TOXICOLOGICAL PROFILE FOR PROPYLENE GLYCOL

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

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Freedom_0007144_0001

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Technical Report for propylene glycol was released in May 1993. This edition supersedes any previously released draft or final profile or report.

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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Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
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Atlanta, Georgia 30333

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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). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

2. 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.

3. 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.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

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PEER REVIEW

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

1. Dr. Gregory Grauer, Associate Professor, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado;

2. Dr. Philip Leber, Private Consultant, Chem-Tox Consulting, Akron, Ohio; and

3. Dr. Kenneth McMartin, Professor, Department of Pharmacology and Therapeutics, Section of Toxicology, Louisiana State University Medical Center, Shreveport, Louisiana.

These experts collectively have knowledge of propylene glycol'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.

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 statement was prepared to give you information about propylene glycol and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,416 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Propylene glycol has been identified in at least 5 of the 1,416 NPL sites.

When a chemical is released from a large source, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as ethylene glycol, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT IS PROPYLENE GLYCOL?

Propylene glycol is a synthetic liquid substance that absorbs water. Propylene glycol is also used to make polyester compounds, and as a base for de-icing solutions. Propylene glycol is used by the chemical, food, and pharmaceutical industries as an antifreeze when leakage might lead to contact with food. The Food and Drug Administration (FDA) has classified propylene glycol as an additive that is “generally recognized as safe” for use in food. It is used to absorb extra water and maintain moisture in certain medicines, cosmetics, or food products. It is a solvent for food

colors and flavors, and in the paint and plastics industries. Propylene glycol is also used to create artificial smoke or fog used in fire-fighting training and in theatrical productions. Other names for propylene glycol are 1,2-dihydroxypropane, 1,2-propanediol, methyl glycol, and trimethyl glycol.

Propylene glycol is clear, colorless, slightly syrupy liquid at room temperature. It may exist in air in the vapor form, although propylene glycol must be heated or briskly shaken to produce a vapor. Propylene glycol is practically odorless and tasteless.

For more information on the sources, properties, and uses of propylene glycol, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO PROPYLENE GLYCOL WHEN IT ENTERS THE ENVIRONMENT

Waste streams from the manufacture of propylene glycol are primarily responsible for the releases into the air, water, and soil. Propylene glycol can enter the environment when it is used as a runway and aircraft de-icing agent. Propylene glycol can also enter the environment through the disposal of products that contains it. It is not likely to exist in large amounts in the air. We have little information about what happens to propylene glycol in the air. The small amounts that may enter the air are likely to break down quickly. If it escapes into the air, it will take between 24 and 50 hours for half the amount released to break down. Propylene glycol can mix completely with water and can soak into soil. It can break down relatively quickly (within several days to a week) in surface water and in soil. Propylene glycol can also travel from certain types of food packages into the food in the package. See Chapters 4 and 5 for more information on propylene glycol in the environment.

1.3 HOW MIGHT I BE EXPOSED TO PROPYLENE GLYCOL?

Propylene glycol has been approved for use at certain levels in food, cosmetics, and pharmaceutical products. If you eat food products, use cosmetics, or take medicines that contain it, you will be exposed to propylene glycol, but these amounts are not generally considered

harmful. People who work in industries that use propylene glycol may be exposed by touching these products or inhaling mists from spraying them. These exposures tend to be at low levels, however. Propylene glycol is used to make artificial smoke and mists for fire safety training, theatrical performances, and rock concerts. These artificial smoke products may also be used by private citizens. These products are frequently used in enclosed spaces, where exposure may be more intense.

See Chapter 5 for more information on exposure to propylene glycol.

1.4 HOW CAN PROPYLENE GLYCOL ENTER AND LEAVE MY BODY?

Propylene glycol can enter your bloodstream if you breathe air containing mists or vapors from either compound. It can also enter your bloodstream through your skin if you come in direct contact with it and do not wash it off. If you eat products that contain propylene glycol, it may enter your bloodstream. Exposure of the general population to propylene glycol is likely since many foods, drugs, and cosmetics contain it.

Propylene glycol breaks down in the body in about 48 hours. However, studies of people and animals show that if you have repeated eye, skin, nasal, or oral exposures to propylene glycol for a short time, you may develop some irritation.

1.5 HOW CAN PROPYLENE GLYCOL AFFECT MY HEALTH?

Propylene glycol breaks down at the same rate as ethylene glycol, although it does not form harmful crystals when it breaks down. Frequent skin exposure to propylene glycol can sometimes irritate the skin.

1.6 ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PROPYLENE GLYCOL?

Propylene glycol is generally considered to be a safe chemical, and is not routinely tested for, unless specific exposure, such as to a medicine or cosmetic, can be linked with the observed bad

symptoms. Since propylene glycol breaks down very quickly in the body, it is very difficult to detect. Refer to Chapters 2 and 6 for more information on these tests.

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

The government has developed regulations and guidelines for propylene glycol. These are designed to protect the public from potential adverse health effects.

The Food and Drug Administration (FDA) has classified propylene glycol as "generally recognized as safe," which means that it is acceptable for use in flavorings, drugs, and cosmetics, and as a direct food additive. According to the World Health Organization, the acceptable dietary intake of propylene glycol is 25 mg of propylene glycol for every kilogram (kg) of body weight. For more information on the regulations and guidelines that apply to propylene glycol, see Chapter 7.

1.8 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 contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfilesTM CD-ROM by calling the toll-free information

and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

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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 of the toxicology of propylene glycol and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for propylene glycol based on toxicological studies and epidemiological investigations.

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

The general population may be exposed to propylene glycol. Propylene glycol is designated as a Generally Recognized As Safe (GRAS) additive by the Food and Drug Administration (FDA) and is widely used in commercial formulations of foods, drugs, and cosmetics (Morshed et al. 1988). Propylene glycol is used as a de-icer, and in heat transfer fluids. It is also an ingredient of many products that are used to produce artificial smoke or mist for theatrical productions, fire safety training, or rock concerts.

Oral exposure to the small amounts of propylene glycol found in foods and drugs is unlikely to cause toxic effects. Dermal exposure to propylene glycol, through cosmetics or drugs, or inhalation of synthetic smoke or mist, may be more frequently associated with reported reactions. Propylene glycol induces remarkably fewer adverse effects in both humans and animals than does ethylene glycol. Data describing either human or animal effects after exposure to propylene glycol were not as prevalent as those found for ethylene glycol. Human data came from case reports of clinical studies, adverse reactions to medical treatment, or accidental exposure. Animal data generally support those effects, or lack thereof, observed in humans.

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 or other areas where they may be exposed to propylene glycol, the information in this section is organized by chemical, and then by health effect-death, systemic, immunological and lymphoreticular, 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 judgement 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. These distinctions are intended to help the users of this document identify the levels of exposure at which adverse health effects start to appear. LOAELs or NOAELs should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these differences 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 or other sites of exposure may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects 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.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for both ethylene glycol and propylene glycol. 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 target organs(s) of effect or the most sensitive health effects(s) for a specific duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of 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 1990a), 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 result from repeated acute insuhs, 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

Information regarding health effects of propylene glycol following inhalation exposure is limited. No studies of health effects in humans were found. Studies in animals were few (Konradova et al. 1978; Robertson et al. 1947; Suber et al. 1989).

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to propylene glycol. Twenty-nine monkeys were continuously exposed to propylene glycol vapor over a period of 13 months, at doses of 32-112 ppm (doses not further specified) (Robertson et al. 1947). Thirteen of the monkeys died or were killed when ill during the course of the experiment (Robertson et al. 1947). Based on the relative lack of data in the literature, it is unlikely that sufficient amounts of propylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area. The LOAEL value from the study by Robertson et al. (1947) for death in monkeys after inhalation exposure to propylene glycol is recorded in Table 2-1 and plotted Figure 2-1.

2.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans, or cardiovascular, musculoskeletal, dermal, ocular, or metabolic effects in animals after inhalation exposure to propylene glycol. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after inhalation exposure are reported in Table 2-1 and plotted in Figure 2-1.

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol – Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
1	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d	Resp		51[b] (nasal hemorrhaging)		Suber et al. 1989
			Hemato	51 F	321 F (decreased white blood cells, and lymphocytes in females)		
				51 M	321 M (decreased sorbitol dehydrogenase, gamma glutamyl transferase)		
			Hepatic	707			
			Renal	51	321 (decreased kidney weight)		
			Bd Wt	51 F	321 F (decreased body weight)		
Immunological/Lymphoreticular							
2	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		707			Suber et al. 1989
CHRONIC EXPOSURE							
Systemic							
3	Monkey (Macacus Rhesus)	13 mo continuous	Resp	112			Robertson et al. 1947
			Gastro	112			
			Hemato		112 (increased hemoglobin)		
			Hepatic	112			
			Renal	112			
			Endocr	112			
			Bd Wt	112			

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TABLE 2-1. Levels of Significant Exposure to Propylene Glycol – Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
4	Rat (NS)	18 mo continuous	Resp	112			Robertson et al. 1947
			Hepatic	112			
			Renal	112			
			Bd Wt		112M (50% increase in body weight)		
	Immunological/Lymphoreticular						
5	Monkey (Macacus Rhesus)	13 mo continuous		112			Robertson et al. 1947
6	Rat (NS)	18 mo continuous		112			Robertson et al. 1947
	Reproductive						
7	Rat (NS)	18 mo continuous		112			Robertson et al 1947

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

[b]Used to derive an intermediate inhalation minimal risk level (MRL) of 0.009 ppm; LOAEL divided an by uncertainty factor of 1,000 (10 for extrapolation from animals to humans, 10 for use of a LOAEL, and 10 for human variability) and multipliedby 6/24 and 5/7 to adjust for intermittent of 6 exposure hours/day, 5 days/week.

Bd Wt = body weight;d = day(s); Endocr= endocrine;F = female; Gastro= gastrointestinal;Hemato = hematological;hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M= male; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified;Resp =respiratory;wk = week(s)

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Figure 2-1. Levels of Significant Exposure to Propylene Glycol - Inhalation
Intermediate (15-364 days)

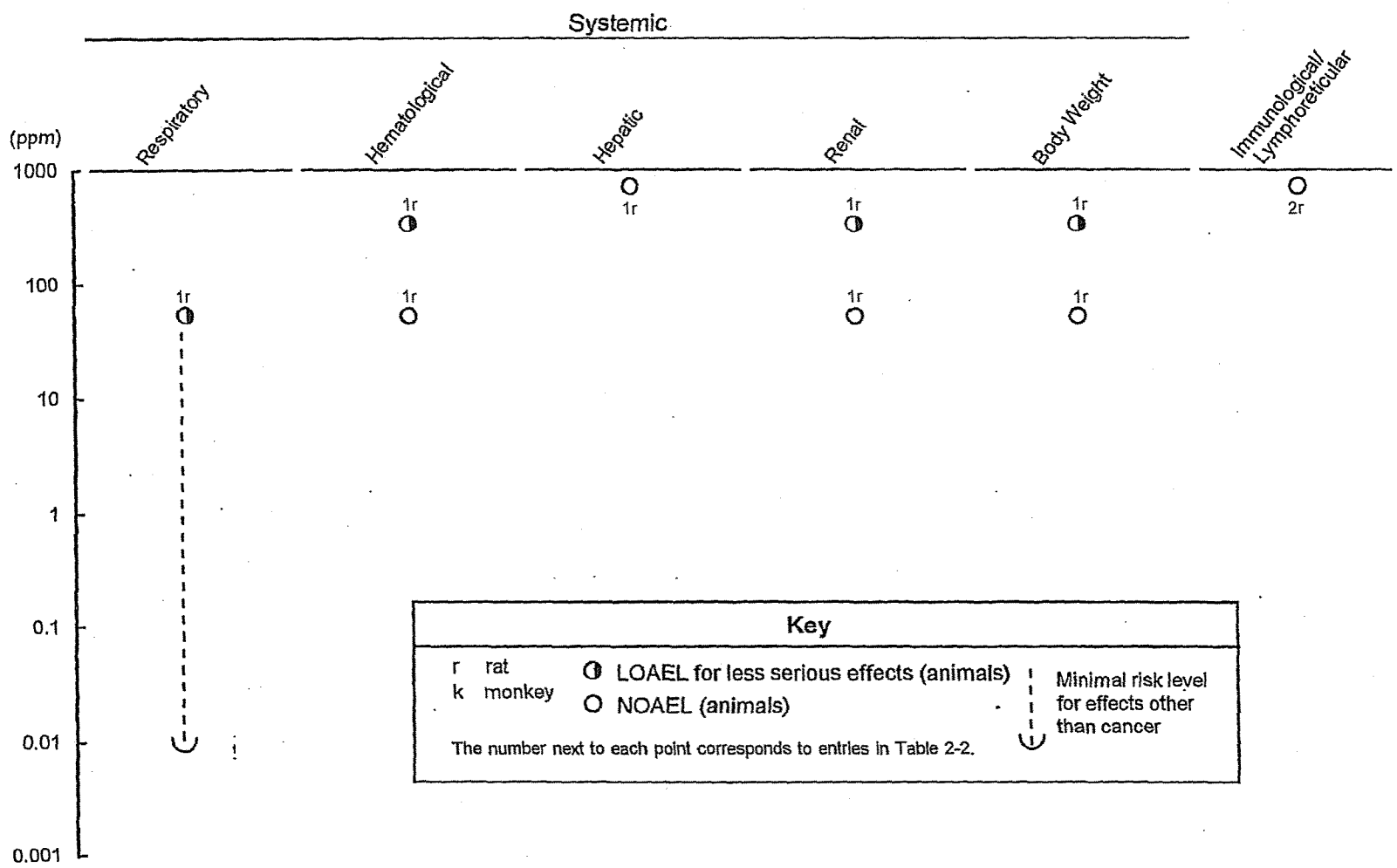

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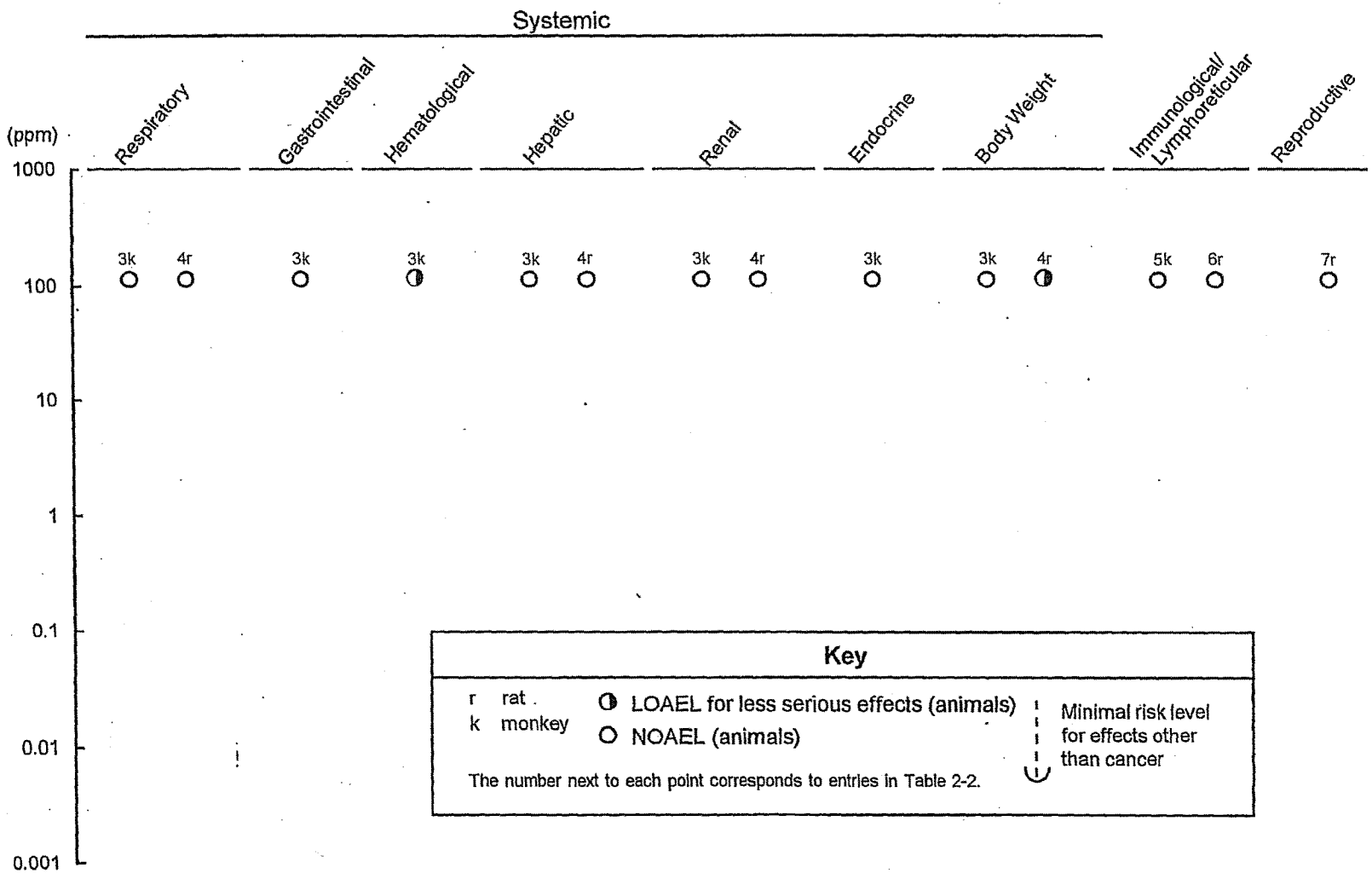
Figure 2-1. Levels of Significant Exposure to Propylene Glycol - Inhalation (continued)

Chronic (≥365 days)



Respiratory Effects. Studies assessing adverse respiratory effects after acute or intermediate inhalation exposure of animals to propylene glycol are inconclusive. The effects of acute inhalation exposure to 10% concentrations of propylene glycol for 20 and 120 minutes in rabbits showed an increased number of degenerated goblet cells in tracheal lining (Konradova et al. 1978). However, the observations made in rats after an intermediate inhalation exposure to propylene glycol did not support those findings. Rats which inhaled 321 ppm of propylene glycol over 90 days had thickened respiratory epithelium with enlarged goblet cells (Suber et al. 1989). Nasal hemorrhaging was also present in rats exposed to a lower dose of 51 ppm propylene glycol, probably caused by dehydration. In rhesus monkeys and rats, continuous exposure to concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the respiratory system (Robertson et al. 1947). These studies do not indicate a basis for concern because comparable exposure conditions do not occur for the general population.

Gastrointestinal Effects. In rhesus monkeys and rats, continuous exposure to air concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the gastrointestinal system (Robertson et al. 1947).

Hematological Effects. Limited information was available on hematological effects of propylene glycol. The results from animal studies indicate that intermediate and chronic exposure to propylene glycol may lead to hemolysis of red blood cells (RBC). After intermediate inhalation exposure to 321 ppm propylene glycol, female rats had decreased white blood cell (WBC) counts, while exposure to 707 ppm of propylene glycol caused decreased mean corpuscular hemoglobin concentrations and white blood cell counts; no dose-related changes in RBCs were observed in male rats under the same regimen (Suber et al. 1989). In rhesus monkeys, continuous exposure to concentrations of propylene glycol in air up to 112 ppm for 13 months caused increased hemoglobin counts compared to the control animals (Robertson et al. 1947). These results indicate that there may, be species differences with regard to the effect of propylene glycol on red blood cells.

Hepatic Effects. The results from animal studies show that there are no adverse hepatic effects in rats after intermediate inhalation exposure to 707 ppm of propylene glycol (Suber et al. 1989). In rhesus monkeys and rats continuous exposure to air concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the hepatic system (Robertson et al. 1947). Based on these findings, it can be assumed that chronic exposures to moderately high levels of propylene glycol will not have adverse hepatic effects in humans. It is not clear if hepatotoxicity would result after an acute

exposure to a high level of propylene glycol. Since levels of propylene glycol in the vicinity of a hazardous waste site would probably be low, it is unlikely that propylene glycol would induce adverse hepatic effects in people living in the area.

Renal Effects. Intermediate inhalation exposure of rats to 707 ppm propylene glycol did not cause adverse renal effects (Suber et al. 1989), although kidney weight was reduced at 321 ppm in males and females. In rhesus monkeys and rats, continuous exposure to concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the renal system (Robertson et al. 1947). These results indicate that exposure to low levels of propylene glycol that may be present at hazardous waste sites is not likely to cause adverse renal effects in the human population living in the vicinity.

Endocrine Effects. In rhesus monkeys and rats, continuous exposure to concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the endocrine system (Robertson et al. 1947).

Body Weight Effects. Rhesus monkeys continuously exposed to air concentrations of propylene glycol up to 112 ppm for 13 months exhibited no adverse body weight effects, whereas rats exposed for 18 months under the same conditions exhibited a 50% decrease in body weight (Robertson et al. 1947). Intermediate inhalation exposure of female rats to 321 ppm caused decreased body weight (Suber et al. 1989).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located specifically regarding adverse immunological effects in humans or animals after inhalation exposure to propylene glycol.

Twenty-nine monkeys were continuously exposed to propylene glycol vapor over a period of 13 months, at doses of 32-112 ppm (Robertson et al. 1947). There was no effect on the spleen. Similarly, rats exposed to 55-112 ppm propylene glycol vapor continuously for 18 months showed no effect on the spleen (Robertson et al. 1947). Young, healthy adult Sprague-Dawley rats divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by nose-only inhalation to mean target aerosol concentrations of 5 1, 321, or 707 ppm propylene glycol, respectively (Suber et al. 1989). The fourth group (control group) was exposed to humidified, filtered room air. There was no effect on spleen weight.

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in each species and duration category for propylene glycol after inhalation exposure are reported in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after inhalation exposure to propylene glycol.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to propylene glycol.

White rats exposed continuously to a concentration of 55-112 ppm propylene glycol for 18 months showed no adverse effects on the ability to produce live young, or on survival of the offspring (Robertson et al. 1947).

The NOAEL value for reproductive effects in rats for the chronic-duration category for propylene glycol after inhalation exposure is reported in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to propylene glycol.

2.2.1.7 Genotoxic Effects

No studies were located regarding in viva genotoxic effects in humans or animals after inhalation exposure to propylene glycol.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals after inhalation exposure to propylene glycol.

2.2.2 Oral Exposure

Propylene glycol is a clear, practically odorless and tasteless liquid that is slightly syrupy at room temperature. Oral exposure to propylene glycol occurs through ingestion of foods, since propylene glycol is approved for use as a food additive. Ingestion by humans is not frequently associated with adverse effects.

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to propylene glycol.

Oral LD_{50} values have been reported in rats (range, 8-46 g/kg), mice (range, 25-32 g/kg), and guinea pigs (range, 18-20 g/kg) after acute oral exposure to propylene glycol (Clark et al. 1979; EPA 1 987a; Ruddick 1972). Male Wistar rats (6/group) were orally dosed with saline or 2,942 mg/kg/day , propylene glycol in water for 10, 20, or 30 days (Morshed et al. 1991a). No death was observed. A fatal case of propylene glycol poisoning occurred in a horse given 3.8 L (7,904 mg/kg) of propylene glycol instead of mineral oil. The horse died of respiratory arrest 28 hours after administration (Dorman and Haschek 1991). It is unlikely that sufficient amounts of propylene glycol can be present or ingested near hazardous waste sites to cause death among people living in the area.

The LD_{50} value for death in rats after acute duration oral exposure to propylene glycol are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans, or musculoskeletal, dermal, or ocular effects in animals after oral exposure to propylene glycol. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after oral exposure are reported in Table 2-2 and Figure 2-2.

TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - 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
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer 344)	once (G)				22800 F (LD_{50})	Clark et al. 1979
	Systemic						
2	Rat (Fischer 344)	once (G)	Gastro			23500 F (hemorrhagic enteritis)	Clark et al. 1979
			Hemato			23500 F (lymphocyte depletion)	
			Endocr			23500 F (adrenocortical hemorrhage)	
3	Cat (NS)	14 d (F)	Hemato		3600 (reticulocytosis, increased Heinz bodies, increased severe mechanical fragility)		Weiss et al. 1992
	Immunological/Lymphoreicular						
4	Cat (NS)	14 d (F)			3600 (decreased haptoglobin concentrations)		Weiss et al. 1992
	Neurological						
5	Rat (Fischer 344)	once (G)				22800 F (lethargy and coma)	Clark et al. 1979
	Reproductive						
6	Mouse (CD-1)	5d 1x/d (GW)		10000			Kavlock et al. 1987

Freedom_0007144_0036

TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - 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
	Developmental							
7	Mouse (CD-1)	5 d 1x/d (GW)		10000				Kavlocket al. 1987
	INTERMEDIATE EXPOSURE							
	Systemic							
8	Cat	13 wk (F)	Hemato		1260	(increased Heinz bodies, decreased RBC survival)		Bauer et al. 1991
9	Cat	13 wk (F)	Hemato		2750	(increased Heinz bodies, increased punctate reticulocytes, decreased RBC survival)		Bauer et al. 1992
10	Cat	5 wk□ (F)	Hemato		1600	(Heinz body formation)		Christopher et al. 1989a
			Renal	1600				
11	Cat	3 wk (F)	Hemato				8000	Christopher et al. 1989a
			Renal		8000	(polyuria, polydipsia)		
12	Cat Mongrel	22-35 d (F)	Renal	1600	8000	(polyuria, polydipsia)		Christopher et al. 1990b
			Metab		1600	(increased anion gap, increased D-lactate)		
13	Cat	17 wk (F)	Hemato		2400	(Heinz body formation)		Weiss et al. 1990

Freedom_0007144_0037

TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - 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
	Neurological						
14	Cat Mongrel	22-35 d (F)		1600		8000 (ataxia, CNS depression, decreased activity)	Christopher et al. 1990b
	Reproductive						
15	Mouse (swiss CD-1)	15-18 wk daily (W)		10118			NTP 1985
	Developmental						
16	Mouse (Swiss CD-1)	15-18 wk daily (W)		10118			NTP 1985
	CHRONIC EXPOSURE						
	Systemic						
17	Rat	2 yr (F)	Resp	2500			Gaunt et al. 1972
			Cardio	2500			
			,Hemato	2500			
			Hepatic	2500			
			Renal	2500			
			Endocr	2500			
18	Dog	2 yr (F)	Hemato	2000	5000 (decreased erythrocytes, hemoglobin, hematocrit)		Weil et al. 1971
			Hepatic	5000			
			Renal	5000			
			Bd Wt	5000			

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TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - 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
			Immunological/Lymphoreticular				
19	Dog	2 yr (F)		5000			Weil et al. 1971

[a]The number corresponds to entries in Figure 2-4.

Bd Wt = body weight; Cardio = cardiovascular; CNS = central nervous sytem; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD50= lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; metab = metabolic; NOAEL = no-observable-adverse-effect level; Resp = respiratory; RBC = red blood cell; (W) = gavage in water; wk = week(s); x = times; yr = year(s)

Freedom_0007144_0039

Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Oral

Acute (≤14 days)

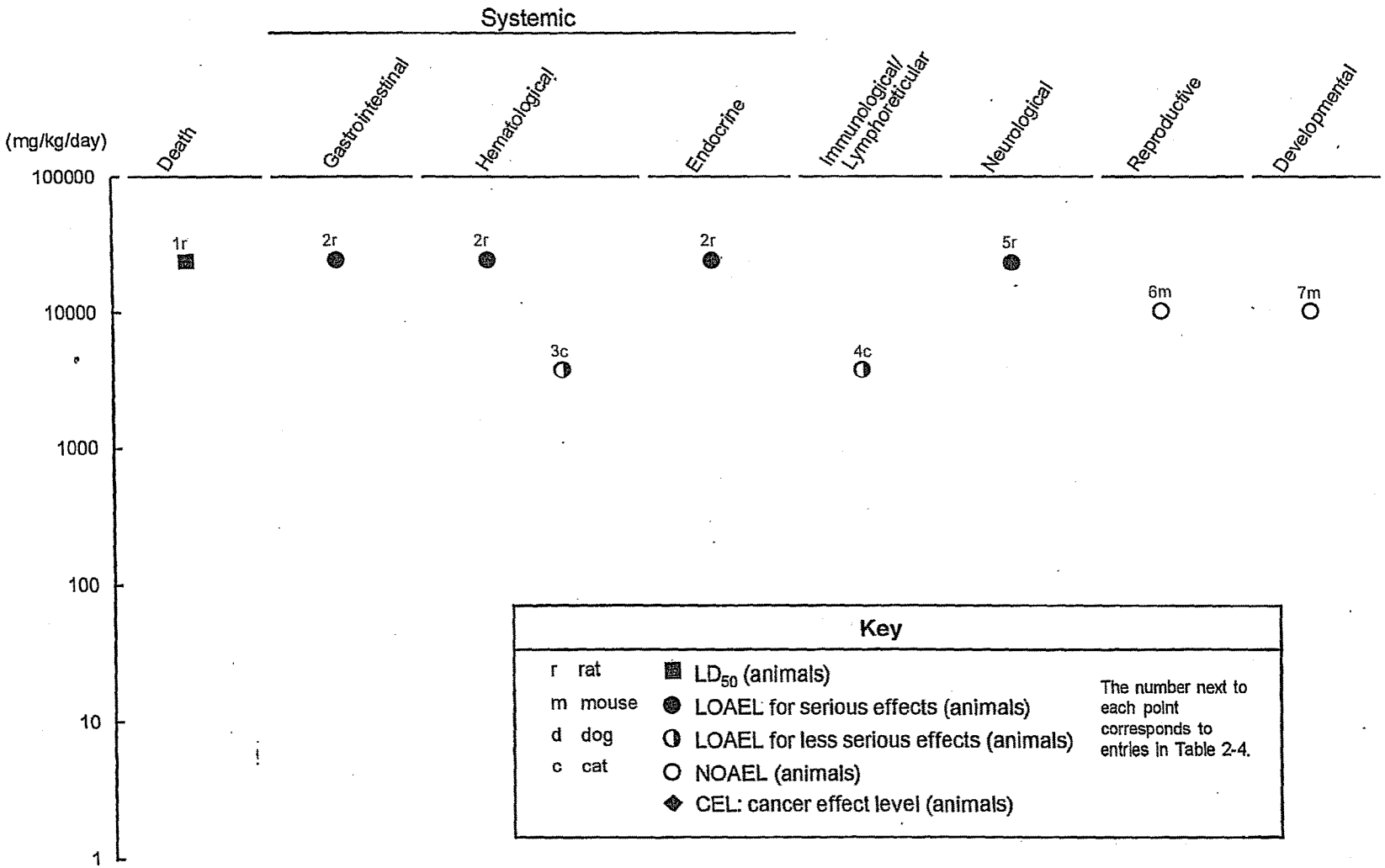


Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Intermediate (15-364 days)

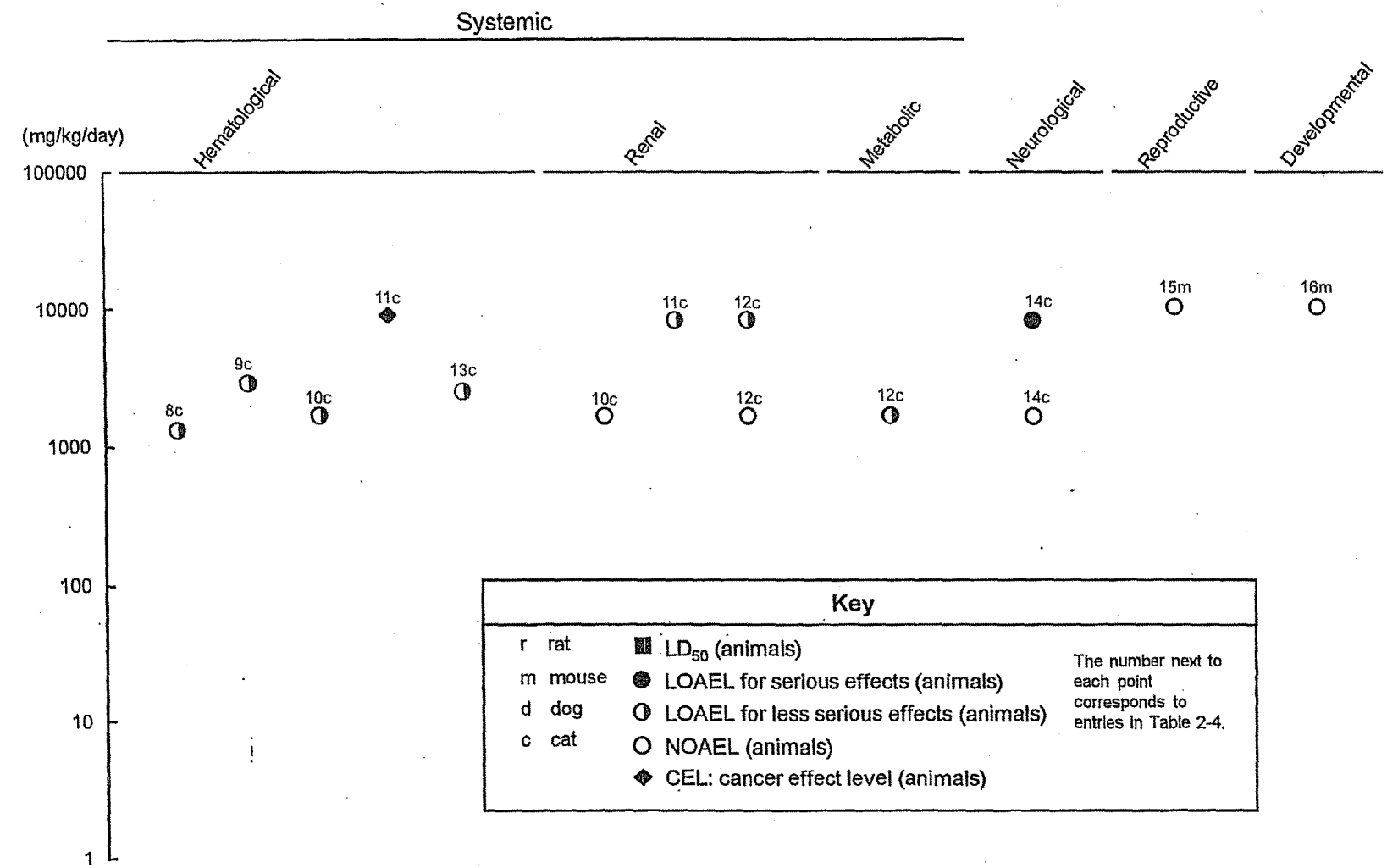
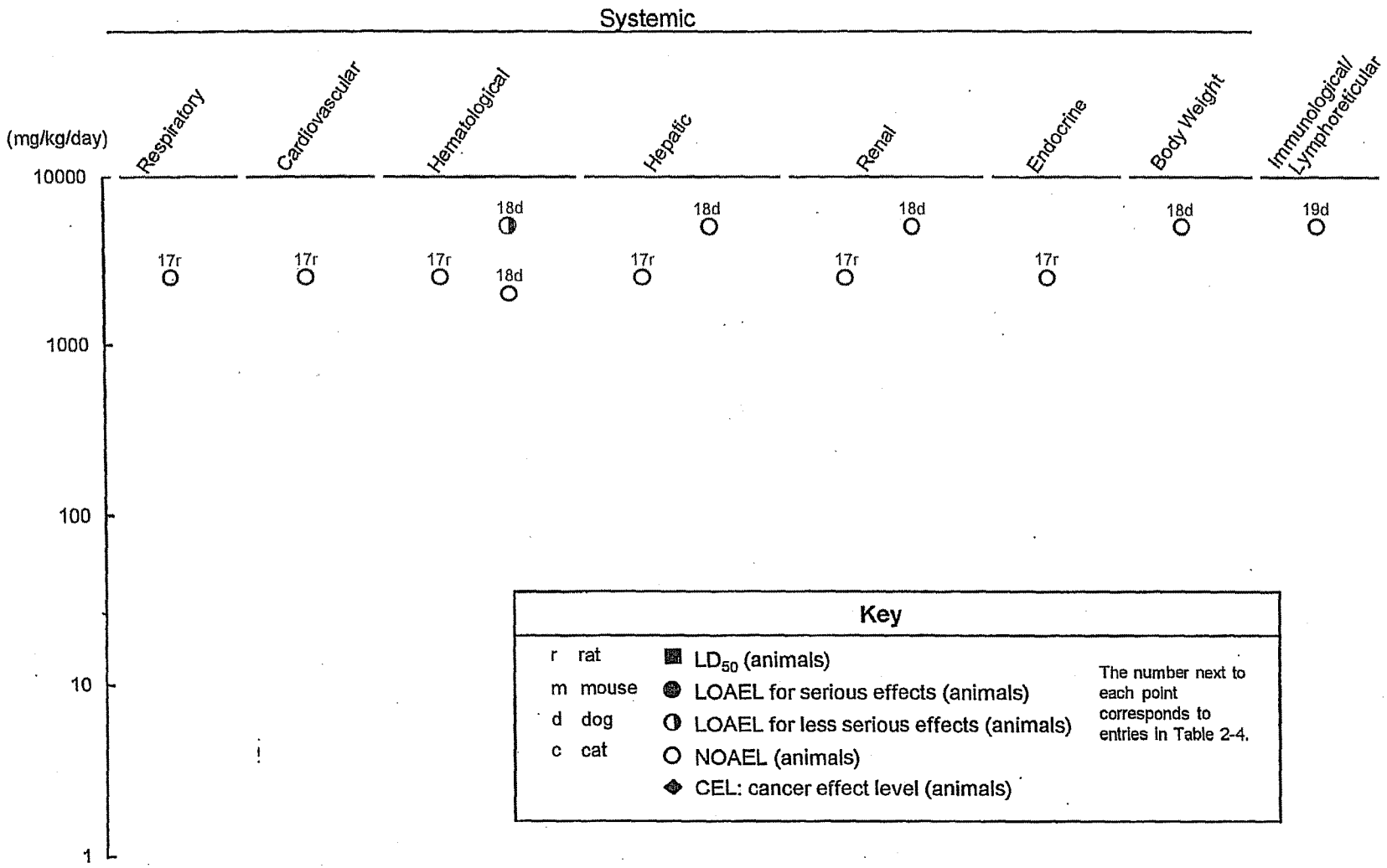


Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Chronic (≥365 days)



Respiratory Effects. In rats there were no changes in any of the respiratory parameters after 2 years of chronic oral exposure to 2,500 mg/kg/day propylene glycol (Gaunt et al. 1972).

Cardiovascular Effects. The heart histopathology of rats after a 2-year oral exposure to 2,500 mg/kg/day of propylene glycol revealed no changes (Gaunt et al. 1972). A similar lack of cardiovascular effects was observed in rats by Morris et al. (1942) after a 23-month exposure to 49,500 mg/kg/day propylene glycol in the feed.

A horse developed myocardial edema prior to death caused by accidental oral administration of 7,904 mg/kg propylene glycol (Dorman and Haschek 1991).

It appears that acute exposure to very high levels of propylene glycol may cause adverse cardiovascular effects, but it is unlikely that such exposures could occur as a result of being in the vicinity of hazardous waste sites.

Gastrointestinal Effects. Fischer 344 rats exhibited hemorrhagic enteritis after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). The effect of orally administered propylene glycol on the brush border membrane from the jejuno-ileum portion of the intestines of rats was investigated *in vivo* (Morshed et al. 1991a). In rats receiving 2,942 mg/kg propylene glycol for 10-30 days, brush border enzymes including sucrase, lactase, and gamma-glutamyl transpeptidase exhibited a tendency toward increased activity. Absorption of D-glucose and calcium was increased after 10 days of treatment, whereas absorption of D-glucose, glycine, L-aspartic acid, L-lysine, and calcium were elevated after 20 or 30 days of treatment. The structural integrity of the jejunal surface was not adversely affected.

Hematological Effects. Limited information was available on hematological effects of propylene glycol in humans after oral exposure. A 39-year-old woman who had ingested propylene glycol and ethanol showed no adverse effects on blood chemistry (Lolin et al. 1988).

The results from animal studies indicate that intermediate and chronic exposure to propylene glycol may lead to hemolysis of red blood cells. Increased numbers of Heinz bodies (sign of red blood cell degeneration) were observed in cats exposed orally to 1,200, 1,600, 2,400, and 3,600 mg/kg of propylene glycol for 2, 5, and 17 weeks, respectively (Christopher et al. 1989a; Weiss et al. 1990, 1992). Other studies indicate increased Heinz body formation and decreased RBC survival in kittens and adult cats

ingesting 3,000 mg/kg and 1,400 mg/kg/day, respectively (Bauer et al. 1992). These findings are further supported by results obtained in dogs after chronic oral exposure to 5,000 mg/kg/day (Weil et al. 1971). Red blood cell hemolysis was evidenced by decreased hemoglobin and hematocrit levels, and decreased total red blood cell counts. In rats, however, there were no changes in any of the hematological parameters after 2 years of chronic oral exposure to 2,500 mg/kg/day propylene glycol (Gaunt et al. 1972). These results indicate that there may be species differences with regard to the effect of propylene glycol on red blood cells. Fischer 344 rats exhibited lymphocyte depletion after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). Hypocellularity of the bone marrow was observed in cats after intermediate oral exposure to 8,000 mg/kg/day of propylene glycol (Christopher et al. 1989a).

Hepatic Effects. The results from chronic-duration animal studies show that there are no adverse hepatic effects in rats fed a diet delivering 2,500 mg/kg/day of propylene glycol for 2 years (Gaunt et al. 1972). Based on these findings, it can be assumed that chronic oral exposures to moderately high levels of propylene glycol will not have adverse hepatic effects in humans. It is not clear if hepatotoxicity would result after an acute exposure to a high level of propylene glycol. Since levels of propylene glycol in the vicinity of a hazardous waste site would probably be low, it is unlikely that propylene glycol would induce adverse hepatic effects would occur in people living in the area.

Renal Effects. No adverse renal effects were observed in cats fed a diet delivering a dose of 1,600 mg/kg/day of propylene glycol for 5 weeks (Christopher et al. 1989a). In the same study, however, cats exposed to 8,000 mg/kg/day of propylene glycol for 3 weeks developed polyuria, considered a less serious adverse effect. In another study, an equal number (5-6) of cats of both sexes w.ere fed 1,600 mg/kg/day propylene glycol for 5 weeks or a high dose diet containing 8,000 mg/kg/day for 22 days (Christopher et al. 1990b). Cats fed the low dose had no adverse clinical signs. Cats fed the high dose had moderate polyuria and polydipsia. Chronic exposure of both rats and dogs to 2,500 and 5,000 mg/kg/day, respectively, for 2 years, had no nephrotoxic effects in either species (Gaunt et al. 1972; Weil et al. 1971). These results indicate that exposure to low levels of propylene glycol that may be present at hazardous waste sites are not likely to cause adverse renal effects in the human population living in the vicinity.

Body Weight Effects. Rats given 2,942 mg/kg propylene glycol by gavage for 10 days exhibited a 41% reduction in body weight, whereas exposure for 20-30 days caused an increase body weight (Morshed et al. 1991a). Dogs exposed to 5,000 mg/kg/day oral propylene glycol for 2 years showed no adverse effect on body weight (Weil et al. 1971).

Metabolic Effects. High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. In a case of acute propylene glycol poisoning (the amount ingested not specified), the patient developed metabolic acidosis (pH of 7.29) with an osmolal gap of 51 mmol/kg (reference concentration is <10 mmol/kg) (Lolin et al. 1988). There is a possibility that this patient also ingested a large amount of ethanol since the serum ethanol level was 90 mg/dL. The level of propylene glycol was 400 mg/dL in the serum and 10 mg/dL in urine.

Rats given oral doses of propylene glycol up to 5,885 mg/kg showed an increase of blood lactate of 2.7 mmol/L, which was prevented by inhibition of propylene glycol metabolism (Morshed et al. 1989). Rabbits given an oral dose of 2,942 mg/kg showed a similar increase in blood lactate of 2.6 mmol/L (Morshed et al. 1991b). In neither study was there a decrease in blood pH, probably because lactic acidosis in clinical situations occurs only when lactate levels rise more than 5 mmol/L (Morshed et al. 1989). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for 5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high-dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Pre-dosing observations were made such that each group of cats served as its own control. In the low dose cats, anion gap increased from 15.5 Meq/liter during the control period to 22.2 Meq/liter on day 24 of exposure. Total CO_2, decreased at the end of the dosing period. Plasma D-lactate increased 24-fold during the dosing period and was significantly correlated with anion gap. L-lactate decreased significantly but in a less dramatic fashion to 31% of control values. Serum sodium increased slightly with dosing, but there were no other notable changes in serum chemistry. In high-dose cats, plasma D-lactate increased rapidly (44-fold) during dosing.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to propylene glycol.

Cats fed 1.2 mg propylene glycol per gram of feed for 14 days showed increased haptoglobin concentration (Weiss et al. 1992). Dogs fed 5,000 mg/kg/day propylene glycol for 2 years showed no adverse immunological effects (Weil et al. 1971).

The highest NOAEL value and the LOAEL value for immunological and lymphoreticular effects in dogs and cats for each duration category for propylene glycol after oral exposure are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Adverse neurological reactions were observed in patients who tested positive in a propylene glycol patch test after an acute oral challenge with 2-15 mL of propylene glycol (Hannuksela and Forström 1978). Although the observed neurotoxicity is attributed to propylene glycol, the study reports that this response was seen in allergic individuals. In a case of acute propylene glycol poisoning, neurotoxic symptoms included stupor and repetitive convulsions (Lolin et al. 1988). The study does not specify the amount of propylene glycol that caused neurotoxicity. Various degrees of propylene glycol neurotoxicity were also observed in a group of 16 outpatients of a neurology clinic after acute oral exposure to 887 mg/kg 3 times per day for at least 3 days, using a formulation containing phenytoin and ethanol (Yu et al. 1985). Very severe mental symptoms (not specified) were observed in one patient who had the highest overall propylene glycol plasma concentration, although patients with lower plasma propylene glycol levels showed similar neurotoxicity. The estimated half-life of propylene glycol is 3.8 hours. This means that there is a measurable accumulation of propylene glycol if it is ingested in the course of a multiple-dosing regimen (Yu et al. 1985). The limitation of the study is that it does not specify if the observed propylene glycol effects may have been associated with the neurological problems already present in those patients or with concomitant ingestion of ethanol.

In a study of oral LD50 values using propylene glycol, lethargy and coma were observed prior to death in rats (Clark et al. 1979). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for 5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Pre-dosing observations were made such that each group of cats served as its own control. Animals were observed for signs of toxicity. Cats receiving the low dose showed no clinical signs of toxicity. Cats receiving the high dose developed decreased activity, mental depression [author's words], and slight to moderate ataxia. These cats had high levels (44-fold higher than control) of D-lactate, thought to contribute to central nervous system toxicity. On the basis of this information, adverse neurological reactions due to exposure to low levels of propylene glycol possibly present at hazardous waste sites are very unlikely.

The LOAEL value for neurological effects in rats for acute-duration category oral exposure propylene glycol is reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to propylene glycol. Pregnant female Swiss mice were given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 (Kavlock et al. 1987). There was no effect of treatment on their ability to produce live pups, or on the survival of those pups. The effects of propylene glycol on reproduction of Swiss (CD-l) mice were tested in a protocol which permitted continuous breeding during a specified interval (NTP 1985). Propylene glycol in drinking water at doses of 0, 1.0, 2.5, and 5.0% yielded mean exposures of 0, 1,819, 4,796, and 10,118 mg/kg/day, based on water consumption. Animals were treated during a l-week pre-cohabitation period and a 14-week monogamous cohabitation 'period. Any offspring produced during the cohabitation period were examined, sexed, weighed, and killed to allow continuous mating of the parental generation. At the end of the cohabitation period, males and females were separated, and the females were allowed to deliver and raise the last litter to weaning. Propylene glycol had no adverse effects on any measure of reproduction, including number of litters, litter size, pup weight, or sex ratio. There was no effect on the reproductive capacity of offspring from the high dose group.

The highest NOAEL values for reproductive effects in each species and duration category for propylene glycol after oral exposure are reported in Tables 2-2 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 propylene glycol.

Pregnant female Swiss mice were given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 (Kavlock et al. 1987). There was no effect of treatment on their ability to produce live pups, or on the survival of those pups. The effects of propylene glycol on reproduction of Swiss (CD-l) mice were tested in a protocol which permitted continuous breeding during a specified interval (NTP 1985). Propylene glycol in drinking water at doses of 0, 1.0, 2.5, and 5.0% yielded mean exposures of 0, 1,819, 4,796, and 10,118 mg/kg/day, based on water consumption. Animals were treated during a l-week pre-cohabitation period and a 14-week monogamous cohabitation period. Any offspring produced during the cohabitation

period were examined, sexed, weighed, and killed to allow continuous mating of the parental generation. At the end of the cohabitation period, males and females were separated, and the females were allowed to deliver and raise the last litter to weaning.

Propylene glycol had no adverse effects on any measure of reproduction, including number of litters, litter size, pup weight, or sex ratio. There was no effect on the reproductive capacity of offspring from the high dose group.

The highest NOAEL values for developmental effects in each species and duration category for propylene glycol after oral exposure are reported in Table 2-2 and Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to propylene glycol.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans after oral exposure to propylene glycol.

In a dietary study of chronic oral exposure of rats to 2,500 mg/kg/day, there were no treatment-related increases in neoplasms (Gaunt et al. 1972). Based on this information, its long history of use in consumer products, and structural activity considerations, it is extremely unlikely that exposure to levels of propylene glycol near hazardous waste sites would influence the incidence of cancer in the population living in the vicinity.

2.2.3 Dermal Exposure

Dermal exposure to propylene glycol most likely occurs through contact with cosmetics or drugs.

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to propylene glycol. Therefore, no LOAELs for death following dermal exposure could be established. Based on the absence of data in the literature, it is unlikely that sufficient amounts of propylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area.

2.2.3.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans, or respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight, or metabolic effects in animals after dermal exposure to propylene glycol.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after dermal exposure are reported in Table 2-3.

Respiratory Effects. Acute respiratory acidosis and cardiorespiratory arrest occurred in an 8-month-old infant with second- and third-degree burns after acute dermal treatment with silver sulfadiazine containing a high amount of propylene glycol. The dose of propylene glycol was 9,000 mg/kg/day (Fligner et al. 1985). Due to the high dose of propylene glycol, and the possible concomitant effects of both the burn injury and the sulfadiazine therapy, the actual source of the respiratory effect in this infant could not be determined, although propylene glycol cannot be ruled out as the causative agent.

Cardiovascular Effects. Very limited and conflicting information is available for humans on cardiovascular effects after dermal exposure to propylene glycol. An 8-month-old infant suffered cardiorespiratory arrest after four dermal exposures to propylene glycol in a silver sulfadiazine medication (Fligner et al. 1985). Due to the high dose of propylene glycol, and the possible concomitant effects of both the burn injury and the sulfadiazine therapy, the actual source of the cardiorespiratory effect in this infant could not be determined, although propylene glycol cannot be ruled out as the causative agent. Other studies of propylene glycol in humans did not evaluate cardiovascular effects.

It appears that acute exposure to very high levels of propylene glycol may cause adverse cardiovascular effects, but it is unlikely that such exposures could occur as a result of being in the vicinity of hazardous waste sites.

TABLE 2-3. Levels of Significant Exposure to Propylene Glycol - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
ACUTE EXPOSURE						
Systemic						
Human	5 d 1x/d	Hemato	6100 mg/kg			Commens 1990
Human	70 hr >1x/d	Resp			9000 M mg/kg (acute respiratory acidosis)	Fligner etal. 1985
		Cardio			9000 M mg/kg (cardiorespiratory arrest)	
		Metab			9000 M mg/kg (increased osmolal gap)	
Human	20-24h	Dermal		3.2% (irritation reaction)		Hannuksela etal. 1975
Human	48hr once	Dermal		10 mg (50% solution, skin edema and erythema)		Kinnunen and Hannuksela 1989
Human	48hr once	Dermal		0.2 mg (1% solution, erythema and edema)		Kinnunen and Hannuksela 1989
Human	7 d 2x/d	Dermal	104 M mg			Trancik and Maibach 1982
Human	once 48 hrs	Dermal		2.5% (erythema, induration, vesiculation)		Warshaw and Herrmann 1952
Human	48 hr once	Dermal	15 mg M	31 mg M (faint, patchy erythema with edema)		Willis etal. 1988
Human	48hr once	Dermal		16 mg M ("basket weave" pattern to stratum corneum)		Willis etal. 1989

Freedom_0007144_0050

TABLE 2-3. Levels of Significant Exposure to Propylene Glycol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
Rabbit (New Zealand)	once	Dermal	0.52 gm F			Clark et al. 1979
Rabbit (New Zealand)	once	Dermal	0.1 gm F			Clark et al. 1979
Immunological/Lymphoreticular						
Human	20-24 hr			3.2% (allergic reaction)		Hannuksela et al. 1975
Neurological						
Human	70 hr >1x/d				9000 mg/kg M (hypoxic encephalopathy)	Fligner et al. 1985
INTERMEDIATE EXPOSURE						
Systemic						
Human	21-22 d	Dermal		207 mg M (erythema)		Trancik and Maibach 1982

Cardio = cardiovascular; d = day(s); F = female; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; NOAEL = no-observable-adverse-effect level; Resp = respiratory; x = times

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Dermal Effects. Propylene glycol does not seem to have significant irritative properties. Skin testing of 42 healthy volunteers showed that 100% propylene glycol caused faint, patchy erythema with edema in 40% of the tested subjects (Willis et al. 1988). In another study, an acute dermal exposure of eczema patients to 0.2 and 22.8 mg/cm2 of propylene glycol caused skin edema and erythema in 3.8% of the 823 patients that were skin tested (Kinnunen and Hannuksela 1989). On the basis of-the findings from these studies, the authors concluded that propylene glycol has marginal irritant properties.

However, some cases of sensitivity have been recorded in the literature. A 51-year-old woman developed a severe itchy erythematous vesicular dermatitis of the upper lip, nose and adjoining right cheek after applying a cream containing 10% propylene glycol (Corrazza et al. 1993). A patch test revealed a sensitivity to propylene glycol. In a test of 1,226 patients, applying 5% propylene glycol in Vaseline, or 10, 30, or 50% in water, caused approximately 208 patients to show some reaction (Aberer et al. 1993). Of these 208 patients, 195 exhibited some form of irritation, whereas only 13 exhibited an allergic reaction (Aberer et al. 1993). The mechanism of the reaction is not understood, but electron microscopy revealed that propylene glycol causes hydration of corneal cells producing a characteristic "basket weave" pattern in the stratum comeum (Willis et al. 1989). In order to determine if propylene glycol can also evoke a hypersensitivity reaction, a total of 15 patients who had positive skin reactions to propylene glycol were exposed to an acute oral propylene glycol challenge (Hannuksela and Forström 1978). The hypersensitivity reaction that developed consisted of exanthem and cleared within 36-48 hours without any medications.

During 1951 and 1952, propylene glycol was applied in a covered patch test to the normal skin of 866 patients (Warshaw and Herrmann 1952). The test sites were examined 48 hours after application of the patches. Undiluted propylene glycol (Brand A, B, and C), and aqueous dilutions of Brand A (2.5, 10, and 50%) were tested. Related compounds, including glycerine, and carbowax 1500, were also tested. Propylene glycol was also applied directly to the skin of some individuals with a glass rod for 20 seconds. The application site was left uncovered. In many of the patients, the patch tests were repeated, but in different locations. When possible, the patients were re-tested after a period of several months. Several patients who reacted to propylene glycol were re-tested with exposure to propylene glycol and dry heat; female patients who reacted to propylene glycol received lipsticks containing propylene glycol for trial use. Positive results were observed in 138 (15.7%) of the skin patch tests of propylene glycol. The reactions ranged from simple erythema to erythema with induration and vesiculation. No differences were noted in reactions to different brands of propylene glycol. Twenty-three persons with reactions to pure

propylene glycol were tested with 50 and 10% dilutions. In general, the reaction to propylene glycol decreased with decreasing concentration. Only 5 of 23 showed any reaction to 10% propylene glycol, and only showed simple erythema. One of three persons tested with 2.5% propylene glycol had a positive reaction. Sixteen patients with positive reactions to the propylene glycol patch test were further patch-tested with glycerine and carbowax 1500, yielding 1 positive reaction to carbowax 1500, and a questionable positive reaction to glycerine. Sixteen patients with positive reactions to the patch test with propylene glycol were retested by simple application of propylene glycol. No positive reactions were observed. The incidence of positive reactions to propylene glycol appeared to fluctuate with the season, and was significantly higher during the cooler and less humid months (14-22% from October to June, 6% from July to September). In 23 of the positive reacting patients, the patch tests with propylene glycol were repeated after a period of 2-12 months. Seventeen of 23 patients showed a positive response, while the other 6 showed no response. Repeated testing with increased heat and moisture, reactivity tended to decrease. One of 15 female patients with a positive reaction to the propylene glycol patch test was also reactive to lipstick containing propylene glycol which was applied to the lips.

Propylene glycol was tested on the skin of 1,556 patients with eczema using a chamber on the back of the patients (Hannuksela et al. 1975). Undiluted propylene glycol was applied to the backs of the patients and left there for 20-24 hours. Readings of the exposure area were made 1, 2, and 4-5 days after application of the chemical. Reactions with redness, with or without infiltration peaking on the first day were considered irritant reactions. Reactions with infiltration with or without vesiculation extending to a considerably larger area than the test area, with the maximum occurring on the second day or later were considered' allergic. Forty-two positive reactors were subjected to patch tests with 3.2, 10, or 32% aqueous propylene glycol. Fifteen patients with allergic reactions to propylene glycol. applied undiluted propylene glycol to their armpits 3 times daily for 4 days. Of the patients tested with undiluted propylene glycol, 12.5% showed positive reactions. Of these, 70% were of primary irritation, and 30% were allergic in appearance. Seasonal variation was observed, with more cases observed in the winter. Forty-two cases of positive reactions to undiluted propylene glycol were retested with aqueous dilutions of the compound. Twelve of 42 showed a positive reaction to 10%, and 9 of 42 had a reaction to 3.2%; 20 of 42 cases reacted to the 32% solution. Eleven of 15 patients who applied propylene glycol to their armpits had no reaction. The 4 reacting patients exhibited itching 4-10 hours and eczema within 24 hours. The symptoms reached their peak at 48 hours and disappeared after 3-5 days. Three of these patients used undiluted propylene glycol and one patient used 10% propylene glycol. In this latter patient, examination of the skin of a lo-hour-old reaction revealed no change in the epidermis, but perivascular infiltration in the dermis, indicative of an allergic reaction.

A 21-day cumulative irritation test was conducted using propylene glycol (Trancik and Maibach 1982). Ten Caucasian males with healthy skin received dermal applications of 207 mg propylene glycol (USP) on their backs in the same spot every day for 21 days. The application site was occluded with gauze and tape for 24 hours following application. Daily readings of test site were conducted at the time the patches were removed. Scoring ranged from no visible reaction to intense erythema with edema and vesicular erosion. In the 21-day cumulative irritation test, only one subject presented with a reaction, which was rated as equivocal irritation, on 20 of the test. All other subjects in the test had no reaction. Results of the 21-day cumulative irritation test indicate that propylene glycol is at least a minimal irritant.

There are few studies of dermal effects of propylene glycol in animals. New Zealand White rabbits exposed to 0.52 g of propylene glycol on skin showed little or no irritation after 72 hours (Clark et al. 1979).

These findings, plus a long history of safe use in medicine, indicate that prolonged dermal exposure to the low levels of propylene glycol present at hazardous waste sites is very unlikely to cause hypersensitivity or other skin reactions in the human population living in the vicinity.

Metabolic Effects. High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. Increased osmolal gap was found in two cases of acute dermal exposure to propylene glycol. An 8-month-old infant with a severe burnswas topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). The osmolal gap reached a maximum of 130 rnilliosmoles/kg 14 days after the treatment started, while serum propylene glycol level peaked at 1,059 mg/dL. Due to the high dose of propylene glycol, and the possible concomitant effects of both the burn injury and the sulfadiazine therapy, the actual source of the metabolic effect in this infant could not be determined, although propylene glycol cannot be ruled out as the causative agent. The burn injury may have contributed to the increased absorption of propylene glycol and hence, the hyperosmolality. However, in another study of acute dermal propylene glycol exposure of 12 adults to 6,100 mg/kg/day for 5 days, propylene glycol had no effect on either serum osmolality or lactic acid levels (Commens 1990). Although the results of these studies are not conclusive, it seems that increased lactate levels leading to acidosis and increased osmolality may develop in humans in the event high levels of propylene glycol are absorbed into the blood stream.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in animals after dermal exposure to propylene glycol.

Since propylene glycol is widely used as a vehicle for dermally applied medications, several studies investigated its potential as both an irritant and contact allergen. Skin testing of 42 healthy volunteers showed that 100% propylene glycol caused faint, patchy erythema with edema in 40% of the tested subjects (Willis et al. 1988). In another study, an acute dermal exposure of eczema patients to 0.2 and 22.8 mg/cm2 of propylene glycol caused skin edema and erythema in 3.8% of the 823 patients that were skin tested (Kinnunen and Hannuksela 1989). On the basis of the findings from these two studies, the authors concluded that propylene glycol has marginal irritant properties. However, some cases of sensitivity have been recorded in the literature. A 51-year-old woman developed a severe itchy erythematous vesicular dermatitis of the upper lip, nose, and adjoining right cheek after applying a cream containing 10% propylene glycol (Corrazza et al. 1993). A patch test revealed a sensitivity to propylene glycol. In a test of 1,226 patients applying 5% propylene glycol in Vaseline, or 10, 30, or 50% in water resulted in approximately 208 patients showing some reaction (Aberer et al. 1993). Of these 208 patients, 195 exhibited some form of irritation, whereas only 13 exhibited an allergic reaction (Aberer et al. 1993). The mechanism of the reaction is not understood, but electron microscopy revealed that propylene glycol causes hydration of corneal cells producing a characteristic "basket weave" pattern in the stratum corneum (Willis et al. 1989): In order to determine if propylene glycol can also evoke a hypersensitivity reaction, a total of 15 patients who had positive skin reactions to propylene glycol were exposed to an acute oral propylene glycol challenge (Hannuksela and Forström 1978). The hypersensitivity reaction that developed consisted of exanthem and cleared within 3 6-48 hours without any medications. Propylene glycol was tested on the skin of 1,556 patients with eczema using a chamber on the back of the patients (Hannuksela et al. 1975). Undiluted propylene glycol was applied to the backs of the patients and left there for 20-24 hours. Readings of the exposure area were made 1, 2, and 4-5 days after application of the chemical. Reactions with redness, with or without infiltration peaking on the first day were considered irritant reactions. Reactions with infiltration with or without vesiculation extending to a considerably larger area than the test area, with the maximum occurring on the second day or later were considered allergic. Forty-two positive reactors were subjected to patch tests with 3.2, 10, or 32% aqueous propylene glycol. Fifteen patients with allergic reactions to propylene glycol applied undiluted propylene glycol to their armpits 3 times daily for 4 days. Of the patients tested with undiluted propylene glycol, 12.5%

showed positive reactions. Of these, 70% were of primary irritation, and 30% were allergic in appearance. Seasonal variation was observed, with more cases observed in the winter. Forty-two cases of positive reactions to undiluted propylene glycol were retested with aqueous dilutions of the compound. Twelve of 42 cases showed a positive reaction to 10%, and 9 of 42 cases had a reaction to 3.2%; 20 of 42 cases reacted to the 32% solution. Eleven of 15 patients who applied propylene glycol to their armpits had no reaction. The 4 reacting patients exhibited itching 4-10 hours and eczema within 24 hours. The symptoms reached their peak at 48 hours and disappeared after 3-5 days. Three of these patients used undiluted propylene glycol and one patient used 10% propylene glycol. In this latter patient, examination of the skin of a 10-hour-old reaction revealed no change in the epidermis, but perivascular infiltration in the dermis, indicative of an allergic reaction.

A 22-day sensitization procedure was conducted using propylene glycol (Trancik and Maibach 1982). For the sensitization procedure, 203 Caucasian males with healthy skin received dermal doses of 207 mg propylene glycol on their backs on Mondays, Wednesdays, and Fridays for 22 days, resulting in a total of 10 doses. The application site was occluded for 48-72 hours (i.e., covered between doses). The test sites were read when the patches were changed. The application site was occluded with gauze and tape for 24 hours following application. Daily readings of test site were conducted at the time the patches were removed. Scoring ranged from no visible reaction to intense erythema with edema and vesicular erosion. In addition, minimal glazing of the skin (roughness) was added to the scoring list. Two weeks after the sensitization phase, a challenge dose was applied to previously untested skin and occluded for 48-72 hours. Rechallenge was performed at 2-week intervals. In the sensitization test, equivocal responses were noted, but no reaction more than equivocal was observed. At the challenge, 19 of 203 showed a positive response. Upon rechallenge, five exhibited an increase in response. The sensitization test indicates that propylene glycol might be a sensitizer.

These findings plus a long history of safe use in medicine indicate that prolonged dermal exposure to the low levels of propylene glycol present at hazardous waste sites is very unlikely to cause hypersensitivity reactions in the human population living in the vicinity.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in animals after dermal exposure to propylene glycol.

Adverse neurological reactions were observed in patients who tested positive in a propylene glycol patch test after an acute oral challenge with 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). Although the observed neurotoxicity is attributed to propylene glycol, the study reports that this response was seen in allergic individuals. An 8-month-old infant with a severe burn was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). After developing respiratory acidosis, the infant experienced cardiac arrest and was resuscitated. Subsequent neurological examination revealed hypoxic damage, which was evident by persistent hypoxic encephalopathy. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the respiratory effect and subsequent neurological damage in this infant could not be determined, although propylene glycol cannot be ruled out as the causative agent.

The LOAEL value for neurological effects in humans for acute effects for propylene glycol after dermal exposure is reported in Table 2-3.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after dermal exposure to propylene glycol.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to propylene glycol.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to propylene glycol.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer effects in humans after dermal exposure to propylene glycol.

No increase in tumors was observed after twice weekly applications of propylene glycol to the skin of Swiss mice for 120 weeks, at doses up to 2 mg (Stenback and Shubik 1974). Based on this information, its long history of use in consumer products, and structural activity considerations, it is extremely unlikely that exposure to levels of propylene glycol near hazardous waste sites would influence the incidence of cancer in the population living in the vicinity.

2.3 TOXICOKINETICS

The toxicokinet ics of propylene glycol is not well defined. Dermal data are most abundant for propylene glycol. Due to the relatively nontoxic nature of the compound, kinetic data are somewhat scarce. Available information is discussed below.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No kinetic data for absorption in humans or animals of propylene glycol after inhalation exposure were found in the literature.

2.3.1.2 Oral Exposure

The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure (Yu et al. 1985). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for 5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Predosing observations were made such that each group of cats served as its own control. Plasma levels of propylene glycol were measured in 2 cats fed the low dose on day 24 of ingestion, and compared to pre-dosing samples. Plasma levels of propylene glycol were 19.1 and 8.4 mmol/liter for the 2 cats.

2.3.1.3 Dermal Exposure

Some studies of the dermal absorption of propylene glycol have been conducted. Patients with second and third degree burns over more than 20% of their total body surface were studied over a period of

30 months (Kulick et al. 1985). Sulfadiazine preparations containing propylene glycol were applied dermally over a period of 3-7 days after admission to the hospital. Serum and urinary levels of propylene glycol were measured. Propylene glycol was detected in the serum of 24 of 45 patients, and in the urine of 40 of 45 patients. Average serum levels were 0.08 mg/mL, with a range of 0-1.3 mg/mL for patient who lived, and 0.82 mg/mL with a range of 0-9.8 mg/mL for patients who died. Propylene glycol levels correlated with total bum surface area and total third degree burn surface area.

In vitro studies of the penetration of propylene glycol through rat abdominal stratum corneum have been conducted (Takeuchi et al. 1993, 1995). Fresh abdominal skin from male Wistar rats was used in experiments in which propylene glycol, or a mixture of propylene glycol and oleic acid were evaluated for absorption properties (Takeuchi et al. 1993). When propylene glycol was applied alone for up to 2 hours, no compound was detected in the dermis. However, when 0.15 M oleic acid was added to the propylene glycol, propylene glycol was detected in the dermis after 30 minutes of exposure, but not after 5 or 15 minutes (Takeuchi et al. 1993). The appearance of propylene glycol seemed to be in three phases when in the presence of a skin penetration enhancer such as oleic acid (Takeuchi et al. 1995). The first stage was the penetration of propylene glycol into the skin barrier, without any change of the dermal structure. The second stage was rapid distribution in and throughout the dermis, presumably accompanied by alteration of the dermal structure. In the third stage, propylene glycol was saturated in the dermis.

Comparison of propylene glycol absorption by skin from humans, hairless mice, and snakes was conducted (Rigg and Barry 1990). Shed snake skin tended to underestimate propylene glycol absorption in human skin, especially in the presence of enhancers, whereas hairless mouse skin greatly overestimated absorption compared to human skin. The authors concluded that human skin should be used for absorption studies whenever possible.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No kinetic data for distribution in humans or animals of propylene glycol after inhalation exposure were found in the literature.

2.3.2.2 Oral Exposure

No studies of the distribution of propylene glycol in humans or animals after oral exposure were found in the literature.

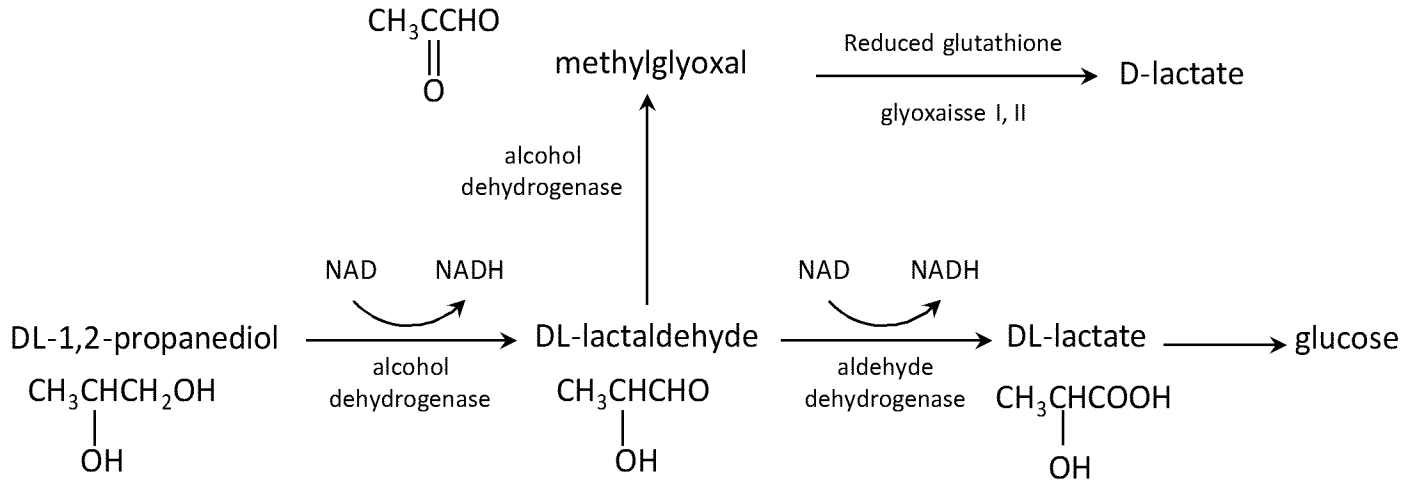
2.3.2.3 Dermal Exposure

In vitro studies of the penetration of propylene glycol through rat abdominal stratum corneum have been conducted (Takeuchi et al. 1993, 1995). Fresh abdominal skin from male Wistar rats was used in experiments in which propylene glycol, or a mixture of propylene glycol and oleic acid were evaluated for absorption properties (Takeuchi et al. 1993). When propylene glycol was applied alone for up to 2 hours, no compound was detected in the dermis. However, when 0.15 M oleic acid was added to the propylene glycol, propylene glycol was detected in the dermis after 30 minutes of exposure, but not after 5 or 15 minutes (Takeuchi et al. 1993). The appearance of propylene glycol seemed to be in three phases when in the presence of a skin penetration enhancer such as oleic acid (Takeuchi et al. 1995). The first stage was the penetration of propylene glycol into the skin barrier, without any change of the dermal structure. The second stage was rapid distribution in and throughout the dermis, presumably accompanied by alteration of the dermal structure. In the third stage, propylene glycol was saturated in the dermis. Additional evaluation indicated that the volume of distribution of propylene glycol in the dermis was influenced by the efficiency of the enhancer compound, with oleic acid and oleylamine being the most efficient, compared to lauric acid, laurylamine, or azone.

2.3.3 Metabolism

The metabolic pathway for propylene glycol in mammals is shown in Figure 2-3. Commercially available propylene glycol is usually a mixture of D- and L-isomers. The major route of metabolism for propylene glycol is via alcohol dehydrogenase to lactaldehyde, then to lactate, via aldehyde dehydrogenase, and on to glucose through gluconeogenic pathways (as summarized in Christopher et al. 1990b; Huff 1961; Miller and Bazzano 1965; Morshed et al. 1989, 1991b; Ruddick 1972). Conversion to methylglyoxal is an alternate route via alcohol dehydrogenase, ending in metabolism to D-lactate through glyoxalase.

Figure 2-3. Propylene Glycol Metabolism in Mammals



From Christopher et al. 1980b

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No kinetic data for excretion in humans or animals of propylene glycol after inhalation exposure were found in the literature.

2.3.4.2 Oral Exposure

The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure, while the elimination half-life is about, 4 hours. The total body clearance is about 0.1 L/kg/hour and seems to be serum-concentration dependent (Yu et al. 1985). Dose-dependent elimination is seen in rats, with saturation of the pathways at doses above 5,880 mg/kg (Morshed et al. 1988). An apparent maximum elimination rate of 8.3 mmol/kg/hour (630 mg/kg/hour) was observed.

2.3.4.3 Dermal Exposure

Excretion of propylene glycol has been studied in humans. Patients with second and third degree bums over more than 20% of their total body surface were studied over a period of 30 months (Kulick et al. 1985). Sulfadiazine preparations containing propylene glycol were applied dermally over a period of 3-7 days after admission to the hospital. Serum and urinary levels of propylene glycol were measured. Propylene glycol was detected in the serum of 24 of 45 patients, and in the urine of 40 of 45 patients. Average urinary levels were 1.3 mg/mL, with a range of 0-17.9 mg/mL for patient who lived, and 2.9 mg/mL with a range of 0-23.0 mg/mL for patients who died. Propylene glycol levels correlated with total bum surface area and total third degree bum surface area.

2.3.5 Mechanism of Action

The mechanism of action of propylene glycol is not well understood.

2.4 RELEVANCE TO PUBLIC HEALTH

Propylene glycol is a colorless, odorless, water-soluble liquid considered safe for use in commercial formulations of foods, drugs, and cosmetics. Propylene glycol, like ethylene glycol, is used as an antifreeze, de-icing solution, and in various paints and coatings. Unlike ethylene glycol, however, propylene glycol has been approved as safe in various food flavorings, drugs, cosmetics, and as a direct additive to food. Propylene glycol is commonly used in the pharmaceutical industry as a solvent for drugs, as a stabilizer for vitamins, and in ointment for medicinal applications. Propylene glycol may be found in canned fruit, packaged coconut, as a solvent in drug and cosmetic preparations, and in flavorings and extracts. Propylene glycol is also used in the generation of artificial mists and fogs used in fire safety training, and theatrical and stage productions: This widespread use of propylene glycol stems from its low level of toxicity.

Minimal Risk Levels for Propylene Glycol

Inhalation MRLs

No MRLs for acute- or chronic-duration inhalation exposure to propylene glycol were derived because data are insufficient. Only one acute-duration inhalation exposure study was found in the available literature, in which rabbits were exposed to only one dose (10% aerosol) of propylene glycol for 20 and 120 minutes (Konradova et al. 1978). An increased number of degenerated goblet cells in the tracheal lining was observed at both doses. Only a single study was found in the available literature for inhalation exposure to propylene glycol for chronic-duration (Robertson et al. 1947) exposure. This study did not provided enough information from which to derive an MRL.

- An MRL of 0.009 ppm has been derived for intermediate-duration (15–364 days) inhalation exposure to propylene glycol.

The MRL was based on the LOAEL of 51 ppm for nasal hemorrhaging in rats (Suber et al. 1989). The MRL was obtained by dividing the LOAEL value by 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and multiplying by factors to adjust the exposure from 6 hours per day (6 or 24) and 5 days per week (5 of 7) to continuous exposure. Young, healthy adult Sprague-Dawley rats were divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by nose-only inhalation to mean target aerosol concentrations of 51, 321, or 707 ppm propylene glycol. The fourth, the control group, was exposed to

humidified, filtered room air. Nasal hemorrhaging occurred in all exposed groups of male and female rats indicating that propylene glycol can act as a dehydrogenating agent. From week 2 to 14, the average of nasal hemorrhaging in male rats was <1, 64, 74, and 75% in controls, low-exposure, medium-exposure, and high-exposure groups, respectively. In females, the average indices were <1% in controls, 14% in the low-exposure group, and 71% in the medium and high-exposure groups. Animals recovered during non-exposure weekend periods. Similar trends were observed for ocular discharge, with females having generally less ocular discharge than males. A significant reduction in body weight of 5-7% starting on day 50 and continuing until the end of the study was observed in female rats receiving the highest dose of 707 ppm propylene glycol. Similar observation was made in the group receiving 321 ppm of propylene glycol but later in the study starting on day 64. This body weight reduction was correlated with a significant reduction in food consumption beginning on study days 43 and 50 for the high- and medium-exposure females, respectively. Female rats exposed to 321 ppm propylene glycol had a significant decrease in white blood cell count and lymphocyte numbers. Female rats exposed to 707 ppm propylene glycol had a significant decrease in hemoglobin concentration, white blood cell count and lymphocyte numbers. Male rats in the medium (321 ppm) and high (707 ppm) groups had a significant decrease in serum sorbitol dehydrogenase and gamma-glutamyl transferase. A significant decrease in total serum protein was observed in male rats treated with high dose (707 ppm) of propylene glycol while females treated with a medium dose (321 ppm) of propylene glycol had an increase in total serum protein. These changes were considered to be sporadic. Kidney weight was decreased at 321 ppm in both sexes. Although there were no treatment-related gross pathology changes, light microscopy revealed thickening of respiratory epithelium with increase in the number of goblet cells and their mucin content in both female and male animals receiving medium and high propylene glycol dose. Minute volume, tidal volume, and respiratory rates were not significantly altered in rats exposed to 51, 321, or 707 ppm propylene glycol for 13 weeks, suggesting that animals adapted to the exposure concentrations.

Oral MRLs

No MRLs for acute-, intermediate-, or chronic-duration oral exposure to propylene glycol were derived because data are insufficient.

Death. There were no reports in the literature of human death due to propylene glycol exposure by any route, at any level, for any length of time. Lethal oral doses for rats, mice, and guinea pigs range from 8,000 to 46,000 mg/kg (Clark et al. 1979; EPA 1987a). Monkeys died after inhalation exposure to

112 ppm propylene glycol after 13 months (Robertson et al. 1947). It is unlikely that sufficient amounts of propylene glycol would be inhaled, ingested, or absorbed through the skin to be fatal.

Systemic Effects

Respiratory Effects. Acute respiratory arrest was observed in an 8-month-old infant being treated for second and third degree bums with an topical antibiotic formulation containing propylene glycol (Fligner et al. 1985). The contribution of the bum injury and the antibiotic therapy to the respiratory arrest, however, is not known. Anecdotal accounts of respiratory irritation after exposure to propylene glycol as a mist or vapor in theatrical productions was found in the literature (Rossol 1990). Studies of laboratory animals are inconclusive with respect to the respiratory effects of propylene glycol (Konradova et al. 1978; Suber et al. 1989).

Cardiovascular Effects. Very limited information is available in humans and animals on cardiovascular effects after exposure to propylene glycol. In the case of the 8-month-old infant mentioned above, cardiac arrest accompanied the respiratory arrest (Fligner et al. 1985). The contribution of the infant's injuries to the observed symptoms is not known. No cardiovascular effects were noted in rats after 2 years of exposure to oral doses of propylene glycol up to 49,500 ppm (Morris et al. 1942). Myocardial edema was observed in a horse prior to death from an accidental oral administration of 7,904 mg/kg propylene glycol (Dorman and Haschek 1991).

Gastrointestinal Effects. There were no reports of the effects of propylene glycol on the gastrointestinal system of humans. Propylene glycol is approved as a direct food additive. Toxicity to the gastrointestinal system has been shown to be negligible. In rats, only a very large oral dose of 23,500 mg/kg caused hemorrhagic enteritis (Clark et al. 1979). Monkeys and rats exposed by inhalation to concentrations of propylene glycol up to 112 ppm for 13-18 months had no gastrointestinal effects (Robertson et al. 1947). The effect of orally administered propylene glycol on the brush border membrane from the jejuno-ileum portion of the intestines of rats was investigated *in vivo* and *in vitro* (Morshed et al. 1991a). In rats receiving 2,942 mg/kg propylene glycol for 10-30 days, brush border enzymes including sucrase, lactase, and gamma-glutamyl transpeptidase exhibited a tendency toward increased activity. Absorption of D-glucose and calcium was increased after 10 days of treatment, whereas absorption of D-glucose, glycine, L-aspartic acid, L-lysine, and calcium were elevated after 20 or 30 days of treatment. The structural integrity of the jejunal surface was not adversely affected. When evaluated *in vitro*, propylene glycol inhibited sucrase, lactase, and maltase, in a non-competitive dose-related manner, with

sucrase being the most affected. Nutrient transport was not altered. These studies suggest that ingested propylene glycol may influence intestinal digestive and absorptive functions, and that the *in vivo* and *in vitro* effects are through different mechanisms.

Hematological Effects. Propylene glycol does not appear to adversely affect hematological parameters in humans (Lolin et al. 1988). In animals, however, intermediate- and chronic-duration exposure to propylene glycol may lead to hemolysis of red blood cells. For example, propylene glycol is used as a moistening agent in cat food. Studies of cats fed 1,200 mg/kg/day and higher doses of propylene glycol for 2-17 weeks exhibited hypocellularity of the bone marrow, increased Heinz body formation and decreased RBC survival (Christopher et al. 1989a; Weiss et al. 1990, 1992). Similar results were seen in dogs after chronic exposure to 5,000 mg/kg/day (Weil et al. 1971).

Musculoskeletal Effects. No *in vivo* data on musculoskeletal effects of propylene glycol were found in the literature. Propylene glycol was shown to cause damage with subsequent creatine kinase release from rat skeletal muscle (Brazeau and Fung 1990). Attempts to elucidate the mechanism of this damage suggested that propylene glycol-mediated damage of skeletal muscle may be caused by an intracellular mechanism rather than by a direct action on the sarcolernma, and that the mechanism may involve calcium. Frog muscle preparations exhibit increased twitch tension in the presence of propylene glycol (Hattori and Maehashi 1993). Propylene glycol appears to facilitate transmitter release from the nerve terminals and raise the acetylcholine sensitivity of the muscle endplate.

Renal Effects. No *in vivo* studies describing frank renal toxicity for propylene glycol alone were found (Christopher et al. 1989a; Gaunt et al. 1972; Robertson et al. 1947; Suber et al. 1989). Polyuria and polydipsia have been observed in cats ingesting 8,000 mg/kg/day propylene glycol for 3 or more weeks (Christopher et al. 1989a, 1990b). Propylene glycol has been shown to damage the membranes of human proximal tubule cells in culture (Morshed et al. 1994). Lactate release was increased and glucose accumulation decreased in human proximal tubule cells prior to observation of membrane damage, indicating that damage was occurring even when the plasma membrane appeared to be unaffected.

Dermal Effects. Propylene glycol has few irritative properties in humans when applied topically, except in the case of unusual sensitivity (Aberer et al. 1993; Corrazza et al. 1993; Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Trancik and Maibach 1982; Warshaw and Herrmann 1952; Willis et al. 1989).

Body Weight Effects. Propylene glycol has little effect on body weight. Exposure of rhesus monkeys to 112 ppm propylene glycol by inhalation for up to 13 months had no effect on body weight, whereas in the same study, rats treated to the same dose for 18 months exhibited a 50% decrease in body weight (Robertson et al. 1947). In another study, rats exposed to 321 ppm for an intermediate period of time had decreased body weight (Suber et al. 1989).

Metabolic Effects. Propylene glycol causes acidosis, through conversion to lactic and pyruvic acids. However, the acidosis from propylene glycol is not as severe as that caused by ethylene glycol. Evidence of this comes from clinical cases of dermal or intravenous treatment with drug formulations containing propylene glycol (Fligner et al. 1985; Glasgow et al. 1983; Huggon et al. 1990; Kelner and Bailey 1985). Acidosis also occurs after ingestion of large amounts of propylene glycol (Lolin et al. 1988). Increased osmolal gap was observed in cats after ingestion of 1,600 mg/kg/day propylene glycol for 5 weeks (Christopher et al. 1990b). It seems possible that metabolic acidosis could develop in humans after exposure to large doses.

High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. An 8-month-old infant with a severe burn was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985).

The osmolal gap reached a maximum of 130 milliosmoles/kg 14 days after the treatment started, while serum propylene glycol level peaked at 1,059 mg/dL. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the metabolic effect in this infant could not be determined, although propylene glycol cannot be ruled out as the causative agent. The burn injury may have contributed to the increased absorption of propylene glycol and hence, the hyperosmolality. Another infant developed increased osmolality after being exposed intravenously to propylene glycol (2.4 mg/kg) used as a vehicle for Enoximone (Huggon et al. 1990). However, in another study of acute dermal propylene glycol exposure of 12 adults to 6,100 mg/kg/day for 5 days, propylene glycol had no effect on either serum osmolality or lactic acid levels (Commens 1990). Increased serum propylene glycol levels, increased lactate, and increased total acid (serum lactate and pyruvate) were also found in a retrospective study of 35 human sera samples and 8 cerebrospinal fluid samples from patients receiving intravenous medications with propylene glycol as the vehicle (Kelner and Bailey 1985). The daily dose of propylene glycol ranged from 57 to 771 mg/kg. None of the sera samples

were specifically collected for determination of propylene glycol levels; therefore, the time between propylene glycol administration and serum collection varied and was not specified in the report. However, statistically significant correlation was found between the lactate levels in serum and cerebrospinal fluid samples and the corresponding propylene glycol concentrations (Kelner and Bailey 1985). Although the results of these studies are not conclusive, it seems that increased lactate levels leading to acidosis and increased osmolality may develop in humans in the event high levels of propylene glycol are absorbed into the blood stream.

Immunological and Lymphoreticular Effects. Since propylene glycol is used in topical formulations, it has been investigated as both an irritant and contact allergen (Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Willis et al. 1988). Results indicate that except in rare cases (Corrazza et al. 1993; Hannuksela et al. 1975; Tranick and Maibach 1982) the irritative properties of propylene glycol are minimal and cannot be classified as allergic reactions (Aberer et al. 1993; Hannuksela and Forström 1978; Willis et al. 1989). There was no effect on the spleen in rats or monkeys exposed to 112 ppm aerosolized propylene glycol for up to 18 months (Robertson et al. 1947; Suber et al. 1989). Propylene glycol in a concentration of 0.5-1.0% has been shown to inhibit natural cytotoxicity and neutrophil chemiluminescence in human cells in vitro (Denning and Webster 1987). The authors suggest that propylene glycol has cytotoxic properties, and should be evaluated in light of this information.

Neurological Effects. Mild neurological effects have been observed in dermally sensitive individuals after an oral challenge dose of 2-15 mL of propylene glycol (Hannuksela and Forström 1978). In the case of ingestion of a large amount of propylene glycol, neurotoxic symptoms including stupor and repetitive convulsions were noted (Lolin et al. 1988). Neurological effects were also noted in patients receiving 887 mg/kg propylene glycol 3 times daily, but those effects were complicated by co-ingestion of ethanol (Yu et al. 1985). Adverse effects have also been observed in rats prior to death (Clark et al. 1979), and in cats (Christopher et al. 1990b). Based on these data, however, it seems unlikely that low level exposure to propylene glycol would cause neurotoxicity.

Reproductive Effects. Studies in humans have not addressed whether propylene glycol adversely affects the reproductive system. In rats and mice, no adverse effects on the reproductive competence of these animals were observed after oral treatment as high as 10,000 mg/kg/day during gestation, or inhalation exposure to 112 ppm for 18 months (Kavlock et al. 1987; NTP 1985; Robertson et al. 1947).

Developmental Effects. Specific in vivo studies have not addressed the developmental toxicity of propylene glycol in humans or animals. In vitro studies of embryonic development suggest that propylene glycol alters the development of mouse zygotes (Damien et al. 1989, 1990). Treatment with propylene glycol caused cell membrane damage and altered pH, resulting in a decrease in embryonic development.

Genotoxic Effects. Studies in humans or animals have not addressed whether adverse genotoxic effects occur after *in vivo* exposure to propylene glycol. Propylene glycol was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (Clark et al. 1979; Pfeiffer and Dunkelberg 1980). Propylene glycol was negative for sister chromatid exchange and changes in alkaline elution rate using Chinese hamster cells or human fibroblasts (Sasaki et al. 1980 as cited in Abe et al. 1982; Swenberg et al. 1976). A summary of genotoxic data for propylene glycol is presented in Table 2-4.

Cancer. There is no evidence that propylene glycol is carcinogenic in humans or animals.

The National Toxicology Program (NTP) has not classified propylene glycol as a carcinogen. The EPA (IRIS 1995) has not assigned propylene glycol a weight-of-evidence classification.

2.5 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).

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). Biomarkers of exposure have been used by industrial hygienists in limited instances as evidence of exposure to certain chemicals. 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

Table 2-4. Genotoxicity of Propylene Glycol *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Clark et al. 1979
	Gene mutation	–	–	Pfeiffer and Dunkelberg 1980
Mammalian cells				
Human fibroblasts	Chromosome aberrations	–	–	Sasaki et al. 1980
Chinese hamster cells	Chromosome aberrations	–	–	Sasaki et al. 1980
Chinese hamster lung cells	DNA damage	–	–	Swenberg et al. 1976

– = negative result

substance and all of its metabolites may have left the body by the time biologic 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 propylene glycol are discussed in Section 2.4.1.

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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect have been used by clinicians to guide them in diagnoses and treatment. Biomarkers of effects caused by propylene glycol are discussed in Section 2.4.2.

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, biologically effective dose, or target tissue response. Biomarkers of susceptibility may be defined, for all practical purposes, as the susceptibility of the individual, relative to its own population. If biomarkers of susceptibility exist, they are discussed in Section 2.6, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Propylene Glycol

Propylene glycol can also be detected in the blood a short time after exposure to a large amount. There are no other specific biomarkers for propylene glycol exposure. Since propylene glycol is considered a safe additive for food, cosmetics, and pharmaceuticals, other specific tests of propylene glycol exposure have not been developed.

2.5.2 Biomarkers Used to Characterize Effects Caused by Propylene Glycol

Propylene glycol is not associated with any specific biomarkers of effect. Dermal irritation may occur after repeated exposure, and suspect drug or cosmetic preparations should be examined closely for propylene glycol content.

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.6 INTERACTIONS WITH OTHER CHEMICALS

In the first step of biotransformation, propylene glycol is catalyzed by alcohol dehydrogenase. 4-Methyl pyrazole is an inhibitor of propylene glycol metabolism (Morshed et al.1988). 4-methyl pyrazole may reduce potential toxic effects of propylene glycol and act as an antidote by interfering with the biodegradation of propylene glycol.

Review of the literature regarding the interaction and influence of other chemicals on the toxicity of propylene glycol revealed that propylene glycol is often used as a vehicle for administration of certain medications such as Valium, Dilantin, Nembutal (Kelner and Bailey 1985), dihydrotachysterol (DHT) (Arulanantham and Genel 1978), Ketoconazole cream (Eun and Kim 1989), and Enoximone (Huggon et al. 1990). Among the observed effects were seizures and cerebral irritability (DHT), increased serum lactate (Valium, Dilantin, and Nembutal), increased serum osmolality (Enoximone), and skin allergy (Ketoconazole cream). All these adverse effects are attributed to propylene glycol and associated with the prolonged administration of these medications using propylene glycol as the vehicle. However, the precise interaction between propylene glycol and these medications was not investigated.

In rats, hexobarbital-induced sleeping time was prolonged in the presence of propylene glycol (Dean and Stock 1974), probably because of competition for drug-metabolizing enzymes. Studies in rabbits have shown that propylene glycol inhibited the elimination of 8-chlorotheophylline and dimenhydrinate from the blood, due to a diminished metabolism of the two drugs (Walters et al. 1993).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to propylene glycol compared to most persons exposed to the same level of propylene glycol in the environment. Reasons include genetic makeup, developmental stage, health and nutritional status, and chemical exposure history. These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or compromised function of target organs. For these reasons, the elderly with declining organ function, people with unusual chemical exposure history, heavy users of alcohol, and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances

than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

No information was found on populations with unusual sensitivity to propylene glycol. However, populations that may show increased sensitivity include very young children, who have immature hepatic detoxification systems, and individuals with impaired liver or kidney function. Studies of burn patients indicate the absorption of propylene glycol from antibiotic preparations can be correlated with total bum surface area and the severity of the bum (Kulick et al. 1985). Thus, burn patients may be at a higher risk for possible adverse effects of propylene glycol. In addition, propylene glycol has been found in the blood of alcoholics with cirrhosis of the liver, in the absence of measurable blood alcohol (Casazza et al. 1987). Thus, alcoholics with liver disease may comprise a population that is unusually susceptible to the effects of propylene glycol.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

2.8.1 Reducing Peak Absorption Following Exposure

No studies on reducing peak absorption of propylene glycol after inhalation exposure were found. The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract after oral exposure is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure, while the elimination half-life is about 4 hours. The total body clearance is about 0.1 L/kg/hour and seems to be serum concentration dependent (Yu et al. 1985). Dose-dependent elimination is seen in rats, with saturation of the pathways at doses above 5,880 mg/kg (Morshed et al. 1988). However, no studies on reducing peak absorption following oral exposure were found.

Studies on the dermal absorption of propylene glycol in rats indicate that absorption into the dermis is enhanced by the addition of fatty acids (Takeuchi et al. 1993, 1995). Thus, cleaning of the skin with a defatting solvent, followed by washing with water, may reduce absorption of propylene glycol after dermal exposure.

2.8.2 Reducing Body Burden

No methods for reducing the body burden of propylene glycol after inhalation, oral, or dermal exposure were found.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Toxicity studies of propylene glycol in laboratory animals can be found in the literature, but findings of adverse effects are rare. Clinical studies in the literature consist of infrequent sensitivity reactions, primarily to drug preparations, where pre-existing conditions requiring the drug come into play. There are two main reasons for that: 1) propylene glycol biodegradation proceeds via lactate to pyruvate in human metabolism, and 2) a significant amount of propylene glycol is excreted unchanged or as glucuronide conjugate via the renal pathway (Hannuksela and Forström 1978). Propylene glycol exhibits few of the toxic properties of ethylene glycol. Since, however, it does cause metabolic acidosis, albeit to a lesser extent that ethylene glycol, correction of the acid-base imbalance would also be helpful in preventing subsequent effects.

2.9 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 propylene glycol 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 propylene glycol.

The following categories of possible data needs have been identified by scientists from ATSDR. 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 fulfilled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be prepared.

2.9.1 Existing Information on Health Effects of Propylene Glycol

Existing information on health effects of propylene glycol is shown in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of propylene glycol, respectively. 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

Figure 2-4. Existing Information on Health Effects of Propylene Glycol

	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

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.

There is very little data on health effects of propylene glycol in humans. No data for humans were found for inhalation exposure of humans. Data exist for inhalation exposure of animals for acute-, intermediate-, and chronic-duration exposure.

Some acute oral data exist for humans, but the information is scanty and includes systemic, and neurological effects after acute exposure. Propylene glycol is considered GRAS by the FDA, and thus oral exposure through foods is considered safe. With respect to this, animal data for oral exposure are more extensive, and all categories of health effects except *in vivo* genotoxicity are included.

Propylene glycol is used extensively in topical drug formulations and cosmetics. The majority of reports of human dermal studies describe sensitivity reaction (or, lack of reaction) to these preparations. Human dermal data includes acute-duration effects, and immunological and neurological effects. Animal data describing dermal exposure are limited to acute-duration effects and an evaluation of immunological and neurological effects.

People living near hazardous waste sites or near sites where propylene glycol is manufactured may be exposed to propylene glycol by ingestion of contaminated water. Since propylene glycol is an approved food additive, ingestion of small amounts would not be considered a health risk. Inhalation exposure is not a likely route for toxic health effects. Dermal exposure to propylene glycol has been associated with sensitivity reactions, although the data are confusing. Increased use of propylene glycol in foods and cosmetics, and as a substitute for ethylene glycol suggests that general exposure to propylene glycol will be more frequent and at higher levels than previously experienced by the general population. Therefore, additional research in these areas may be warranted.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. No information was available for acute-duration inhalation exposure to propylene glycol in humans. Only one study in animals was found to provide some information for acute-duration inhalation exposure (Konradova et al. 1978). Rabbits were exposed to only one dose (10%

aerosol) of propylene glycol for 20 or 120 minutes, and an increased number of degenerated goblet cells in the tracheal lining was observed. No other data were available from this study and the importance of these findings is unclear. Information regarding acute-duration oral exposure to propylene glycol in humans (Frosch et al. 1990; Hannuksella and Forstrom 1978; Lolin et al. 1988; Nelson et al. 1987) and animals is more abundant (Clark et al. 1979; Dorman and Haschek 1991; Kavlock et al:1987; Morshed et al. 1991a; Ruddick 1972; Studer et al. 1993; Weiss et al. 1992). Acute-duration dermal exposure to propylene glycol in humans (Commens 1990; Corazza et al. 1993; Eun and Kim 1989; Fligner et al. 1985; Kinnunen and Hannuksela 1989; Kulick et al. 1985; Willis et al. 1988) and animals has been reported (Clark et al. 1979), although data are scarce.

Death has been shown to occur after acute-duration oral exposure to propylene glycol (Clark et al. 1979; Dorman and Haschek 1991; Gordon and Hunter 1982; Ruddick 1972). With the exception of hematological effects in cats after oral exposure (Weiss et al. 1992), there does not appear to be a target system for propylene glycol effects. Sensitization reactions have been reported in humans after acute-duration dermal exposure (Corazza et al. 1993; Hannuksella and Forstrom 1978).

No acute-duration inhalation MRL could be derived for propylene glycol because no adequate studies were found. In the single acute-duration inhalation study found in the literature (Konradova et al. 1978), only one dose was used, and sufficient information was not provided on which to base and MRL. No acute-duration oral MRL could be derived for propylene glycol because no adequate studies were found. With regard to the human studies (Frosch et al. 1990; Hannuksella and Forstrom 1978; Lolin et al. 1988; Nelson et al. 1987), only one dose was tested, data were sparse, or the exact dose was not known. Acute-duration oral studies in animals focused on death (Clark et al. 1979; Ruddick 1972), involved a single dose (Dorman and Haschek 1991; Kavlock et al 1987; Morshed et al. 1991a; Studer et al. 1993), or discussed species-specific effects (Weiss et al. 1992). Thus, none of these studies were adequate for deriving an MRL.

Intermediate-Duration Exposure. No studies of intermediate-duration inhalation exposure of humans to propylene glycol were found. One intermediate-duration inhalation study of propylene glycol in rats was found in the literature (Suber et al. 1989). No studies of intermediate-duration oral exposure of humans to propylene glycol were found. Studies of intermediate-duration oral exposure of animals were more abundant (Bauer et al. 1991; Christopher et al. 1989a; Morshed et al. 1991a; NTP 1985; Weiss et al. 1990). No studies of intermediate-duration dermal exposure to propylene glycol were found in animals.

One intermediate-duration dermal exposure study in humans described primarily dermal irritative effects of propylene glycol (Trancik and Maibach 1982).

No reports of death in animals after intermediate-duration exposure to propylene glycol were found. Systemic effects after inhalation exposure of rats included nasal hemorrhaging, hematological effects, and decreased kidney and body weight (Suber et al. 1989). Cats exhibit characteristic hematotoxicity (Heinz body formation) after intermediate-duration oral exposure (Bauer et al. 1991; Christopher et al. 1989a; Weiss et al. 1990), although no other targets for toxicity were apparent.

An intermediate-duration inhalation MRL was derived for propylene glycol based on nasal hemorrhaging in rats (Suber et al. 1989). No intermediate-duration oral MRL could be derived due to a lack of suitable studies. Of the intermediate-duration oral exposure studies found, none were in humans; animal studies included species-specific effects in cats (Bauer et al. 1991; Christopher et al. 1989a; Weiss et al. 1990), studies with a single dose (Morshed et al. 1991a), or studies with no adverse effects observed (NTP 1985).

Chronic-Duration Exposure and Cancer. No chronic-duration studies of human exposure to propylene glycol alone by inhalation, oral, or dermal administration were found in the literature. One study of chronic-duration inhalation exposure of animals (Robertson et al. 1947), and one study of dermal exposure of animals (Stenback and Shubik 1974) were found. Data for chronic-duration oral exposure of animals to propylene glycol is more abundant (Gaunt et al. 1972; Morris et al. 1942; Weil et al. 1971). Tumorigenesis was evaluated after inhalation and dermal exposure (Robertson et al. 1947; Stenback and Shubik 1974).

After inhalation exposure to propylene glycol for 13 months, 13 of 29 rhesus monkeys died (Robertson et al. 1947). Death was not observed in rats or dogs after exposure to oral doses of propylene glycol of 2,500 or 5,000 mg/kg/day, respectively, for 2 years (Gaunt et al. 1972; Weil et al. 1971). No reports of death after dermal exposure were found. Systemic effects noted after inhalation. exposure of animals to propylene glycol were few, and included increased hemoglobin in monkeys and increased body weight in rats (Robertson et al. 1947). Similarly, only hematological effects, including decreased erythrocytes, hemoglobin, and hematocrit were observed in dogs at 5,000 mg/kg/day (Weil et al. 1971).

No evidence of tumorigenesis was noted after oral exposure of rats to doses of propylene glycol up to 2,500 mg/kg/day for 2 years (Gaunt et al. 1972), or dermal exposure of mice to 20 mg applied twice weekly for 120 weeks (Stenback and Shubik 1974).

No MRLs for chronic-duration inhalation exposure to propylene glycol could be derived due to a lack of appropriate studies in the literature. No studies were found for humans, and in the one animal study found (Robertson et al. 1947), the effects cited (increased hemoglobin and body weight) were not appropriate effects on which to base an MRL. No MRLs for chronic-duration oral exposure to propylene glycol could be derived due to a lack of appropriate studies in the literature. In the one study found (Gaunt et al. 1972), no adverse effects were noted.

Immunological and Lymphoreticular Effects. Since propylene glycol is used in topical formulations, it has been investigated as both an irritant and contact allergen (Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Tranick and Maibach 1982; Willis et al. 1988). Results indicate that except in rare cases (Corrazza et al. 1993; Hannuksela et al. 1975; Trancik and Maibach 1982) the irritative properties of propylene glycol are minimal (Aberer et al. 1993; Hannuksela and Forström 1978; Willis et al. 1989). There was no effect on the spleen in rats or monkeys exposed to 112 ppm aerosolized propylene glycol for up to 18 months (Robertson et al. 1947; Suber et al. 1989).

Propylene glycol in a concentration of 0.5-1.0% has been shown to inhibit natural cytotoxicity and neutrophil chemiluminescence in human cells in vitro (Denning and Webster 1987). The authors suggest that propylene glycol has cytotoxic properties and should be evaluated in light of this information.
The data describing the immunotoxicity of propylene glycol is not clear. Further in vivo animal studies would be helpful in defining the immunotoxic effects of propylene glycol.

Neurological Effects. Mild neurological effects have been observed in dermally sensitive individuals after an oral challenge dose of 2-15 mL of propylene glycol (Hannuksela and Forström 1978). In the case of ingestion of a large amount of propylene glycol, neurotoxic symptoms including stupor and repetitive convulsions were noted (Lolin et al. 1988). Neurological effects were also noted in patients receiving 887 mg/kg propylene glycol 3 times daily, but those effects were complicated by co-ingestion of ethanol (Yu et al. 1985). Adverse effects have also been observed in rats prior to death (Clark et al. 1979) and in cats (Christopher et al. 1990b). Based on these data, however, it seems unlikely that low level exposure to propylene glycol would cause neurotoxicity. Further studies of the neurological effects of propylene glycol would be helpful in defining the toxicity of the compound.

Genotoxicity. Although propylene glycol has been extensively evaluated in genetic toxicity test systems, the existing studies provide convincing evidence that it is not genotoxic.

Studies in humans or animals have not addressed whether adverse genotoxic effects occur after in vivo exposure to propylene glycol. However, propylene glycol was not mutagenic in S. typhimurium strains with and without metabolic activation (Clark et al. 1979; Pfeiffer and Dunkelberg 1980). In addition, propylene glycol was negative for sister chromatid exchange and changes in alkaline elution rate using Chinese hamster cells or human fibroblasts (Sasaki et al. 1980 as cited in Abe et al. 1982; Swenberg et al. 1976). Based on these results, it seems likely that propylene glycol does not represent a genotoxic risk to exposed persons. An in vivo study would complete the database of the genotoxic effects of propylene glycol.

Reproductive Toxicity. Studies in humans have not addressed whether propylene glycol adversely affects the reproductive system. In rats and mice, no adverse effects on the reproductive competence of these animals were observed after oral treatment at doses as high as 10,000 mg/kg/day during gestation of 1 generation or for multiple litters and 2 generations of mice (Kavlock et al. 1987; NTP 1985) or inhalation exposure to 112 ppm for 18 months (Robertson et al. 1947). Further evaluation of the reproductive toxicity of propylene glycol is not necessary.

Developmental Toxicity. Propylene glycol does not appear to be a developmental toxicant in animals. Pregnant female Swiss mice given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 showed no adverse developmental effects (Kavlock et al. 1987). No adverse effects of propylene glycol on the development of Swiss (CD-l) mice were noted after doses of approximately 10,000 mg/kg/day (NTP 1985). In vitro studies of embryonic development suggest that propylene glycol alters the development of mouse zygotes (Damien et al. 1989, 1990). Treatment with propylene glycol caused cell membrane damage and altered pH, resulting in a decrease in embryonic development. The relevance of these results to in vivo exposure is not clear. Further studies of developmental toxicity of propylene glycol do not appear to be necessary.

Epidemiological and Human Dosimetry Studies. No reliable epidemiological studies of propylene glycol exposure are available. Increased use of propylene glycol in food and in drugs and cosmetics suggests that oral and dermal exposures are the most important routes of exposure for the general population. In addition, the substitution of propylene glycol in applications where ethylene glycol

was previously used will create new subpopulations for exposure. Epidemiological and human dosimetry studies of these subpopulations would be helpful in evaluating propylene glycol toxicity in these increased applications of use.

Biomarkers of Exposure and Effect.

Exposure. Propylene glycol can be detected in the blood a short time after exposure to a large amount. There are no other specific biomarkers for propylene glycol exposure. Since propylene glycol is considered a safe additive for food, cosmetics, and pharmaceuticals, other specific tests of propylene glycol exposure have not been developed. Further evaluation of possible biomarkers of exposure to propylene glycol would be helpful, especially in light of increased use of propylene glycol in food, cosmetics, and drugs.

Effect. Propylene glycol is not associated with any specific biomarkers of effect. Dermal irritation may occur after repeated exposure, and suspect drug or cosmetic preparations should be examined closely for propylene glycol content. In light of the increased use of propylene glycol in foods, cosmetics, and drugs, identification of biomarkers of propylene glycol effect would be useful in evaluating biological effects of propylene glycol exposure.

Absorption, Distribution, Metabolism, and Excretion. No kinetic data for absorption, distribution, metabolism, or excretion in humans or animals of propylene glycol after inhalation exposure were found in the literature. Few data were found in the literature describing the kinetics of propylene glycol in humans after oral exposure (Yu et al. 1985), but more data were found for animals (Christopher et al. 1990b; Huff 1961; Miller and Bazzano 1965; Morshed et al. 1988, 1989, 1991 a). Since propylene glycol is used in topical drug preparations, limited data are available for kinetic parameters in humans after dermal exposure (Fligner et al. 1985; Kulick et al. 1985; Rigg and Barry 1990), and in animals (Rigg and Barry 1990; Takeuchi et al. 1993, 1995). Most of these data concern acute exposures and are limited because propylene glycol is considered a safe and innocuous compound. No data were located regarding kinetic parameters of propylene glycol after inhalation exposure. Studies are needed in order to adequately assess the rates and extent of the toxicokinetic parameters for this route. In light of increased use of propylene glycol as a food additive, and in cosmetics and topically applied drugs, additional studies of the absorption, distribution, metabolism, and excretion of propylene glycol after oral and dermal exposure for acute-, intermediate-, and chronic-duration exposure would be helpful in assessing the kinetic properties of the compound by these routes.

Comparative Toxicokinetics. The kinetics of propylene glycol have been studied in animals (Morshed et al. 1988; Rigg and Barry 1990; Takeuchi et al. 1993, 1995) and to a lesser extent in humans (Fligner et al. 1985; Kulick et al. 1985; Rigg and Barry 1990; Yu et al. 1985). However, information on the toxicokinetic properties of propylene glycol are limited, based on its nontoxic status. No specific target organs have been identified for propylene glycol, although neurological effects have been noted after oral exposure (Clark et al. 1979; Hannuksela and Forström 1978; Lolin et al. 1988; Yu et al. 1985). Propylene glycol also causes metabolic acidosis, although to a lesser extent than ethylene glycol (Lolin et al. 1988; Morshed et al. 1989, 1991b). Little data exist to assist in interspecies comparison of kinetic parameters. In light of increased use of propylene glycol in foods, cosmetics, and drugs, and as a substitute for ethylene glycol, additional inhalation, oral, and dermal kinetic studies would be helpful in predicting human kinetic response to propylene glycol exposure.

Methods for Reducing Toxic Effects. No studies related to reducing absorption of propylene glycol after inhalation or oral exposure were found. Studies on the dermal absorption of propylene glycol in rats indicate that absorption into the dermis is enhanced by the addition of fatty acids (Takeuchi et al. 1993, 1995). Thus, cleaning of the skin with a defatting solvent, followed by washing with water, may reduce absorption of propylene glycol after dermal exposure.

Toxicity studies of propylene glycol in laboratory animals can be found in the literature, but findings of adverse effects are rare. Clinical studies in the literature consist of infrequent sensitivity reactions, primarily to drug preparations, where pre-existing conditions requiring the drug come into play. There are two main reasons for that: 1) propylene glycol biodegradation proceeds via lactate to pyruvate in human metabolism, and 2) a significant amount of propylene glycol is excreted unchanged or as glucuronide conjugate via the renal pathway (Hannuksela and Forström 1978). Propylene glycol exhibits few of the toxic properties of ethylene glycol. Since it does cause metabolic acidosis, although to a lesser extent that ethylene glycol, correction of the acid-base imbalance would also be helpful in preventing subsequent effects, and the same therapies that are useful in preventing ethylene glycol acidosis would also be useful for propylene glycol. Since propylene glycol is significantly less toxic than ethylene glycol, extensive study of methods to reduce the possible toxic effects of exposure does not seem warranted.

2.9.3 Ongoing Studies

The following ongoing studies regarding the health effects of propylene glycol were reported .in the Federal Research in Progress File (FEDRIP 1995) database and in recent literature:

Regulation of Lipid Metabolism in High Producing Dairy Cattle. The principal investigator is R. Grummer from the University of Wisconsin School of Dairy Science in Madison, Wisconsin. The objective is to determine the regulation of lipid metabolism in adipose tissue, liver and mammary glands of high producing dairy cattle. Propylene glycol will be used for reducing plasma nonesterified fatty acids during feed restriction.

Modifying Milk Fat Composition for Improved Manufacturing Qualities and Consumer Acceptability. The principal investigator is D. Palmquist from Ohio State University School of Animal Sciences in Wooster, Ohio. The objective is to identify and characterize important regulatory steps in fatty acid synthesis and desaturation and their positional distribution on glycerol in milk fat, and to quantify modification of milk fat composition by manipulating the diet of the cow. Propylene glycol will be used as an oral drench to modify energy balance.

Microbial Safety Criteria for Foods Contacting Reuse Water in Food. The principal investigator is A. Miller from the Eastern Regional Research Center in Wyndmoor, Pennsylvania. The objective is to identify microbiological risks to food by reuse water during slaughter and further processing, to study bacterial attachment mechanisms and develop approaches to dislodge or prevent adhesion of pathogens to food surfaces, and to investigate the potential for expanded applications of reuse water to the food plant environment. Propylene glycol will be evaluated in the control of microbial growth.

The Effect of Vitamin E on the Propylene Glycol-Induced Formation of Heinz Bodies. The principal investigator is Diane Hatchell from the Department of Veterans Affairs Medical Center, Durham, North Carolina. The objective is to test the efficacy of vitamin E as a means of inhibiting the propylene glycol-induced formation of Heinz bodies in cat blood.

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3. CHEMICAL AND PHYSICAL INFORMATION

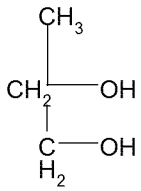
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of propylene glycol is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of propylene glycol is located in Table 3-2.

Table 3-1. Chemical Identity of Propylene Glycol[a]

Characteristic	Information
Chemical name	Propylene glycol
Synonyms and trade names	1,2-Dihydroxypropane; 1,2-propanediol; 1,2-propylene glycol; 2,3-propanediol; hydroxy-propanol; alpha-propylene glycol; methyl glycol; methylethyl glycol; monopropylene glycol; trimethyl glycol.
Registered trade name(s)	PG-12; Sirlene
Chemical formula	$C_3H_8O_2$
Chemical structure[b]	
Identification numbers:	
CAS registry	57-55-6
NIOSH RTECS	TY2000000
EPA hazardous waste	No data
OHM/TADS	7216877
DOT/UN/NA/IMDG shipping	No data
HSDB	174
NCI	No data

[a]All information obtained from HSDB 1994b, except where noted.
[b]EPA 1987a

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances 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 Propylene Glycol[a]

Property	Propylene glycol
Molecular weight	76.11[b]
Color	Colorless[d]
Physical state	Liquid[b]
Melting point	-60 °C[e,b] (forms glass)
Boiling point	187.6; 188.2 °C[b]
Density:	
at 20 °C (g/cm^3)	1.0361[c]
Odor	Odorless
Odor threshold	No data
Solubility:	
Water at 20 °C	Miscible with water
Organic solvent(s)	Soluble in alcohol, ether, benzene, soluble in acetone, chloroform[b].
Partition coefficients:	
Log K_{ow}	-0.92[f,g]
Log K_{oc}	0.88[f], 0.76[g]
Vapor pressure at 20 °C	0.07 mm Hg[also d]
Henry's law constant at 25 °C	1.2×10^{-8} atm-m^3/mole; 1.7×10^{-8} atm-m^3/mole[g]
Autoignition temperature	421.26 °C[h]; 371 °C[i]
Flashpoint	99.04 °C[h,i]
Flammability limits	2.6–12.5%[h,i]
Conversion factors	1 ppm = 3.11 mg/m^3[j] 1 mg/L = 321.6 ppm[j]
Explosive limits	No data

[a]All information obtained from HSDB 1995b, except where noted.
[b]Merck 1989
[c]Weast 1988
[d]Lewis 1993
[e]Daubert and Danner 1980
[f]EPA 1987a
[g]ASTER 1995
[h]Daubert and Danner 1989
[i]NFPA 1994
[j]Rowe and Wolf 1982

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4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Propylene glycol is produced commercially from the hydration of propylene oxide (Merck 1989). Propylene glycol also is produced by the liquid-phase high pressure reaction (600 atmospheres) of synthetic gas in the presence of a rhodium cluster complex (Kirk-Othmer Encyclopedia of Chemical Technology 1978).

The companies that produce propylene glycol in the United States, their production sites, and the annual capacities in millions of pounds for 1993 (the most recent year for which figures are available) are shown below (SRI 1993).

Company	Production Site	Capacity
ARCO Chemical Company	Bayport, TX	374
Dow Chemical USA	Freeport, TX	250
	Plaquemine, LA	150
Eastman Chemical Company	South Charleston, WV	72
Olin Corporation	Brandenburg, KY	70
Texaco Chemical Company	Port Neches, TX	120
Total Production		**1,036**

Over the past few years, production of propylene glycol has remained relatively constant at a level of approximately 1,000 million pounds per year (SRI 1989, 1991, 1993, 1995). The production volumes were 935, 1,000, 980, and 1,036 million pounds in 1989, 1991, 1993, and 1995, respectively.

There is no information on facilities that manufacture or process propylene glycol in the United States available in the Toxic Release Inventory because information on this chemical is not required to be reported (EPA 1995c).

4.2 IMPORT/EXPORT

Propylene glycol has been imported into the United States in ever increasing quantities over the last several years. Import volume increased from 198,031 kg (0.4 million pounds) in 1992, to 2,167,664 kg (4.8 million pounds) in 1993, to 5,249,265 kg (11.6 million pounds) in 1994 (NTDB 1995).

Propylene glycol also has been exported over the last several years with export volume greatly exceeding the import volume in any given year. Export volume for propylene glycol has declined slightly since 1990, but has averaged 77,000,000 kg per year (170 million pounds per year). Export volumes for propylene glycol were 94,606,830 kg (209 million pounds), 64,850,502 kg (143 million pounds), 62,940,802 kg (139 million pounds), 81,531,357 kg (180 million pounds), and 78,997,747 kg (174 million pounds) in 1990, 1991, 1992, 1993, and 1994, respectively (NTDB 1995).

4.3 USE

Propylene glycol has been used extensively in many different industrial applications because of its chemical and physical properties. Propylene glycol dissolves in water and is miscible with alcohol, acetone, chloroform, and other organic solvents; has the capacity to hold large amounts of heat before boiling; and lowers the freezing point of water (EPA 1987a; Lewis 1993). In addition, propylene glycol is hygroscopic, is suitable for use as an industrial humectant, and possesses excellent solvent properties (Lewis 1993; Merck 1989; Rowe and Wolf 1982). Approximately 41% of all propylene glycol produced is used for unsaturated polyester resin production, 29% is exported, 11% is used in foods, pharmaceutical products, and cosmetics, 7% is used in semi-moist pet food, 4% is used as a humectant for tobacco, 4% is used in functional fluids, and 4% is for miscellaneous uses (HSDB 1995b).

The major use of propylene glycol is as an intermediate in the manufacture of cross-linked polyesters and hydroxylated polyester resins. In the airline industry, ethylene glycol has been used as a base component of de-icing fluids for aircraft, runways, and taxiways (Klecka et al. 1993; Kirk-Othmer Encyclopedia of Chemical Technology 1978). Propylene glycol is a solvent and humectant for various pharmaceuticals, hair colorant formulations, and food and tobacco products (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Merck 1989). In addition, the use of small amounts of propylene glycol is permitted in foods as an anticaking agent, antioxidant, dough strengthener, emulsifier, processing aid, stabilizer and thickener, surface active agent or texturizer (EPA 1979). In veterinary medicine, propylene glycol is used in oral medications for ruminants and as a solvent for various drugs (Merck 1983). As a nontoxic antifreeze, propylene glycol is used in breweries and dairy establishments and as an inhibitor of fermentation and mold growth (Merck 1989). The chemical has been used as an emollient in pharmaceutical and cosmetic creams because it readily absorbs water. Propylene glycol has even been used in vapor form as an air sterilizer in hospitals and public buildings, and in veterinary applications to protect animals against the spread of airborne bacteria and influenza virus (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Rowe and Wolf 1982). Used as a mist, propylene glycol is deployed as a

special effect fog/smoke during theatrical performances, rock concerts, private parties, and in fire training programs to simulate fire fighting conditions (Rossol 1993).

4.4 DISPOSAL

Propylene glycol is currently listed as a Generally Recognized as Safe (GRAS) additive in foods (FDA 1982) and is not listed as a toxic substance under Section 313 of the Emergency Planning and Community Right-to Know Act under Title III of the Superfund Amendments and Reauthorization Act (EPA 1995c).

Two methods for treatment of waste water containing propylene glycol include a methane fermentation process and a newly developed biotreatment process that uses mixed cultures of bacteria to degrade the compound. The methane fermentation process has proven to be a reliable as well as cost and energy efficient method for the treatment of domestic sludges and certain industrial waste water containing propylene glycol and other organic compounds (Chou et al. 1979). Propylene glycol in effluents from propylene oxide production plants contains both high biological oxygen demand/chemical oxygen demand (BOD/COD) loads and high chloride concentrations. The high salinity poses problems to waste water treatment such as activated sludge and activated carbon absorption processes A novel and economically viable propylene glycol biotreatment process recently has been developed that uses a mixed culture of engineered bacterial species from the genera *Pseudomonas* and *Aerobacter*. The *Pseudomonas* use propylene glycol to produce volatile acids, while *Aerobacter* were effective in degrading the volatile acids to carbon dioxide and water (Raja et al. 1991).

A new encapsulated biooxidation method has shown potential for the remediation of soil contaminated with propylene glycol (Vesper et al. 1994). The encapsulated biooxidation method proposes that sodium percarbonate encapsulated in polyvinylidene chloride be inserted in subsurface soil by a method called hydraulic fracturing. Oxygen slowly released from the encapsulated sodium percarbonate increases the number of glycol-degrading organisms. In a laboratory experiment conducted over a 30-day period at 12 °C that simulated subsurface soil temperatures, the concentration of propylene glycol was reduced lo-fold and the number of propylene glycol degrading organisms increases 10-fold compared to live controls without the encapsulated sodium percarbonate. This method is expected to remediate soils contaminated with glycols via enhanced aerobic biodegradation in subsurface soils. The hydraulic fracturing technique that would be used to deliver the encapsulated sodium percarbonate to the subsurface soils involves creating horizontal pancake-shaped fractures that are 5 meters in diameter and 1-2 cm in thickness. These fractures are stacked vertically in the subsoil, and granular material is injected into each fracture (Vesper

et al. 1994). The advantage of this method is that oxygen can be delivered deep into contaminated subsurface soil and then made available slowly to stimulate bacterial growth.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Propylene glycol is released to the environment in manufacturing and processing waste streams and as the result of disposal of industrial and consumer products containing this compound. The major sources of releases are from the use and disposal of this compound in de-icing solutions. Because of its solubility in water and lack of adsorption and partitioning to soils, propylene glycol will have high mobility in soil and potential to leach into groundwater. Upon release to the environment, the compound is expected to partition to and be transported in surface water and groundwater. Propylene glycol is rapidly degraded in all environmental media; it is not expected to persist or bioaccumulate in aquatic organisms. Biodegradation is the most important transformation process in surface waters and soils. Assuming first order kinetics, the half-life of propylene glycol in water is estimated to be 1-4 days under aerobic and 3-5 days under anaerobic conditions. The half-life of propylene glycol in soil is expected to be equal to or slightly less than that for water. Vapors released to the atmosphere readily undergo rapid photochemical oxidation via reaction with hydroxyl radicals with an estimated half-life of 0.8 days. Little information was found on concentrations of this compound in any environmental media. Propylene glycol is a Generally Recognized as Safe (GRAS) food additive that is widely used in food and tobacco products, pharmaceuticals, and cosmetics.

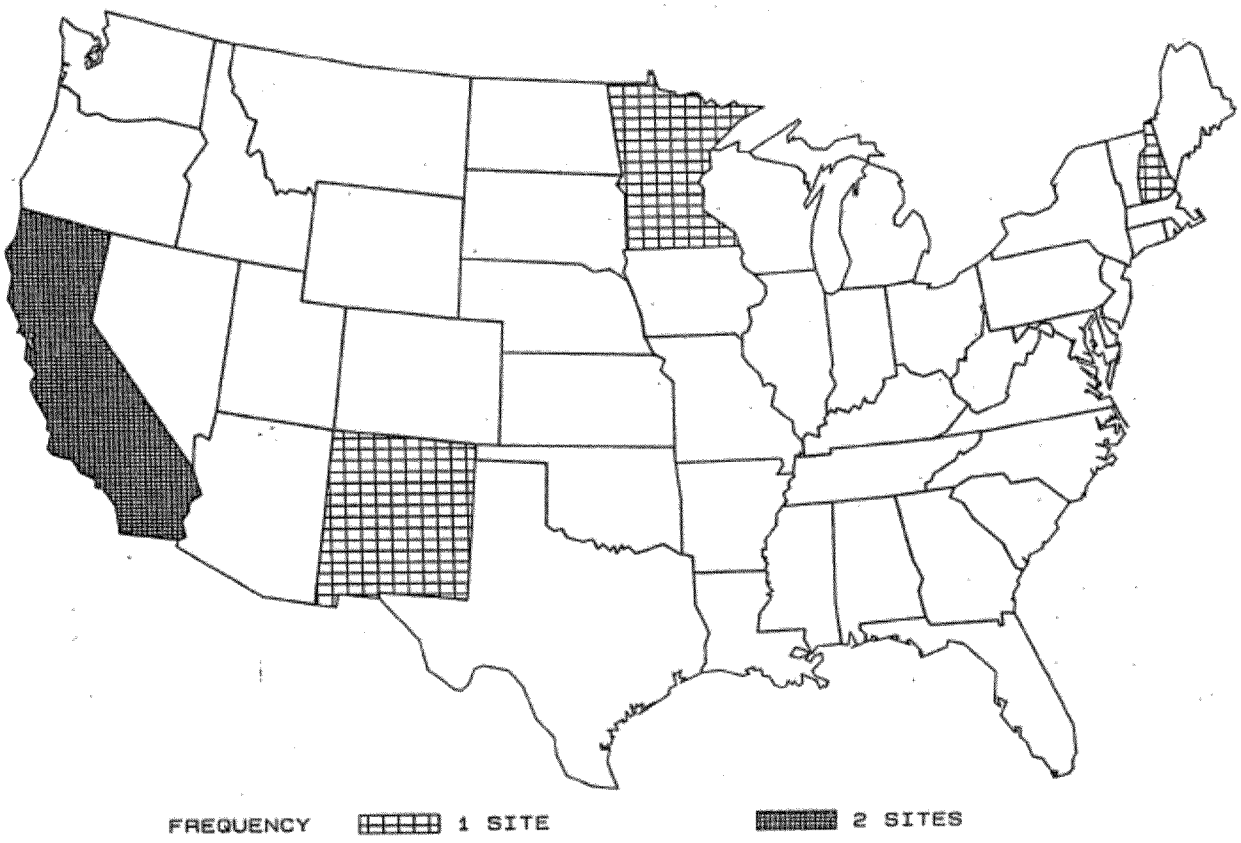
The most important routes of exposure to propylene glycol for members of the general population are ingestion and dermal contact with products containing this compound. The general public also may be exposed to small amounts of propylene glycol released from newly installed carpet with polyvinyl backing. In occupational settings, workers are exposed via dermal contact and possibly inhalation in applications involving the heating or spray application of fluids containing this compound.

Propylene glycol has been identified in at least 5 of 1,416 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 1995). However, the number of sites evaluated for propylene glycol is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

Releases of propylene glycol are not required to be reported under SARA Section 313; consequently there are no data for this compound in the 1993 Toxic Release Inventory (EPA 1995c). There are at least 5 NPL

Figure 5-1. Frequency of NPL Sites with Propylene Glycol Comtamination*



*Derived from HazDat 1995

hazardous waste sites where propylene glycol has been identified in some environmental media (HazDat 1995).

5.2.1 Air

Little information was found regarding the release of propylene glycol to the atmosphere. Propylene glycol used as a solvent in paints, inks, and coatings will slowly volatilize to the atmosphere (EPA 1987a). During the application of de-icing solutions to aircraft, an estimated 49-80% of de-icing solutions containing both ethylene glycol and propylene glycol are released on airport runway aprons. The remainder is retained on the aircraft or is immediately dispersed to the air (Sills and Blakeslee 1992); however, release to the atmosphere is expected to be limited by the compound's low vapor pressure.

There is no information on releases of propylene glycol to the atmosphere from domestic manufacturing and processing facilities because these releases are not required to be reported (EPA 1995c). Propylene glycol has not been detected in air samples collected at any hazardous waste sites where it was detected in some environmental media (HazDat 1995).

5.2.2 Water

Propylene glycol is released to surface waters in waste water from production and processing facilities and from spills and in runoff (e.g., through the use of the compound in de-icing fluids). Propylene glycol concentrations up to 19,000 mg/L (ppm) were detected in storm water runoff at the Salt Lake City Airport in Utah (Sills and Blakeslee 1992). Propylene glycol was detected, but the concentration was not quantified in effluents from a chemical manufacturing plant in Memphis, Tennessee (EPA 1976). Propylene glycol may also be released to surface waters as a metabolite of propylene glycol dinitrate which is a military propellant found in waste water streams from munitions facilities (EPA 1979, 1987a; Kaplan et al. 1982; Walker and Kaplan 1992).

There is no information in the Toxic Release Inventory (TRI) on releases of propylene glycol to surface or groundwater from domestic manufacturing and processing facilities because these releases are not required to be reported (EPA 1995c).

Groundwater samples collected from a perched water table at the Ottawa Airport in Canada contained 4 mg/L (ppm) of propylene glycol (Sills and Blakeslee 1992). Propylene glycol also has been detected in

groundwater samples collected at two hazardous waste sites where it was detected in various environmental media (HazDat 1995).

5.2.3 Soil

The major sources of propylene glycol releases to soil are the disposal of used antifreeze fluids and de-icing fluids containing the compounds (EPA 1979, 1987a).

There is no information in the TRI on releases of propylene glycol to soil from domestic manufacturing and processing facilities because these releases are not required to be reported (EPA 1995c). Propylene glycol has not been detected in any soil samples collected at hazardous waste sites although it has been detected in other environmental media (HazDat 1995).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Propylene glycol has a low vapor pressure (0.07 mm Hg at 20 °C) and is miscible with water (see Table 3-2). If released to the atmosphere (e.g., as vapors generated at elevated temperatures), propylene glycol should exist almost entirely in the vapor phase (Eisenreich et al. 1981). The high solubility of propylene glycol in water ensures at least partial removal of the compound will occur by wet deposition (EPA 1987a). Therefore, upon release to the environment, the compound is expected to be transported primarily in aqueous media (EPA 1979). The low Henry's law constant values for the compound ($1.2x10^{-8}$ to $1.7x10^{-8}$ atm-m^3/mole range; see Table 3-2) suggest that releases to surface water will not partition to the atmosphere via volatilization (Simmons et al. 1976; Thomas 1990). Adsorption to sediment or soil particulates is also not expected to be significant on the basis of the low K_{oc} value (see Table 3-2).

Based on the low K_{oc} value, propylene glycol is expected to have a very high mobility in soil and could leach into groundwater (Swarm et al. 1983). The low octanol/water partition coefficient (K_{ow}) (see Table 3-2) suggests that bioconcentration and biomagnification are also not likely to occur. No measured BCF values were located for this compound.

Propylene glycol is expected to be highly mobile in moist soils and may leach to groundwater upon release to surface soils; however, rapid biodegradation is expected to limit the extent of the leaching (see

Section 5.3.2) (EPA 1987a). The compound may also volatilize from dry surface soils (EPA 1979, 1987a; Hine and Mookerjee 1975).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Propylene glycol released to the atmosphere is expected to undergo rapid photochemical oxidation via reaction with hydroxyl radicals. The half-life for the photochemical oxidation of propylene glycol has been estimated to be 20-32 hours (EPA 1987a; Howard et al. 1990).

5.3.2.2 Water

Biodegradation by a variety of acclimated and unacclimated microorganisms, under both aerobic and anaerobic conditions, is the most important transformation process for propylene glycol in surface waters. The half-lives for the biotransformation of propylene glycol generally range from 1 to 4 days under aerobic conditions and from 3 to 5 days under anaerobic conditions (EPA 1987a).
Propylene glycol rapidly disappears from culture flasks containing activated sludge microorganisms under both aerobic and anaerobic conditions (Kaplan et al. 1982). Some propylene glycol was lost from sterile cultures after 9 days. An 8% and 16% loss of propylene glycol was observed in sterile anaerobic and aerobic cultures, respectively. In active cultures, propylene glycol was not detected after 2 days in aerobic nutrient broth. When used as a sole carbon source, propylene glycol disappeared after 4 days under aerobic and 9 days under anaerobic conditions. Raja et al. (1991) reported a novel biotreatment process using *Pseudomonas* and *Aerobacter* bacteria. The *Pseudomonas* were able to use the propylene glycol to produce volatile acids, while *Aerobacter* degraded the volatile acids quickly to carbon dioxide and water.

Propylene glycol is not expected to undergo significant abiotic transformation in surface waters via hydrolysis or oxidation (EPA 1979, 1987a). Glycols generally are resistant to hydrolysis (Harris 1990). For example, the half-life for reaction of propylene glycol with hydroxyl radicals in aqueous solution has been estimated to be 1.3-2.3 years (Harris 1990).

5.3.2.3 Sediment and Soil

Biodegradation by a variety of microorganisms under both aerobic and anaerobic conditions is the most important transformation process for propylene glycol in soils, with half-lives similar to or less than those in surface waters (EPA 1 987a). The soil microbe *C. glycolicum* degraded propylene glycol under anaerobic conditions to acid and alcohol end products (Gaston and Stadtman 1963). Ouattara et al. (1992) reported anaerobic degradation of propylene glycol by strains of the sulfate-reducing bacteria Desulfovibrio isolated from anoxic soil of a rice field. Propylene glycol was degraded to acetate in the presence of sulfate with the production of carbon dioxide. The rates of biodegradation of propylene glycol in soi ls are significantly dependent on substrate concentrations, soil types, and ambient soil temperatures, but nutritional supplements had minimal effects (Klecka et al. 1993). Generally, the rate of propylene glycol biodegradation was faster in soils with low glycol concentrations, high organic carbon content, and higher ambient soil temperatures (in the range of -2-25 °C). Propylene glycol present in soils at concentrations <6,000 mg/kg (ppm) biodegraded at an average rate of 2.3 mg/kg soil/day at -2 °C, 27.0 mg/kg (ppm) soil/day at 8 °C and at an average rate of 93.3 mg/kg (ppm) soil/day at 25 °C (Klecka et al. 1993). Based on these results, biodegradation is expected to play a major role in removing propylene glycol residues from soils adjacent to airport runways and taxiways.

As in surface waters, abiotic transformation of propylene glycol in soil is not expected to be a significant process (EPA 1987a).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No information was located on the concentration of propylene glycol in the ambient atmosphere. Propylene glycol was detected in air samples collected in a large scale environmental chamber analyzing volatile organic emissions. Quasi-steady-state emission rates of the propylene glycol at 24 hours and 168 hours after the start of the experiment were 690 $\mu g/m^2$/hour and 193 µg/m2/hour, respectively from newly installed carpet with polyvinylchloride backing (Hodgson et al. 1993).

5.4.2 Water

Available information on the environmental impact of de-icing solutions on airport storm water runoff has been summarized in a recent review article by Sills and Blakeslee (1992). Monitoring data from several

contractor and airport authority reports reveal that storm water runoff from airports may contain several hundred to several thousand mg/L (ppm) glycols. Propylene glycol levels up to 19,000 mg/L (ppm) were detected in storm water from the Salt Lake City International airport. Although the potential for groundwater contamination is quite low for many airports with predominantly heavy soil, the movement of glycols through unsaturated silty sand can be potentially high (Sills and Blakeslee 1992). At the Ottawa International Airport in Canada, groundwater in the perched water table, which contained sandy soil, was found to contain propylene glycol at levels up to 4 mg/L (ppm). Peak concentrations occurred in June and declined to nondetectable levels by the fall.

5.4.3 Sediment and Soil

No information was found on soil concentrations of propylene glycol.

5.4.4 Other Environmental Media

Propylene glycol has been identified in negligible amounts in the water-soluble component of cigarette smoke (Schumacher et al. 1977).

Propylene glycol has also been found to migrate into a number of foods from regenerated cellulose films containing the compound as a softening agent. The compound was detected in chocolates at 20-1,460 mg/kg (ppm) after 5.5 months of storage and at 25-1,890 mg/kg (ppm) after 15 months, in fruit cakes at 10-154 mg/kg (ppm) after 84-336 days of storage, in meat pies at <10-118 mg/kg (ppm) after 3-7 days of storage, in toffee at <10-1,530 mg/kg (ppm) after 168-450 days of storage, in madeira cake at <10-365 mg/kg (ppm) after 2 1-28 days storage, and in boiled sweets at <10-272 mg/kg (ppm) after 168-450 days storage (Castle et al. 1988a).

Propylene glycol is also used in some cosmetic and oral drug formulations and is a GRAS additive in foods (FDA 1982), where it is used as an emulsifying and plasticizing agent, humectant, surfactant, and solvent. Propylene glycol is added to foods at concentrations ranging from <0.001% in eggs and soups to up to 97% in seasonings and flavors (EPA 1979). Propylene glycol is a naturally occurring by-product in the fermentation of some beers and has been detected in the concentration range of 1.0-51.0 mg/L (ppm) in several commercially packaged beers (Williamson and Iverson 1993).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to propylene glycol primarily through ingestion of food and pharmaceutical products and through dermal contact with cosmetic products containing the compound (EPA 1979, 1 987a). The average daily dietary intake of propylene glycol in Japan, where the compound is used as a food additive stabilizer, was estimated to be 43 mg per person in 1982 (Louekari et al. 1990). Public school children and the general public who participate in fire fighting exercises/demonstrations where propylene glycol is used to simulate fire conditions are exposed to small amounts of propylene glycol (Rossol 1993). The general public is exposed to low. concentrations of propylene glycol mist from propylene glycol-containing theatrical fog/smoke used in producing special effects during theatrical performances, rock concerts, and private parties (Rossol 1993). The general public is also exposed to small concentrations of propylene glycol from carpets with polyvinyl chloride backing. The quasi-steady-state specific emission rate of propylene glycol from these carpets was calculated to be 690 µg/m2/hour at 24 hours and 193 µg/m2/hour at 168 hours after carpet installation (Hodgson et al. 1993).
NOSH estimated that about 2.5 million individuals were potentially exposed to propylene glycol in the workplace in 1970; the estimate for 1980 was 80,200 workers (HSDB 1995b). Dennal contact is expected to be the main route of worker exposure; however, inhalation of vapors or mists may also occur when the compound is heated, agitated, or sprayed (e.g., in de-icing formulations) (Rowe and Wolf 1982).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries involved in the manufacture or use of products containing high concentrations of propylene glycol (e.g., antifreeze, coolants, de-icing fluids, brakes fluids, solvents) may be exposed to concentrations of the compounds at levels higher than the general population, particularly in operations involving heating or spraying of these materials. Performers and workers in theatrical productions that use propylene glycol-containing fog/smoke for special effects are likely to be exposed to higher concentrations of propylene glycol than the general population (Rossol 1993). Fire fighters who participate in frequent fire-fighting exercises involving propylene glycol fog/smoke may also belong to the high exposure group (Rossol 1993).

5.7 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 propylene glycol 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 propylene glycol.

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.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. As seen in Table 3-2, the relevant physical and chemical properties of propylene glycol are known (ASTER 1995b; Daubert and Danner 1989; EPA 1987a; HSDB 1995b; Merck 1989). No further information is required.

Production, Import/Export, Use, Release, and Disposal. Production data are available for propylene glycol (SRI 1989, 1991, 1993, 1995). Similarly, data on the import/export volumes for propylene glycol for the last several years are available (NTDB 1995). Information on the various uses of this compound are also available (EPA 1987a; HSDB 1995b; Lewis 1993; Merck 1989; Rowe and Wolf 1982). Propylene glycol enters the environment primarily during its use as an intermediate in the synthesis of polyester fibers and resins, as a component of automotive antifreeze/coolants, and as a de-icing fluid for aircraft (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Klecka et al. 1993; Lewis 1993; Merck 1989; Rowe and Wolf 1982). Propylene glycol is also used in pharmaceutical products, hair colorant formulations, food and tobacco products, as a non-toxic antifreeze in the food industry, as an air sterilant in hospitals or animal facilities, and as a special effects fog/smoke in theatrical performances or in fire training programs (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Klecka et al. 1993; Merck 1989; Rossol 1993; Rowe and Wolf 1982). Information regarding the disposal of propylene glycol containing waste waters (Chou et al. 1979; Raja et al. 1991) and for remediation of propylene glycol contaminated soils (Drajun 1991; Vesper et al. 1994) is 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 1988-1993, became available in

May of 1995. This database will be updated yearly and should provide a list of industrial facilities and emissions. No TRI data are available for propylene glycol because this chemical is not required to be reported by chemical producers (EPA 1995c).

Environmental Fate. Information regarding the fate of propylene glycol in the air is available that suggests the compound would be primarily found in the vapor phase and would likely be removed from the atmosphere via wet deposition (Eisenreich et al. 1981; EPA 1979, 1987a). Propylene glycol undergoes rapid photochemical oxidation via reaction with hydroxyl radicals with an estimated half-life of 20 hours in the atmosphere (EPA 1987a). Because of its high solubility in water, the compound is expected to be transported primarily in aqueous media and will not partition to the atmosphere via volatilization from water (EPA 1979, 1987a; Thomas 1990). Adsorption to sediment or soil particles is not expected to be significant based on the low K_{oc} value and therefore propylene glycol is expected to have a high mobility in soil and potential to leach into groundwater (Swarm et al. 1983). Propylene glycol is transformed in both water and soil by microorganisms (EPA 1987a; Gaston and Stadtman 1963; Klecka et al. 1993). The half-lives for the biotransformation of propylene glycol in surface waters generally range from 1 to 4 days under aerobic conditions and from 3 to 5 days under anaerobic conditions, with half-lives in soil similar to or less than those in surface waters (EPA 1987a). No additional information on degradation of propylene glycol in air or water are required; however, additional quantitative information on the degradation of propylene glycol in soil would be useful.

Bioavailability from Environmental Media. Available information regarding the rate of propylene glycol absorption following inhalation, oral, or dermal contact has been discussed in the Toxicokinetics section (see Section 2.3). Although no data on propylene glycol's bioavailability from contaminated air are available, the bioavailability from inhalation exposure is expected to be high because propylene glycol is likely to be present in the vapor phase (Eisenreich et al. 1981) and not in the particulate phase in the adsorbed state. Similarly, no data on the bioavailability of propylene glycol from water, soil or plant material are available; however, propylene glycol is readily miscible in water and does not adsorb readily to soil. Propylene glycol, therefore, is expected to be readily bioavailable from soil and water. Information on the bioavailability of propylene glycol from actual environmental media is not required as propylene glycol is a GRAS chemical (FDA 1982).

Because the FDA (1982) has classified propylene glycol as a GRAS chemical, no monitoring data for concentrations of propylene glycol in contaminated media at hazardous waste sites are needed to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Food Chain Bioaccumulation. Based on its low K_{oc} value, propylene glycol is not expected to bioconcentrate in aquatic food chains; however, no measured BCF values were located for any invertebrate or fish species. Information is also lacking regarding the biomagnification potential of propylene through aquatic food chains although it is unlikely because of the rapid degradation rate for the chemical in aquatic systems. No further information on the bioconcentration or biomagnification potential of propylene glycol is required as it is a GRAS chemical (FDA 1982).

Exposure Levels in Environmental Media. No information was located on the concentration of propylene glycol in ambient air. Propylene glycol was detected in air samples collected in a large scale environmental chamber analyzing volatile organic emissions from newly installed carpet with polyvinylchloride backing (Hodgson et al. 1993). No data on the level of propylene glycol in drinking water were located, although propylene glycol has been detected at up to 4 mg/L (ppm) in groundwater in the vicinity of an airport (Sills and Blakeslee 1992) and at unspecified concentrations in groundwater samples collected at two hazardous waste sites (HazDat 1995). Little information on the levels of propylene glycol in soils was located. Data on propylene glycol levels in foods, particularly those stored in cellulose films or in PET bottles, are available (Castle et al. 1988a; EPA 1979; Kashtock and Breder 1980; Williamson and Iverson 1993) and a recent estimate of human dietary intake of propylene glycol in Japan is available (Louekari et al. 1990). Reliable monitoring data for the levels of propylene glycol in various environmental media are not needed as this compound is a GRAS additive in foods (FDA 1982).

Exposure Levels in Humans. Little quantitative information on propylene glycol levels in various human tissues and body fluids of a control population, populations near hazardous waste sites, or occupationally exposed groups in the United States is available. Most information is available for oral exposures (Yu et al. 1985). Data on the levels of propylene glycol and its metabolites in body tissues and fluids are not needed because this chemical is a GRAS food additive (FDA 1982).

Exposure Registries. No exposure registries for propylene glycol 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.

5.7.2 Ongoing Studies

No additional information was located on ongoing studies that would fill existing data needs for propylene glycol (FEDRIP 1995).

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring propylene glycol in biological samples or in environmental media. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify propylene glycol. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect propylene glycol in environmental samples are the methods approved by federal 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 refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Table 6-1 is a summary of some of the most commonly used methods reported in the literature for detecting propylene glycol in biological samples. The primary method for measuring propylene glycol in biological samples is derivatization followed by gas chromatography (GC) using either a flame ionization detector (FID) or mass spectrometry (MS) for quantification. GC is the preferred analytical method because of the ease of sample preparation and the accuracy of the quantification of sample concentrations. Alkali flame ionization detectors have also been used for ethylene glycol analysis and give a response ratio of 3:1 compared with PID (Bogusz et al. 1986). Capillary gas chromatography with a constant current ^{63}Ni electron capture detector (ECD) has also been used successfully to detect propylene glycol (Needham et al. 1982).

Sample preparation for GC is important and proceeds through several steps: acidification, esterification, and extraction into an organic solvent. The use of internal standards is necessary for quantification. In clinical cases involving ethylene glycol poisoning, propylene glycol should not be used as an internal standard for quantitation because certain sedatives (Valium and Ativan) may contain propylene glycol (Apple et al. 1993).

Detection of propylene glycol in biological samples using GC with either FID or MS is very sensitive, with detection limits ranging from sub to low ppm. The coefficient of variation (CV) varies with the concentration of glycol used but typically ranges from 0.4% to 27% and is usually less than 10%. In gas chromatographic procedures, the glycols and their acid metabolites are derivatized to form esters in order

Table 6-1. Analytical Methods for Determining Propylene Glycol in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human plasma	Deproteinization with acetic acid; vortex; centrifugation; supernatant spiked with internal standard; reaction with butyl-boronic acid; neutralize with NH_4OH, extraction with dichloromethane; concentration.	HRGC/MS	1 ppm	94–106	Giachetti et al. 1989
Human serum	Acetonitrile with internal standard added to sample; centrifugation; concentration; extraction with *p*-bromo-phenyl boric acid in ethyl acetate.	HRGC/ECD	0.38 ppm	>90	Needham et al. 1982
Human blood	Deproteinization with $HClO_4$; centrifugation; pH adjustment; centrifugation	GC/MS	0.6 ppm	NR	Sisfontes et al. 1986
Human serum and urine	Internal standard added; centrifugation; derivatization with phenylboronate in methanol.	HRGC/FID	1.0 ppm	89–98	Houźe et al. 1993
Human serum (glycolic acid)	Colorimetric: precipitation of protein with trichloroacetic acid followed by centrifugation, addition of chromotropic acid, heating, and dilution; gas chromatographic: addition of internal standard and acetone followed by centrifugation, addition of NaOH, evaporation to dryness, and formation of methyl ester.	Absorbance at 580 nm or GC/FID as appropriate	1.0 mmol/L (60 ppm, w/v) for both methods; 3–6% RSD	NR	Fraser and MacNeil 1993
Humans serum (glycolic acid)	Extraction from salted, acidified serum using methyl ethyl ketone followed by removal of organic phase and evaporation to dryness and derivatization with PNBDI.	HPLC/UV	0.05 mmol/L (3 ppm, w/v); 1% RSD	NR	Hewlett et al. 1986

Table 6-1. Analytical Methods for Determining Propylene Glycol in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human plasma, urine (oxalate)	Heparinized blood deproteinated by addition of acetonitrile and phosphate buffer (pH=7), centrifugation, removal of solvent and evaporation to dryness; derivatization as for urine; urine acidified and derivatized using 1,2-diaminobenzene, adjustment of pH to 5-6, centrifugation.	HPLC/UV	Plasma: 0.15 mg/L (ppm, w/v); 7.5% RSD; urine: 0.5 mg/L (ppm, w/v); 5% RSD.	85	Brega et al. 1992

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; $HClO_4$ = chloroform; HPLC = high-performance liquid chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; NH_4OH = ammonium hydroxide; NR = not reported; PNBDI = O-*p*-nitrobenzyl-N,N'-diisopropylisourea; RSD = relative standard deviation; UV = ultraviolet detector; w/v = weight:volume

to facilitate quantitative elution from the chromatographic columns (see Table 6-1). Simple and rapid methods are also available for the quantitation of the glycols in urine, serum, or deproteinated whole blood. These methods use direct sample injection without prior solvent extraction and derivatization (Aarstad et al. 1993; Edinboro et al. 1993; Jonsson et al. 1989). However, such methods, particularly those that use packed columns may misidentify propionic acid (found in patients with methylmalonic acidemia) as ethylene glycol (Shoemaker et al. 1992).

High-resolution proton nuclear magnetic resonance spectroscopy has potential use in the identification and quantification of propylene glycol and other chemicals in cerebrospinal fluid (CSF) and serum (Petroff et al. 1986). The technique has two advantages: 1) it requires no pretreatment of the specimens prior to analysis and no advance knowledge of possible compounds present in fluids and 2) results are extremely rapid. Propylene glycol was detected at 1 ppm in CSF (Petroff et al. 1986).

No information was located on detecting propylene glycol in feces, adipose tissue, or human milk.

6.2 ENVIRONMENTAL SAMPLES

As with biological samples, GC is the major technique used to determine propylene glycol concentrations in environmental samples whether in air, water, food, drugs, or other substances. Capillary gas chromatography with FTD or ECD, possibly followed by MS, generally gives good quantitative results down to the ppm range with recovery usually greater than 80%. The determination of propylene glycol in air requires adsorption onto a surface and subsequent extraction. Water samples may be analyzed without preparation (EPA 1995a, 1995b). Detection of propylene glycol in foods and drugs may be accomplished by chromatography of the sample; for substances with a high fat content, extraction with hexane may be used to remove the fat. Table 6-2 is a summary of some of the most commonly used methods reported in the literature for detecting propylene glycol in environmental samples. The specific techniques used for each analytical method are listed in the table if that information was provided by the author(s).

The presence of propylene glycol in foods packaged with plastic films containing the compounds has been studied, as have ethylene glycol levels in drugs sterilized with ethylene oxide. Sample preparation is important because procedures vary depending on the fat content of the food sample. Foods with low fat content can be extracted with ethyl acetate, derivatized to a trimethylsilyl ether, and then injected into the gas chromatograph. For foods with a high fat content, hexane is used as the defatting agent prior to derivatization. Quantifying ethylene glycol or propylene glycol in wines requires no preparation of the

Table 6-2. Analytical Methods for Determining Propylene Glycol in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Sample adsorbed on Amberlite® XAD-2 with personal sampling pump; extraction with diethyl ether.	GC/FID	NR	75–98	Andersson et al. 1982
Water	Direct injection (Method 8015b).	GC/FID	NR	NR	EPA 1995a
Water	Direct injection (Method 8430).	GC/FTIR	120 mg/L (ppm, w/v)	NR	EPA 1995b
Plastics	Sample extraction from plastic with carbon disulfide.	GC/FID	16.5 ng	58–61	Muzeni 1985
Plastics	Sample extraction with solvent of ethylacetate-water-methanol.	GC/FID	2 ppm	NR	DeRudder et al. 1986
Cosmetics	Co-distillation with isooctane	GC/FID	NR	NR	Helrich 1990a
Ground tobacco	Extraction with anhydrous methanol.	GC/FID	NR	NR	Helrich 1990b
Aqueous solution	Sample concentration, then dilution with water; concentration with helium gas; redilution.	GC/FID	50 ppb	97–103	Kashtock and Breder 1980
Beer	Addition of ammonium sulfate and extract with ethyl acetate.	HRGC/FID	0.73 ppm	88	Williamson and Iverson 1993
Vanilla extract	Refluxing with heptane and addition of KIO_4, $NaHCO_3$, KI, and starch to aqeous phase followed by titration with $KasO_2$.	Titration	NR	NR	Helrich 1990c
Food	Addition of hot water to sample to obtain slurry; extraction with hexane; precipitation of sugars with calcium hydroxide; concentration; derivatization with BSTFA.	HRGC/FID; GC/MS	10 ppm	78–107	Castle et al. 1988b
Anchovies	Extraction with methanol and concentration.	HRGC/MS/MS (PICI)	12.5 ppb	NR	Matusik et al. 1993

BSTFA = bis(trimethylsilyl)trifluoroacetamide; FID = flame ionization; GC = gas chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; MS/MS = tandem mass spectrometry; PICI = positive ion chemical ionization

samples prior to analysis (Kaiser and Rieder 1987; Klaus and Fischer 1987). Drugs in aqueous solutions may be analyzed directly, water insoluble drugs should be extracted in water, and ointments may be dissolved in hexane and then extracted with water. Recovery is between 80 and 114%, with detection limits in the low-ppm range (Hartman and Bowman 1977; Manius 1979). The use of ion exchange chromatography with sulfuric acid as the mobile phase has also given good recovery (98-101%) with a detection limit of 5 μg/mL propylene glycol from pharmaceuticals (Iwinski and Jenke 1987). Although the use of TLC (Ballarin 1980) has been recommended, it has been superseded by GC.

Propylene glycol in cigarette smoke has been detected using electrostatic precipitation or filter pad, with extraction and separation with capillary gas chromatography (Borgerding et al. 1990).

No information was located on techniques for detecting and analyzing propylene glycol in soil.

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 ethylene glycol and propylene glycol is available. Where adequate information is not available, ATSDR, in conjunction with 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 propylene glycol.

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. Methods for the determination of propylene glycol in blood and urine are available (Giachetti et al. 1989; House et al. 1993; Needham et al. 1982; Sifontes et al. 1986) with sensitivities in the sub-ppm range.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for the determination of propylene glycol have been reported for air (Andersson et al. 1982; NIOSH 1984), water or aqueous solutions (EPA 1995a, 1995b; Kashtock and Breder 1980), and

foods (Castle et al. 1988b; Matusik et al. 1993; Williamson and Iverson 1993). Methods have also been developed for the determination of glycols that leach from plastics (DeRudder et al. 1986; Muzeni 1985) and that can end up in foods stored in containers made from the plastics. An MRL of 0.009 ppm for intermediate inhalation exposure to propylene glycol has been defined and none of the methods reported would be adequate without modification. It is likely that the LODs of some of the methods could be reduced but this remains to be shown.

6.3.2 Ongoing Studies

No ongoing research on analytical methods for the determination of propylene glycol was found.

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7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding propylene glycol in air, water, and other media are summarized in Table 7-1. An MRL of 0.009 ppm has been derived for intermediate-duration inhalation exposure (1.5-364 days) to propylene glycol based on a LOAEL of 51 ppm for nasal hemorrhaging (Suber et al. 1989).

Propylene glycol is regulated under Clean Air Act New Source Performance Standards for the synthetic organic chemical manufacturing industry (EPA 1993b). Propylene glycol is regulated by the Clean Water Act Effluent Guidelines for organic chemicals, plastics, and synthetic fibers (OCPSF). The waste water generated by the production of these chemicals has effluent limitations on biochemical oxygen demand (BOD5), total suspended solids (TSS), and pH (EPA 1987d).

Table 7-1. Regulations and Guidelines Applicable to Propylene Glycol

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
WHO	Acceptable daily intake	0-25 mg/kg	FAO/WHO 1974
NATIONAL			
Regulations and guidelines:			
a. Air			
EPA OAR	App. A – Chemicals defining synthetic organic chemical and polymer manufacturing	Yes	40 CFR 52 EPA 1972a
	Subpart VV – Std. of performance for equipment leaks of VOC in SOCMI: Chemicals produced by affected facilities	Yes	40 CFR 60.489 EPA 1983
	Definitions of emissions from polymer manufacturers: Definition of "polymerization reaction section"	Yes	40 CFR 60.561 EPA 1990b
	Subpart NNN – Std. of performance for VOC emissions from SOCMI distillation operations: Chemical affected	Yes	40 CFR 60.667 EPA 1990b
	Subpart RRR – Std. of performance for VOC emissions from SOCMI process reactors: Chemicals affected	Yes	40 CFR 60.707 EPA 1993b
	New source performance standard	Yes	58 FR45962 EPA 1993c
b. Water			
EPA OW	Bulk organic chemicals under the Clean Water Act	Yes	40 CFR 414.70 EPA 1987d
	App. A – Non-complexed metal-bearing waste	Yes	40 CFR 414 EPA 1987d
EPA OWRS	Pesticide subject to registration and reregistration	Yes	40 CFR 152.146 EPA 1989b EPA 1989a
c. Food			
FDA	Generally recognized as safe	Yes	21 CFR 184.1666 FDA 1982
	2,4-D: Food tolerances for residues 2,4-D Applied in the form of polyethylene glycol and/or propylene glycol		40 CFR 180.142 EPA 1982
	Max. 2,4-D tolerance: Pasture and rangeland grasses	1,000 ppm	
	Min. 2,4-D tolerance: Blueberries and rice	0.1 ppm	

Table 7-1. Regulations and Guidelines Applicable to Propylene Glycol

Agency	Description	Information	Reference
	Inert ingredients exempt from tolerances	Yes	40 CFR 180.1001 EPA 1971
NATIONAL *(cont.)*			
d. Other			
EPA OPTS	Temperature correction factors for organic solvents	0.043 K°C/mmHg	40 CFR 796.1220 EPA 1985a
	Avian dietary testing procedures – sample diluents	Yes	40 CFR 797.2050 EPA 1985b
	Sample Diluents for Bobwhite reproductive tests	Yes	40 CFR 797.2130 EPA 1985b
	Sample diluents for Mallard reproductive Tests	Yes	40 CFR 797.2150 EPA 1985b
	Sample carriers for avian acute toxicity test	Yes	40 CFR 797.2175 EPA 1985b
STATE			
Regulations and guidelines:			
a. Air:	Acceptable ambient air concentrations		
VA	24 hours	1.10×10^3 µg/m^3	NATICH 1991

EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NATICH = National Air Toxics Information Clearinghouse; OAR = Office of Air and Radiation; OPTS = Office of Pesticides and Toxic Substances; OW = Office of Water; OWRS = Office of Waste Regulations and Standards; SOCMI = Synthetic Organic Chemical Manufacturing Industry; VOC = Volatile Organic Compound

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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 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 that 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 of people that 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 uncertainties 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 occurs. 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.

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.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

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.

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 that 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 that 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 uncertainty 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) that 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosp hate 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 dynamic behavior of a material in the body, used to predict 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, whereas 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 that 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.

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) concentration 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.

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 causal 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 group.

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 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 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

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Propylene glycol
CAS Numbers: 57-55-6
Date: December 1995
Profile Status: Third Draft Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 1
Species: Rat

Minimal Risk Level: 0.009 [ ] mg/kg/day [X] ppm

Reference: Suber et al. 1989

Experimental design: Young, healthy adult Sprague-Dawley rats were divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by nose-only inhalation to mean target aerosol concentrations of 51, 321, or 707 ppm propylene glycol. The fourth, the control group, was exposed to humidified, filtered room air. Nasal hemorrhaging occurred in all exposed groups of male and female rats indicating that propylene glycol can act as a dehydrogenating agent. From week 2-14, the average of nasal hemorrhaging in male rats was <1%, 64%, 74%, and 75% in controls, low-exposure, medium-exposure, and high-exposure groups, respectively. In females, the average indices were < 1% in controls, 14% in the low-exposure group, and 71% in the medium and high-exposure groups. Animals recovered during non-exposure weekend periods. Similar trends were observed for ocular discharge, with females having generally less ocular discharge than males. A significant reduction in body weight of 5-7% starting on day 50 and continuing until the end of the study was observed in female rats receiving the highest dose of 707 ppm propylene glycol. Similar observation was made in the group receiving 321 ppm of propylene glycol but later in the study starting on day 64. This body weight reduction was correlated with a significant reduction in food consumption beginning on study day 43 and 50 for the high- and medium-exposure females, respectively. Female rats exposed to 321 ppm propylene glycol had a significant decrease in white blood cell count and lymphocyte numbers. Female rats exposed to 707 ppm propylene glycol had a significant decrease in hemoglobin concentration, white blood cell count and lymphocyte numbers. Male rats in the medium (321 ppm) and high (707 ppm) groups had a significant decrease in serum sorbitol dehydrogenase and gamma-glutamyl transferase. A significant decrease in total serum protein was observed in male rats treated with high (707 ppm) dose of propylene glycol while females treated with a medium (321 ppm) dose of propylene glycol had an increase in total serum protein. These changes were considered as being sporadic. Kidney weight was decreased at 321 ppm in both sexes. Although there were no treatment-related gross pathology changes, light microscopy revealed thickening of respiratory epithelium with increase in the number of goblet cells and their mucin content in both female and male animals receiving medium and high propylene glycol dose. Minute volume, tidal volume, and respiratory rates were not significantly altered in rats exposed to 51, 321, or 707 ppm propylene glycol for 13 weeks, suggesting that animals adapted to the exposure concentrations.

Effects noted in study and corresponding doses: Nasal hemorrhaging was observed in all PG-treated groups:

51 ppm PG = low dose (64% in males, 14% in females; less serious LOAEL)

321 ppm PG = mid dose (74% in males, 71% in females)

707 ppm PG = high dose (75% in males, 71% in females)

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [ ] 3 [X] 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: No conversion was used.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Doses were converted from mg/L to ppm:

0.16 mg/L x 1,000 = 160 mg/m3. 160 mg/m^3 x 24.45/76.09 (MW PG) = 51.4 ppm

1.0 mg/L = 321.3 ppm

2.2 mg/L = 706.9 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: Animals were exposed for 6 hours per day, 5 days per week. Since the effect (nasal hemorrhaging) subsided when exposure was discontinued during the weekend periods, it seemed relevant to adjust the exposure period not only to a continuous 24 hour, but also to a 7-day exposure. Therefore conversion factors of 6/24 and 5/7 were used:
51 ppm x 6/24 x 5/7 = 9 ppm

Other additional studies or pertinent information that lend support to this MRL: This was the only suitable intermediate-duration inhalation exposure study available

Agency Contacts (Chemical Managers): Ed Murray

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

Relevance to Public Health

This chapter 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 chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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 chapter.

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 Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

MRLs 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, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point 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 end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) 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 two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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 regimens 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 "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 end point 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 9 of the profile.

(11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate 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, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL 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 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

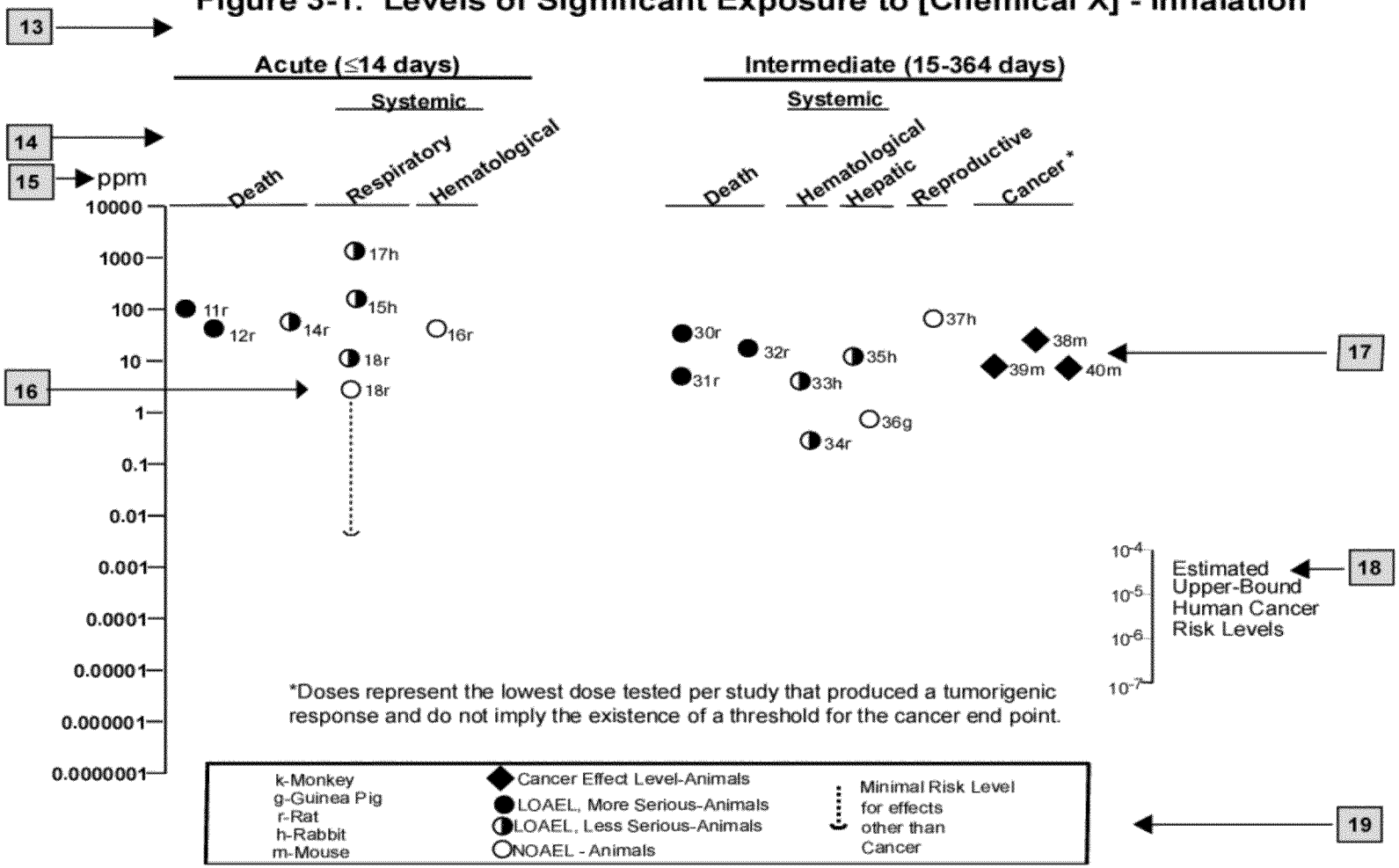
	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer						11 ↓	
	38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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).

Freedom_0007144_0168

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
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
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
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
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
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/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
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
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
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_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contamin ant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
OR	odds ratio
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
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
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 carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	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