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 figure[a]	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			

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

Key to figure[a]	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)

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

Intermediate (15-364 days)

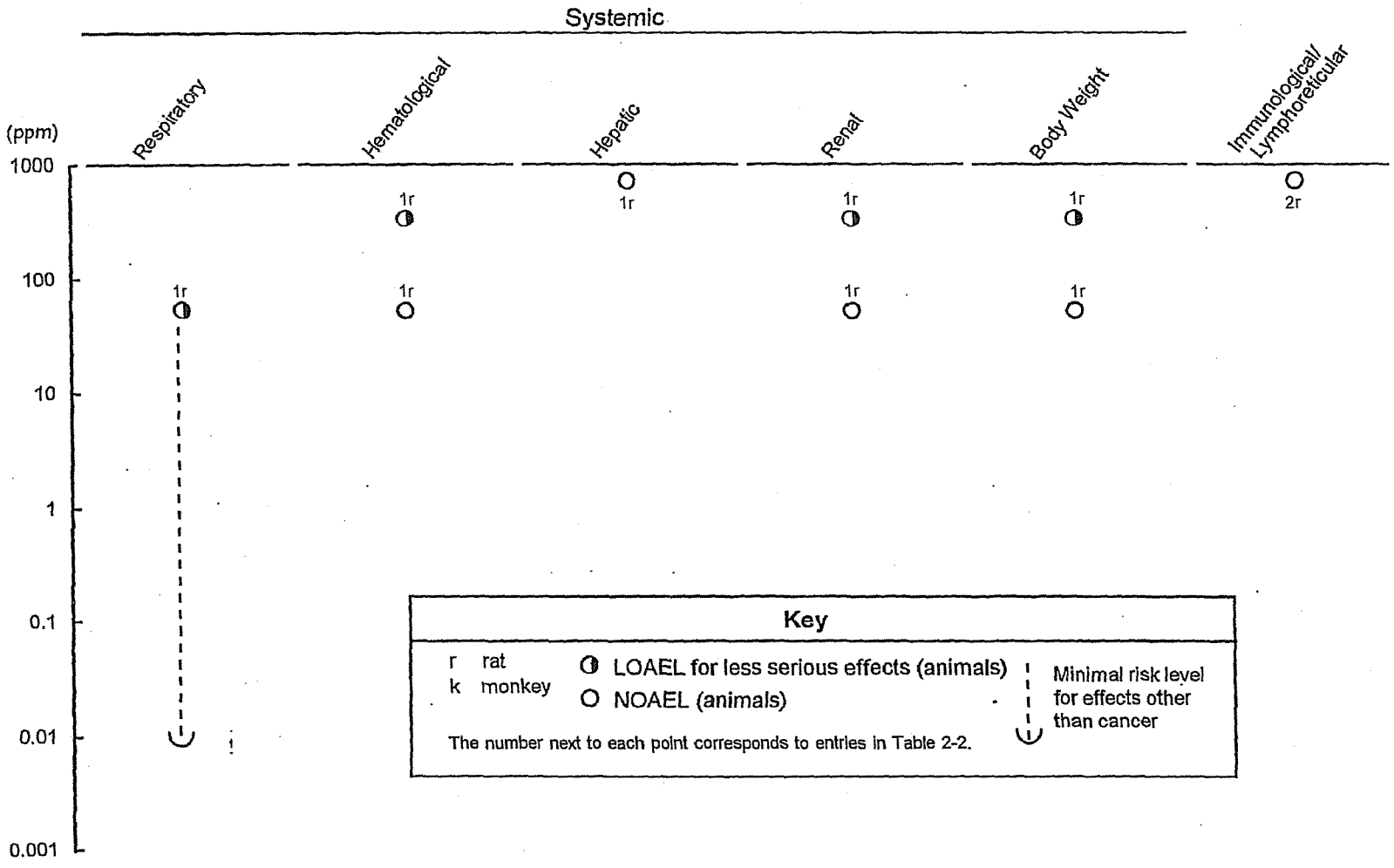
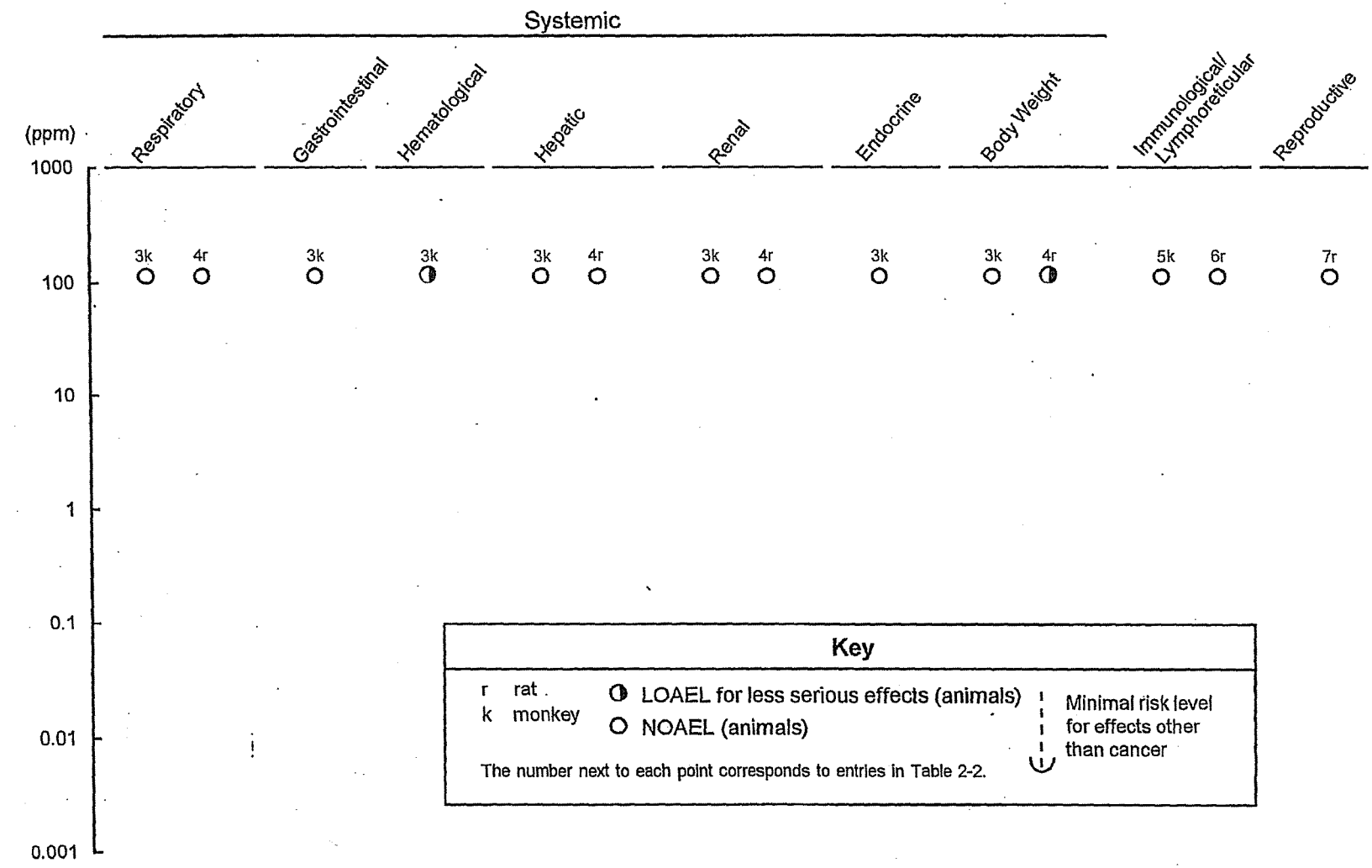


Figure 2-1. Levels of Significant Exposure to Propylene Glycol - Inhalation (continued)

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

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

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 Cardio ,Hemato Hepatic Renal Endocr	2500 2500 2500 2500 2500 2500				Gaunt et al. 1972
18	Dog	2 yr (F)	Hemato Hepatic Renal Bd Wt	2000 5000 5000 5000	5000	(decreased erythrocytes, hemoglobin, hematocrit)		Weil et al. 1971

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

Key to figure[a]	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)

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

Acute (≤14 days)

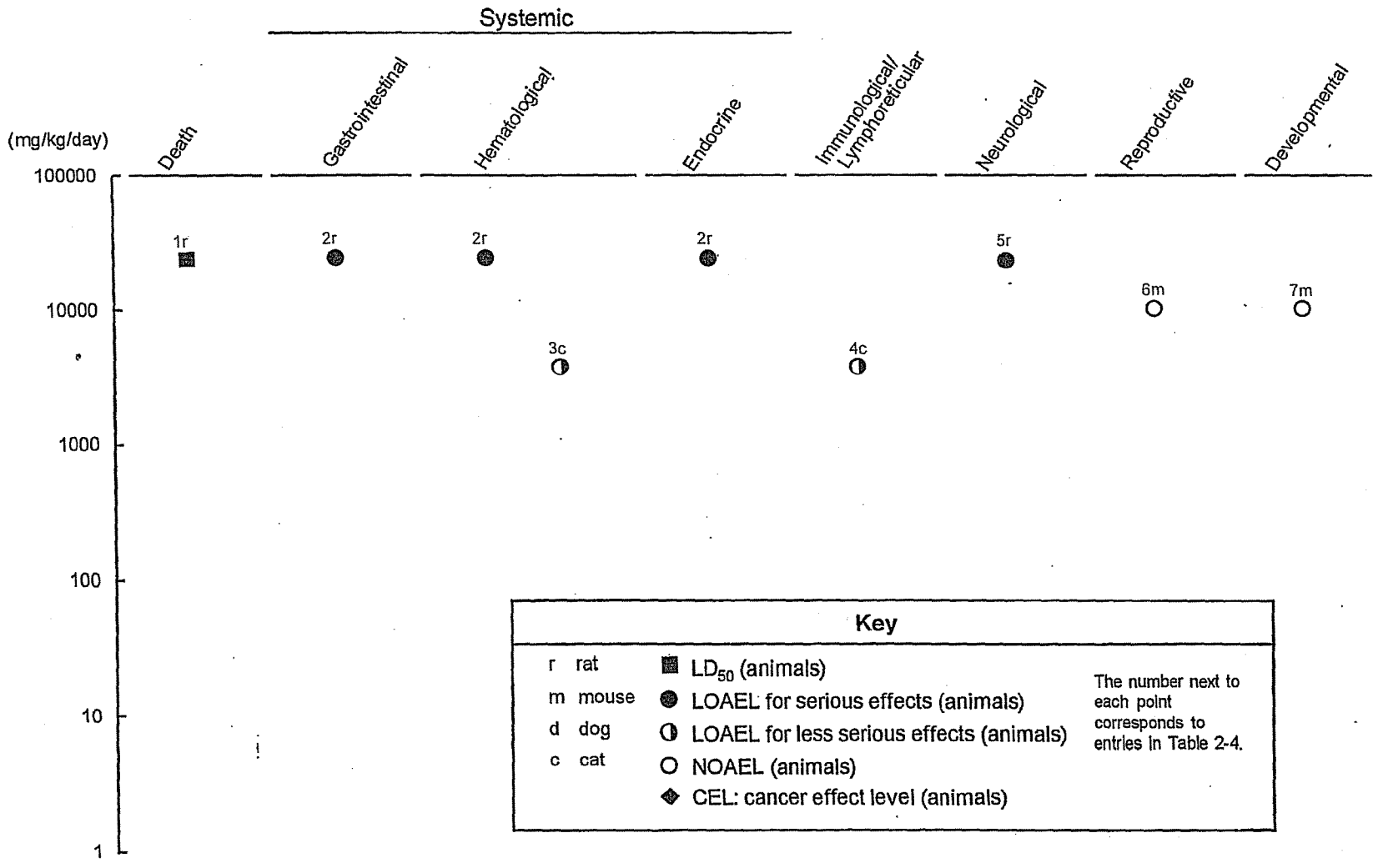


Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Intermediate (15-364 days)

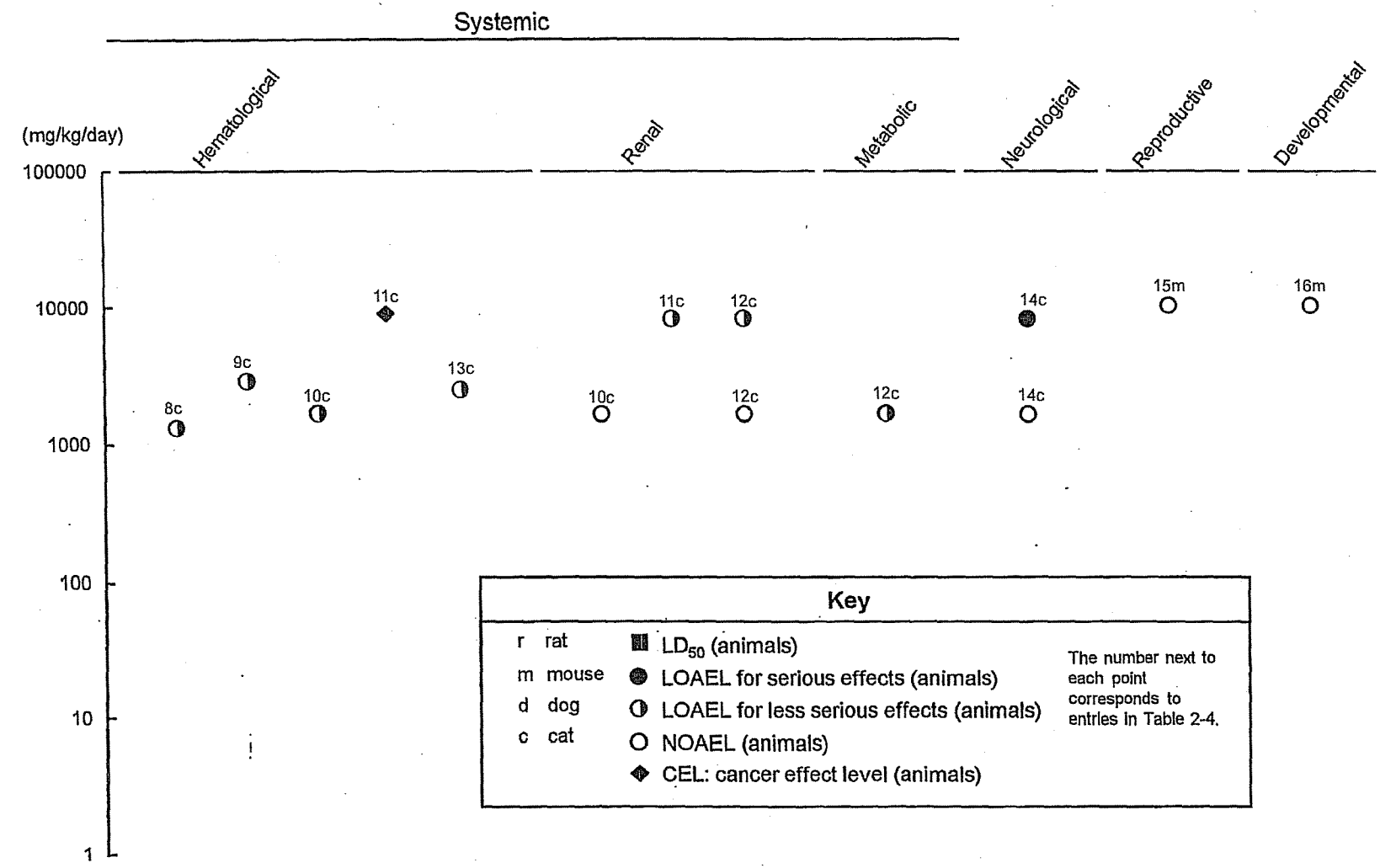
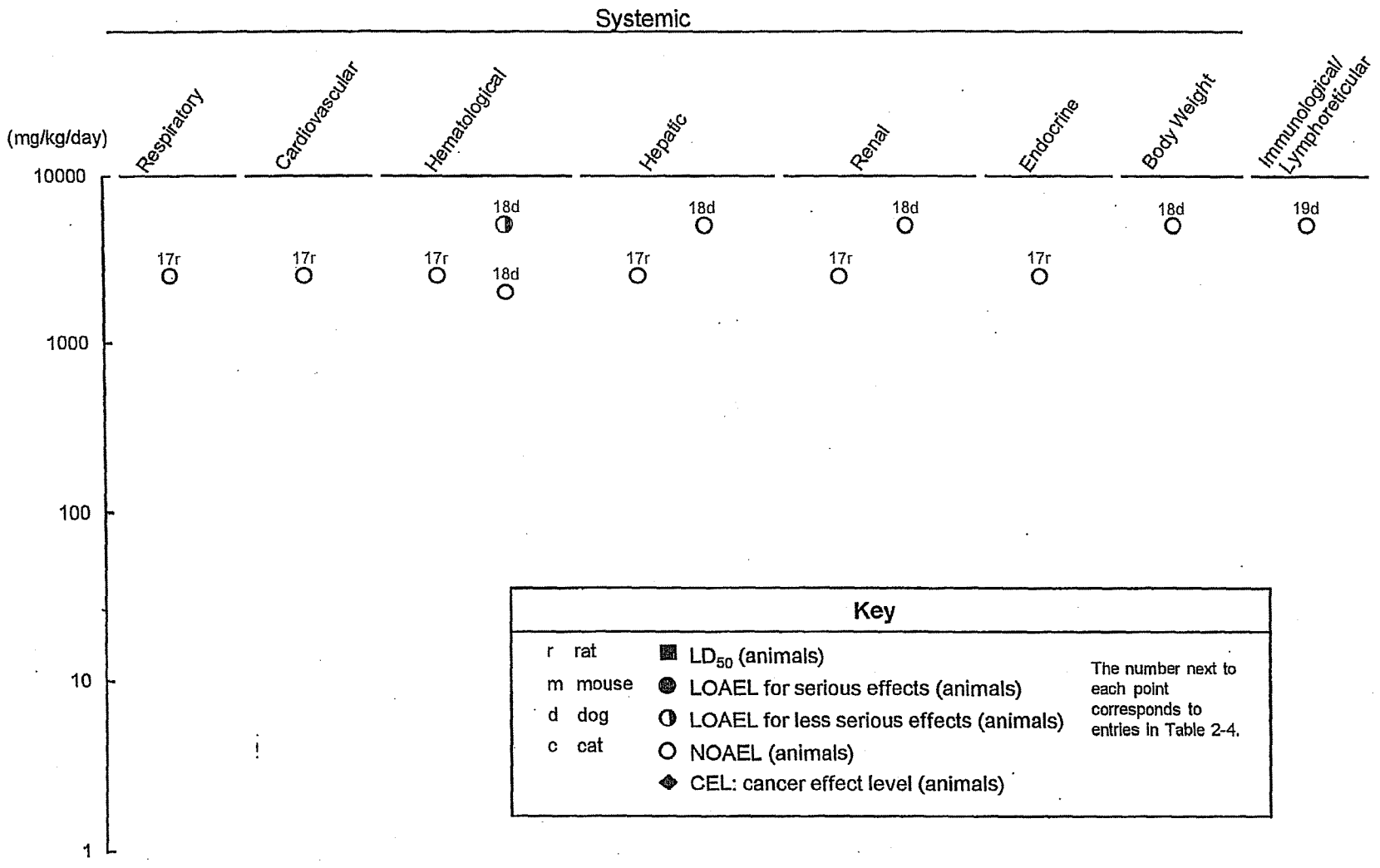


Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

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 <l0 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

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

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Rabbit (New Zealand)	once	Dermal	0.52 F gm			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 M (hypoxic encephalopathy) mg/kg	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-effectlevel; M = male; Metab = metabolic; NOAEL = no-observable-adverse-effectlevel; Resp = respiratory; x = times

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 cornea1 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 l0%, 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 l0-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 toxicokinetics 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.

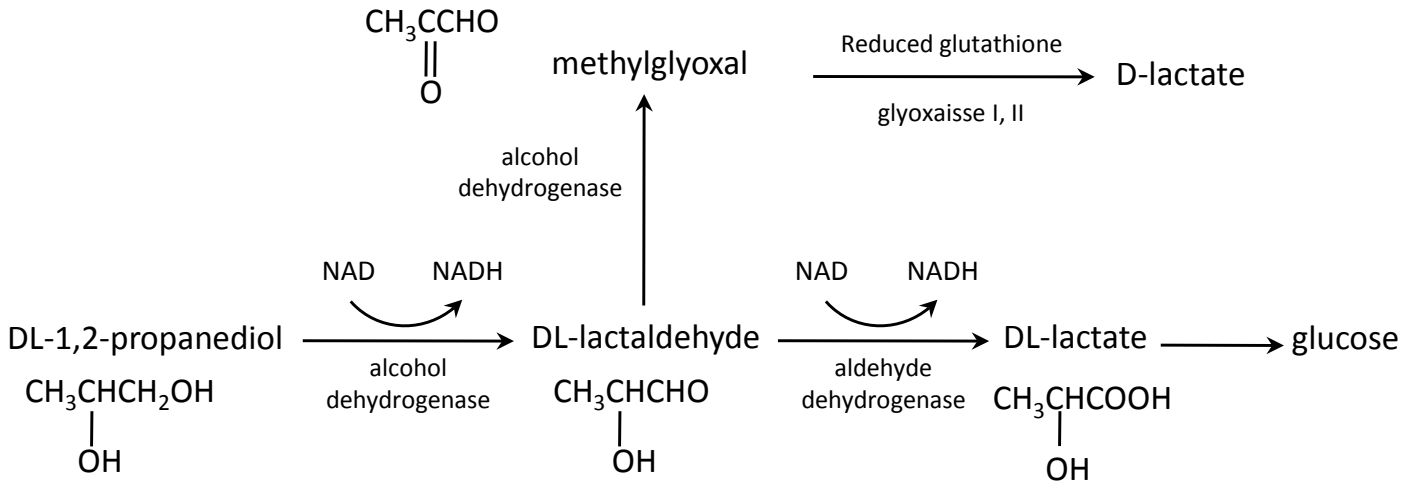
2.3.2.3 Dermal Exposure

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

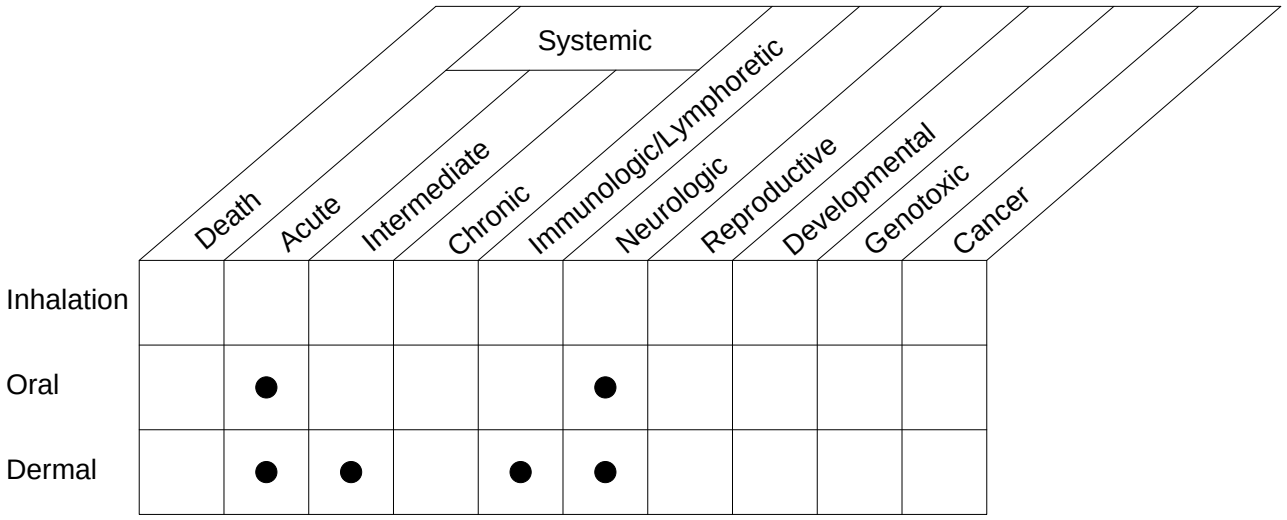
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of propylene glycol is available. Where adequate information 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.

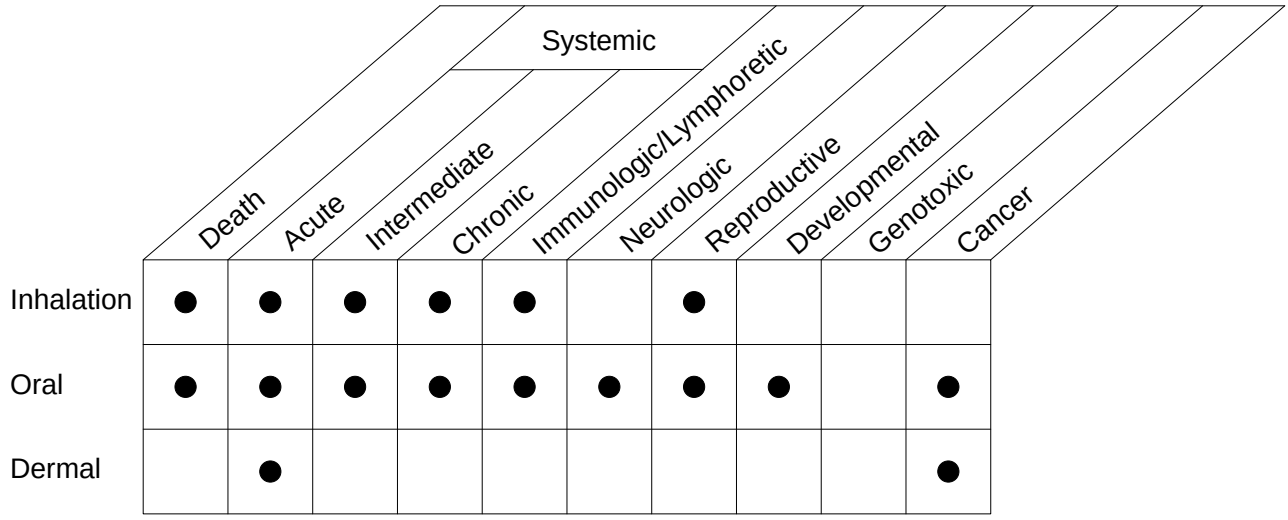
2.9.1 Existing Information on Health Effects of Propylene Glycol

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



Human



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.