueous solution of sodium bisulfite (NIOSH 1989a; Petreas et al. 1986); an acidic, aqueous solution of 2,4-dinitrophenylhydrazine (DNPH) (EPA 1988d); or buffered Girard T reagent (NIOSH 1989b). Formaldehyde released into air from textiles has been collected onto moist filter paper (Naruse et al. 1995). Cofer and Edahl (1986) have reported a sampling device that uses a nebulization/reflux approach that is essentially a modification of the impinger device capable of collecting samples at high flow rates (7–8 L/minute). Formaldehyde trapped into water or aqueous bisulfite is subjected to chemical derivatization prior to analysis (see below). Formaldehyde collected into water has been shown to degrade rapidly (a 50% loss in 50 hours) upon ambient and refrigerated storage (Daggett and Stock 1985) while those samples in bisulfite are stable for periods ranging from 1 week (Daggett and Stock 1985) to 4 weeks (Balmat and Meadows 1985). The method of EPA (1988d) traps the formaldehyde as it reacts with DNPH to form the 2,4-dinitrophenylhydrazone derivative. The formation of the formaldehyde dinitrophenylhydrazone has been extended to solid-phase samplers including DNPH-coated silica (Grosjean et al. 1993; Millipore Corporation 1992), DNPH-coated glass fiber filters (Dalene et al. 1992), and annular denuders coated with DNPH (Possanzini et al. 1987). These solid-phase samplers are much more convenient, especially for personal samples where impinger-based devices can easily be spilled. Commercially prepared DNPH-silica cartridges are available from Millipore Corporation (Milford, Massachusetts) and Supleco (Bellefonte, Pennsylvania). Nondek et al. (1991, 1992) have collected formaldehyde as dansylhydrazone through reaction of formaldehyde as it passed through dansylhydrazine-coated porous glass particles. Yet another approach is based on the collection of formaldehyde as its oxazolidine derivative using the polymeric sorbent XAD-2 coated with hydroxymethyl piperidine (NIOSH 1994a). A passive collection device is also available commercially and is based on the stabilization of formaldehyde as its adduct with sulfite after passage of formaldehyde through a membrane (3M Company 1985). Formaldehyde adsorbed to particulate matter has also been recovered using a water extraction of the particles prior to the formation of the DNPH derivative (NIOSH 1994b).

Table 6-2. Analytical Methods for Determining Formaldehyde in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Drawing of air through two impingers in series each of which contains 1% sodium bisulfite. Addition of chromotropic acid and concentrated sulfuric acid, heating to 95 C for 15 minutes, cooling to room temperature (Method 3500).	Absorbance at 580 nm	0.05 μg/m^3 (0.04 ppb in 100 L sample)	No data	NIOSH 1989a
Air	Drawing of air through an XAD-2 sorbent coated with 10% 2-hydroxymethyl piperidine, elution of the oxazolidine derivative with toluene (Method 2541).	GC/FID (can use GC/NPD for improved sensitivity)	0.028 mg/m^3 (23 ppb in 36 L sample)	No data	NIOSH 1994a
Air particulates (textile or wood)	Drawing of air through 25 mm PVC filter (5 μm pore size), extraction of formaldehyde from particulates into water, derivatization with 2,4-dinitrophenylhydrazine (Method 5700).	HPLC/UV	0.076 μg/m^3 (0.062 ppb)	96 (1.1% RSD at 7 μg/sample)	NIOSH 1994b
Air	Drawing of air through a midget bubbler containing 15 mL buffered (pH = 4.5) Girard T reagent (NIOSH 3501).	DC polarography	0.3 mg/m^3 (0.24 ppm)	100	NIOSH 1989b
Air	Preparation of passive monitor (3M 3721), formaldehyde in air diffuses through a membrane and adsorbs onto bisulfite-impregnated paper, desorption with water, addition of chromotropic acid and concentrated sulfuric acid.	Absorbance at 580 nm	<34 μg/m^3 (<0.028 ppm)	100 (±5%)	3M Company 1985
Air	Drawing of sample through impinger containing 2N HCL/0.05% 2,4-dinitrophenylhydrazine and isooctane; removal of isooctane layer, extraction of aqueous layer with 70/30 hexane/ methylene chloride, combining of organic layers and evaporation of solvent; redissolution in methanol (TO5-1).	HPLC/UV	1.2–2.4 μg/m^3 (1–2 ppb)	>75 (15–20% RSD)	EPA 1988d
Air	Drawing of air through DNPH-coated silica SPE, elution with acetonitrile.	HPLC/UV	0.49 μg/m^3 (0.40 ppb)	96 (7.1% RSD)	Grosjean et al. 1993

Table 6-2. Analytical Methods for Determining Formaldehyde in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Drawing of air through DNPH-coated silica; elution with acetonitrile.	HPLC/UV	<1.2 μg/m^3 (< 1 ppb)	>95 for sampling rates up to 2 L/min	Millipore Corporation 1992
Air (tropospheric)	Drawing of filtered air through a nebulization/reflux concentrator (scrubber) at rate of 7–8 L/min where formaldehyde is reacted to form DNPH derivative.	HPLC/UV	0.12 μg/m^3 (0.1 ppb)	90–96	Cofer and Edahl 1986
Air	Drawing of air through impinger filled with 1% sodium bisulfite; addition of CTA, concentrated sulfuric acid; equilibration for 1 hour.	Absorbance at 580 nm	No data	98.7±4.7	Petreas et al. 1986
Air	Drawing of air through impinger containing water; addition of pararosaniline (PRA) hydrochloride, sodium sulfite, and equilibration for 60 minutes at room temperature.	Absorbance at 570 nm	No data	91.9±6.9	Petreas et al. 1986
Air	Drawing of air through glass fiber filter impregnated with DNPH. After collection, elution of derivative with acetonitrile and elution through a cation exchange column to remove excess reagent; evaporation of solvent and redissolution in toluene containing internal standard.	GC/TSD	10 μg/m^3 (8.1 ppb)	92 at 600 ng (5% RSD)	Dalene et al. 1992
Air	Drawing of air through tube that contains a smaller, concentric tube made of Nafion (semipermeable) through which water flows in the opposite direction and serves to trap formaldehyde; addition of 1,3-cyclo-hexanedione, in acidified ammonium acetate to form dihydropyridine derivative in flow injection analysis system.	Fluorescence (FIA)	0.011 μg/m^3 (9 ppt)	50 (%RSD at 0.07 ppb = 1.5%)	Fan and Dasgupta 1994
Air	Drawing of air through impingers containing pH 7 phosphate buffer and EDTA; addition of bisulfite, reaction of excess bisulfite with 5,5'-dithiobis(2-nitrobenzoic acid) (indirect measure of formaldehyde).	Absorbance at 412 nm	12 μg/m^3 (0.01 ppm in 88 L)	99.9 (1.7% RSD)	Hoogenboom et al. 1987

Table 6-2. Analytical Methods for Determining Formaldehyde in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Drawing of air through microcartridges packed with porous glass particles impregnated with dansylhydrazine; cartridge placed in-line with HPLC mobile phase.	online HPLC/Fluorescence	0.01 μg/L (0.01 ppb in 1 L)	No data	Nondek et al. 1992
Air (off-gassing from textiles)	Placement of filter paper moistened with distilled water into a vial and incubation of the open vial with textiles at 40 C for 24 hours in 12.7 L chamber; addition to vial of solution containing ammonium acetate, water, acetic acid, and acetylacetone and incubation at 40 C for 30 min.	Absorbance at 414 nm	< 15 ppm	No data	Naruse et al. 1995
Atmospheric water	Reaction of formaldehyde in water with ammonium acetate and 2,4-pentanedione in FIA system to form 3,5-diacetyl-1,4-dihydrolutidine.	FIA/fluorescence	3 μg/L (3 ppb)	No data	Dong and Dasgupta 1987
Drinking water	Reaction of 1 L water with DNPH in 2M acid, extraction with chloroform, solvent exchange to methanol.	HPLC/UV	20 μg/L (20 ppb)	>90 at 20–200 μg/L	Tomkins et al. 1989
Drinking water	Buffering a volume of water to pH 3 followed by derivatization at 40 C for 1 hour with DNPH. Derivative recovered using C_{18} SPE and elution with methanol (Method 554).	HPLC/UV	8.1 μg/L	96 (7.9% RSD) at 250 μg/L.	EPA 1992b
Fog water	Free formaldehyde: addition of 200 μL of DNPH solution in 2N HCl was added to 200 μL of sample followed by addition of 400 μL of iso-octane and reaction for 45 minutes; direct analysis of an aliquot of organic layer. Total formaldehyde: addition of NaOH to increase pH to 13 to decompose formaldehyde-bilsulfite adduct followed by addition of DNPH in 2.7 N HCl and isooctane; direct analysis of an aliquot of the organic layer.	HPLC/UV	3 μM (90 ppb)	No data (analytical variability stated as ±1 μM)	Facchini et al. 1990

Table 6-2. Analytical Methods for Determining Formaldehyde in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Maple syrup	Distillation of 3 mL of water from 20 g of sample, addition of Nash reagent (ammonium acetate, acetic acid, acetyl acetone) followed by heating for 30 minutes at 37 C (Method 964.21).	Absorbance at 415 nm.	<1 ppm (<1 mg/L)	No data	Helrich 1990
Milk	Addition of acidified DNPH and hexane to 2 mL of sample, reaction with stirring for 30 minutes at room temperature; filtration through Celite, washing with hexane; evaporation of solvent; redissolution in acetonitrile.	HPLC/UV	Estimated at 0.009 mg/kg (9 ppb)	89.9±3.9 (0.1 μg/mL)	Kaminski et al. 1993b
Fish flesh	Heating of 100 g of fish to 200 C and purging of volatiles through two impingers in series, each containing cysteamine solution; equilibration for 30 minutes to form thiazolidine derivative; extraction with methylene chloride, cleanup using silica-gel; addition of internal standard.	GC/NPD	5.8 pg (for GC detection only; not a method LOD)	No data	Yasuhara and Shibamoto 1995
Coffee	Addition of 0.75 g cysteamine to 250 mL of brewed or reconstituted instant coffee to liquid-liquid continuous extractor; adjustment of pH to 8 and extraction with 70 mL chloroform for 3 hours; removal of water using sodium sulfate, addition of internal standard, volume adjustment.	GC/NPD	No data	>100 at 1 ppm	Hayashi et al. 1986

CTA = chromotropic acid; DNPH = 2,4-dinitrophenylhydrazine; EDTA = ethylene diaminetetraacetic acid; FIA = flow injection analysis; GC = gas chromatography;; HPLC = high-performance liquid chromatography; LOD = level of detection; NPD =nitrogen-phosphorus detector; PRA = pararosaniline; RSD = relative standard deviation; SPE = solid phase extraction; TSD = thermionic specific detection; UV = ultraviolet absorbance detection

Most of the measurement methods reported rely on spectrophotometry or chromatography, either GC or HPLC, although one of the NIOSH methods (Method 3501, NIOSH 1989b) is based on polarography. There are many spectrophotometric methods available. Method 3500 (NIOSH 1989a) is often used as a reference method during the development of new methods. This method relies on the reaction of the formaldehyde-bisulfite adduct with chromotropic acid (4,5-dihyroxynaphthalene-2,7-disulfonic acid) in the presence of concentrated sulfuric acid to form a highly colored product that is measured by its absorbance at 580 nm. Phenols in 8-fold excess over formaldehyde produce a -10 to -20% bias; small negative interferences can also result from ethanol and higher molecular-weight alcohols, olefins, aromatic hydrocarbons, and cyclohexanone (NIOSH 1989a). Little interference is seen from other aldehydes.

The method of Fan and Dasgupta (1994) relies on the reaction of formaldehyde with 1,3-cyclohexane-dione in acidified ammonium acetate to form the fluorescent dihydropyridine derivative in a flow injection analysis system. Formaldehyde trapped in water can be reacted with pararosaniline and sodium sulfite under mild conditions (neutral pH, room temperature equilibration) to produce a colored product that is measured at 570 nm (Petreas et al. 1986). The presence of bisulfite is an interference in this reaction so the method cannot be used to sample atmospheres that contain sulfur dioxide. In addition, the method is reported to suffer from interferences resulting from the presence of other aldehydes and phenol (Hoogenboom et al. 1987). The indirect method of Hoogenboom et al. (1987) relies on the reaction of excess bisulfite in an aqueous solution of formaldehyde with 5,5'-dithiobis(2-nitrobenzoic acid) to form a colored product, the absorbance of which is measured at 412 nm. The method reported by Naruse et al. (1995) relies on the formation of a colored product obtained by reacting the aqueous formaldehyde with acetylacetone and ammonium acetate in acetic acid. Absorbance is measured at 414 nm.

The separation of dinitrophenylhydrazones using HPLC and absorbance detection is widely used for the measurement of formaldehyde and other carbonyl compounds (EPA 1988d; Grosjean et al. 1993; Millipore Corporation 1992; NIOSH 1994b). The reactivity of carbonyl compounds other than formaldehyde with DNPH requires the use of a chromatographic method to resolve the derivatives of the other compounds from that of formaldehyde. Ozone present in the atmosphere being sampled reacts with DNPH and the DNPH derivative of formaldehyde (Arnts and Tejada 1989), especially when using DNPH-coated silica gel cartridges. Ozone can be scrubbed from the sample stream by passing the air through a copper tube coated with potassium iodide before passing the air through the DNPH-coated silica (Millipore Corporation 1992). In some cases, the DNPH derivatives are separated using GC, but

this mode of analysis requires an additional cleanup step to remove the excess DNPH reagent (Dalene et al. 1992). Caution must be used to avoid exposure of DNPH-silica cartridges or eluted samples to aldehyde and ketone sources. Laboratory air often holds high concentrations of acetone. Labeling inks, adhesives, and packaging containers (including vials with plastic caps) are all possible sources of contamination (Millipore Corporation 1992). Field blanks should always be used.

Methods for the collection and determination of formaldehyde in water show great similarity to those methods for air described above. The methods of Tomkins et al. (1989) and EPA (1992b) for formaldehyde in drinking water and the method of Facchini et al. (1990) for formaldehyde in fog water all rely on the formation of the DNPH derivative followed by HPLC. The method of Dong and Dasgupta (1987) relies on the reaction of formaldehyde in atmospheric water with a diketone (2,4-pentanedione) and ammonium acetate to form a fluorescent derivative that is measured spectrophotometrically in a flow injection analysis system.

A few methods for the determination of formaldehyde in foods were found in the literature. The method of Kaminski et al. (1993b) for formaldehyde in milk relies on the formation of the DNPH derivative with analysis by HPLC and absorbance detection. Formaldehyde in maple syrup (Helrich 1990) is determined spectrophotometrically after the reaction of formaldehyde with acetyl acetone (Nash reagent or 2,4-pentanedione) in the presence of ammonium acetate in an acidic solution. Formaldehyde in fish flesh (Yasuhara and Shibamoto 1995) and in coffee (Hayashi et al. 1986) has been determined through the formation of the thiazolidine derivative (a reaction product of formaldehyde with cysteamine) followed by GC in conjunction with nitrogen-phosphorus detection. Yasuhara and Shibamoto (1995) noted that the accuracy of formaldehyde determination can be affected by the adsorption of formaldehyde onto glass surfaces and the generation of artificial formaldehyde during heating of nitrogen-containing compounds such as trimethylamine oxide.

Two other methods for the determination of formaldehyde in gases and liquids have been described but are too complex, given the simplicity of the other methods available. One method is based on enzymatic processes (Barzana et al. 1989; Ho and Richards 1990) followed by spectrophotometry; the other is based on pH changes associated with formaldehyde metabolism by genetically altered cells (Korpan et al. 1993).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of formaldehyde is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of formaldehyde.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods for the determination of formaldehyde in blood (Heck et al. 1985), breath (Lin et al. 1995), and urine (Shara et al. 1992) have been published. However, formaldehyde concentration in body fluids or expired air is not expected to be a reliable biomarker of exposure, even for acute exposure, because of its high reactivity and rapid metabolism. Methods for the detection of formate, the principal metabolite of formaldehyde, in urine are also available, but urinary levels of formate did not appear to be consistently associated with exposure levels in studies of students exposed to formaldehyde in anatomy laboratories (Einbrodt et al. 1976; Gottschling et al. 1984). One plausible contributing factor to the lack of consistency in the use of formate concentrations as a measure of exposure is that the metabolism of other chemicals can lead to the formation of formate. Further research to increase the sensitivity or reliability of methods to quantify formaldehyde or formate does not seem warranted.

In contrast, DNA-protein cross links in white blood cells (Shaham et al. 1996a) and the presence of serum IgG antibodies to formaldehyde conjugated to human serum albumin (Carraro et al. 1997) are

potentially useful biomarkers of intermediate- or chronic-duration exposure to formaldehyde that may be developed further with additional research.

Methods to detect DNA-protein cross links have been published (Cohen et al. 1990; Shaham et al. 1996a; Zhitkovich and Costa 1992) that reportedly have greater sensitivity than earlier methods that relied on alkaline elution techniques (Brutlag et al. 1969). Although the formation of DNA-protein cross links is not specific to formaldehyde (i.e., other agents can form them), Shaham et al. (1996a) demonstrated that cultured human white blood cells showed increasing quantities of DNA-protein cross links when cultured in media with increasing formaldehyde concentrations and that a small group of formaldehyde-exposed persons had a significantly greater mean amount of DNA-protein cross links in their white blood cells than did a group of non-exposed persons. Additional research to apply these methods to larger groups of occupationally exposed and non-exposed persons may help to determine the reliability of this variable as a biomarker of exposure and to determine the extent to which individuals vary in this response to formaldehyde. Additional research to apply the DNA-protein cross link methods to nasal biopsy specimens may lead to an increased sensitivity of this potential biomarker of exposure and effect.

Carraro et al. (1997) developed an indirect competitive immunoenzyme assay to detect serum IgG antibodies against formaldehyde conjugated to human serum albumin. This technique was used to compare the presence or absence of the antibodies in 219 healthy subjects who differed in smoking habits (tobacco smoke is a significant source of formaldehyde exposure) and occupational exposure to formaldehyde. The indirect competitive immunoenzyme assay was developed and applied as a qualitative method. Additional research is needed to determine if the method can be modified to provide a reliable and precise measure to quantify exposure level or exposure duration.

Effect. As discussed in the previous section, DNA-protein cross links and anti-formaldehyde-human serum albumin IgG antibodies are potential biomarkers of effect and exposure. Whereas detection of these biomarkers can represent biological responses to repeated exposure to formaldehyde (the first is not specific to formaldehyde, but the second is), it is uncertain to what degree their detection indicates that adverse health effects will occur. Further research on relationships between formaldehyde-induced upper respiratory tract tissue damage and/or dysfunction and: (1) DNA-protein cross links in either white blood cells or nasal biopsy tissue; or (2) levels of formaldehyde-specific IgG antibodies may help in determining if improved detection methods are needed.

Various methods have been published to examine nasal lavage fluid for cellular and chemical contents that may be indices of acute allergic or inflammatory responses to formaldehyde or other respiratory irritants (Pin et al. 1992; Prat et al. 1993; Wang et al. 1995). Increased eosinophil concentration and increased albumin and total protein levels have been found in nasal lavage fluid taken from subjects exposed to 0.4 ppm formaldehyde for 2 hours (Krakowiak et al. 1998; Pazdrak et al. 1993). Although these variables are not expected to be specifically influenced by formaldehyde, they appear to provide biomarkers of acute respiratory irritation from airborne formaldehyde or other upper respiratory irritants. Further research on relationships between concentrations of these variables in nasal lavage fluid and prevalence or severity of respiratory symptoms in humans exposed acutely to varying concentrations of formaldehyde may help to confirm their use as biomarkers of effect.

Histological changes in nasal biopsy tissue samples have been observed in several cross-sectional studies of formaldehyde-exposed and non-exposed workers (Ballarin et al. 1992; Boysen et al. 1990; Edling et al. 1988; Holmstrom et al. 1989c). Each of these studies used a morphological grading method that assigned an increasing point value for histological changes ranging in severity from loss of ciliated cells to the presence of malignant cells. Prevalence of different types of changes and mean histological scores were compared between exposed and non-exposed groups. As with the use of cellular and biochemical changes in nasal lavage fluid, the changes are not expected to be only due to formaldehyde, but appear to provide biomarkers of upper respiratory tract tissue damage. Further research on the possible progression of nasal tissue damage in workers with increasing duration of exposure may help in determining if methods for detecting and quantifying nasal epithelial tissue damage need further improvement.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available for the determination of formaldehyde in air, water, and a limited number of foods. Regarding methods for air, very low limits of detection (LODs) are possible. The chromotropic acid method (NIOSH 3500) (NIOSH 1989a) has an LOD of 0.04 ppb. Typical LODs possible using dinitro phenyl hydrazine (DNPH) derivatization, either from an impinger-based sample collection procedure or through derivatization on DNPH-coated silica, are 1–2 ppb (EPA 1988d), 0.4 ppb (Grosjean et al. 1993), and less than 1 ppb (Millipore Corporation 1992). Other methods that form fluorescent derivatives, such as the method of Nondek et al. (1992), can provide greater sensitivity (LOD reported to be 0.01 ppb) and are applicable; however, they require specialized equipment not available in most laboratories. Assuming an intermediate inhalation exposure minimal

risk level (MRL) of 0.01 ppm, all of the above methods are adequate. If a chronic-duration inhalation MRL of 0.0008 ppm (0.8 ppb) is assumed, the methods of NIOSH (1989a), Grosjean et al. (1993), and Nondek et al. (1992) are adequate. For monitoring of air, formaldehyde concentrations at the intermediate (0.01 ppm) and acute (0.05 ppm) MRLs, the above methods, in addition to those of Millipore Corporation (1992) and EPA (1988d), are adequate. No additional methods for formaldehyde in air are needed.

Methods for the determination of formaldehyde in drinking water are available and they utilize the same detection methods as those utilized for the analysis of formaldehyde in air, with LODs reported to be 20 ppb (Tomkins et al. 1989) and 8.1 ppb (EPA 1992b). The MRL for chronic oral exposure to formaldehyde is 0.2 mg/kg/day. If a 70-kg person is assumed, the maximum intake is 14 mg/day. If a daily intake of 2 L of water or 2 kg/day of food per day is assumed, then any analytical method must have an LOD of less than 7 mg/L for water or 7 mg/kg (ppm) for food. The cited methods for detecting formaldehyde in water have LODs far below the needed value and are sensitive enough to measure background levels in the environment; no additional methods for formaldehyde detection in water are required. Other than for milk (Kaminski et al. 1993b, LOD=9 ppb), no methods for formaldehyde detection in food were found. Additional methods for detection of formaldehyde in foods are needed. Methods for the detection of formaldehyde in soil are not adequately described in the available literature.

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of formaldehyde and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry which gives detection limits in the low-parts-per-trillion (ppt) range.

The information in Table 6-3 was found as a result of a search of Federal Research in Progress (FEDRIP 1996).

Table 6-3. Ongoing Studies on Formaldehyde

Investigator	Affiliation	Research description	Sponsor
Creighton University		Studying products of altered lipid metabolism, including formaldehyde, associated with exposures to TCDD, endrin, and lindane in pregnant mice. Specifically, they are concerned with the exposures of the fetus to these products and will be determining formaldehyde concentrations in maternal serum and amniotic fluid.	NIEHS
Albion Instruments	Salt Lake City, UT	Investigating the utility of solid-state lasers for monitoring escaped clinical gases.	DHHS
Spectral Sciences, Inc.	Burlington, MA	Development of diode laser-based remote monitoring of trace gas concentrations over long open-air paths. The target analytes include those covered by the Clean Air Act (CAA), formaldehyde among them.	DOE
Southwest Sciences	Santa Fe, NM	Diode laser-based sensors for gases, including formaldehyde, in harsh high-temperature, high-pressure environments.	DOE

DHHS = Department of Health and Human Services; DOE = Department of Energy; NIEHS = National Institute of Environmental Health

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding formaldehyde in air, water, and other media are summarized in Table 7-1.

ATSDR has derived an acute inhalation MRL of 0.04 ppm on the basis of clinical symptoms (increased itching, sneezing, mucosal congestion, transient burning sensation of the eyes and of the nasal passages) and nasal alterations (elevated eosinophil counts and a transient increase in albumin content of nasal lavage fluid) in humans (Pazdrak et al. 1993). This MRL is based on a minimal LOAEL of 0.4 ppm and an uncertainty factor of nine (three for use of a minimal LOAEL and three for human variability).

An intermediate-duration inhalation MRL of 0.03 ppm was derived based on a NOAEL of 0.98 ppm and a LOAEL of 2.95 ppm (22 hours/day, 5 days/week for 26 weeks) for clinical signs of nasopharyngeal irritation (hoarseness and nasal congestion and discharge) and lesions in the nasal epithelium (squamous metaplasia and hyperplasia) observed in monkeys (Rusch et al 1983). An uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) was used to derive the MRL.

A chronic inhalation MRL of 0.008 ppm was derived based on a minimal LOAEL of 0.24 ppm for histological evidence of mild damage to the nasal epithelial tissue (squamous metaplasia, loss of ciliated cells, goblet cell hyperplasia, and mild dysplasia in biopsied tissue) in formaldehyde exposed chemical workers (Holmstrom et al. 1989c). To derive the MRL, the minimal LOAEL was divided by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability).

An intermediate oral MRL of 0.3 mg/kg/day was based on a NOAEL and LOAEL of 25 and 125 mg/kg/day for gastrointestinal tract effects in rats exposed for 4 weeks to formaldehyde in drinking water (Til et al. 1988b). An uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL to derive the MRL.

ATSDR derived a chronic oral MRL of 0.2 mg/kg/day based on a NOAEL and LOAEL of 15 and 82 mg/kg/day for gastrointestinal tract effect in rats exposed for up to 2 years to formaldehyde in drinking water (Til et al. 1989). An uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL to derive the MRL.

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification	Group 2A[a]	IARC 1995
WHO	Drinking-water guideline values for health-related organics	None	WHO 1984
NATIONAL			
Regulations:			
a. Air:			
OSHA	Permissible Exposure Limit (PEL)	0.75 ppm	29 CFR 1910.1048 OSHA 1992
	8-hr. Time weighted average (TWA)		
	15-min. Short-term exposure limit (STEL)	2 ppm	
EPA-OAR	Hazardous Air Pollutants	Yes	Clean Air Act Amendment Title III, Section 112 (b) U.S. Congress 1990
	Standards of Performance for New Stationary Sources		
	Equipment Leaks of VOCs in the Synthetic Organic Chemicals Manufacturing Industry (SOCMI)	Yes	40 CFR 60.489 EPA 1983a
	VOC Emissions from SOCMI Air oxidation unit processes-chemicals affected	Yes	40 CFR 60.617 EPA 1990a
	VOC Emissions from SOCMI Distillation operation-chemical affected	Yes	40 CFR 60.667 EPA 1990b
	VOC Emissions from SOCMI Reactor processes-chemicals affected	Yes	40 CFR 60.707 EPA 1993a
	National Emission Standards for Organic Hazardous Air Pollution from the Synthetic Organic Chemical Manufacturing Industry-Delegation of Authority	Yes	40 CFR 63.106 EPA 1994a
	Chemical Accident Prevention Provisions-Regulated Toxic Substances and Threshold Quantities for Accidental Release Prevention-Formaldehyde Solution	15,000 pounds	40 CFR 68.130 EPA 1994b

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde (continued)

Agency	Description	Information	References
NATIONAL (cont.)			

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde (continued)

Agency	Description	Information	References
EPA-OAR	Regulation of Fuels and Fuel Additives-Reformulated Gasoline-Simple Emission Model	Yes	40 CFR 80.42 EPA 1994c
	Complex emissions models; baseline exhaust emission	Phase I Summer Winter (mg/mile) 4.85 7.27 Phase II Summer Winter (mg/mile) 9.38 15.84	40 CFR 80.45 EPA 1994d
	Vehicle test procedures	Yes	40 CFR 80.51 EPA 1994e
	Measurement methods for formaldehyde and actelaldehyde	Yes	40 CFR 80.56 EPA 1994f
	Conventional gasoline baseline emissions determinations	Yes	40 CFR 80.90 EPA 1994g
	Control of Air Pollution from New and In-use Motor Vehicles and New and In-use Motor Vehicle Engines-Certification and Test Procedures	Yes	40 CFR 86 EPA 1977a
	NESHAP for Source Category; Pulp and Paper Production (proposed rule)	Yes	58 FR 66078 EPA 1993b
	List of Regulated Substances and Thresholds for Accidental Release Prevention (proposed rule)	500 pounds (threshold)	58 FR 5102 EPA 1993c
	Control of Air Pollution from New and In-use Motor Vehicles and engines; Technical Amendments to the Test Procedures for Methanol-fueled Motor Vehicles and Motor Vehicle Engines and Petroleum-fueled Motor Vehicles (proposed rule)	Yes	58 FR 11816 EPA 1993d
	HAP: Proposed Regulations Governing Constructed, Reconstructed or Modified Major Sources (proposed rule)	Yes	59 FR 15504 EPA 1994h
b. Water			
EPA-OW	Designation of Hazardous Substances-List of Hazardous Substances, Table 116.4	Yes	40 CFR 116.4 EPA 1978

NATIONAL (cont.)

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde (continued)

Agency	Description	Information	References
	Determination of Reportable Quantities for Hazardous Substances- RQ Pursuant to Section 311 CWA, Table 117.3	100 pounds	40 CFR 117.3 EPA 1985b
	EPA Permit Programs: NPDES-Toxic Pollutants and Hazardous Substances Required to be Identified by Existing Dischargers if Expected to be Present, Table V	Yes	40 CFR 122, App. D EPA 1983b
	Criteria and Standards for the NPDES-Instructions for Form 2C, Application for Permit to Discharge Wastewater	Yes	40 CFR 125 EPA 1984
	Organic Chemicals, Plastics, and Synthetic Fibers		
	Commodity organic chemicals (applicability)	Yes	40 CFR 414.60 EPA 1987a
c. Food:			
FDA	Indirect Food Additives: Adhesives and Components of Coatings	Yes	21CFR 175.105 FDA 1977a
	Indirect Food Additives: Paper and Paperboard		
	Components of paper and paperboard in contact with aqueous and fatty foods	Yes	21 CFR 176.170 FDA 1977 b
	Components of paper and paperboard in contact with dry food	Yes	21 CFR 176.180 FDA 1977c
d. Other:			
EPA-OERR	List of Hazardous Substances and Reportable Quantities	1000 pounds (453.6 kg) (statutory) 100 pounds (45.4 kg) (final RQ)	40 CFR 302.4 EPA 1985a
EPA-OSW	Identification and Listing of Hazardous Waste		
	Definition of a Hazardous Waste	Yes	40 CFR 261.3 EPA 1992a
	Discarded commercial chemical products, off-specification, container residues, and spills	Yes	40 CFR 261.33 EPA 1980

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Basis for listing hazardous wastes-constituent for listing (K010)	Yes	40 CFR 261, App. VII EPA 1981
	Basis for listing - hazardous constituent (U122)	Yes	40 CFR 261, App. VIII EPA 1988b
	Standards for Management of Specific Hazardous Wastes Facilities		
	Regulation of residues	Yes	40 CFR 266.112 EPA 1985c
	Methods Manual for Compliance with BIF Regulations (Method 0011A, Analysis of Aldehydes and Ketones by High Performance Liquid Chromatography)	Yes	40 CFR 266, App. IX EPA 1991b
	Land Disposal Prohibition and Establishment of Treatment Standards-Waste to be evaluated by 8/8/88	Yes	40 CFR 268.10 EPA 1986a
	Treatment Standards-Applicability	Yes	40 CFR 268.4 EPA 1987b
	Emergency Planning and Notification-Extremely Hazardous Substances and Their Threshold Planning Quantities	100 pounds (RQ) 500 pounds (threshold)	40 CFR 355, App. A EPA 1987c
	Toxic Chemical Release Reporting: Community Right-to-Know--Specific Chemical Listing-Chemicals and Chemical Categories	Yes	40 CFR 372.65 EPA 1988c
	Hazardous Waste Management System; Carbamate Production Identification and Listing of Hazardous Waste and CERCLA Hazardous Substance Designation and Reportable Quantities (notice of proposed rulemaking-K157 waste)	1 pound (statutory RQ)	59 FR 9808 EPA 1994i
	Land Disposal Restrictions for Newly Identified and Listed Hazardous Wastes and Hazardous Soil	Yes	62 FR 7502 EPA 1997

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Treatment standards, U122 waste	Wastewater WETXO or CHOXD; CARBN; or INCIN Nonwastewater CMBST	
Guidelines:			
a. Air:			
ACGIH	Ceiling Limit for Occupation Exposure (TLV-STEL)	0.3 ppm (0.37 mg/m^3)	ACGIH 1998
NIOSH	Recommended Exposure Limit for Occupation Exposure (8-hr TWA)	0.016 ppm	NIOSH 1992
	Recommended Exposure Limit for Occupation Exposure (15-min Ceiling)	0.1 ppm	
	Immediately Dangerous to Life and Health	20 ppm	
b. Water:			
EPA	1-d Health Advisory (child)-draft	10 mg/L	EPA 1995; IRIS 1999
	10-d Health Advisory (child)-draft	5 mg/L	
	Lifetime Health Advisory (adult)-draft	1 mg/L	
	Longer-term Health Advisory-draft	5 mg/L (child) 20 mg/L (adult)	
d. Other:			
ACGIH	Group (Cancer Ranking)	A2[b]	ACGIH 1998
EPA	Cancer Classification	B1[c]	IRIS 1999
	RfD	0.2 mg/kg/day	
NIOSH	Cancer Classification	Ca[d]	NIOSH 1992, 1994c
STATE			
Regulations and Guidelines:			
a. Air:	Average Acceptable Ambient Air Concentrations		EPA 1992c
AZ	1 hour	2x10^1 µg/m^3	
	24 hours	1.2x10^1 µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde (continued)

Agency	Description	Information	References
STATE (cont.)			
	Annual	$8x10^{-2}$ µg/m^3	
CT	8 hours	$1.2x10^{1}$ µg/m^3	
FL-FtLdle	8 hours	$1.5x10^{-2}$ µg/m^3	
FL-Pinella	8 hours	4.5 µg/m^3	
	24 hours	1.8 µg/m^3	
	Annual	$7.7x10^{-2}$ µg/m^3	
IN	8 hours	6 µg/m^3	
	Annual	$7.7x10^{-2}$ µg/m^3	
IN-Innap	8 hours	$1.8x10^{1}$ µg/m^3	
KS	Annual	$7.69x10^{-2}$ µg/m^3	
KS-KC	Annual	$7.69x10^{-2}$ µg/m^3	
LA	Annual	7.69 µg/m^3	
MA	24 hours	$3.3x10^{-1}$ µg/m^3	
	Annual	$8x10^{-2}$ µg/m^3	
ME	15 minutes	$6.7x10^{1}$ µg/m^3	
	1 year	$4x10^{-2}$ µg/m^3	
MI	Annual	$8x10^{-2}$ µg/m^3	
NC	15 minutes	$1.5x10^{-1}$ µg/m^3	
NC-Forco	15 minutes	$1.5x10^{1}$ µg/m^3	
ND	NA	BACT	
NV	8 hours	$7.1x10^{-2}$ µg/m^3	
NY	1 year	5x10 µg/m^3	
OK	24 hours	$1.2x10^{1}$ µg/m^3	
PA-Phil	1 year	7.2 µg/m^3	
	Annual	4.82 ppb	
SC	24 hours	7.5 µg/m^3	
SD	8 hours	$1.2x10^{1}$ µg/m^3	
TX	30 minutes	$1.5x10^{1}$ µg/m^3	
	Annual	1.5 µg/m^3	
VA	24 hours	$1.2x10^{1}$ µg/m^3	
VT	Annual	$8x10^{-2}$ µg/m^3	
WA-Olympia		$5x10^{-2}$ ppm	
STATE (cont.)			

Table 7-1. Regulations and Guidelines Applicable to Formaldehyde (continued)

Agency	Description	Information	References
WA-SWEST	Annual	$7.7x10^{-2}$ µg/m^3	
b. Water			
	Water Quality Criteria: Human Health		
CA	Drinking water (guideline)	30 µg/L	FSTRAC 1995
MD	Drinking water (guideline)	10 µg/L	
ME	Drinking water (guideline)	30 µg/L	
NJ	Drinking water (guideline)	100 µg/L	

[a] 2A = probable human carcinogen
[b] A2 = suspected human carcinogen
[c] B1 = probable human carcinogen
[d] Ca = potential occupational carcinogen

BACT = Best Available Control Technology; BIF = Boilers and Industrial Furnaces; CARBN = Carbon adsorption; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CHOXD = Chemical or electrolytic oxidation; CMBST = Combustion; CWA = Clean Water Act; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal State Toxicology and Regulatory Alliance committee; FSUBS = Fuel Substitution; HAP = Hazardous Air Pollutants; IARC = International Agency for Research on Cancer; INCIN = Incineration; MCLG = Maximum Contaminant Level Goal; NA = not applicable; NAS = National Academy of Sciences; NESHAP= National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollution Discharge Elimination System; OAR - Office of Air and Radiation; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; PEL = Permissible Exposure Limit; RCRA = Resource Conservation and Recovery Act; RfD = Reference Dose; RQ = Reportable Quantities; SOCMI = Synthetic Organic Chemicals Manufacturing Industry; STEL = Short-term exposure Limit; TLV= Threshold Limit Value; TWA = Time-weighted Average; VOC = Volatile Organic Compound; WHO = World Health Organization; WETOX = Wet Air Oxidation

No acute-duration oral MRL value was derived for formaldehyde. A more detailed discussion of MRLs for formaldehyde is presented in Section 2.5 and in Appendix A of this profile.

The EPA oral reference dose (RfD) for formaldehyde is 0.2 mg/kg/day for causing gastrointestinal damage. No reference concentration (RfC) was reported for the compound (IRIS 1999).

The National Toxicology Program (1998) noted that formaldehyde is reasonably anticipated to be a human carcinogen. The International Agency for Research on Cancer (IARC) has classified formaldehyde as 2A, probably carcinogenic to humans, based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals (IARC 1995). The EPA has classified formaldehyde as a B1 compound, probable human carcinogen based on limited evidence in humans and sufficient evidence in animals (EPA 1991a; IRIS 1999).

Formaldehyde is on the list of chemicals subject to the requirements of "The Emergency Planning and Community Right-to-Know act of 1986" (EPCRA) (EPA 1988a). Section 313 of Title III of EPCRA, requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media (U.S. Congress 1986).

OSHA requires employers of workers who are occupationally exposed to formaldehyde to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use controls and practices, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 0.75 ppm. The 15-minute, short-term exposure limit (STEL) for formaldehyde is 2 ppm (OSHA 1992).

The EPA regulates formaldehyde under the Clean Air Act (CAA) and has designated formaldehyde as a hazardous air pollutant (HAP). The major source category for which formaldehyde emissions are controlled is the synthetic organic chemicals manufacturing industry (SOCMI)—equipment leaks, air oxidation unit processes, and distillation operations (EPA 1983a, 1990a, 1990b).

Formaldehyde is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Section 414, of the Code of Federal Regulations (EPA 1987a). The point source category for which specific Regulatory Limitations are listed is the waste water discharge from the manufacture of formaldehyde as a commodity organic chemical (EPA 1987a). The Resource Conservation and Recovery Act (RCRA) identifies formaldehyde as a toxic waste if it is discarded as a commercial product, manufacturing intermediate, or off-specification commercial chemical product. Formaldehyde is assigned the hazardous waste number, U122 (EPA 1980).

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), owners of vessels or facilities are required to immediately report release of formaldehyde equal to or greater than the reportable quantity of 100 pounds (45.4 kg) (EPA 1985a). When formaldehyde is used as a post-harvest fungicide for various raw agricultural commodities that are used only as animal feed (e.g., barley, corn, rye grass soybean hay, and oats), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) exempts formaldehyde from the tolerance requirement for residues in or on the commodity (EPA 1975).

The Food and Drug Administration (FDA) identifies formaldehyde as an indirect food additive for use only as a component of adhesives (FDA 1977a). When used in accordance with specified conditions, the food additive formaldehyde may be safely used in the manufacture of animal feeds (FDA 1976).

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9. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainities of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurrs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

$FEFR_{25-75}$—Forced expiratory flowrate between 25 and 75%.

$FEV_{1.0}$—Forced expiratory volume in 1.0 seconds.

FVC—Forced vital capacity.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects—Functional changes in the immune response.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) —An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainity factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments

which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

ppbv—Parts per billion by volume.

ppmv—Parts per million by volume.

Proportionate Mortality Ratio (PMR)—The ratio of a cause-specific mortality proportion in an exposed group to the mortality proportion in an unexposed group; mortality proportions may be adjusted for confounding variables such as age. Cause-specific mortality proportions can be calculated when the cohort (the population at risk) cannot be defined due to inadequate records, but the number of deaths and the causes of deaths are known.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect

various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Relative Risk (RR)—The risk expressed as a ratio of the incidence of diseased subjects exposed to a particular risk factor to the incidence of diseased subjects in a non-exposed referent group.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—The ratio of a cause-specific mortality rate in an exposed cohort during a given period to the mortality rate of an unexposed cohort; mortality rates are often adjusted for age or other confounding variables.

Standardized Proportionate Incidence Ratio (SPIR)—Similar to a Proportionate Mortality Ratio (PMR) in that it is a ratio of a proportion of a specific disease in an exposed group compared with the proportion in an unexposed group.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Formaldehyde
CAS number(s): 50-00-0
Date: April 20, 1999
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 15
Species: Human

MRL: 0.04 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Pazdrak, K, Gorski, P, Krakowiak, A and Urszula, R (1993). Changes in Nasal Lavage Fluid Due to Formaldehyde Inhalation. Int Arch Occup Environ Health 64: 515-519.

Experimental design: This study investigated the effects of formaldehyde exposure on the severity of symptoms of nasal and eye irritation and the cellular makeup of nasal discharge in occupationally exposed patients with skin hypersensitivity to formaldehyde and unexposed (control) patients. The study was comprised of 2 study groups, all of whom were non-smokers. Group 1 consisted of 7 male and 3 female volunteers, all of whom suffered from skin hypersensitivity to formaldehyde; group 2 consisted of 11 healthy males with no history of allergic diseases, normal serum IgE levels, and negative skin tests to common allergens. Nasal washings were performed in both groups immediately before and after a 2-hour exposure to 0 (placebo) and 0.5 mg/m^3 (0.4 ppm) formaldehyde, and at 4 and 18 hours after completion of the 2-hour exposure periods. Washings were analyzed for eosinophil, neutrophil, basophil, and mononuclear cells, and albumin content. Symptoms of irritation (number of sneezes, degree of mucosal edema, rhinorrhea, and itchy eyes) were evaluated through the exposure period and through 4- and 18-hour periods after the exposure period. A symptom score was compiled for each subject by summation of points assigned to the following symptoms (maximum score = 7): sneezing (0 points/0 sneezes; 1 point/1-4 sneezes; 2 points/ > 4 sneezes); rhinorrhea (0 points /none; 1 point/mild; 2 points/abundant); mucosal edema (0 points/none; 1 point/mild; 2 points/nasal block); and itching (0 points/none; 1 point/itchy eyes).

Effects noted in study and corresponding doses: In both groups, placebo inhalation periods were without effects on nasal wash cellular contents or symptom score. During exposure to 0.4 ppm formaldehyde, both groups showed statistically significantly increased average symptom scores compared with average placebo scores (about 4 versus <0.5). Symptom scores were no longer elevated 18 hours after exposure. In both groups, eosinophil counts were elevated at all time points after 0.4 ppm formaldehyde exposure, while the proportion of epithelial cells declined after formaldehyde exposure. Albumin levels also increased in both groups after formaldehyde exposure, but remained elevated only briefly (10 minutes). There were no significant differences between allergic and healthy patients in nasal washing characteristics after formaldehyde exposure. No changes in basophil numbers were noted in either patient group and there was no evidence of mast cell degranulation. The authors concluded that the symptoms observed were the result of a non-specific, non-allergic process in response to low-level formaldehyde vapor exposure. The authors also noted that further study is required to understand the significance of the increased release of eosinophils noting that eosinophils may have both protective (e.g., they can neutralize histamine) and damaging (e.g., they may liberate mediators that damage epithelial surfaces) properties.

Dose and end point used for MRL derivation:

The only concentration tested, 0.4 ppm, is a minimal LOAEL for nasal and eye irritation

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL- the observed symptoms of irritation were mild and reversible, and the clinical significance of the changes in nasal lavage fluid content is uncertain at present .
[ ] 10 for extrapolation from animals to humans
[X] 3 for human variability - the observed symptoms of irritation were observed in a potentially sensitive group of subjects (they displayed dermal sensitivity to formaldehyde).

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

NA

Was a conversion used from intermittent to continuous exposure?

NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Other additional studies or pertinent information that lend support to this MRL:

The Anderson and Molhave (1983) study identified an apparent effect level (0.2 ppm), based on subjective reports of irritation that is lower than the effect levels (0.35-0.4 ppm) in the studies by Pazdrak et al. (1993), Krakowiak et al. (1998), and Bender et al. (1993), which used more objective measures of acute irritation (eosinophil counts and protein concentrations in nasal lavage fluid or time to first reporting of irritation: see section 2.2.1.2 Systemic Effects - Respiratory Effects Acute Controlled Exposure Human Studies.) Because of the use of objective measures of toxicity and the general weight of the available data indicating that some people will not experience eye or upper respiratory tract irritation from formaldehyde even at 1 ppm (see Day et al. 1984; Kulle et al. 1987, Weber Tschopp et al. 1977, and Witek et al. 1986), the Pazdrak et al. (1993) LOAEL of 0.4 ppm was considered a minimal LOAEL in a group of potentially sensitive individuals (some subjects had dermal hypersensitivity to formaldehyde) and selected as the basis of the acute MRL.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Formaldehyde
CAS number: 50-00-0
Date: April 20, 1999
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 49
Species: Cynomolgus Monkey

MRL: 0.03 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Rusch, G, Clary, JJ, Rinehart WE and Bolte, HF (1983). A 26 Week Inhalation Toxicity Study with Formaldehyde in the Monkey, Rat and Hamster. Toxicol Appl Pharmacol 68: 329-343.

Experimental design: Groups of 6 male Cynomolgus monkeys were exposed to 0, 0.19±0.02, 0.98±0.08, or 2.95±0.18 ppm for 22 hours per day, 7 days per week for 26 weeks. All monkeys were weighed and clinically assessed weekly. At sacrifice, adrenals, kidneys, liver, and heart were weighed. Sections of lung, nasal turbinate, trachea, and any other tissue with gross abnormalities were prepared for histologic examination.

Effects noted in study and corresponding doses: Body weights in the monkeys were normal in all groups throughout the study. Monkeys in the 2.95-ppm group exhibited increasing hoarseness, nasal congestion, and nasal discharge, especially during the last 13 weeks of the study. While some nasal symptoms were noted in the 0.19- and 0.98-ppm groups, they were observed to be inconsistent and were not substantiated histologically. All organ weight data were unremarkable. No treatment-related effects were noted in internal organs upon gross inspection. A statistically significant increased incidence of squamous metaplasia and hyperplasia of the nasal epithelium was clearly observed in the 2.95-ppm group, but no significant increase in the incidence of epithelial squamous metaplasia/hyperplasia was found in the 0.19 and 0.98-ppm groups. The response was seen most clearly in the mid-region of the nasoturbinates. No ultrastructural changes were noted in other sections of the turbinates, trachea, or lungs at any of the doses of formaldehyde tested.

Dose and end point used for MRL derivation:

Clinical signs of nasopharyngeal irritation (hoarseness and nasal congestion and discharge) and lesions in the nasal epithelium (squamous metaplasia and hyperplasia) were observed at 2.95 ppm; no effects were observed at 0.98 ppm. Thus, the NOAEL and LOAEL for nasopharyngeal irritation are 0.98 and 2.95 ppm, respectively.

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans - an uncertainty factor of 3 was used, instead of 10, because similar nasal effects have been reported at similar concentrations in different species and different studies indicating few pharmacodynamic differences in species susceptibility

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

NA

Was a conversion used from intermittent to continuous exposure?

The exposure concentration was not adjusted to a continuous exposure basis based on evidence that concentration is more important than the product of concentration and duration of exposure in determining the severity of formaldehyde-induced epithelial damage in the upper respiratory tract (Wilmer et al. 1987).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

In the absence of reference nasal cavity surface areas and minute ventilations for Cynomolgus monkeys, a default regional gas dose ratio of 1 was assumed (EPA 1994).

Other additional studies or pertinent information that lend support to this MRL:

Although there are numerous human studies of acute inhalation toxicity from formaldehyde (controlled-exposure and occupational exposure studies) and numerous investigations of toxic effects from chronic occupational exposures, studies of humans exposed for intermediate durations were not located. In contrast, the database for studies of animals (including primates) exposed by inhalation to formaldehyde is rich, providing data describing exposure-response relationships for formaldehyde-induced effects on the upper respiratory tract system in several species (rats, mice, hamsters, and monkeys) . The study by Rusch et al. (1983) examined a number of species and identified the lowest effect level among the available sets of data. Given this observation, the absence of human intermediate-duration data, and the putatively greater relevance of monkeys, compared with rodents, to humans, the monkey NOAEL of 0.98 ppm and LOAEL of 2.95 ppm for clinical signs of nasopharyngeal irritation were selected as the basis of the intermediate-duration MRL.

Agency Contact (Chemical Manager) : Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Formaldehyde
CAS number: 50-00-0
Date: April 20, 1999
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [] Acute [ ] Intermediate [X] Chronic
Key to figure: 86
Species: Human

MRL: 0.008 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Holmstrom M, Wilhelmsson B, Hellquist H, et al. 1989c. Histological changes in the nasal mucosa in persons occupationally exposed to formaldehyde alone and in combination with wood dust. Acta Otolaryngol (Stockh) 107:120-129.

Experimental design: Holmstrom et al. (1989c) examined histological changes in nasal tissue specimens from a group of 70 workers in a chemical plant that produced formaldehyde and formaldehyde resins for impregnation of paper, a group of 100 furniture factory workers working with particle board and glue components, and a nonexposed, control group of 36 office workers in the same village as the furniture factories. Mean durations of employment in the groups were 10.4 years (SD 7.3, range 1–36 years) for the chemical workers and 9.0 years (SD 6.3, range 1–30 years) for the furniture workers. Estimates of personal breathing zone air concentrations ranged from 0.04 to 0.4 ppm (median 0.24±0.13 ppm) for the chemical workers, from 0.16 to 0.4 ppm (median 0.20±0.04 ppm) for the furniture workers, and from 0.07 to 0.13 ppm in the late summer for the office workers with a year-round office worker median reported as 0.07 ppm with no standard deviation. The mean wood dust concentration in the furniture factory was reported to have been between 1 and 2 mg/m^3. Nasal mucosa specimens were taken from the medial or inferior aspect of the middle turbinate. Histology scores were assigned to each specimen based on a 0–8 scale, identical to the scale used by Edling et al. (1988; described previously). Nasal mucosal biopsy sections for each subject were examined and assigned scores as follows: 0 - normal respiratory epithelium; 1- loss of ciliated epithelium cells; 2 - mixed cuboid/squamous epithelium, metaplasia; 3 - stratified squamous epithelium; 4 - keratosis; 5 - budding of epithelium; 6 - mild or moderate dysplasia; 7 - severe dysplasia; and 8 - carcinoma.

Effects noted in study and corresponding doses: Nasal histology scores ranged from 0 to 4 (mean 2.16; n=62) for the chemical workers, from 0 to 6 (mean 2.07; n=89) for the furniture workers, and from 0 to 4 (mean 1.46; n=32) for the office workers. The mean histological score for the chemical workers, but not the furniture workers, was significantly different from the control score, thus supporting the hypothesis that the development of the nasal lesions is formaldehyde-related and not obligatorily related to possible interaction between formaldehyde and wood dust. The most severe epithelial change found (light or moderate epithelial dysplasia) was found in two furniture workers. Among the chemical workers (not exposed to wood dust), loss of cilia, goblet cell hyperplasia and cuboidal and squamous cell metaplasia replacing the columnar epithelium occurred more frequently than in the control group of office workers. Within both groups of formaldehyde-exposed workers, no evidence was found for associations between histological score and duration of exposure, index of accumulated dose, or smoking habit.

Dose and end point used for MRL derivation:

Clinical symptoms of mild irritation of the eyes and upper respiratory tract and mild damage to the nasal epithelium were observed in workers exposed for 10.4 years (range 1-36 years) to an average TWA concentration of 0.24 ppm (range: 0.04 to 0.4 ppm). The LOAEL of 0.24 ppm is considered to be a minimal LOAEL.

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[X] 3 for use of a LOAEL - the exposed histological effects are considered to be mild and subclinical in nature, suitable for 0.24 ppm to be designated as a minimal LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

NA

Was a conversion used from intermittent-to-continuous exposure?

The exposure concentration was not adjusted to a continuous exposure basis based on evidence that concentration is more important than the product of concentration and duration of exposure in determining the severity of formaldehyde-induced epithelial damage in the upper respiratory tract (Wilmer et al. 1987).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Other additional studies or pertinent information that lend support to this MRL:

Several cross-sectional studies of groups of formaldehyde-exposed workers chronically exposed to estimated concentrations ranging from about 0.1 to 0.6 ppm (Holmstrom et al. 1989c; Edling et al. 1988; Boysen et al. 1990; Ballarin et al. 1992) have found histological evidence for mild damage to nasal epithelial tissue such as the damage described for exposed workers in the Holmstrom et al. (1989c) study. The observed effects were consistently mild, but each study reported a statistically significant, albeit small, increase in average histological score (increasing scores indicating increasing severity of change) for exposed groups compared with nonexposed control groups: 2.8 exposed versus 1.8 on an 8-point scale (Edling et al., 1988); 2.16 versus 1.46 on an 8-point scale (Holmstrom et al., 1989c); 1.9 versus 1.4 on a 5-point scale (Boysen et al., 1990); and 2.3 versus 1.6 on a 6-point scale (Ballarin et al., 1992). The Holmstrom et al. (1989c) study was selected as the basis of the MRL from among these four cross-sectional studies (they each examined equivalent endpoints and are of similar quality of design) primarily because the statistically significant effects were found in a group exposed to formaldehyde in the absence of potentially confounding exposures to wood dust. A full uncertainty factor of 10 was used to account for human variability because the observed mild effects were seen in groups of chronically exposed workers that were otherwise in apparent good health; a healthy worker effect may have operated causing sensitive individuals to avoid employment in the studied workplaces.

Additional supporting evidence for mild histological changes to the nasal epithelium with chronic exposure to concentrations below 1 ppm comes from rat studies. Although several studies of rats exposed for life (generally with an exposure protocol of 6 hours/day, 5 day/week) found no statistically significant increases in incidences of nonneoplastic lesions in the nasal epithelium of rats exposed to 0.1 to 2 ppm [Kerns et al. 1983b (F344 rats); Monticello et al. 1996 (F344 rats); Woutersen et al. 1989 (Wistar rats)], Kamata et al. (1997) reported that some F344 rats, after 28 months of exposure, displayed a mild response at 2 ppm and even at 0.3 ppm. A statistically significantly increased incidence for nasal epithelial squamous metaplasia without hyperplasia was observed in rats exposed to 2 ppm compared with control rats (5/32 versus 0/32); the incidence for nasal epithelial cell hyperplasia with squamous metaplasia was also significantly elevated compared with controls (7/32 versus 0/32). In rats exposed to 0.3 ppm, incidences of the same respective nasal epithelial lesions were also greater than control incidences (1/32 versus 0/32 and 4/32 versus 0/32), but not to a statistically significant degree.

Agency Contact (Chemical Manager) : Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Formaldehyde
CAS number(s): 50-00-0
Date: Aprile 20, 1999
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 17
Species: Rat

MRL: 0.3 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Til HP, Woutersen RA, Feron VJ, Clary JJ (1988b). Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking-water study in rats. Fd. Chem. Toxic 26: 447–452.

Experimental design: Groups (10 males and 10 females) of weanling, SPF-bred rats (Cpb:WU; Wistar random) received 0, 5, 25, or 125 mg/kg/day formaldehyde in their drinking water for 4 weeks. Fresh formaldehyde dosing solutions were made once per week; however, the authors did not provide information on if or how often the dosing solutions were analyzed for actual formaldehyde content. Due to this procedural discrepancy, it is unclear how much formaldehyde each animal actually received in the drinking water, since polymerization, oxidation, or evaporation may have occurred during the study. Control groups (20 males and 20 females) were given unsupplemented tap water. A water-restricted group (10 males and 10 females) received the same amount of unsupplemented drinking water as the amount of liquid consumed by the group given the highest dose of formaldehyde. Rats were weighed weekly and observed daily for condition and behavior. Food and water intake were measured over weekly periods throughout the study. Hematological parameters (hemoglobin concentration, packed-cell volume, erythrocyte and leucocyte counts) were determined. Whole blood from fasted animals was examined for glucose. Blood samples were analyzed for alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, total bilirubin, urea, creatinine and calcium, inorganic phosphate, chloride, and sodium and potassium. In week 4 of treatment, rats were deprived of water for 24 hours and of food for 16 hours. Urine was collected during the last 16 hours of the deprivation period. Density and volume of urine were determined. The rats were killed in week 5, organs (adrenals, brain, liver, heart, kidneys, spleen, testes, thymus, thyroid, and ovaries) were weighed and organ-to-body weight ratios determined. Histopathological examination was performed on the liver, kidneys, tongue, pharynx, esophagus, stomach, and nose. The fur of rats receiving 125 mg/kg/day formaldehyde showed yellowish discoloration from week 3 onward. Food intake was significantly reduced at all dose levels for female rats. At 125 mg/kg/day formaldehyde, water intake was significantly reduced in both sexes; body weight was not affected. There was no effect on the density (except that in 5 mg/kg treated males and water-restricted males, density significantly decreased) or volume of the urine collected. Hematological parameters showed no significant changes in animals treated with formaldehyde at any dose level. Male rats given 125 mg/kg/day formaldehyde showed statistically significant decrease in plasma protein and albumin concentrations. Female rats given 25 mg/kg/day formaldehyde showed statistically significant decrease in plasma alkaline phosphatase; alanine aminotransferase activities also decreased but was not significant. At 125 mg/kg, kidney weights in females were significantly increased. There were no other organ weight changes observed at any dose level, treatment-related, or histopathological changes in any of the tissues examined except the stomach. Necropsy findings revealed thickening of the limiting ridges and hyperkeratosis in the forestomach and focal atrophic inflammation in the glandular stomach in animals given the high concentration of formaldehyde. Moderate papillomatous hyperplasia was seen in one female given a high concentration of formaldehyde. Types of lesions in

males given 125 mg/kg formaldehyde are as follows: slight-to-moderate focal hyperkeratosis of forestomach, slight-to-moderate focal gastritis (location in stomach not reported), and slight-to-moderate submucosal mononuclear-cell infiltrate (location in stomach not reported). Types of lesions in females given 125 mg/kg formaldehyde are as follows: very slight, slight-to-moderate focal hyperkeratosis of forestomach; very slight, slight-to-moderate focal gastritis (location in stomach not reported); focal papillomatous hyperplasia (location in stomach not reported); and polymorphonuclear leucocytic infiltration.

Effects noted in study and corresponding doses:

25 mg/kg/day: NOAEL for gastrointestinal effects.

125 mg/kg/day: Thickening of the limiting ridges and hyperkeratosis in the forestomach and focal atrophic inflammation in the glandular stomach; slight-to-moderate focal hyperkeratosis of forestomach. Slight-to-moderate focal gastritis, and slight-to-moderate submucosal mononuclear-cell infiltrate in males (location in stomach not reported); very slight, slight-to-moderate focal hyperkeratosis of forestomach. Very slight, slight-to-moderate focal gastritis and focal papillomatous hyperplasia (location in stomach not reported). Polymorphonuclear leucocytic infiltration in females, moderate papillomatous hyperplasia in one female (less serious LOAEL).

Dose end point used for MRL derivation: NA

[X] NOAEL [ ] LOAEL 25 mg/kg/day

Uncertainty factors used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: None

Was a conversion used from intermittent to continuous exposure?
If so, explain: None

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL : Gastrointestinal irritation and damage have been observed in both humans and animals after ingestion of formaldehyde. In human poisoning studies, effects observed include: ulceration and sloughing of the soft palate and posterior pharyngeal wall; ulceration of the epiglottis, pyriform fossae and arytenoids; edematous and ulcerated esophageal mucosa with patches of black, sloughed tissue along the entire length; hyperemic areas of the stomach; and superficial ulceration in the distal body and antrum after a single dose of 234 mg/kg formaldehyde (Kochhar et al. 1986); abdominal pain and retching; hard, white and leathery stomach after a dose of 517 mg/kg (Burkhart et al. 1990), or abdominal pain at 624 mg/kg (Eells et al. 1981). In human poisoning studies in which the dose of formaldehyde is not known, gastrointestinal symptoms including mucosal damage, ulceration and bleeding of the buccal cavity and tonsils, and dysphagia due to esophageal mucosal damage (Freestone and Bentley 1989), necrosis of the esophagus and stomach, extensive congestion, peptic plaques in esophagus and stomach, colitis, congestion, diffuse necrosis and

hemorrhage of gastric and duodenal mucosa, burns in gastrointestinal mucosa, and ileitis (Koppel et al. 1990). In animals, gastrointestinal irritation and damage (Til et al. 1989; Tobe et al. 1989), and neoplastic lesions (Soffritti et al. 1989; Takahashi et al. 1986a) have been observed in other studies in which formaldehyde was administered orally for longer periods of time. Vargova et al. (1993) reported immunological effects related to formaldehyde exposure (increased relative lymph node weight and a decrease in combined IgM and IgG titers), while Dean et al. (1984) failed to produce observable changes in immunological parameters. The Vargova et al. (1993) study was not used for MRL calculation because actual individual IgG and IgM titers were not significantly reduced until the dose reached 40 mg/kg/day, and because it used a gavage method of dosing, which is less relevant to human exposure than the drinking water study of Til et al. (1988b). It appears from the available data that immunological changes resulting from formaldehyde exposure are unclear and perhaps not a viable toxicological endpoint for determining formaldehyde toxicity. Thus, gastrointestinal effects appear to be an appropriate indicator of an adverse reaction to oral exposure to formaldehyde.

Agency Contact (Chemical Manager) : Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Formaldehyde
CAS number(s): 50-00-0
Date: April 20, 1999
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 38
Species: Rat

MRL: 0.2 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Til HP, Woutersen RA, Feron VJ, Hollanders VHM, Falke HE, Clary JJ (1989). Two-year drinking-water study of formaldehyde in rats. Fd. Chem. Toxic 27: 77-86.

Experimental design: Target concentrations of 5, 25, and 125 mg/kg/day formaldehyde (95% paraformaldehyde) were administered to groups of weanling SPF-bred rats (Cpb:WU; Wistar random) in their drinking water for 2 years. Actual formaldehyde concentrations reported in this study were 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females when adjusted for body weight. Fresh formaldehyde dosing solutions were made once per week; however, the authors did not provide information on if or how often the dosing solutions were analyzed for actual formaldehyde content. Due to this procedural discrepancy, it is unclear how much formaldehyde each animal actually received in the drinking water, since polymerization, oxidation, or evaporation may have occurred during the study. Daily observations were made of the condition and behavior of the rats. Body weights were recorded at the start of the study, at weekly intervals in the first 12 weeks, and once every 4 weeks thereafter. Water intake was measured over weekly periods throughout the study and food intake was determined over weekly periods during the first 12 weeks, then over 2-week periods every 3 months. Hematological parameters (hemoglobin concentration; packed-cell volume; erythrocyte, leucocyte, and thrombocyte counts) were determined in weeks 26 and 103 from 10 rats/sex/group. Whole blood taken from 10 rats/sex/group after overnight fasting in weeks 27, 52, 78, and 104 was examined for glucose. Blood samples taken from 10 rats/sex/group on weeks 26, 53, 79, and 105 were analyzed for alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, total bilirubin, urea, creatinine, cholesterol, g-glutamyl transferase and calcium, inorganic phosphate, chloride, sodium, and potassium. Urinalysis was performed from pooled urine samples collected in weeks 27 and 104 and observed for protein, glucose, occult blood, ketones, urobilinogen, and bilirubin. pH determinations were carried out in weeks 27, 52, 78 and 104. Surviving rats of the first (10 rats/sex/group), second (10 rats/sex/group) and third (50 rats/sex/group) subsets were killed in weeks 53, 79, and 105, respectively. Organs (adrenals, brain, heart, kidneys, liver, ovaries, pituitary, spleen, testes, and thyroid) were weighed and organ-to-body weight ratios determined. Microscopic examination was performed on the these organs and samples of the skin, skeletal muscle, mammary glands (females), Harderian and exorbital lachrymal glands, nose, lungs, aorta, parotid, submandibular and sublingual salivary glands, esophagus, forestomach, glandular stomach, small and large intestine, pancreas, urinary bladder, epididymides, prostate, uterus, sternum, mesenteric and axillary lymph nodes, spinal cord, sciatic nerve, and eye in control and high-dose groups. The liver, lungs, stomach, and nose of the low- and mid-dose groups were examined as well as the adrenals, kidneys, spleen, testes, thyroid, ovaries, and pituitary and mammary glands (females) of the third subset killed in week 105. Necropsies were performed on rats found dead or killed when moribund in the course of the study. A slight yellowing of the fur in the rats given mid- and high-dose levels were observed from week 3 onward; this effect was more pronounced in the high-dose group. Liquid consumption decreased 40% in high-dose animals of both sexes; in mid-dose groups,

liquid consumption decreased as compared to controls, but the differences were not statistically significant. Food consumption at the high dose was significantly decreased in males but showed a less pronounced effect in females. The mean body weights of the high-dose group were decreased from week 1 onward in males and from week 24 onward in females. At the end of the study, there had been a 15% decrease in body weight in males at the 82 mg/kg/day dose and a 10% decrease in females at the 109 mg/kg/day dose. There were no significant differences in the hematological parameters monitored. In the high-dose groups, increased urine density and decreased volume of urine in males (in weeks 27 and 52) and females (in week 27) were observed. Occult blood was found in males of all dose groups in week 27 and in females of the mid- and high-dose groups in week 104. Clinical chemistry variables evaluated between groups during weeks 53 and 105 showed no statistically significant differences and, therefore, no toxicological significance was attached to the slight changes in plasma alkaline phosphatase activity, total plasma protein content, plasma urea level, cholesterol levels, and plasma potassium concentration in weeks 27 and 79 of the study. Absolute heart and liver weights in high-dose males were significantly decreased in weeks 79 and 105, testes weight in week 79, and kidney weight in week 105. These decreases in weight were attributed to lower body weights of animals in this group. Relative kidney weight in females increased in the high-dose group in weeks 53, 79, and 105. Relative brain weight significantly increased in high-dose males in weeks 53, 79, and 105 and in females in week 105. Relative testes weight increased in the high-dose groups in week 105. Necropsy findings of high-dose rats killed in weeks 53, 79, and 105 revealed a raised and thickened limiting ridge of the forestomach. The limiting ridge of the forestomach was raised and thickened in most male and female rats of the high-dose group, and in some males and females of the other groups, including the control group. Also, several rats in the high-dose groups showed irregular mucosal thickenings in the forestomach and/or glandular stomach. These changes were also found in rats of the other groups as well as the control groups. The incidence of discoloration and an irregular surface of the kidneys, which was frequently accompanied by enlarged parathyroids, was lower in males of the high-dose group (12%) than in the controls (33%) in week 105. The incidence of testicular atrophy in the high-dose group (6%) was also remarkably low as compared to controls (24%). In high-dose animals, histopathological examination revealed gastric changes including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach, and focal chronic atrophic gastritis, occasionally accompanied by ulceration and/or glandular hyperplasia, in the glandular stomach. Histopathological examinations of the kidneys showed that the incidence and degree of renal papillary necrosis increased in week 105 in high-dose animals. Non-neoplastic lesions found in organs other than the stomach or kidneys were not treatment-related. There were no gastric tumors observed apart from two benign papillomas, one in the male of the low-dose group and one in a female control rat.

Effects noted in study and corresponding doses:

15 mg/kg/day: NOAEL for gastrointestinal effects in males.

82 mg/kg/day: gastric changes including papillary epithelial hyperplasia accompanied by hyperkeratosis and focal ulceration in the forestomach and focal chronic atrophic gastritis, occasionally accompanied by ulceration and/or glandular hyperplasia, in the glandular stomach (less serious LOAEL in males), and renal papillary necrosis.

Dose end point used for MRL derivation: NA

[X] NOAEL [ ] LOAEL 15 mg/kg/day

Uncertainty factors used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a LOAEL)

[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: None

Was a conversion used from intermittent to continuous exposure?
If so, explain: None

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL : Gastrointestinal irritation and damage have been observed in both humans and animals after ingestion of formaldehyde. In human poisoning studies, effects observed include: ulceration and sloughing of the soft palate and posterior pharyngeal wall; ulceration of the epiglottis, pyriform fossae and arytenoids; edematous and ulcerated esophageal mucosa with patches of black, sloughed tissue along the entire length; hyperemic areas of the stomach; and superficial ulceration in the distal body and antrum after a single dose of 234 mg/kg formaldehyde (Kochhar et al. 1986); abdominal pain and retching; hard, white and leathery stomach after a dose of 517 mg/kg (Burkhart et al. 1990), or abdominal pain (Eells et al. 1981). In human poisoning studies, in which the dose of formaldehyde is usually not known with any accuracy, the gastrointestinal symptoms include mucosal damage, ulceration and bleeding of the buccal cavity and tonsils, and dysphagia due to esophageal mucosal damage (Freestone and Bentley 1989). In addition, necrosis of the esophagus and stomach, extensive congestion, peptic plaques in esophagus and stomach, colitis, congestion, diffuse necrosis and hemorrhage of gastric and duodenal mucosa, burns in gastrointestinal mucosa, and ileitis (Koppel et al. 1990) have also been reported. In animals, gastrointestinal irritation and damage also occurs, which includes thickening of the limiting ridges and hyperkeratosis in the forestomach and focal atrophic inflammation in the glandular stomach. In addition, slight-to-moderate focal hyperkeratosis of forestomach, slight-to-moderate focal gastritis, slight-to-moderate submucosal mononuclear-cell infiltrate (males), focal papillomatous hyperplasia, polymorphonuclear leucocytic infiltration (females), and moderate papillomatous hyperplasia in one female were noted in rats after administration of 125 mg/kg/day formaldehyde in the drinking water for 4 weeks (Til et al. 1988b). Tobe et al. (1989) noted forestomach hyperkeratosis in rats given 50 mg/kg/day formaldehyde in the drinking water for 15–24 months; neoplastic lesions (Soffritti et al. 1989; Takahashi et al. 1986a) have been observed in other studies in which formaldehyde was administered orally for longer periods of time. Thus, gastrointestinal effects appear to be an appropriate indicator of an adverse reaction to oral exposure to formaldehyde.

It was also noted that the data showed that at 104 weeks of administering 15 mg/kg/day formaldehyde, 27 male rats in the 15 mg/kg group died, which differed significantly from corresponding control values. However, the deaths were not dose-related, since deaths at 82 mg/kg/day were not significantly different from control animals. Otherwise, no toxicologically significant difference in mortality was found between controls and treated animals. This study was also used to derive the EPA Reference Dose (RfD) of 0.2 mg/kg/day, which is the same number as this chronic oral MRL.

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APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-4, and 2-5) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-4, and 2-5, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

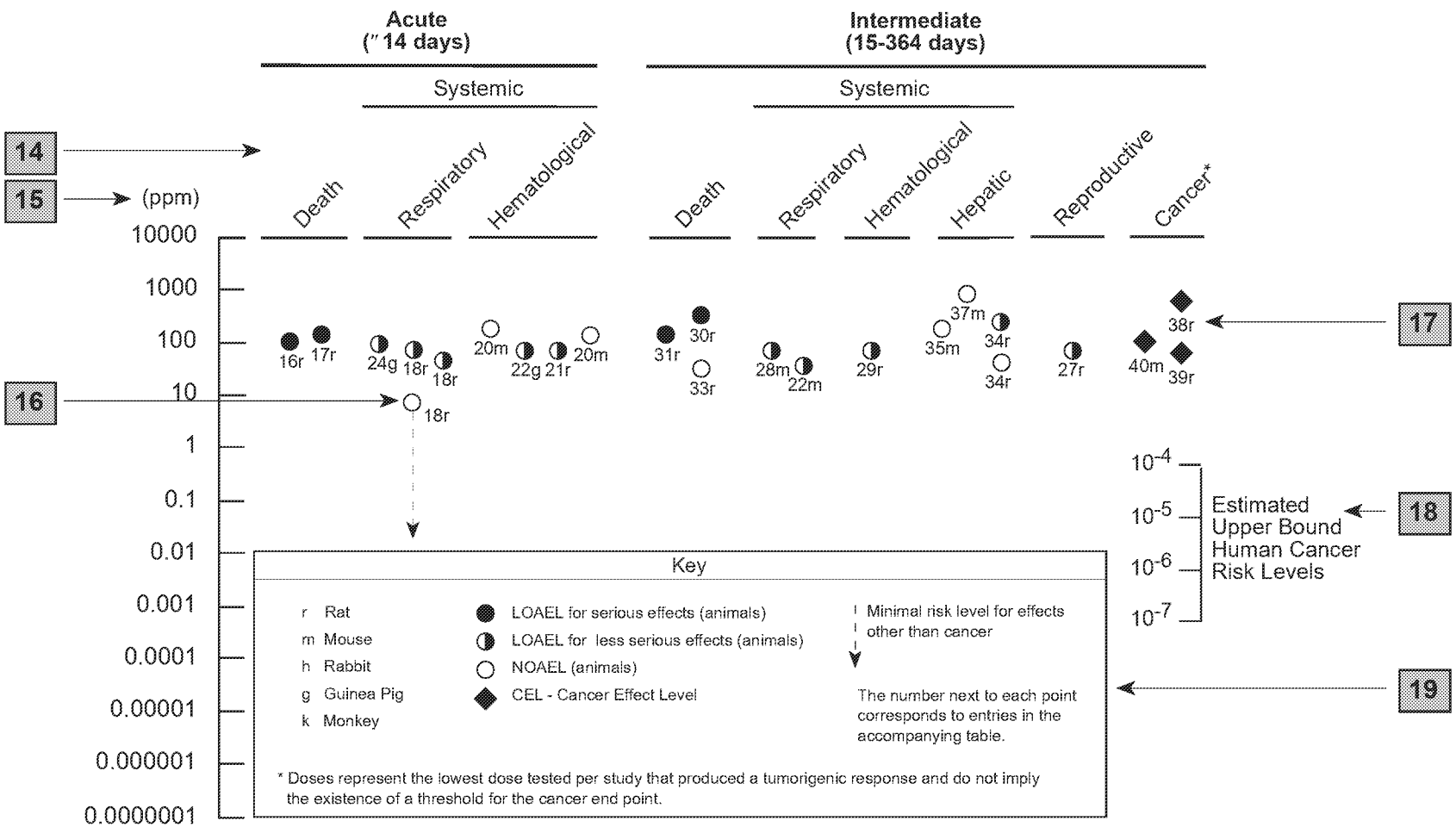
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 Systemic							
4 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure. MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFD	computational fluid dynamics
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/
DWEL	Drinking Water Exposure Level
ECD	electron capture detection

ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FDH	Formaldehyde dehydrogenase
$FEFR_{25-75}$	forced expiratory flow rate between 25% and 75% FVC
FEMA	Federal Emergency Management Agency
FEV_1	forced expiratory volume in 1 second
f-HSA	formaldehyde-human serum albumin
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
FVC	forced vital capacity
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level

mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NA/IMCO	North America/International Maritime Dangerous Goods Code
NAAQS	National Ambient Air Quality Standard
NaOH	sodium hydroxide
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEFR	peak expiratory flow rate
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppbv	parts per billion volume
ppm	parts per million
ppm	parts per million volume
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sd	standard deviation
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standardized mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
UFFI	urea-formaldehyde foam insulation
VOC	Volatile Organic Compound
yr	year

WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result