

## APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Bromoform  
CAS Number: 75-25-2  
Date: August 2005  
Profile Status: Final Draft of Post-Public Comment Toxicological Profile  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 13  
Species: Mice

Minimal Risk Level: 0.7  mg/kg/day  mg/m<sup>3</sup>

Reference: Condie LW, Smallwood CL, Laurie RD. 1983. Comparative renal and hepatotoxicity of halomethanes: Bromodichloromethane, bromoform, chloroform, dibromochloromethane and methylene chloride. Drug Chem Toxicol 6:563-578.

Experimental design:

Groups of 5–16 male CD-1 mice received daily gavage doses of 0, 72, 145, or 289 mg/kg/day bromoform in corn oil for 14 days. Body weight was measured on days 1 and 14. Blood was collected for clinical chemistry at study termination. Renal cortical slices of kidney tissue were collected for measurement of para-aminohippurate (PAH) uptake, and samples of liver and kidney tissue were collected for histopathological examination.

Effects noted in study and corresponding concentrations:

No significant alterations in body weight gain were observed. PAH uptake by kidney slices was decreased by 30% in the 289 mg/kg/day group; a significant increase in SGPT was also observed at this dose. Minimal to moderate liver and kidney histological alterations were observed. Liver effects included centrilobular pallor at 145 and 289 mg/kg/day and focal inflammation at 289 mg/kg/day. Kidney effects consisted of epithelial hyperplasia at 289 mg/kg/day and mesangial nephrosis at 145 and 289 mg/kg/day.

Concentration and end point used for MRL derivation:

The MRL is based on a NOAEL of 72 mg/kg/day and a LOAEL of 145 mg/kg/day for hepatic centrilobular pallor in mice.

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

10 for extrapolation from animals to humans  
 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

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Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL:

Several acute-duration studies support the identification of the liver as the most sensitive target of bromoform toxicity. The observed effects include hepatocellular vacuolization and swelling (Chu et al. 1982a; Coffin et al. 2000), centrilobular pallor (Condie et al. 1983), increased absolute and relative liver weights (Munson et al. 1982), alterations in serum chemistry enzymes such as SGPT (Munson et al. 1982), and impaired liver function (Munson et al. 1982). The highest NOAEL for liver effects is 72 mg/kg/day in mice (Condie et al. 1983); in this study, centrilobular pallor (Condie et al. 1983), which was considered to be indicative of liver degeneration, was observed at 145 mg/kg/day. At 125 mg/kg/day, increases in liver weight were observed (Munson et al. 1982) and hepatocellular vacuolization and swelling were observed at 200 mg/kg (164 mg/kg/day) (Coffin et al. 2000). Other adverse effects that have been observed at similar or higher dose levels include mesangial nephrosis at 145 mg/kg/day (NOAEL of 72 mg/kg/day) (Condie et al. 1983), impaired immune function at 125 mg/kg/day (NOAEL of 50 mg/kg/day) (Munson et al. 1982), skeletal anomalies in the offspring of rats exposed to 200 mg/kg/day (NOAEL of 100 mg/kg/day) (Ruddick et al. 1983), and central nervous system depression at  $\geq 600$  mg/kg (Balster and Borzelleca 1982; Bowman et al. 1978; NTP 1989a). Although several adverse effects have been reported at 100–200 mg/kg/day, the liver was selected as the critical target because the adverse liver effects are consistently observed in animals following acute-, intermediate-, and chronic-duration exposure.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Bromoform  
CAS Number: 75-25-2  
Date: August 2005  
Profile Status: Final Draft of Post-Public Comment Toxicological Profile  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 26  
Species: Rat

Minimal Risk Level: 0.2  mg/kg/day  mg/m<sup>3</sup>

Reference: NTP. 1989a. Toxicology and carcinogenesis studies of tribromomethane (bromoform) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Technical Report Series No. 350. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Experimental design:

Groups of F344/N male and female F344/N rats (10/sex/group) received gavage doses of 0, 12, 25, 50, 100, or 200 mg/kg bromoform in corn oil 5 days/week for 13 weeks. The rats were observed twice per day and weighed weekly. At sacrifice, all animals were necropsied and tissues from the vehicle control and high dose groups were examined histologically.

Effects noted in study and corresponding concentrations:

None of the rats died before the end of the study. Final mean body weights were similar in dosed and control groups. Lethargy was observed in all male rats exposed to 100 or 200 mg/kg and in all females exposed to 200 mg/kg. Hepatocellular vacuolization was observed in male rats (3/10, 6/10, 5/10, 8/10, 8/10, and 10/10 in the 0, 12, 25, 50, 100, and 200 mg/kg groups, respectively); the response reached statistical significance (Fisher exact one-tailed p-value of 0.03) at 50 mg/kg/day. Severity data were not reported for this lesion, but the study authors noted that vacuoles were more numerous in the 200 mg/kg group. Corresponding hepatic effects were not observed in females.

Concentration and end point used for MRL derivation:

The MRL is based on a NOAEL of 25 mg/kg (duration-adjusted to 18 mg/kg/day) and a LOAEL of 50 mg/kg (duration-adjusted to 36 mg/kg/day) for hepatic lesions (hepatocellular vacuolization).

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

10 for extrapolation from animals to humans  
 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

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Was a conversion used from intermittent to continuous exposure?

The NOAEL was adjusted for intermittent exposure:  $25 \text{ mg/kg} \times 5 \text{ days}/7 \text{ days} = 18 \text{ mg/kg/day}$

Other additional studies or pertinent information that lend support to this MRL:

A number of animal studies have identified the liver as the critical target of bromoform oral toxicity. An intermediate-duration study in rats (Aida et al. 1992) supports the identification of 50 mg/kg as the critical dose. In this study, a LOAEL of 56.4 mg/kg/day was identified for hepatocellular vacuolization and swelling in rats exposed to bromoform in the diet for 1 month. At a higher dose (207.5 mg/kg/day), a decrease in serum triglycerides and an increase in serum cholesterol levels were found; these findings are consistent with the liver histological alterations. Mice appear to be less sensitive to the toxicity of bromoform than rats. NOAEL and LOAEL values of 100 and 200 mg/kg (5 days/week) for hepatocellular vacuolization were identified in the intermediate-duration mouse NTP study (NTP 1989a). Melnick et al. (1998) found hydropic degeneration and increases in SGPT and sorbitol dehydrogenase levels in mice receiving gavage doses of 500 mg/kg, 5 days/week for 3 weeks. Acute- and chronic-duration studies have also identified the liver as the most sensitive target of toxicity.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Bromoform  
CAS Number: 75-25-2  
Date: September 2005  
Profile Status: Final Draft of Post-Public Comment Toxicological Profile  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 38  
Species: Rat

Minimal Risk Level: 0.02  mg/kg/day  mg/m<sup>3</sup>

Reference: NTP. 1989a. Toxicology and carcinogenesis studies of tribromomethane (bromoform) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Technical Report Series No. 350. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Experimental design:

Groups of male and female F344/N rats (50/sex/group) were administered via gavage 0, 100, or 200 mg/kg bromoform in corn oil 5 days/week for 103 weeks. Animals were observed for clinical signs throughout the study. Body weights were measured weekly for 12 weeks and monthly thereafter. At termination, all study animals were necropsied. Full histopathological examination was performed on all control and high dose animals and on low dose males. Selected tissues including esophagus, gross lesions, kidney, liver, lymph nodes, mammary gland, pancreas, pituitary gland, salivary glands, thyroid gland, trachea, and uterus were examined in low-dose females.

Effects noted in study and corresponding concentrations:

Significantly increased mortality was observed in male rats exposed to 200 mg/kg after week 91 (36–78% vs. 26–32%). Survival was comparable to vehicle controls in males exposed to 100 mg/kg and in females exposed to 100 or 200 mg/kg. Bromoform-related clinical signs included lethargy in both sexes and aggressiveness in males. After 15 weeks, the difference between control body weights and body weights of males exposed to 200 mg/kg males was consistently  $\geq 10\%$ ; terminal body weights were 21% lower than controls. In the females exposed to 200 mg/kg, the difference in body weights was  $\geq 10\%$  after week 41; terminal body weights were 25% lower than controls. Body weights in the 100 mg/kg groups were typically within 10% of controls. Bromoform-related hepatic lesions included fatty change (characterized as hepatocellular vacuolization) in 23/50, 49/50, and 50/50 males exposed to 0, 100, or 200 mg/kg, respectively, and 19/50, 39/49, and 46/50 females; chronic active inflammation (male: 0/50, 29/50, and 23/50; female: 9/50, 8/49, and 27/50); and necrosis (male: 7/50, 3/50, and 20/50; female: 11/50, 3/49, and 2/50). Other lesions with significantly increased incidences included salivary gland duct squamous metaplasia at 100 and 200 mg/kg (males: 0/50, 15/50, and 31/48; females: 0/49, 10/49, and 16/50) and chronic active inflammation (male: 0/50, 14/50, and 22/48; female: 0/49, 9/49, and 18/50); ulcers of the forestomach in males at 200 mg/kg (1/49, 5/50, and 10/50); chronic active inflammation in the lungs in males at 100 and 200 mg/kg (1/50, 7/50, and 15/50); squamous metaplasia in the prostate gland at 200 mg/kg (2/49, 6/46, and 12/50); hyperplasia of the anterior lobe of the pituitary gland in males at 100 mg/kg (9/48, 26/50, and 15/50); and spleen pigmentation in females at 200 mg/kg (7/49, 6/28, and 29/50), which was characteristic of hemosiderin. The occurrence of ulcers in the forestomach may have resulted from gavage bolus dose delivery. Lesions observed in the lungs and salivary glands were reported to be consistent with infection by sialodacryoadenitis (SDA) virus. However, since the

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occurrence of these lesions was clearly dose-related, the study authors concluded that they were likely to represent a combination of viral and chemical-related effects.

It should be noted that the study authors did not report statistical analysis data for nonneoplastic lesions. An independent statistical analysis was conducted; statistical significance was determined using a Fisher exact test, one tailed  $p < 0.05$ ).

Concentration and end point used for MRL derivation:

The MRL is based on a LOAEL of 100 mg/kg (duration-adjusted to 71 mg/kg/day) for histopathological changes (vacuolization) in the liver.

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

- 3 for use of a minimal LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Modifying Factors used in MRL derivation:

- 10 to account for the identification of a lower LOAEL in the 13-week NTP (1989a) study.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? Yes.

The LOAEL was adjusted for intermittent exposure:  $100 \text{ mg/kg} \times 5 \text{ days/7 days} = 71 \text{ mg/kg/day}$

Other additional studies or pertinent information that lend support to this MRL:

Two studies have examined the chronic toxicity of bromoform (NTP 1989a; Tobe et al. 1982). Both studies identified the liver as the most sensitive target of toxicity. Both the NTP (1989a) rat and mouse studies identified LOAEL values of 100 mg/kg (5 days/week) for hepatocellular vacuolization. The rat study was selected over the mouse study because the effects were observed in both sexes. This study is supported by a 2-year dietary study conducted by Tobe et al. (1982). Yellowing of the liver and increases in absolute and liver weights were observed in female rats exposed to 140 mg/kg/day; histological examinations were not conducted. Alterations in several clinical chemistry parameters are also indicative of liver damage. Increases in SGOT and SGPT and decreases in serum triglycerides and cholesterol were observed at 590–720 mg/kg/day. A number of intermediate-duration studies (Aida et al. 1992; Chu et al. 1982b; Melnick et al. 1998; NTP 1989a) support the identification of the liver as the critical target of bromoform toxicity.

Agency Contact (Chemical Managers): John Risher, Dennis Jones



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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Dibromochloromethane  
CAS Number: 124-48-1  
Date: August 2005  
Profile Status: Final Draft of Post-Public Comment Toxicological Profile  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 16  
Species: Mouse

Minimal Risk Level: 0.1  mg/kg/day  mg/m<sup>3</sup>

Reference: Condie LW, Smallwood CL, Laurie RD. 1983. Comparative renal and hepatotoxicity of halomethanes: Bromodichloromethane, bromoform, chloroform, dibromochloromethane and methylene chloride. Drug Chem Toxicol 6:563-578.

Experimental design:

Groups of 5–16 male CD-1 mice received daily gavage doses of 0, 37, 74, or 147 mg/kg/day dibromochloromethane in corn oil for 14 days. Body weight was measured on days 1 and 14. Blood was collected for clinical chemistry at study termination. Renal cortical slices of kidney tissue were collected for measurement of para-aminohippurate uptake, and samples of liver and kidney tissue were histopathological examination.

Effects noted in study and corresponding concentrations:

No deaths or treatment-related clinical signs were reported. No significant alterations in body weight gain were observed. Para-aminohippurate uptake by kidney slices was decreased by approximately 30% in the 147 mg/kg/day group; a significant increase in SGPT was also observed at this dose. Minimal to moderate liver and kidney histological alterations were observed. Liver effects included hepatocellular vacuolization at 37 mg/kg/day and higher (1/16, 3/5, 4/10, and 8/10 in the 0, 37, 74, and 147 mg/kg/day groups, respectively) and mitotic figures at 147 mg/kg/day (0/16, 0/5, 2/10, and 4/10). Kidney effects consisted of mesangial hypertrophy was observed at 37 mg/kg/day and higher (0/16, 4/5, 7/10, and 7/10).

Concentration and end point used for MRL derivation:

The MRL is based on a LOAEL of 37 mg/kg/day for hepatocellular vacuolization (Condie et al. 1983).

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

- 3 for use of a minimal LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

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If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL:

There are numerous studies that support the identification of the liver as the critical target of dibromochloromethane toxicity. Hepatocellular vacuolization and/or swelling were observed in mice exposed to 100 and 300 mg/kg (9 doses in an 11-day period) (Coffin et al. 2000), at  $\geq 50$  mg/kg in rats and mice exposed to dibromochloromethane for an intermediate duration (Aida et al. 1992; Daniel et al. 1990; NTP 1985) and in rats and mice exposed to  $\geq 40$  for 2 years (NTP 1985). At higher doses, hepatocellular necrosis is observed (Aida et al. 1993; Daniel et al. 1990; NTP 1985) in rats and mice exposed to  $\geq 100$  mg/kg for intermediate durations.

The Condie et al. study (1983) also identified the 37 mg/kg/day dose as a LOAEL for kidney effects, mesangial cell hyperplasia. Other animal studies have also found kidney lesions following oral exposure to dibromochloromethane. Nephropathy, characterized by tubular cell degeneration and tubular cast formation was noted in 80% of male rats and 100% of female rats, but was not found in the controls or other dose groups exposed to dibromochloromethane in corn oil for 13 weeks (NTP 1985). The liver was selected as the critical target because the results of other studies suggest that it may be the more sensitive target of toxicity.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Dibromochloromethane  
CAS Number: 124-48-1  
Date: August 2005  
Profile Status: Final Draft of Post-Public Comment Toxicological Profile  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 46  
Species: Rat

Minimal Risk Level: 0.09  mg/kg/day  mg/m<sup>3</sup>

Reference: NTP. 1985. Toxicology and carcinogenesis studies of dibromochloromethane in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Technical Report Series No. 282. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Experimental design:

Groups of 50 male and 50 female F344/N rats received 0, 40, or 80 mg/kg gavage doses of dibromochloromethane in corn oil 5 days/week for 2 years. Clinical signs were recorded weekly. Body weights were recorded weekly for the first twelve weeks of the study and monthly thereafter. Necropsy was performed on all animals. Histopathological examination was conducted on tissues from all dose groups.

Effects noted in study and corresponding concentrations:

Survival was comparable in all study groups. Body weight gain was within 10% of controls throughout the study. In the liver, fatty change (male: 27/50, 47/50, and 49/50; female: 12/50, 23/50, and 50/50) and "ground glass" cytoplasmic changes (male: 8/50, 22/50, and 34/50; female: 0/50, 1/50, and 12/50) were observed. A dose-related increase in nephrosis was observed in female rats (7/50, 11/50, and 14/50); however, the incidences in exposed rats was not statistically higher than in vehicle controls assessed using the Fisher exact test.

It should be noted that the study authors did not report statistical analysis data for nonneoplastic lesions. An independent statistical analysis was conducted; statistical significance was determined using a Fisher exact test, one tailed  $p < 0.05$ .

Concentration and end point used for MRL derivation:

The MRL is based on a LOAEL of 40 mg/kg (duration-adjusted to 28 mg/kg/day) for liver histopathology (fatty change) (NTP 1985).

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

- 3 for use of a minimal LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

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Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure?

The LOAEL was adjusted for intermittent exposure:  $40 \text{ mg/kg} \times 5 \text{ days}/7 \text{ days} = 28 \text{ mg/kg/day}$

Other additional studies or pertinent information that lend support to this MRL:

The identification of the liver as the critical target is supported by numerous acute-duration studies in rats and mice exposed to  $\geq 37 \text{ mg/kg}$  (Chu et al. 1982a; Coffin et al. 2000; Condie et al. 1983; Hewitt et al. 1983; Munson et al. 198; NTP 1985),  $50 \text{ mg/kg}$  for intermediate durations (Aida et al. 1992; Daniel et al. 1990; Melnick et al. 1998; NTP 1985), and  $40 \text{ mg/kg}$  for chronic durations (NTP 1985; Tobe et al. 1982). The identification of the LOAEL of  $40 \text{ mg/kg}$  for fatty changes in the liver is supported by the NTP (1985) mouse study and a rat study by Tobe et al. (1982). Fatty metamorphosis was found in mice receiving gavage doses of  $50 \text{ mg/kg}$ , 5 days/week for 2 years (NTP 1985). Necrosis was observed at  $100 \text{ mg/kg}$ . In the Tobe et al. (1982) study, groups of rats were exposed to dibromochloromethane in diet for 2 years. No histological examinations were conducted; however, hypertrophy and yellowing of the liver was found at  $85 \text{ mg/kg/day}$ . Alterations in a number of clinical chemistry parameters, which are indicative of liver damage, were also observed. Decreases in serum triglycerides were observed at  $20 \text{ mg/kg/day}$  and decreases in serum cholesterol were observed at  $540 \text{ mg/kg/day}$ .

Agency Contact (Chemical Managers): John Risher, Dennis Jones

## APPENDIX B. USER'S GUIDE

### Chapter 1

#### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

### Chapter 2

#### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

#### Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

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meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

## **Chapter 3**

### **Health Effects**

#### **Tables and Figures for Levels of Significant Exposure (LSE)**

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

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

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

- (1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).
- (7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

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- (8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").
- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference. The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND**

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

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.
- (14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).



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- (17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

## SAMPLE

1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

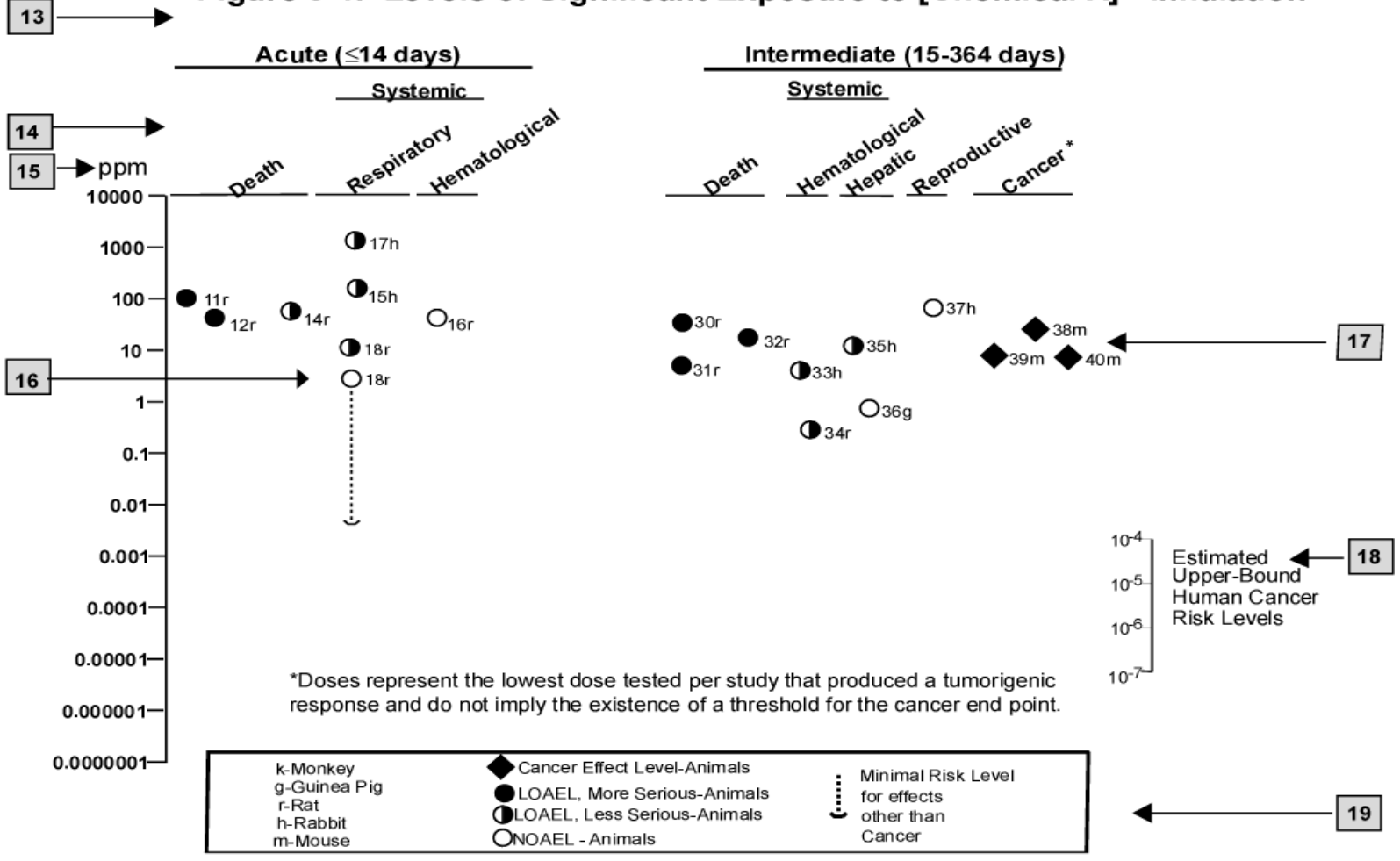
Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 →	INTERMEDIATE EXPOSURE						
3 →	Systemic	↓	↓	↓	↓	↓	↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981
	CHRONIC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

12 → <sup>a</sup> The number corresponds to entries in Figure 3-1.

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

**SAMPLE**

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





**APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS**

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase (also known as SGPT)
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase (also known as SGOT)
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

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DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F <sub>1</sub>	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K <sub>d</sub>	adsorption ratio
kg	kilogram
kkg	metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>50</sub>	lethal concentration, 50% kill
LC <sub>Lo</sub>	lethal concentration, low
LD <sub>50</sub>	lethal dose, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LDH	lactic dehydrogenase
LH	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT <sub>50</sub>	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie

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MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

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OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (also known as AST)
SGPT	serum glutamic pyruvic transaminase (also known as ALT)
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization



## APPENDIX C

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q <sub>1</sub> *	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result



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