Toxicological Profile for 1,2,3-Trichloropropane

Draft for Public Comment

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Agency for Toxic Substances and Disease Registry

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FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

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

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

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

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VERSION HISTORY

Date	Description
May 2019	Update of data in Chapters 2, 3, and 7
August 2011	Addendum to the toxicological profile released
September 1992	Draft for public comment toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for 1,2,3-Trichloropropane* was released in 1992. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2, 3, and 7 were revised to reflect the most current health effects and regulations/guidelines data. In some cases, other sections of the profile were updated as needed or for consistency or with the updated health effects data. However, the focus of the update to this profile is on health effects information.

1,2,3-Trichloropropane ($C_3H_5Cl_3$; CAS number 96-18-4) is a man-made chemical that is present in the environment as a result of anthropogenic activity. It is primarily used in the production of other chemicals. In the past, it was used as a solvent and extractive agent. Exposure can occur through ingestion of contaminated food and water, inhalation, and dermal contact. Data regarding the concentrations of 1,2,3-trichloropropane in the environment are limited; low levels have been found in a few rivers and bays, drinking water, groundwater, and hazardous waste sites in the United States.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of 1,2,3-trichloropropane primarily comes from studies conducted in experimental animals. Three studies have evaluated the toxicity of 1,2,3-trichloropropane in humans. Approximately 30 experiments have been conducted in experimental animals, although there are less than 15 publication or unpublished studies. Approximately 50% of the studies are by the oral route, 30% by inhalation, and the remainder are dermal/ocular studies. As illustrated in Figures 1-1 and 1-2, the most sensitive effects appear to be liver damage, kidney damage, respiratory tract damage, hematological effects, heart damage, and cancer.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,2,3-Trichloropropane

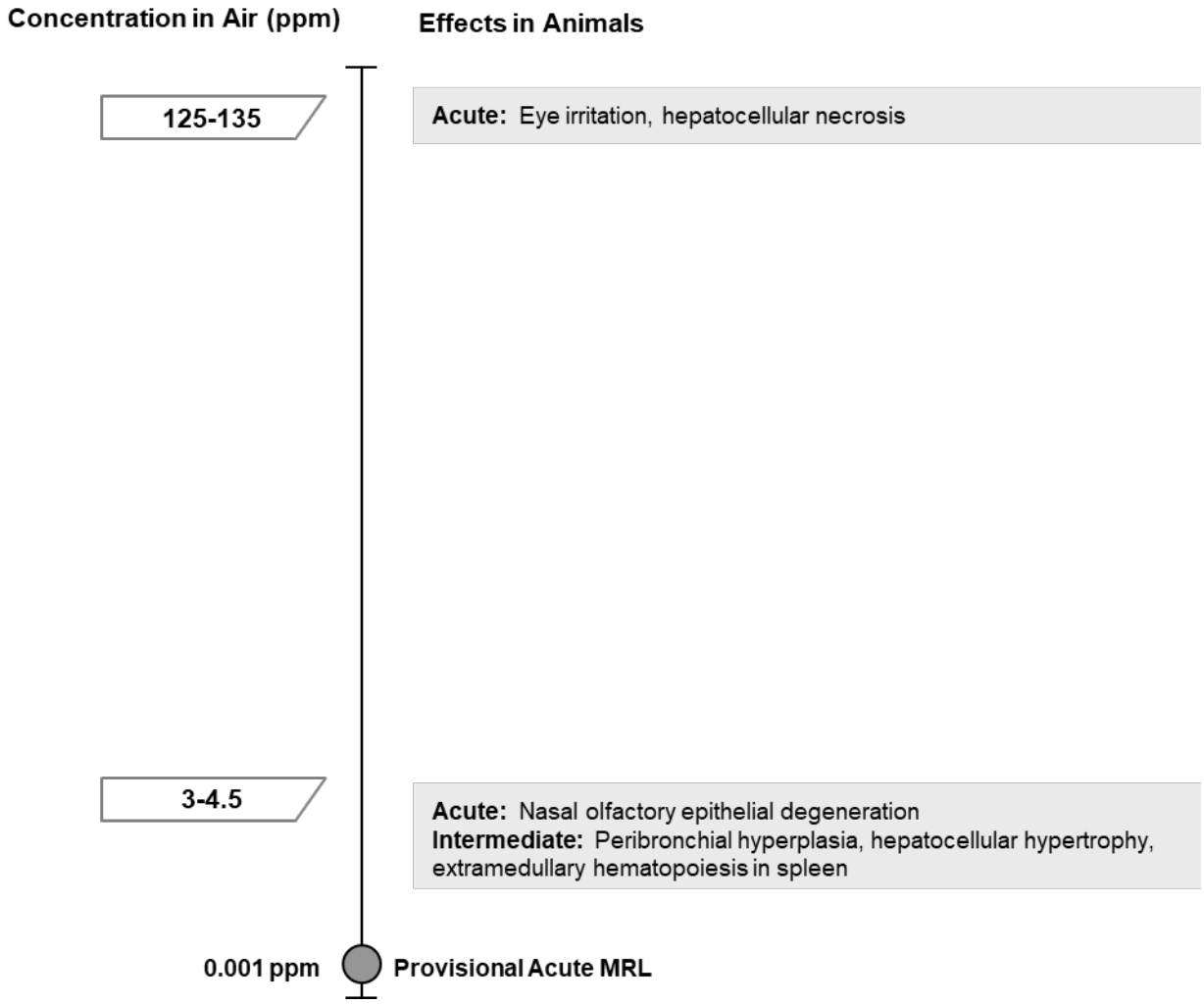
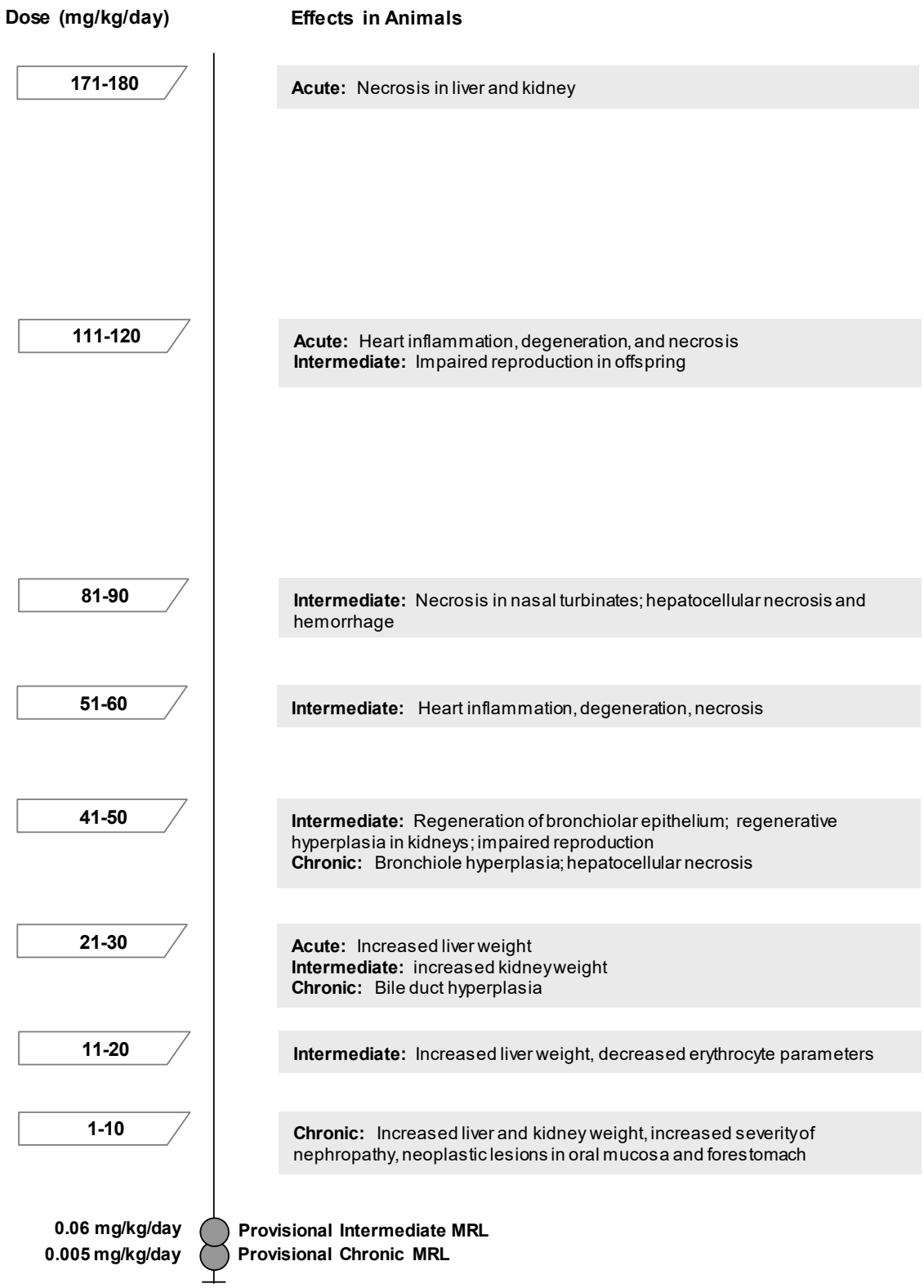


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2,3-Trichloropropane



Respiratory Effects. Throat irritation was observed in humans exposed to 1,2,3-trichloropropane for 15 minutes (Silverman et al. 1946). The respiratory tract, specifically the nasal olfactory epithelium, is the most sensitive target of toxicity in experimental animals following inhalation exposure to 1,2,3-trichloropropane. The earliest sign of toxicity in the olfactory epithelium is a decrease in epithelial thickness; at higher concentrations, degeneration, inflammation, and fibrosis occur (Miller et al. 1986a, 1986b). Peribronchial hyperplasia has also been observed in rats following inhalation exposure (Johannsen et al. 1988). Oral exposure to relatively high doses of 1,2,3-trichloropropane also resulted in inflammation and necrotic lesions in the nasal cavity of rats and mice following acute- or intermediate-duration exposure (NTP 1993) and regenerative hyperplasia of bronchiolar epithelium in mice following chronic exposure (NTP 1993). Additionally, lung hemorrhages have resulted in rabbits administered a lethal dermal dose of 1,2,3-trichloropropane (Alpert 1982; Union Carbide 1958).

Cardiovascular Effects. Heart inflammation, degeneration, and necrosis have been observed in rats administered 1,2,3-trichloropropane for an acute- or intermediate-duration exposure (Merrick et al. 1991). However, other oral studies and inhalation studies have not found histological alterations in the heart (Johannsen et al. 1988; Miller et al. 1986a; NTP 1993; Villeneuve et al. 1985).

Hematological Effects. Decreases in hematocrit, hemoglobin, and erythrocyte levels have been observed in rats following intermediate-duration oral exposure (NTP 1993); the resulting anemia appeared to be due to depressed erythropoiesis. Similar decreases in hematological parameters were also observed in rats and mice following chronic oral exposure, but this may have been due to blood loss associated with tumors (NTP 1993). In addition to the alterations in hematological parameters, splenic extramedullary hematopoiesis has been observed following inhalation (Johannsen et al. 1988) and oral (NTP 1993) exposures.

Liver Effects. Human data on the hepatotoxicity of 1,2,3-trichloropropane is limited to a case report of an individual with rapid progressive degeneration of liver function after ingesting 1,2,3-trichloropropane (Han 2010). Evidence of liver damage has been observed in rats and mice following inhalation or oral exposure. Observed effects include increases in liver weight, often observed at lower doses than those associated with histological damage; clinical chemistry alterations including alterations in serum enzymes, increases in serum bilirubin, and decreases in pseudocholinesterase levels; hepatocellular vacuolization; hepatocellular necrosis; and bile duct hyperplasia (Johannsen et al. 1988; Merrick et al. 1991; NTP 1993; Villeneuve et al. 1985). Following oral exposure, liver damage is one of the most sensitive effects.

Kidney Effects. The kidney is one of the most sensitive targets of toxicity following oral exposure. Increases in kidney weight were observed at lower doses; at higher doses, regenerative hyperplasia, tubular necrosis, and increases in the severity of chronic nephropathy have been observed (NTP 1993; Villeneuve et al. 1985). In contrast, renal effects have not been observed following inhalation exposure (Johannsen et al. 1988; Miller et al. 1986a).

Cancer Effects. The carcinogenicity of 1,2,3-trichloropropane was evaluated in rats and mice in a chronic gavage study (NTP 1993). In both species, forestomach squamous cell papillomas or carcinomas were observed at the lowest doses tested. Other sites with neoplastic lesions included the oral mucosa, liver, renal tubules, clitoral gland, mammary gland, preputial gland, harderian gland, and Zymbal's gland.

The U.S. Department of Health and Human Services categorized 1,2,3-trichloropropane as reasonably anticipated to be a human carcinogen (NTP 2016), the U.S. Environmental Protection Agency (EPA) categorized it as likely to be carcinogenic to humans (EPA 2009b), and the International Agency for Research on Cancer (IARC) categorized it as a suspected human carcinogen (IARC 2017).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of a provisional acute-duration inhalation MRL for 1,2,3-trichloropropane. The data were not considered adequate for derivation of an intermediate-duration inhalation MRL and no chronic inhalation studies were identified. As presented in Figure 1-3, the available inhalation data for 1,2,3-trichloropropane suggest that the respiratory tract, hematological erythrocyte, liver, and eyes are sensitive targets of toxicity.

The oral database was considered adequate for derivation of a provisional intermediate-duration oral MRL and a provisional chronic-duration oral MRL for 1,2,3-trichloropropane. The liver, kidney, erythrocytes, and cancer are sensitive targets following oral exposure to 1,2,3-trichloropropane. Reproductive and cardiovascular endpoints also have relatively low lowest-observed-adverse-effect level (LOAEL) values, as illustrated in Figure 1-4. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of 1,2,3-Trichloropropane – Inhalation

The respiratory tract, liver, erythrocyte, and eye are the most sensitive targets of 1,2,3-trichloropropane.

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.

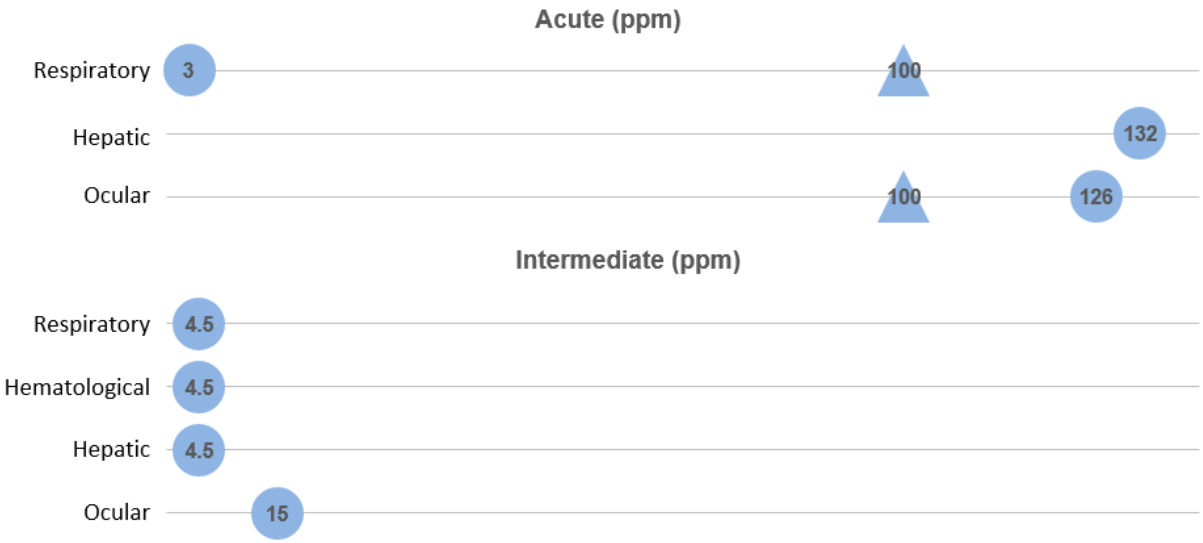


Figure 1-4. Summary of Sensitive Targets of 1,2,3-Trichloropropane – Oral

The heart, liver, erythrocyte, and kidney are the most sensitive targets of 1,2,3-trichloropropane.
Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.

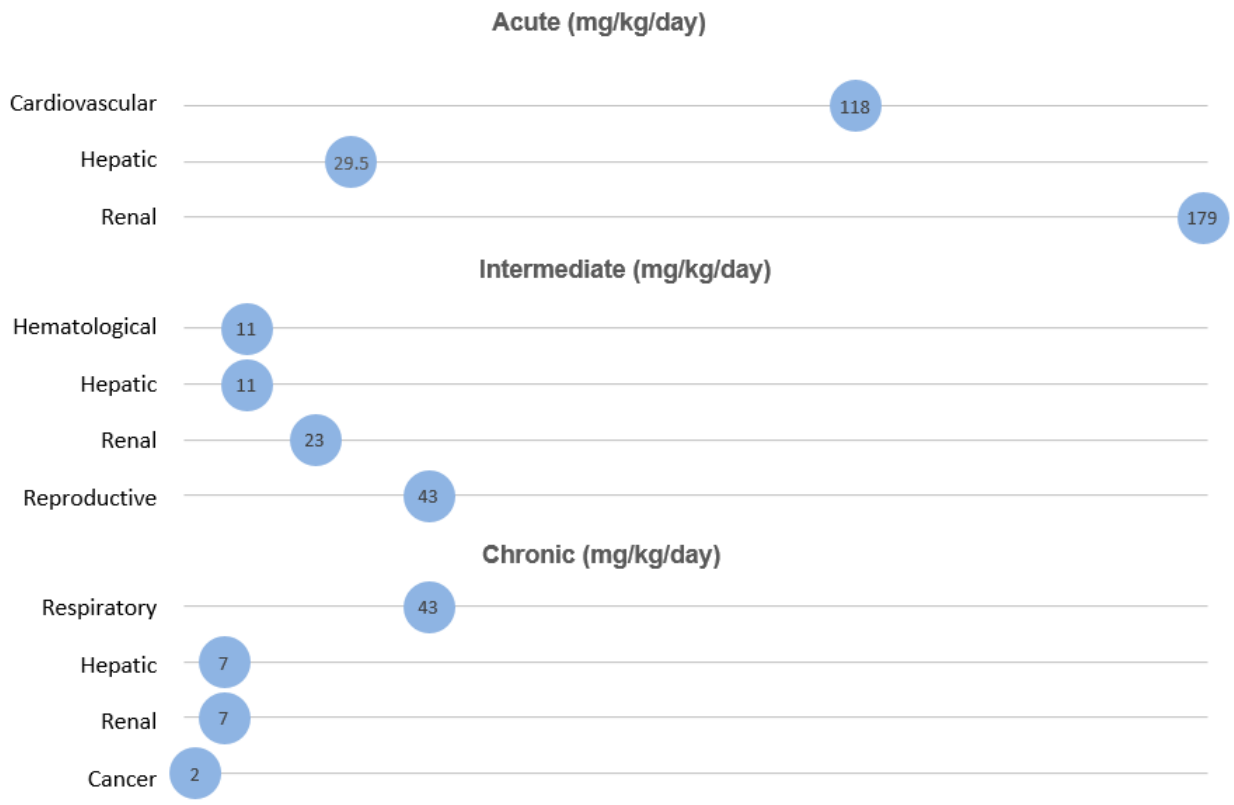


Table 1-1. Minimal Risk Levels (MRLs) for 1,2,3-Trichloropropane[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute (provisional)	0.001	Decreased thickness of nasal olfactory epithelium	$NOAEL_{HEC}$ of 0.03 ppm	30	Miller et al. 1986b
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate (provisional)	0.06	Increased absolute liver weight and decreased hemoglobin and erythrocyte levels	NOAEL of 5.7 mg/kg/day	100	NTP 1993
Chronic (provisional)	0.005	Bile duct hyperplasia	$BMDL_{10}$ of 0.47 mg/kg/day	100	NTP 1993

[a]See Appendix A for additional information.

BMDL = benchmark dose, 95% lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level;

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,2,3-trichloropropane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,2,3-trichloropropane, but may not be inclusive of the entire body of literature.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal/ocular studies are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint 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 endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of 1,2,3-trichloropropane are indicated in Table 2-2 and Figure 2-3.

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

The health effects of 1,2,3-trichloropropane have been primarily evaluated in experimental animal studies. As illustrated in Figure 2-1, approximately half of the health effects data come from oral exposure studies in animals. Animal data are available for each health effect category and exposure duration category. The most examined endpoints in inhalation and oral studies were hepatic, body weight, respiratory, and renal; approximately 40% of the studies examine each of these endpoints. Dermal/ocular exposure studies primarily focused on portal-of-entry effects. Human data are limited to three studies examining portal-of-entry effects following exposure to airborne 1,2,3-trichloropropane, developmental toxicity in the general population, and a case report of liver effects following ingestion. Based on these data, the following targets of toxicity have been identified:

- **Respiratory Endpoints:** Damage to the nasal olfactory epithelium have been observed in rats and mice following acute and intermediate inhalation exposure. Necrosis has also been observed in the nasal cavity following oral exposure. Throat irritation was reported in humans following a short exposure to a relatively high concentration of 1,2,3-trichloropropane. Peribronchial hyperplasia, bronchiolar epithelial regenerative hyperplasia, and lung hemorrhages have been observed in experimental animals following inhalation, oral, and dermal exposure, respectively.

- **Hepatic Endpoints:** Hepatic effects have been observed in a case study of an individual ingesting 1,2,3-trichloropropane and in experimental animal studies following acute and intermediate inhalation exposure and acute, intermediate, or chronic oral studies. Increases in liver weight, hepatocellular vacuolization, and bile duct hyperplasia were observed in these studies.

- **Renal Endpoints:** Renal effects have been observed in experimental animals following acute, intermediate, and chronic oral exposure. Effects included increases in kidney weight,

regenerative tubular hyperplasia, tubular necrosis, and increases in the severity of chronic nephropathy.

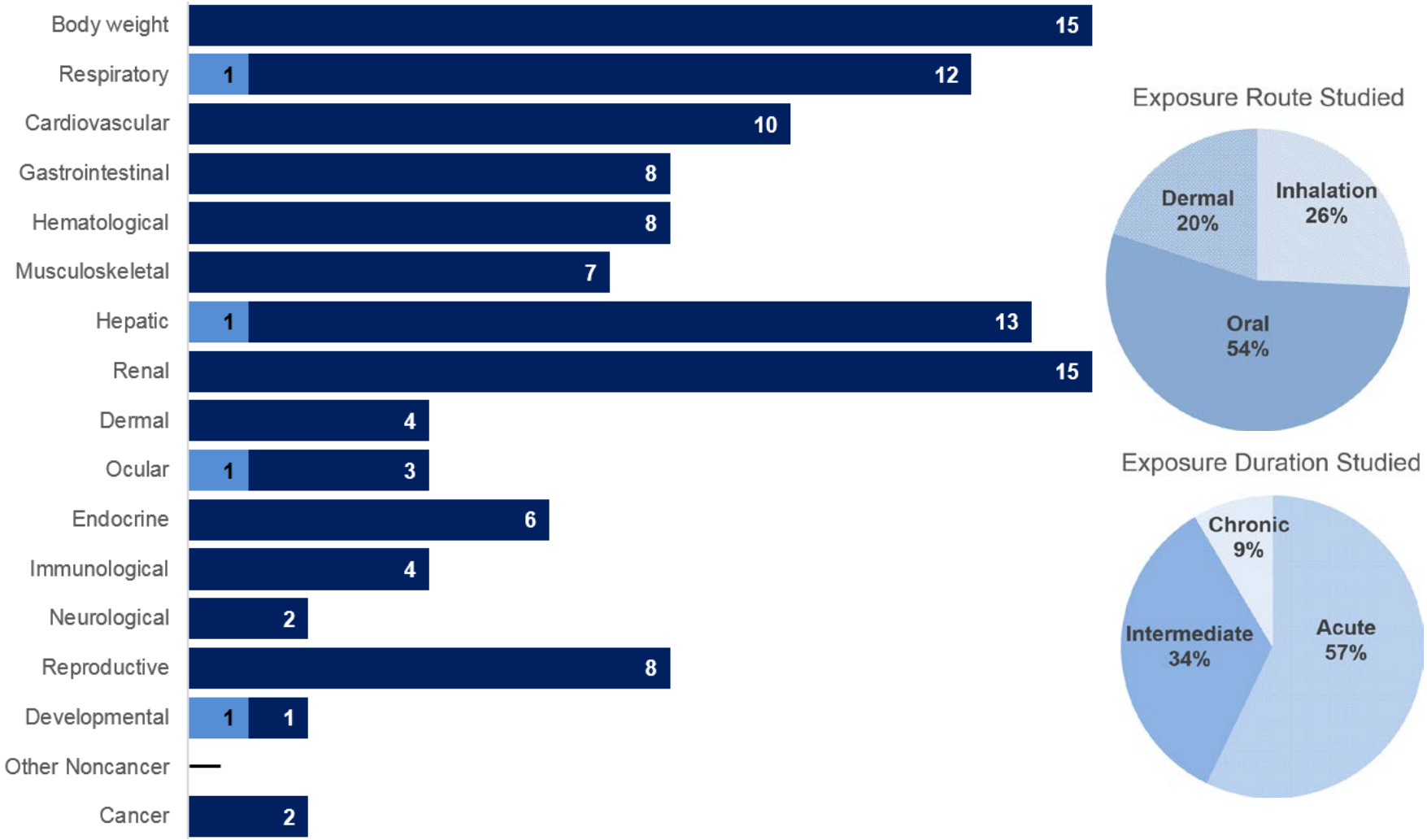
- **Hematological Endpoints:** Anemia, as evidenced by decreases in hematocrit, hemoglobin, and erythrocyte levels, and/or splenic extramedullary hematopoiesis have been observed in experimental animals following inhalation and oral exposure.

- **Cancer Endpoints.** Chronic oral exposure resulted in increases in neoplastic lesions in multiple sites in rats and mice. The most sensitive target tissue appears to be the forestomach; squamous cell papillomas and carcinomas in the forestomach were observed at the lowest doses tested. Other targets included the oral mucosa, liver, and kidneys.

- **Other Endpoints.** Alterations in body weight, lacrimation, impaired reproduction, and developmental toxicity have also been observed in inhalation and/or oral exposure studies in experimental animals; however, these do not appear to be sensitive targets of 1,2,3-trichloro-propane toxicity.

Figure 2-1. Overview of the Number of Studies Examining 1,2,3-Trichloropropane Health Effects

Most studies examined the potential hepatic, respiratory, body weight, and renal effects of 1,2,3-trichloropropane.
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 32 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Human 12	1 days 15 minutes/day	50, 100	CS	Resp		100		Throat irritation
					Ocular		100		Eye irritation
Silverman et al. 1946									
2	Rat (F344) 6 M	1 day 4 hours/day	0, 126, 343, 697, 2,160	CS, GN	Death			697	100% death at 697 and 2,160 ppm
					Ocular		126		Eye irritation
Gushow and Quast 1984									
3	Rat (CD) 5 M, 5 F	1 day 6 hours/day	0, 888	CS	Death			888	9/10 died
Johannsen et al. 1988									
4	Rat (F344) 5 M, 5 F	11 days 9 exposures 6 hours/day	0, 13, 40, 132	HP, BC, BI, OW, BW	Death				No deaths observed
					Bd wt	40	132		10–15% decrease in body weight gain
					Resp		13		Degeneration and inflammation of nasal olfactory epithelium at ≥13 ppm; multifocal fibrosis in nasal submucosa at 132 ppm
					Cardio	132			
					Gastro	132			
					Hemato	132			
					Musc/skel	132			
					Hepatic	40	132		Very slight hepatocellular necrosis
					Renal	132			
					Endocr	132			
					Immuno	132			No histological alterations in thymus or lymphoid tissue

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
					Neuro	132			No histological alterations in brain, spinal cord, or peripheral nerves
					Repro	132			No histological alterations in reproductive tissues
Miller et al. 1986a									
5	Rat (F344) 5 M, 5 F	11 days 9 exposures 6 hours/day	0, 1, 3, 10	HP, OW, GN, BW	Resp	1[b]	3		Decreased thickness of olfactory epithelium
Miller et al. 1986b									
6	Rat (Carworth-Wistar) 6 NS	1 day 4 hours/day	1,000	CS	Death			1,000	5/6 died within 14-day observation period
Smyth et al. 1962									
7	Rat (NS) 6 F	1 day 1–4 hours/day	500, 1,000, 2,000, 5,650	CS	Death			500	4/6 died
Union Carbide 1958									
8	Mouse (B6C3F1) 6 M	1 day 4 hours/day	0, 126, 343, 697, 2,160	CS, GN	Death			343	100% death at 697 and 2,160 ppm
Gushow and Quast 1984									
9	Mouse (B6C3F1) 6 M	11 days 9 exposures 6 hours/day	0, 13, 40, 132	CS, GN	Death				No deaths observed
					Bd wt	132			
					Resp		13		Decreased thickness of olfactory epithelium at 13 ppm and subacute inflammation of olfactory epithelium at ≥40 ppm

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
					Cardio	132			
					Gastro	132			
					Hemato	132			
					Musc/skel	132			
					Hepatic	40	132		Hepatocellular vacuolization
					Renal	132			
Miller et al. 1986a									
10	Mouse (B6C3F1) 5 M, 5 F	11 days 9 exposures 6 hours/day	0, 1, 3, 10	HP, OW, GN, BW	Resp	3	10		Nasal olfactory inflammation
Miller et al. 1986b									
INTERMEDIATE EXPOSURE									
11	Rat (CD) 5 M, 5 F	4 weeks 5 days/week 6 hours/day	0, 95, 297, 579	BW, OW, GN, CS	Death			579	3/10 rats died
					Bd wt	297			Decreased weight gain
					Resp	597			
					Hepatic		95		Increased liver weight
					Renal	579			
					Immuno		579		Decreased spleen weight
					Neuro	579			No histological alterations
					Repro	579			No histological alterations
Johannsen et al. 1988									
12	Rat (CD) 15 M, 15 F	13 weeks 5 days/week 6 hours/day	0, 0.5, 1.54, 4.5, 15, 49	OW, GN, HP, BC, UR, CS	Resp	1.54	4.5		Peribronchial hyperplasia
					Cardio	49			
					Gastro	49			
					Hemato		4.5F		Extramedullary hematopoiesis in spleen

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
					Musc/skel	49			
					Hepatic	1.54M	4.5M		Midzonal hepatocellular hypertrophy
					Renal	49			
					Ocular	4.5	15		Excessive lacrimation
Johannsen et al. 1988									
13	Rat (CD) 10 M, 20 F	10 weeks premating period, 30–40 day mating period, and GDs 0–14 5 days/week 6 hours/day	0, 0.49, 1.47, 4.5, 15	OW, CS, OF, GN, HP, DX	Repro	15			
Johannsen et al. 1988									

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.001 ppm; NOAEL dose adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

BC = blood chemistry; Bd Wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; DX = developmental toxicity; Endocr = endocrine; F = female(s); Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Resp = respiratory; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation
Acute (≤14 days)

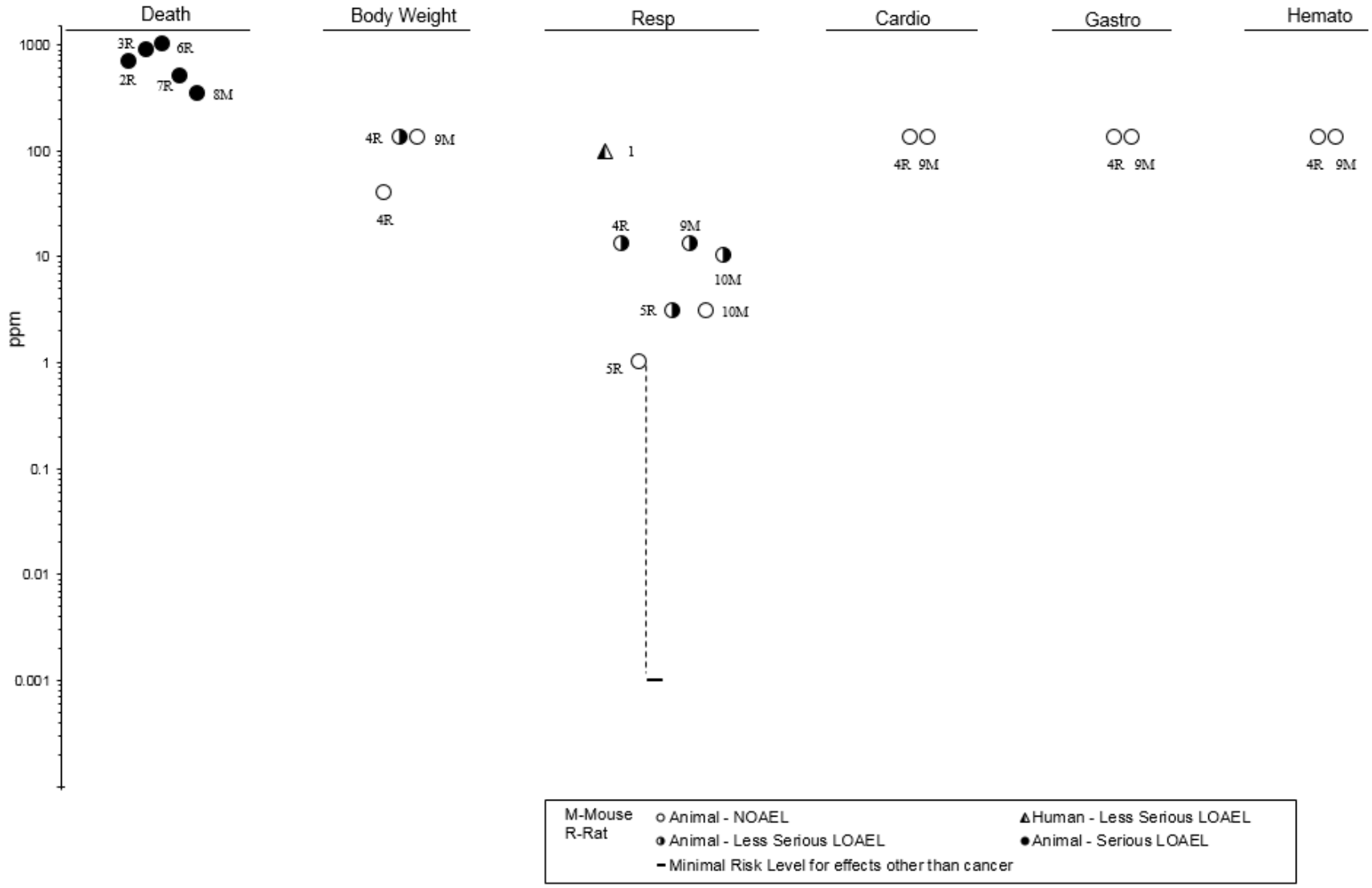


Figure 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation
Acute (≤14 days)

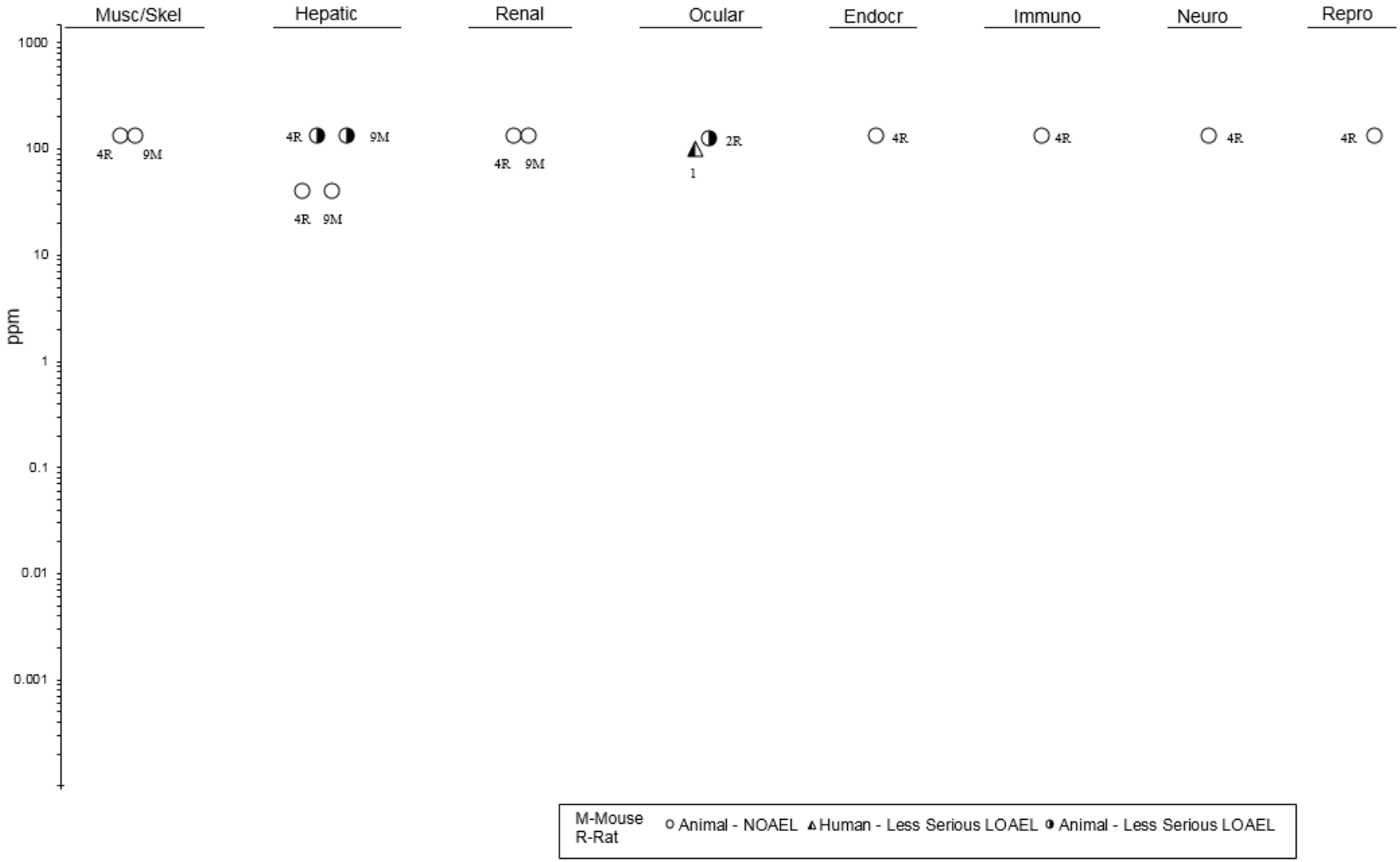


Figure 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation
Intermediate (15-364 days)

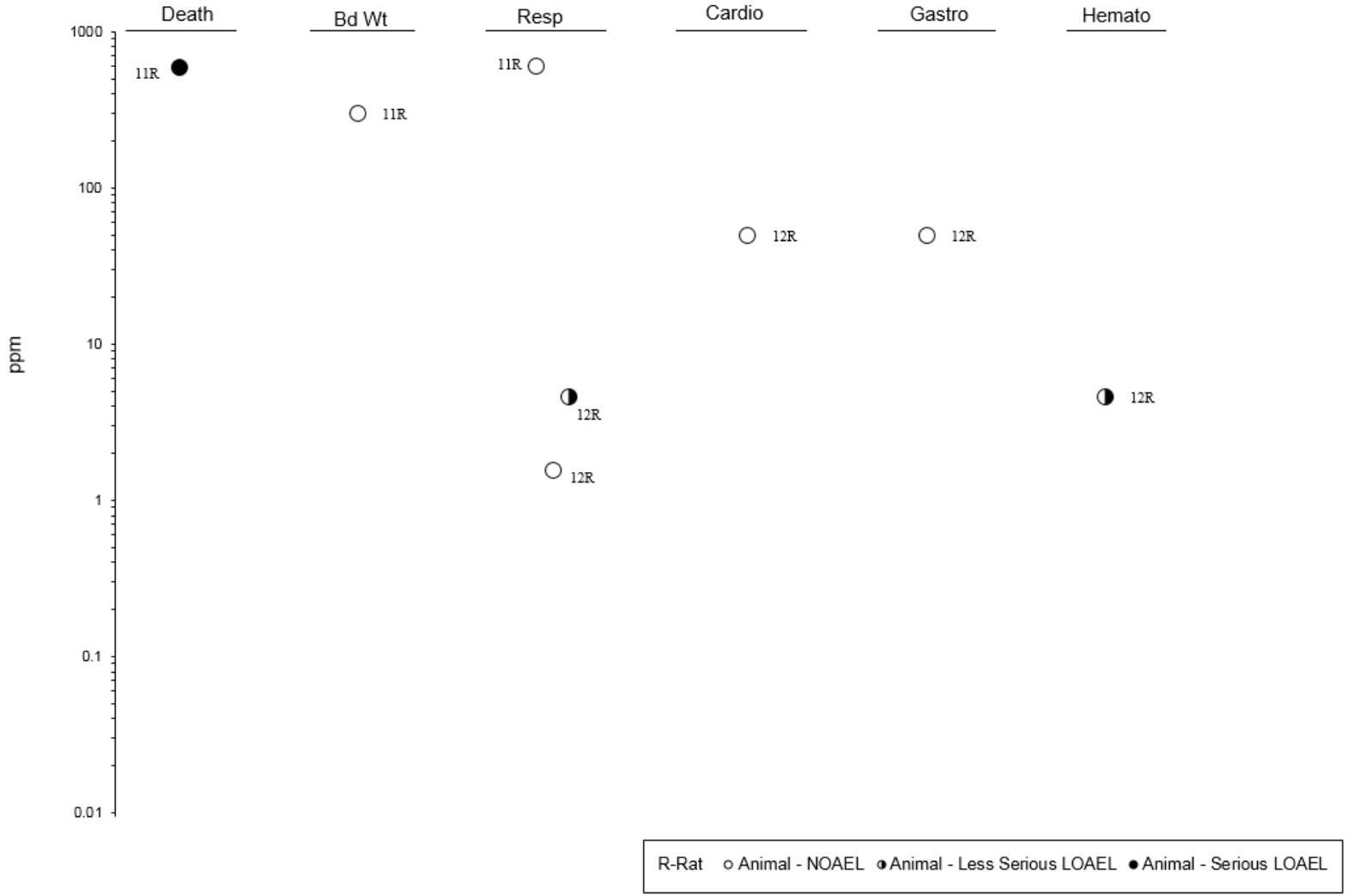


Figure 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation
Intermediate (15-364 days)

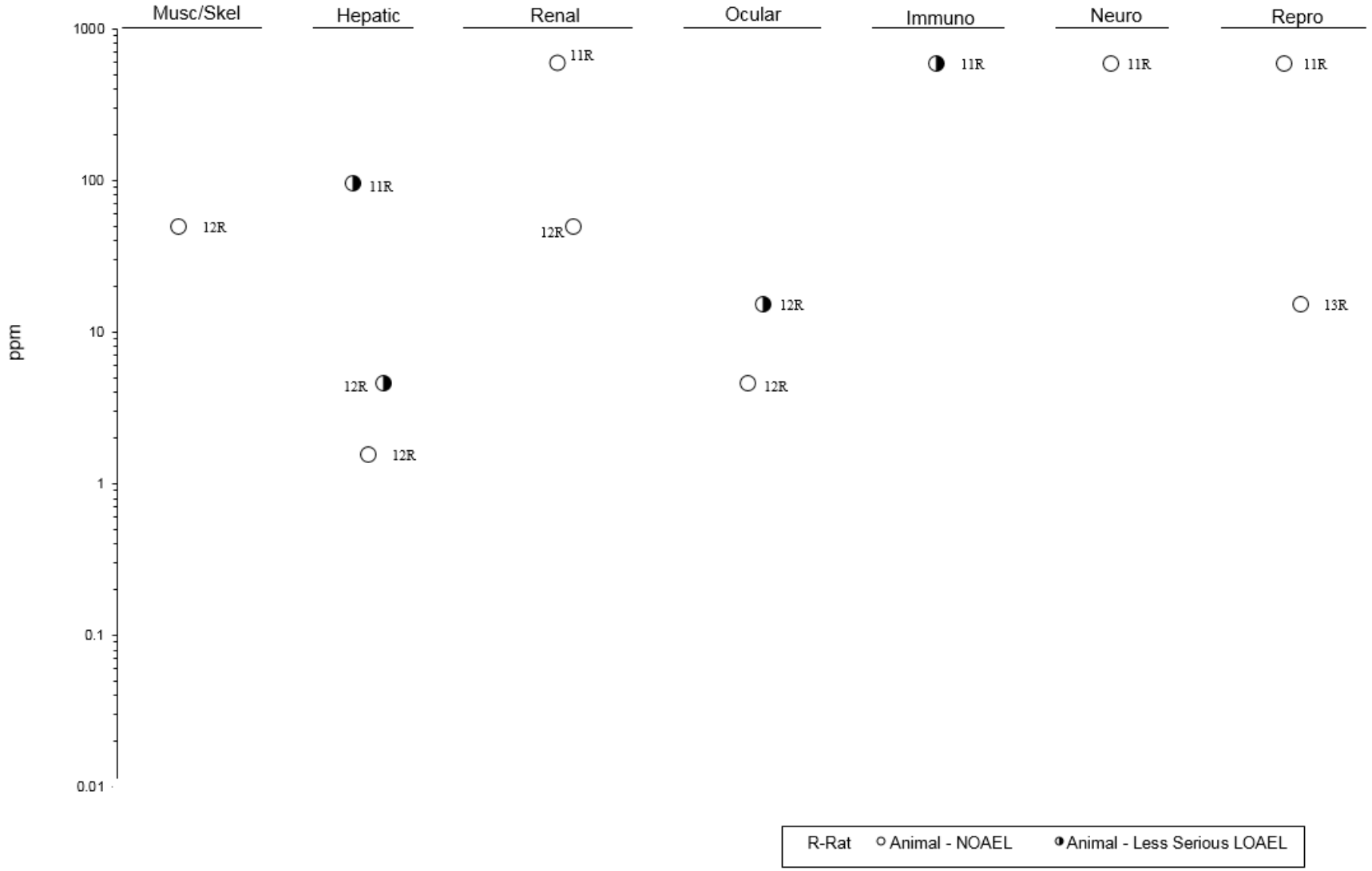


Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 5 M, 5 F	1 time (G)	78, 139, 250, 445, 778, 1,390, 2,500	GN, CS	Death			150	LD_{50}
Alpert 1982									
2	Rat (Wistar) 10 M	14 days 1 time/day (GO)	0, 15, 60	HP	Bd Wt	60			
					Renal	60			
					Repro	60			No histological alterations in male reproductive tissues
Dix 1979									
3	Rat (Sprague-Dawley) 10 M, 10 F	10 days (GO)	0, 1.5, 7.4, 29.5, 118	BW, OW, HP	Bd wt	29.5	118		22–25% decrease body weight gain
					Cardio	29.5	118		Heart inflammation, degeneration, and necrosis
					Hepatic	7.4	29.5		Increased relative liver weight
					Immuno	29.5	118		Diffuse thymic atrophy
Merrick et al. 1991									
4	Rat (F344) 20 M, 20 F	2 weeks 5 days/week (GO)	0, 8, 16, 32, 63, 125, 250	GN, CS, HP	Death			250	100% mortality
					Resp		250		Nasal necrosis
					Hepatic			250	Necrosis
					Renal			250	Necrosis
NTP 1993									

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
5	Rat (NS) 15 M	5 days 1 time/day (GO)	0, 80	HP, OF, FX	Repro	80			No evidence of dominant lethality or histological alterations in testes
Saito-Suzuki et al. 1982									
6	Rat (Carworth-Wistar) 5 M	1 time (G)		CS	Death			444	LD_{50}
Smyth et al. 1962									
7	Mice (Swiss) 8 M, 8 F	14 days (GO)	0, 12,5, 25,0, 50.0, 100.0, 200.0	CS, BW	Bd wt	200			
NTP 1990									
INTERMEDIATE EXPOSURE									
8	Rat (Sprague-Dawley) 10 M, 10 F	90 days (GO)	0, 1.5, 7.4, 14.7, 58.9	BW, OW, HP	Bd wt	14.7	58.9		14–20% decrease in body weight gain
					Cardio	14.7	58.9		Heart inflammation, degeneration, and necrosis
					Hepatic	7.4	14.7		Increased relative liver weight at ≥14.7 mg/kg/day; bile duct hyperplasia at 58.9 mg/kg/day
					Immuno	14.7	58.9		Plasma cell hyperplasia in mandibular lymph nodes
Merrick et al. 1991									

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
9	Rat (F344) 20 M, 20 F	17 weeks 5 days/week (GO)	0, 8, 16, 32, 63, 125, 250	OW, GN, HP, BC, FI	Death			125	One male and five females died
					Bd Wt	32 M	63 M		11 and 21% decreases in body weight gain in males at 63 and 125 mg/kg; 24% decrease in females at 125 mg/kg
					Resp	63	125		Necrosis in nasal turbinates
					Cardio	125			
					Gastro	125			
					Hemato	8[b]	16		Decreases in hematocrit, hemoglobin, and erythrocyte levels after 8 and 17 weeks
					Musc/skel	125			
					Hepatic	8 F[b]	16 F		Increases in liver weight in females at ≥16 mg/kg; hepatocellular necrosis and hemorrhage and bile duct hyperplasia in females at ≥125 mg/kg
					Renal	16 M	32 M		Increases in absolute and relative kidney weights in males at ≥32 mg/kg; Regenerative hyperplasia after 8 weeks of exposure at ≥63 mg/kg
					Endocr	125			

NTP 1993

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
10	Rat (Sprague-Dawley) 10 M,10 F	13 weeks 7 days/week (W)	M: 0, 0.17, 1.7, 17, 113; F: 0, 0.26, 2.6, 17.6, 149	OW, BC, GN, HP, BI, WI	Death				No deaths were observed
					Bd Wt	17	113		Reduced body weight gain
					Cardio	149			
					Hemato	149			
					Hepatic	17 M	113 M		Anisokaryosis, accentuated zonation and fatty vacuolation
					Hepatic	17.6 F	149 F		Biliary hyperplasia in females only
					Renal	17	113		Eosinophilic inclusions, pyknosis, nuclear displacement, fine glomerular adhesions, interstitial reactions, and histologic proteinuria
					Endocr	17	113		Angular collapse of some follicles, reduced colloid density, increased epithelial height in thyroid
Villeneuve et al. 1985									
11	Mouse (B6C3F1) 20 M, 20 F	17 weeks 5 days/week (GO)	0, 8, 16, 32, 63, 125, 250	HP, OW, BC, BI, GN, OF, FI	Death			250	Majority of deaths occurred by week 2 in females and week 4 in males
					Bd Wt	250			
					Resp	32 F	63 F		Regeneration of bronchiolar epithelium in the lungs of males at ≥125 mg/kg and females at ≥63 mg/kg
					Cardio	250			

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Gastro	32 F	63 F		Hyperkeratosis and acanthosis of forestomach
					Hemato	250			
					Musc/skel	250			
					Hepatic	63	125		Increased liver weights at ≥125 mg/kg; focal hepatocellular necrosis at 250 mg/kg
					Renal	125		250	Multifocal tubular necrosis in animals dying early
					Endocr	125			
NTP 1993									
12	Mice (Swiss) 20 M, 20 F	98 days (GO)	0, 30.0, 60.0, 120.0	CS, BW, FX	Repro	30	60		Decreased number of live pups in 5th litter and decreased fertility; at 120 mg/kg/day: decreased number of litters starting at the 3rd breeding, increased days to litter in the 4th and 5th litters, and decreased number of live pups per litter in 2–5 litters
					Repro	120 M			No alterations in epididymal sperm motility, count, or morphology
					Repro		120 F		Ovarian amyloidosis; no alterations in average estrous cycle length
NTP 1990									

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
13	Mice (Swiss) 20 M, 20 F	Prenatal exposure, post weaning, mating, and gestation exposure	0, 30.0, 60.0, 120.0	CS, BW, FX	Develop	60	120		Decreases in mating, fertility, and pregnancy indices.
NTP 1990									
CHRONIC EXPOSURE									
14	Rat (F344/N) 60 M, 60 F	2 years 5 days/week (GO)	0, 3, 10, 30 mg/kg	CS, BW, HE, BC, OW, HP	Death			10	Decreased survival
					Bd wt	10 F	30 F		15% decrease in body weight gain in females
					Resp	30			
					Cardio	30			
					Gastro	3	10		Hyperkeratosis of esophagus and acute inflammation of tongue in females at ≥10 mg/kg and males at 30 mg/kg
					Hemato	3	10		Hematopoietic cell proliferation in spleen at ≥10 mg/kg; decreased hemoglobin, increased leukocytes, increased segmented neutrophils (measured after 15 months) at 30 mg/kg
					Musc/skel	30			

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Hepatic	3 M[c]	10 M		Bile duct hyperplasia in males at 10 mg/kg at 15 months (at 30 mg/kg after 2 years); increased liver weight at ≥10 mg/kg
					Renal		3 M		Increased absolute kidney weight at ≥3 mg/kg; renal tubular hyperplasia at ≥10 mg/kg (males only) and increased severity of nephropathy (males only); renal tubular hyperplasia in females at 30 mg/kg
					Endocr		3		Focal hyperplasia of pancreatic acini
					Repro	10	30		Interstitial cell hyperplasia in testes

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Cancer			3	CEL: squamous cell papillomas or carcinomas in forestomach and adenomas of the pancreas; at ≥10 mg/kg: squamous cell papillomas or carcinomas in oral mucosa, adenoma in renal tubules, adenoma or carcinoma of the clitoral gland, and adenocarcinoma of the mammary gland (females only); at 30 mg/kg: adenoma or carcinoma in preputial gland, carcinoma in Zymbal gland (females only)
NTP 1993									
15	Mouse (B6C3F1) 60 M, 60 F	2 years 5 days/week (GO)	0, 6, 20, 60 mg/kg	CS, BW, HE, SC, OW, HP	Death			6	Decreased survival
					Bd wt	20	60		12–18% decrease in body weight gain
					Resp	20	60		Bronchiole hyperplasia
					Cardio	60			
					Gastro		6		Squamous hyperplasia in forestomach in females

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Hemato		6		Hematopoietic cell proliferation in spleen at ≥6 mg/kg; decreased erythrocyte, hematocrit and hemoglobin and increased leukocyte and segmented neutrophil counts at 60 mg/kg
					Musc/skel	60			
					Hepatic	20	60		Hepatocellular necrosis and increases in relative liver weight
					Renal	60			
					Ocular	60			No histological alterations were observed in the eye
					Endocr	60			
					Repro	60			No histological alterations

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Cancer			6	CEL 6 mg/kg: squamous cell papilloma or carcinoma in forestomach, hepatocellular adenoma or carcinoma in males; 20 mg/kg: harderian gland adenoma in males; 60 mg/kg: squamous cell papilloma or carcinoma in oral mucosa in females, harderian gland adenoma in females; uterine stromal polyps and endometrial adenoma or adenocarcinoma

NTP 1993

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.06 mg/kg/day based on duration-adjusted NOAEL of 5.7 mg/kg/day divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic oral MRL of 0.005 mg/kg/day based on a duration adjusted $BMDL_{RD10}$ of 0.47 mg/kg/day and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Bd Wt = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage, not specified; GN = gross necropsy; (GO) = gavage in oil vehicle; Gastro = gastrointestinal; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose; 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; No = number; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW= organ weight; Repro = reproductive; Resp = respiratory; (W) = drinking water; WI = water intake

Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Acute (≤14 days)

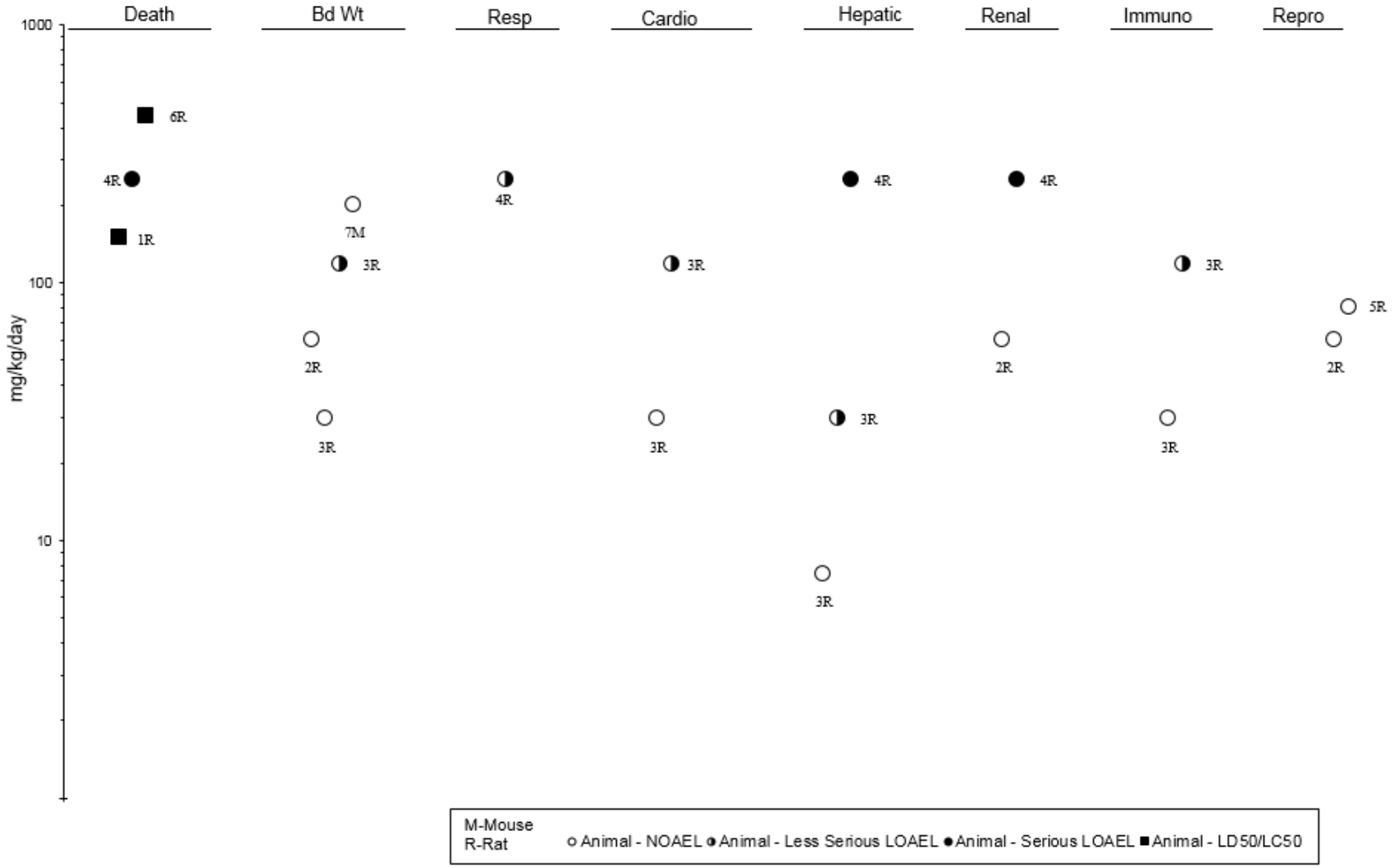


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Intermediate (15-364 days)

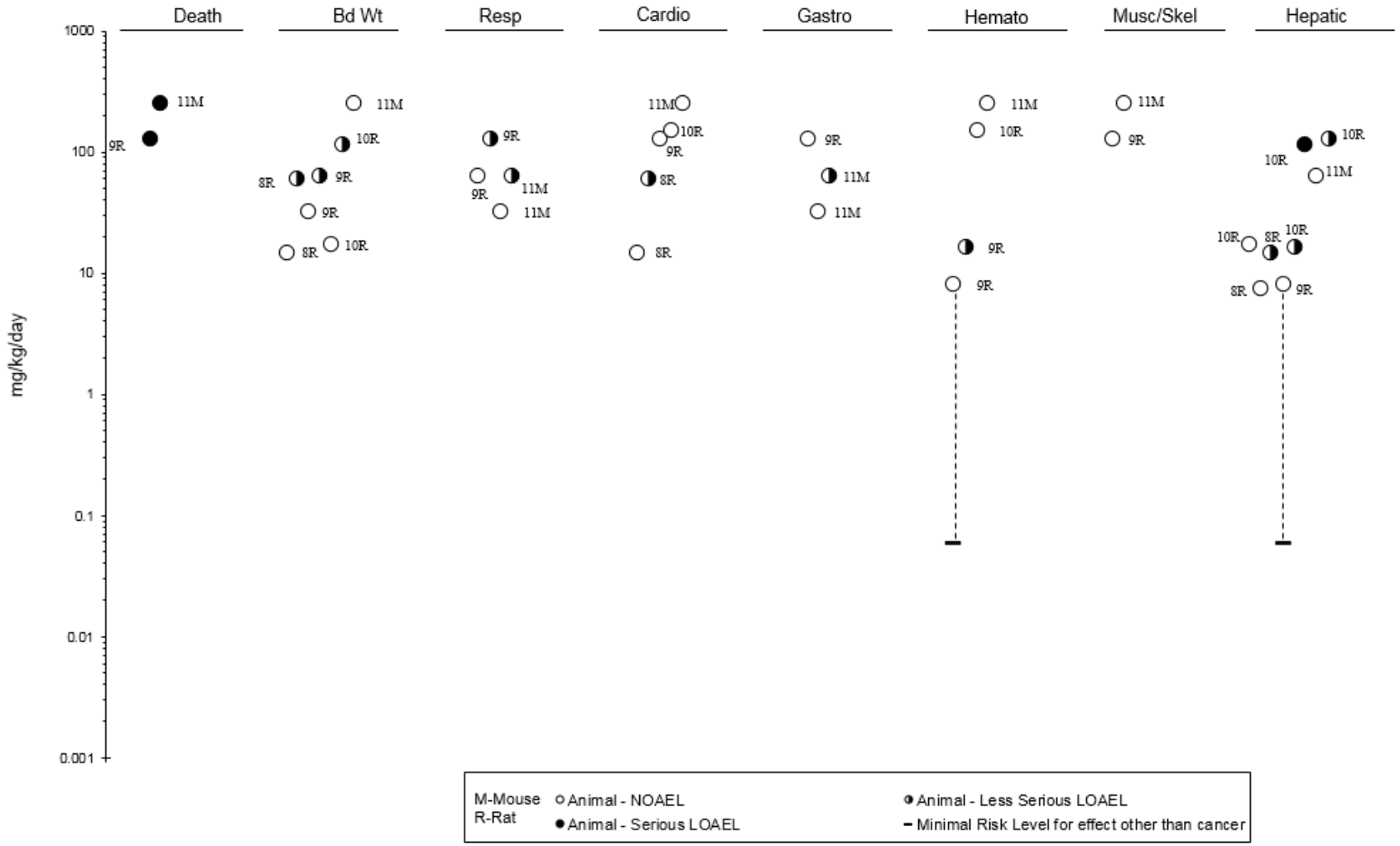


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Intermediate (15-364 days)

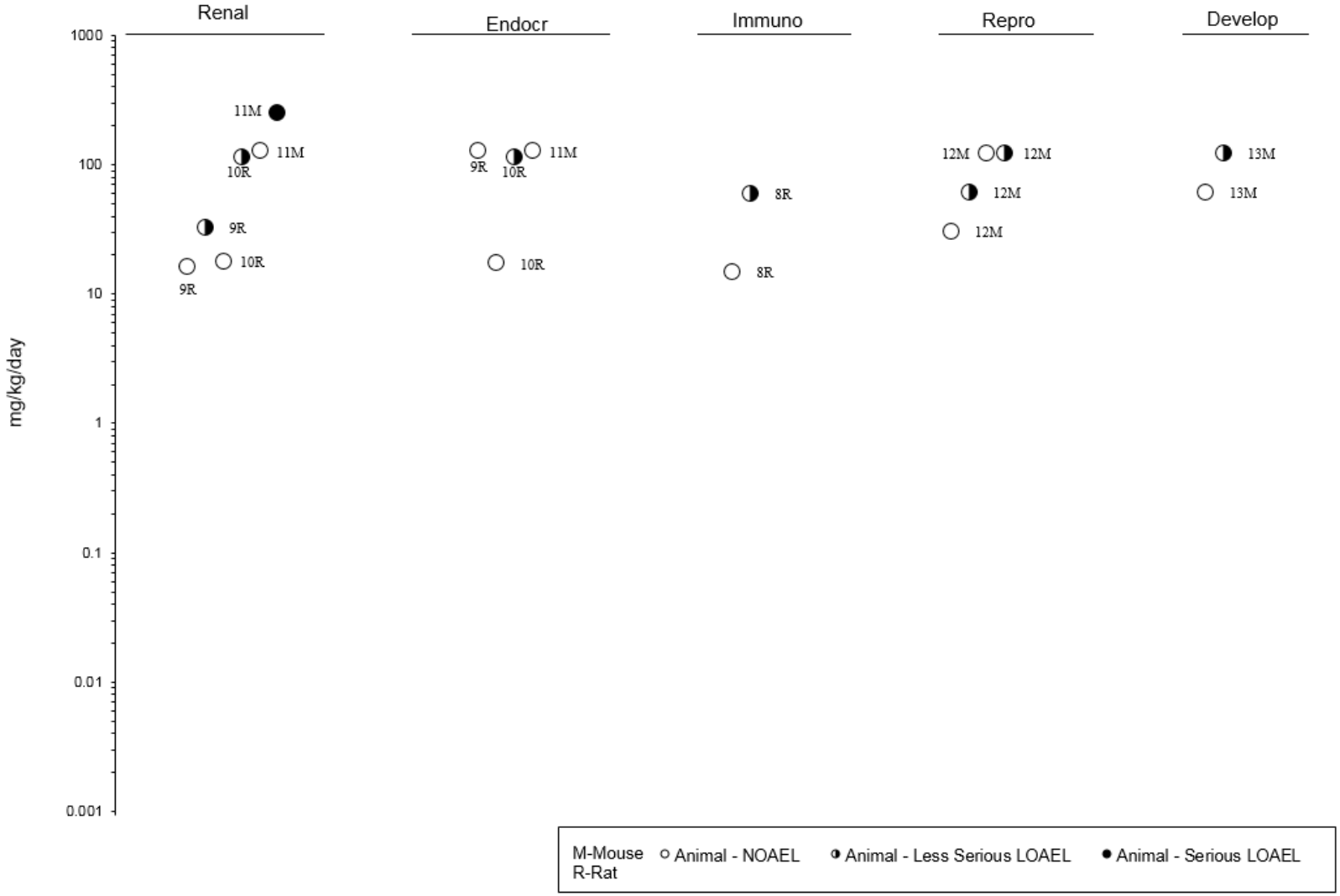


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Chronic (≥365 days)

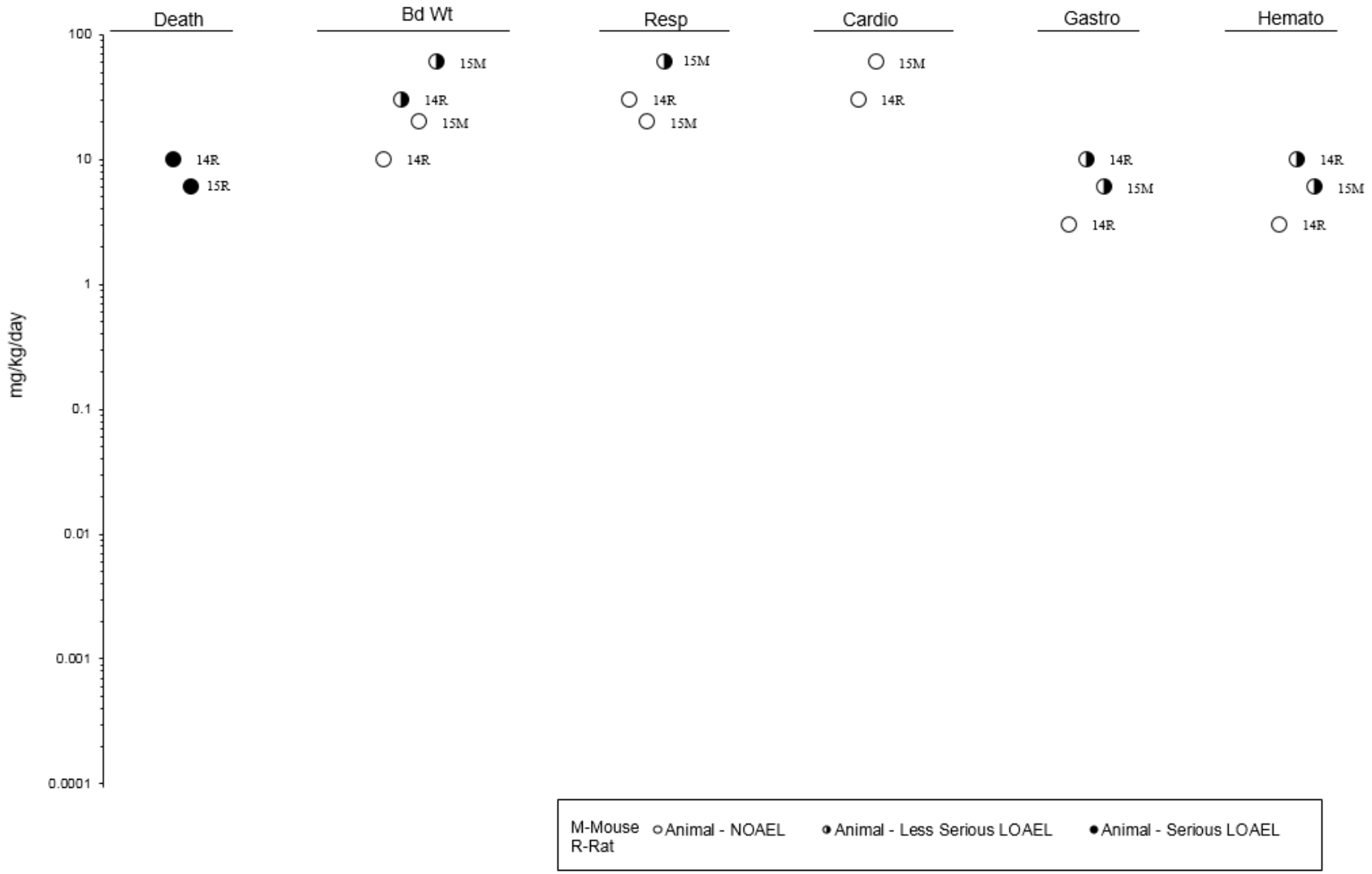


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Chronic (≥365 days)

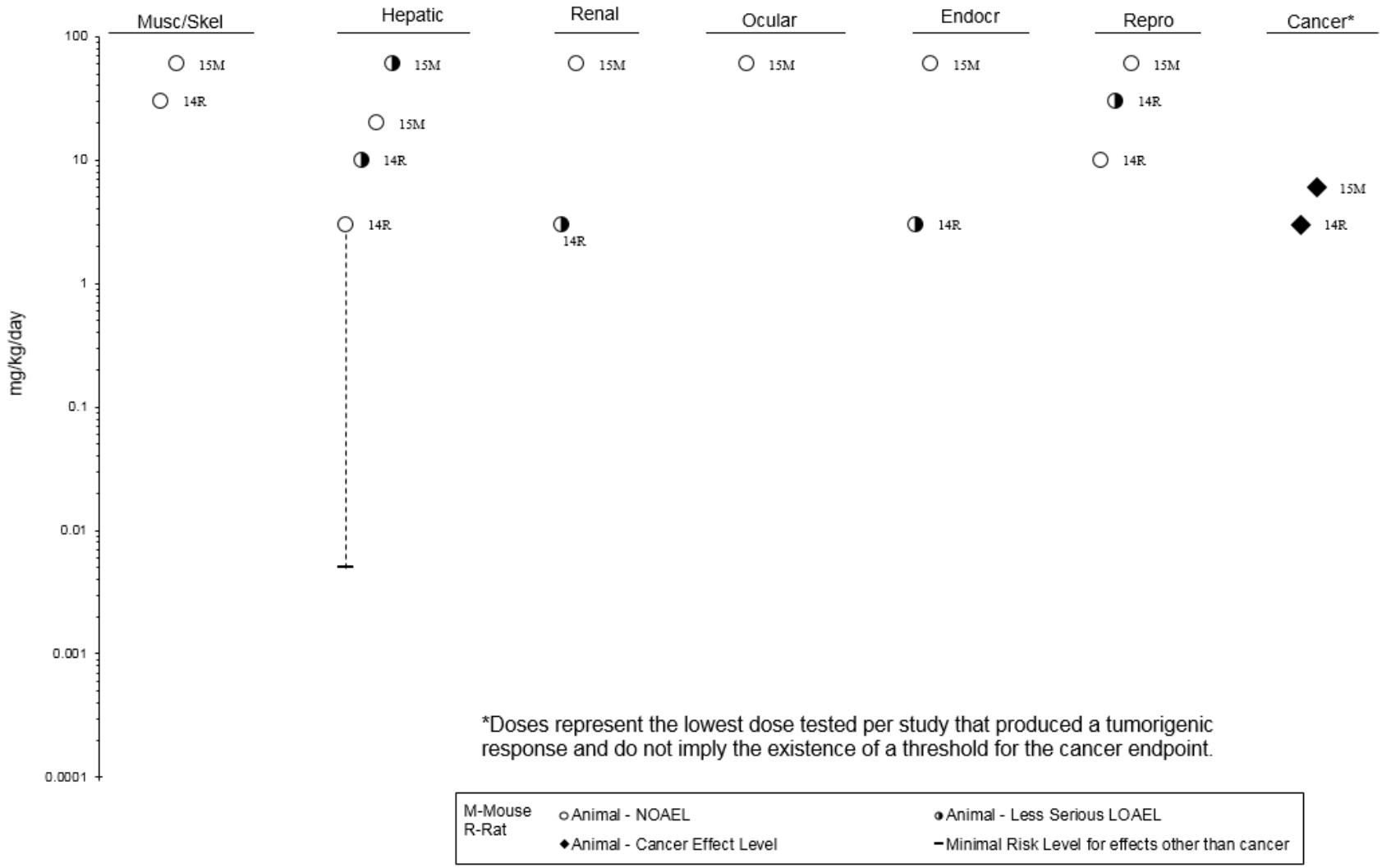


Table 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Rat 4 M, 4 F	24 hours	278, 556, 695, 1,112, 1,390 mg/kg	CS	Death			836 mg/kg	LD_{50}
Clark 1977								
Rabbit (New Zealand white) 6 M,6 F	24 hours	250, 445, 723, 1,084, 1,390, 2,500, 4,450 mg/kg	CS	Death			250 mg/kg	2/6 males died
				Resp			250 mg/kg	Lung discoloration
				Gastro			250 mg/kg	Stomach ulceration
				Hepatic			250 mg/kg	Liver discoloration
				Renal			250 mg/kg	Discoloration of kidneys and bladder contents
Alpert 1982								
Rabbit (New Zealand white) 6 M,6 F	24 hours	278 mg/kg	CS	Dermal		278 mg/kg		Skin irritation
Alpert 1982								
Rabbit (New Zealand white) 6 M,3 F	1 time	0.1 mL	CS	Ocular		0.1 mL		Eye irritation
Alpert 1982								
Rabbit (NS) 4M,4F	24 hours	0, 174 mg/cm^2	GN, CS	Dermal		174 mg/cm^2		Severe skin irritation
Clark 1977								
Rabbit (NS) 4 NS	1 time	NS	CS	Ocular		0.1 mL		Eye irritation
Clark 1977								

Table 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
Rabbit (NS) 7 NS	10 times in 15 minutes	2 mL	GN, CS	Dermal		2 mL		Intense skin irritation, subdermal bleeding
McOmie and Barnes 1949								
Rabbit (NS) 4 M	1 day 24 hours/day	Log series	CS	Death			2,458 mg/kg	LD_{50}
Smyth et al. 1962								
INTERMEDIATE EXPOSURE								
Guinea pig (Duncan-Hartley) 5 M, 5 F	3 weeks 1 days/week 6 hours/day	0, 1.83	CS	Dermal	0.51 mL[a]			
Alpert 1982								

[a]Challenge dose applied to sensitized and virgin skin for 6 hours 14 days after the last sensitizing dose. Both sensitizing and challenge doses were covered.

CS = clinical signs; F = female(s); GN = gross necropsy; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose, 50% kill; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

No studies were located regarding death in humans after exposure to 1,2,3-trichloropropane.

Inhalation exposure to 1,2,3-trichloropropane for 4–6 hours caused death in mice at concentrations as low as 343 ppm (Gushow and Quast 1984) and rats at concentrations as low as 500 ppm (Gushow and Quast 1984; Johannsen et al. 1988; Smyth et al. 1962; Union Carbide 1958). In a repeated-exposure studies, no deaths were observed in rats or mice exposed to concentrations as high as 132 ppm (Miller et al. 1986a) for 11 days or in rats exposed to 49 ppm for 13 weeks (Johannsen et al. 1988). The cause of death in the acute studies is unclear, but signs suggestive of central nervous system (CNS) impairment (e.g., incoordination and convulsions) have been observed prior to death in both species.

Oral LD_{50} values of 150 mg/kg (Alpert 1982) and 444 mg/kg (Smyth et al. 1962) have been determined for rats. Variations in LD_{50} values are apparent, which could be due to differences in animal strain, sex, fed/fasted state or compound purity. The cause of death is unclear, but signs suggestive of CNS impairment (e.g., piloerection, salivation, ataxia, coma) prior to death and hemorrhagic damage in visceral tissues (e.g., liver, kidney) were observed. Repeated gavage administration (5 days/week) of 1,2,3-trichloropropane caused death due to liver and kidney toxicity in 15% of female rats by the 13^{th} week at a dose of 125 mg/kg, in 100% of female rats by week 2 at 250 mg/kg, and in 80% of female mice by week 4 at 250 mg/kg (NTP 1993). Doses as high as 149 mg/kg/day were not lethal in rats, however, when administered in the drinking water for the 13 weeks (Villeneuve et al. 1985). Although absorption of 1,2,3-trichloropropane from drinking water could have been decreased due to use of a solubilizer, this suggests that 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. In chronic studies, decreases in survival were observed in rats and mice administered via gavage 10 or 6 mg/kg 5 days/week for 2 years (NTP 1993); the early deaths were likely secondary to neoplastic lesions.

Single dermal doses as low as 250 mg/kg caused death in rabbits (Alpert 1982). Dermal LD_{50} values of 836 mg/kg in rats (Clark 1977) and 2,458 mg/kg in rabbits (Smyth et al. 1962) have been identified. The treated skin of the animals in these studies was covered with an impervious barrier for 24 hours to prevent evaporation of the volatile compound. The cause of death is unclear, but symptoms suggestive of CNS impairment (e.g., ataxia, tremors, coma) and internal hemorrhage have been observed.

2.3 BODY WEIGHT

Intermittent exposure to 1,2,3-trichloropropane concentrations as high as 132 ppm for 11 days did not adversely affect body weight gain in rats or mice (Miller et al. 1986a). Body weight gain was decreased in rats that were intermittently exposed to lethal concentrations (≥297 ppm) of 1,2,3-trichloropropane for 4 weeks and concentrations as low as 15 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988). The decreased weight gain was more severe at higher concentrations and there was initial weight loss at 600 ppm in the 4-week study.

Reduced body weight gain occurred in rats treated with 1,2,3-trichloropropane by gavage at doses ≥58.9 mg/kg for acute- (Kimura et al. 2016) or intermediate-durations (Kimura et al. 2016; Merrick et al. 1991; NTP 1993; Villeneuve et al. 1985). No effect on body weight gain was observed in mice administered 250 mg/kg (5 days/week) for 17 weeks (NTP 1993). Less than 20% decreases in body weight gain were observed in rats and mice administered 30 or 60 mg/kg, respectively, 5 days/week for 2 years (NTP 1993).

2.4 RESPIRATORY

Limited information indicates that brief exposure (15 minutes) to 100 ppm 1,2,3-trichloropropane (purity unknown) can cause throat irritation in humans (Silverman et al. 1946). Repeated exposure of animals to 1,2,3-trichloropropane concentrations much lower than 100 ppm causes respiratory system effects that are indicative of irritant action. Intermittent 6-hour exposures for 11 days produced alterations in nasal tissues, particularly of the olfactory epithelium, of rats and mice (Miller et al. 1986a, 1986b). These changes included decreased thickness of the olfactory epithelium in rats and mice at 3 ppm, degeneration of the olfactory epithelium in rats at ≥10 ppm concentrations, and inflammation and decreased thickness of the olfactory epithelium in mice at 3–13 ppm with degeneration at higher concentrations. At 132 ppm, nasal submucosal fibrosis was observed in rats (Miller et al. 1986a). Intermittent exposure to ≥4.5 ppm for 13 weeks caused focal peribronchial hyperplasia in rats (Johannsen et al. 1988).

Nasal effects have also been observed in rats and mice orally administered 1,2,3-trichloropropane. These changes were produced by daily doses of 250 mg/kg (rats and mice) for 2 weeks and 125 mg/kg (rats) or 250 mg/kg (mice) for up to 17 weeks. Effects were similar in both species; these typically included inflammation, attenuation of the epithelial lining, and necrotic alterations, and principally occurred in the dorsal posterior areas of the nasal passages. The oral doses that produced the nasal alterations were in the

near lethal range. Repeated daily exposure of mice to lower doses of 1,2,3-trichloropropane (as low as 63 mg/kg) by oral intubation over a period of 17 weeks or 60 mg/kg for 2 years caused regenerative changes (e.g., hyperplasia) in the bronchiolar epithelium (NTP 1993).

Lung hemorrhage and apparently related effects (e.g., discoloration of the lungs and liquid in the thoracic cavity) have been observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982; Union Carbide 1958).

2.5 CARDIOVASCULAR

No studies were located regarding cardiovascular effects in humans after exposure to 1,2,3-trichloropropane. There were no histopathological changes in the hearts of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988).

Animal studies found that administration by gavage of 1,2,3-trichloropropane resulted in heart inflammation, degeneration, and necrosis in rats administered 118 mg/kg/day for 10 days (Merrick et al. 1991) or 58.9 mg/kg/day for 90 days (Merrick et al. 1991). In contrast, other studies have not found histological alterations in the heart of rats administered 125 mg/kg by gavage 5 days/week for 17 weeks (NTP 1993), 149 mg/kg/day by drinking water for 13 weeks (Villeneuve et al. 1985), or 30 mg/kg administered by gavage 5 days/week for 2 years (NTP 1993), or in mice administered 250 mg/kg 5 days/week for 17 weeks (NTP 1993) or 60 mg/kg 5 days/week for 2 years (NTP 1993).

2.6 GASTROINTESTINAL

No studies were located regarding gastrointestinal effects in humans after exposure to 1,2,3-trichloropropane.

There were no histopathological changes in the stomach and intestines of rats and mice that were intermittently exposed to airborne concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988).

In mice administered 63 mg/kg 1,2,3-trichloropropane for 17 weeks (5 days/week), hyperkeratosis and acanthosis of the forestomach were observed (NTP 1993). Chronic exposure also resulted in gastrointestinal lesions. Hyperkeratosis of the esophagus and acute inflammation of the tongue were observed in female rats administered via gavage (5 days/week) 10 mg/kg and in male rats administered 30 mg/kg (NTP 1993). In female mice, squamous hyperplasia was observed in the forestomach following 5 days/week administration of 6 mg/kg (NTP 1993). Ulceration of the stomach wall was observed in rabbits dermally exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982).

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans after exposure to 1,2,3-trichloropropane. Hematological evaluations were normal in rats and mice that were intermittently exposed to inhalation concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a). Hematological evaluations of rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks also were normal, but splenic extramedullary hematopoiesis was increased at ≥4.5 ppm (Johannsen et al. 1988). Although increased splenic hematopoiesis was observed, other hematology parameters were unremarkable. Spleen weights were decreased in rats that were intermittently exposed to 579 ppm 1,2,3-trichloropropane for 4 weeks, but the hematological significance of this effect cannot be determined because evaluation of hematology and histology was not performed (Johannsen et al. 1988).

An oral study found evidence of anemia, indicated by decreased hematocrit, hemoglobin, and erythrocyte counts, in rats that were administered 1,2,3-trichloropropane by gavage (5 days/week) at doses as low as 16 mg/kg over a period of 17 weeks (NTP 1993). The anemia was mild at the lower doses and appears to be nonregenerative and associated with depressed erythropoiesis. 1,2,3-Trichloropropane did not produce significant hematological alterations in rats when administered in the drinking water at doses as high as 149 mg/kg/day for 13 weeks (Villeneuve et al. 1985) or in mice administered up to 250 mg/kg via gavage (5 days/week) for 17 weeks (NTP 1993). Chronic administration of 10 mg/kg in rats and 6 mg/kg in mice resulted in hematopoietic cell proliferation in the spleen (NTP 1993); higher doses (30 and 60 mg/kg in rats and mice, respectively) resulted in decreased erythrocyte, hematocrit, and hemoglobin concentrations. The investigators noted that the hematological effects were likely due to depressed erythropoiesis or from blood loss associated with forestomach and/or oral mucosal neoplasms (NTP 1993). The NTP study also reported that increases in leukocyte levels, particularly segmented neutrophils, in the rats and mice were likely due to neoplasm-induced inflammation.

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans after exposure to 1,2,3-trichloropropane. There were no histopathological changes in the skeletal muscle or bone of rats and mice intermittently exposed via inhalation to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988). Similarly, no pathological effects in bone or skeletal muscle of rats and mice that were administered via gavage 1,2,3-trichloropropane at doses as high as 125 and 250 mg/kg, respectively, over a period of 17 weeks (NTP 1993) or 30 or 60 mg/kg, respectively, for 2 years (NTP 1993).

2.9 HEPATIC

Data on the hepatic toxicity of 1,2,3-trichloropropane are limited to a case report of a man consuming 10–15 mL of an unknown liquid; 1,2,3-trichloropropane exposure was suspected based on elevated levels of 1,2,3-trichloropropane in the blood (Han 2010). Rapid progressive deterioration of liver function was noted 2 days post-exposure.

Acute- and intermediate-duration inhalation exposure to 1,2,3-trichloropropane resulted in histological alterations in the livers of rats and mice. Exposure to 132 ppm for 2 weeks resulted in very slight hepatocellular necrosis in rats and hepatocellular vacuolization in mice (Miller et al. 1986a). Following intermediate-duration inhalation exposure, mild hepatocellular hypertrophy was observed in rats exposed to ≥4.5 ppm in a 13-week study (Johannsen et al. 1988).

Oral studies clearly support the identification of the liver as a target of 1,2,3-trichloropropane toxicity. The most sensitive effect appears to be decreases in liver weight which have been observed in acute studies at ≥29.5 mg/kg/day (Merrick et al. 1991), intermediate-duration studies at ≥14.7 mg/kg/day (Merrick et al. 1991; NTP 1993), and chronic studies at ≥10 mg/kg (NTP 1993). The NTP (1993) 17-week study also found decreases in pseudocholinesterase at low doses (≥8 mg/kg) in rats; the investigators noted that the decrease in pseudocholinesterase may be due to a hepatocellular damage-induced decrease in synthesis (NTP 1993). Increases in serum total bilirubin and alanine aminotransferase (ALT) have also been observed in rats exposed to ≥63 mg/kg (5 days/week) for 17 weeks (NTP 1993). Histological alterations have been observed following acute, intermediate, and chronic oral exposure. Gavage administration of 250 mg/kg (5 days/week) produced hepatocellular necrosis in rats and mice within 2 weeks; the liver effects were considered a contributing factor to the

early mortality (NTP 1993). Necrotic changes also occurred in the livers of rats and mice treated with daily gavage doses as low as 125 mg/kg over a period of 17 weeks (NTP 1993). Exposure to 113 or 149 mg/kg/day 1,2,3-trichloropropane administered in drinking water for 13 weeks produced mild hepatic changes (e.g., occasional fatty vacuolization and biliary hyperplasia) in rats (Villeneuve et al. 1985), suggesting that 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. Hepatocellular necrosis has also been observed in mice chronically administered 60 mg/kg 5 days/week for 2 years (NTP 1993). In addition to the reported hepatocellular effects, several oral studies have found bile duct hyperplasia in rats administered 58.9 mg/kg/day 1,2,3-trichloropropane for 90 days (Merrick et al. 1991), 113 mg/kg/day for 13 weeks (Villeneuve et al. 1985), or 30 mg/kg 5 days/week for 2 years (NTP 1993). Turgid and discolored livers were observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982; Union Carbide 1958). These macroscopic alterations are consistent with oral and inhalation evidence of hepatotoxicity.

2.10 RENAL

No studies were located regarding renal effects in humans after exposure to 1,2,3-trichloropropane. Based on available data, the kidney does not appear to be a sensitive target following inhalation exposure to 1,2,3-trichloropropane. No histological alterations were observed in rats and mice exposed to 132 ppm for 2 weeks (Miller et al. 1986a) or 49 ppm for 13 weeks (Johannsen et al. 1988); increases in kidney weights were observed in the 13-week study, but this was not considered adverse in the absence of other indicators of renal toxicity.

In contrast to the inhalation studies, oral exposure studies have reported kidney toxicity. Daily gavage doses of 250 mg/kg produced serious renal toxicity (e.g., tubular nephropathy, necrosis) in rats and mice within 2 weeks (NTP 1993). The kidney damage in rats was severe enough to contribute to death. At a lower dose, regenerative hyperplasia in the outer medulla and proximal tubule karyomegaly were observed after 3 or 7 days of administration of 125 mg/kg/day 1,2,3-trichloropropane (Kimura et al. 2016). Increases in relative and absolute kidney weights have been observed at ≥32 and ≥64 mg/kg, respectively, following intermediate-duration exposure (Kimura et al. 2016; NTP 1993). Regenerative hyperplasia was observed in rats after 28 day of administration of 125 mg/kg/day (Kimura et al. 2016), 8 weeks of administration of 63 mg/kg 5 days/week (NTP 1993) and at 125 mg/kg after 17 weeks of exposure (NTP 1993). Similar doses of 1,2,3-trichloropropane (113 or 149 mg/kg) administered in drinking water for 13 weeks produced mild renal changes (e.g., pyknosis, fine glomerular adhesions, and occasional histologic proteinuria) in rats (Villeneuve et al. 1985). The mild renal changes suggest that

1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. Necrotic changes occurred in the kidneys of mice treated with daily gavage doses of 250 mg/kg over a period of 17 weeks (NTP 1993). Chronic administration (5 days/week) resulted in several renal effects (NTP 1993): increases in absolute kidney weights in males at ≥3 mg/kg, increases in absolute kidney weight in females and relative kidney weights in males and females at ≥10 mg/kg, renal hyperplasia in rats at ≥10 mg/kg, and an increase in the severity of nephropathy in male rats, as compared to controls at 30 mg/kg. NTP (1993) noted that the renal hyperplasia was part of the continuum with renal adenomas; thus, this lesion could be considered precancerous. No renal effects were observed in mice chronically administered doses as high as 60 mg/kg 5 days/week (NTP 1993).

Limited information is available on the renal toxicity of 1,2,3-trichloropropane following oral administration. Discolored kidneys and hematuria were observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982; Union Carbide 1958). These macroscopic alterations are consistent with oral and inhalation evidence of renal toxicity.

2.11 DERMAL

No studies were located regarding dermal or ocular effects in humans after exposure to 1,2,3-trichloropropane. Daily gavage administration of 1,2,3-trichloropropane at doses ≥63 mg/kg for up to 17 weeks caused alopecia but no gross eye irritation in rats (NTP 1993). Mice that were similarly treated with up to 250 mg/kg 1,2,3-trichloropropane had no macroscopic skin lesions or gross eye irritation (NTP 1993).

Dermal application of 1,2,3-trichloropropane causes severe skin irritation in rabbits. Evidence suggests that prolonged exposure (e.g., for 24 hours) or repeated daily application (e.g., for 2 weeks) may be necessary to cause irritation (Clark 1977; McOmie and Barnes 1949). The results of one study suggest that 1,2,3-trichloropropane in corn oil vehicle was a very mild skin sensitizer in guinea pigs (Clark 1977). Another study that used a less sensitive procedure found no evidence of skin sensitization by undiluted 1,2,3-trichloropropane in guinea pigs (Alpert 1982). This study also found that corn oil itself was a mild skin sensitizer in guinea pigs, indicating that there is a possibility that the vehicle may enhance the weak effect observed by Clark (1977).

2.12 OCULAR

Limited information indicates that brief (15-minute) exposure to 100 ppm 1,2,3-trichloropropane vapor causes eye irritation in humans (Silverman et al. 1946). A single 4-hour exposure to vapor concentrations

as low as 126 ppm 1,2,3-trichloropropane (Gushow and Quast 1984) caused eye irritation in rats and mice. Repeated intermittent exposure to vapor concentrations as low as 15 ppm for 13 weeks (Johannsen et al. 1988) caused eye irritation in rats. Ocular application of 1,2,3-trichloropropane caused eye irritation in rabbits (Alpert 1982; Clark 1977).

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans after exposure to 1,2,3-trichloropropane. Two studies have reported effects in endocrine tissues in rats. A 13-week drinking water study reported histological alterations in the thyroid of rats exposed to 113 mg/kg/day (Villeneuve et al. 1985); alterations included reduced colloid density, increased epithelial height, and angular collapse of some follicles. NTP (1993) reported focal hyperplasia of pancreatic acini in rats administered ≥3 mg/kg 1,2,3-trichloropropane by gavage 5 days/week for 2 years. The endocrine system does not appear to be a sensitive target of 1,2,3-trichloropropane toxicity based on the inconsistency of affected tissues in the studies finding effects and that most studies examining the endocrine system including a 2-week rat inhalation study identifying a NOAEL of 132 ppm (Miller et al. 1986a), 17-week gavage studies in rats and mice both identifying a NOAEL value of 125 ppm (NTP 1993), and a 2-year gavage study in mice with a NOAEL of 60 mg/kg (NTP 1993) have not found effects.

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after exposure to 1,2,3-trichloropropane. Information on the potential effect of 1,2,3-trichloropropane on immune function is limited to an *in vitro* assay that reported weak inhibition of B-cell lymphocyte mitogenesis and no inhibition of T-cell lymphocyte mitogenesis in C3H/He mouse splenic cells (Sakazaki et al. 2001).

There were no histopathological alterations in the thymus, spleen, lymphoid tissue, or bone marrow of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm for 13 weeks (Johannsen et al. 1988). Intermittent exposure to a higher (lethal) concentration (579 ppm) for 4 weeks caused decreased spleen weight in rats (Johannsen et al. 1988). Due to the lack of histological examinations and immunoassays, the immunological significance of the decreased spleen weight cannot be determined.

Merrick et al. (1991) reported diffuse thymic atrophy in rats administered 188 mg/kg/day for 10 days and plasma cell hyperplasia in the mandibular lymph nodes of rats administered 58.9 mg/kg/day for 90 days. NTP (1993) reported lymphoid depletion in the spleen and thymus of rats administered 1,2,3-trichloropropane at doses ≥63 mg/kg/day over 17 weeks and dying early (NTP 1993); the incidence of these lesions were not reported. Mice that were similarly treated with lethal doses (250 mg/kg) showed splenic lymphoid depletion with occasional lymphoid necrosis and increased thymus weight (incidences were not reported) (NTP 1993). The immunological significance of these effects are not known.

As indicated in the discussion of dermal effects (Section 2.11), one study provides limited evidence that 1,2,3-trichloropropane may be a very weak dermal sensitizer in animals (Clark 1977).

2.15 NEUROLOGICAL

There are limited data on the neurotoxicity of 1,2,3-trichloropropane in humans. Case reports describe neurological signs in individuals exposed to airborne 1,2,3-trichloropropane (Mi et al. 2013) or ingesting 1,2,3-trichloropropane (Han 2010). In both cases, exposure to 1,2,3-trichloropropane was assumed based on elevated levels in the blood; it was not known if they were exposed to other compounds. Observed signs included confusion and agitation (Han 2010) and headache, and intermittent drowsiness (Mi et al. 2013).

Data on the effects of 1,2,3-trichloropropane on the nervous system is limited to studies examining histopathology; no studies tested for neurofunction. Clinical signs were observed in animals exposed to lethal airborne concentrations of 1,2,3-trichloropropane; prostration was observed in rats exposed to 888 ppm for 6 hours (Johannsen et al. 1988) and hypoactivity was observed in rats exposed to 579 ppm 6 hours/day for 4 weeks (Johannsen et al. 1988). Histopathological examination of nervous tissue was not conducted for either groups of rats.

No histopathological effects were observed in the brain, spinal cord, and peripheral nerves of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 2 weeks (Miller et al. 1986a). No effect was observed on brain and spinal cord histology and brain weight in rats that were intermittently exposed to up to 49 ppm for 13 weeks (Johannsen et al. 1988). There were no treatment-related changes in brain weight or brain histology in rats and mice that were administered 1,2,3-trichloropropane doses as high as 250 mg/kg/day for periods as long as 17 weeks (NTP 1983a, 1983b).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after exposure to 1,2,3-trichloropropane. In the only inhalation reproductive study of 1,2,3-trichloropropane, male and female rats were intermittently exposed to concentrations of 0.49–15 ppm prior to mating, during mating, and during gestation (Johannsen et al. 1988). There were no effects on mating performance or fertility in either sex, but the data for the males at ≥4.5 ppm concentrations are inconclusive because the control group for these males had low mating performance compared to another male control group. No effects on mating or fertility were found in male rats administered by gavage 80 mg/kg/day 1,2,3-trichloropropane for 5 days in a dominant lethal mutation study (Saito-Suzuki et al. 1982). In a continuous breeding study, decreases in the number of litters produced and decreases in the number of live pups per litter were observed in rats administered ≥60 mg/kg/day for five litters (approximately 98 days) (NTP 1990). An increase in the days to litter was also observed at 120 mg/kg/day. To assess whether the observed effects were due to effects in the male or female animals, a cross-over mating study was conducted after the fifth litter was born (NTP 1990). A decrease in the number of live pups were observed when females administered 120 mg/kg/day were mated with control males. In the cross-over mating study, no alterations in epididymal sperm motility, count, or morphology or estrous cycle length were observed (NTP 1990).

Other inhalation and oral studies have examined potential histological alterations in reproductive tissues. Intermittent inhalation exposure to ≤132 ppm for 2 weeks (Miller et al. 1986b) or ≤49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988) had no effect on the weights or histology of the reproductive organs of male and female rats. In gavage studies, no histological alterations were observed in the testes of rats administered 80 mg/kg/day 1,2,3-trichloropropane for 5 days (Saito-Suzuki et al. 1982); no alterations were observed in male or female reproductive tissues in rats or mice administered ≤125 mg/kg (5 days/week) for 17 weeks (NTP 1993), rats administered ≤30 mg/kg 5 days/week for 2 years (NTP 1993), or in mice administered ≤60 mg/kg 5 days/week for 2 years (NTP 1993). In the cross-over mating study (NTP 1990), amyloidosis was observed in the ovaries of rats administered 120 mg/kg/day for at least 98 days.

2.17 DEVELOPMENTAL

One epidemiology study examined the possible association between 1,2,3-trichloropropane exposure and birth defects (Brender et al. 2014). Using data from the Texas Birth Defect Registry, the study found associations for several birth defects, including any neural tube defect, spina bifida, and septal heart

defects; the odds ratios (OR) and confidence intervals (CI) are presented in Table 2-4. Exposure was quantified based on maternal residential proximity and estimated pounds of chemical emitted. For spina bifida and cleft palate, associations were only found at the highest exposure intensity (OR 2.62, 95% CI 1.55–4.46 and OR 1.91, 95% CI 1.01–3.63, respectively). For septal heart defects, an association was found in the medium-intensity group (OR 1.31, 95% CI 1.12–1.52), but not in the high-intensity group (OR 1.02, 95% CI 0.86–1.21). Although the study found associations, it does not establish causality; it is also noted that the study found associations for a number of chemicals.

Table 2-4. Possible Associations Between Maternal Residential Proximity to 1,2,3-Trichloropropane Air Emissions and Birth Defects

Defect	Adjusted odds ratio[a]	95% Confidence interval
Any neural tube defect	1.49	1.08–2.06
Anencephaly	1.15	0.56–2.36
Spina bifida	1.78	1.22–2.59
Any oral cleft defect	1.16	0.89–1.51
Cleft palate alone	1.48	0.97–2.25
Cleft lip without cleft palate	1.03	0.73–1.44
Conotruncal heart defects	1.01	0.74–1.37
Obstructive heart defects	1.06	0.79–1.42
Septal heart defects	1.13	1.02–1.24
Any type of limb deficiency	1.10	0.72–1.67
Longitudinal limb deficiency	1.08	0.58–1.99
Transverse limb deficiency	0.95	0.53–1.71

[a]Adjustments for birth year and maternal age, education, race/ethnicity, and public health region of residence.

Source: Brender et al. 2014

Limited information regarding developmental effects of inhaled 1,2,3-trichloropropane in animals is available from a reproduction study in which male and female rats were intermittently exposed to concentrations as high as 15 ppm prior to mating, during mating, and during gestation (Johannsen et al. 1988). There were no effects on gestation length, and pup viability and weight at birth and during lactation were normal. In an oral developmental toxicity study utilizing the offspring of rats tested in the continuous breeding study (NTP 1990, see Section 2.16), decreases in mating and fertility indices were observed at 120 mg/kg/day. No alterations in the number of live pups, sex ratio, or pup body weight were

observed at a dose of ≤120 mg/kg/day (NTP 1990). Increases in average estrous cycle length was observed at 30, 60, and 120 mg/kg, but the increase was not dose-related.

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals after exposure to 1,2,3-trichloropropane.

2.19 CANCER

No studies were located regarding carcinogenicity in humans after exposure to 1,2,3-trichloropropane.

Information on the carcinogenicity of 1,2,3-trichloropropane is based on chronic duration gavage studies in rats and mice (NTP 1993). Increases in the incidence of neoplastic lesions were observed at all doses tested. In rats administered ≥3 mg/kg (5 days/week), squamous cell papillomas or squamous cell carcinomas were observed in the forestomach and adenomas were observed in the pancreas. At ≥10 mg/kg, squamous cell papillomas or squamous cell carcinomas in the oral mucosa, adenomas in renal tubules, adenoma or carcinoma of the clitoral gland, and adenocarcinomas of the mammary gland were observed. At the highest dose tested (30 mg/kg), adenoma or carcinoma in the preputial gland, and carcinoma in the Zymbal's gland (males only) were also observed. Clear evidence of carcinogenicity was also found in male and female mice treated with ≥6 mg/kg (NTP 1993). The evidence consisted of increased incidences of squamous cell papilloma or carcinoma in the forestomach and hepatocellular adenoma or carcinoma (males only) at 6 mg/kg; harderian gland adenoma in males at 20 mg/kg; and squamous cell papilloma or carcinoma of the oral mucosa (females only), harderian gland adenoma (females only), and uterine stromal polyps and endometrial adenoma or adenocarcinoma at 60 mg/kg.

The Department of Health and Human Services has determined that 1,2,3-trichloropropane is reasonably anticipated to be a human carcinogen (NTP 2016). EPA concluded that it is likely to be carcinogenic to humans (EPA 2009b), and IARC considers is to be a suspected human carcinogen (IARC 2017).

2.20 GENOTOXICITY

The genotoxicity of 1,2,3-trichloropropane has been investigated in a small number of *in vitro* studies, which are summarized in Table 2-5. 1,2,3-Trichloropropane was mutagenic in certain strains of *Salmonella typhimurium* when assayed with exogenous metabolic activation preparation (Haworth et al.

1983; Kubo et al. 2002; Låg et al. 1994; Mersch-Sundermann et al. 1994; NTP 1993; Ratpan and Plaumann 1988; Stolzenberg and Hine 1980). It did not induce gene mutations in *Escherichia coli* (Mersch-Sundermann et al. 1994). In eukaryotic organisms, 1,2,3-trichloropropane induced gene mutations in mouse lymphoma cells (NTP 1994), DNA damage in human lymphocytes (Tafazoli and Kirsch-Volders 1996), sister chromatid exchange in Chinese hamster V79 and ovary cells (NTP 1993; Von Der Hude et al. 1987), and chromosomal aberrations in Chinese hamster ovary cells (NTP 1993). In most cases, the positive results were only observed with activation. 1,2,3-Trichloropropane did not increase micronuclei formation in human lymphocytes (Tafazoli and Kirsch-Volders 1996).

Table 2-5. Genotoxicity of 1,2,3-Trichloropropane *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Prokaryotic organisms				
Salmonella typhimurium (plate incorporation test)	Gene mutation	+	–	Stolzenberg and Hine 1980
S. typhimurium strains (liquid preincubation test)	Gene mutation	+	–	Haworth et al. 1983
S. typhimurium TA97, TA98, TA100, and TA1535, (liquid preincubation test)	Gene mutation	+	–	NTP 1993
S. typhimurium TA1537 (liquid preincubation test)	Gene mutation	–	–	NTP 1993
S. typhimurium (plate incorporation test)	Gene mutation	+	–	Ratpan and Plaumann 1988
S. typhimurium TA98 (Ames assay)	Gene mutation	–	–	Kubo et al. 2002
S. typhimurium TA100 (Ames assay)	Gene mutation	+	–	Kubo et al. 2002
S. typhimurium TA100 (Ames assay)	Gene mutation	+	–	Låg et al. 1994
S. typhimurium TA100 (Ames assay)	Gene mutation	+	–	Mersch-Sundermann et al. 1994
Escherichia coli (SOS chromotest)	Gene mutation	–	–	Mersch-Sundermann et al. 1994
Eukaryotic organisms				
L5178Y mouse lymphoma cells	Gene mutation	+	–	NTP 1993
Human lymphocytes (comet assay)	DNA damage	+	+	Tafazoli and Kirsch-Volders 1996
Human lymphocytes	Micronuclei formation	–	–	Tafazoli and Kirsch-Volders 1996

Table 2-5. Genotoxicity of 1,2,3-Trichloropropane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Chinese hamster V79 cells	Sister chromatid exchange	+	–	Von Der Hude et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	+	–	NTP 1993
Chinese hamster ovary cells	Chromosomal aberrations	+	–	NTP 1993

+ = positive results; – = negative results

A small number of studies have evaluated the *in vivo* genotoxicity (Table 2-6). In *Drosophila*, exposure to 1,2,3-trichloropropane increased the frequency of somatic mutations and recombinations (Chroust et al. 2007). In mammalian species, 1,2,3-trichloropropane did not induce dominant lethal mutations when administered orally to rats (Saito-Suzuki et al. 1982) (see Section 2.16) or increase the frequency of micronucleated polychromatic erythrocytes in mice (Crebelli et al. 1999).

Table 2-6. Genotoxicity of 1,2,3-Trichloropropane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster	Somatic mutation and recombination	+	Chroust et al. 2007
CD-1 mice (intraperitoneal)	Micronucleated polychromatic erythrocytes	–	Crebelli et al. 1999

– = negative result; + = positive result

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

No studies were located regarding 1,2,3-trichloropropane toxicokinetics in humans, but there are limited data from studies in animals. These data are summarized below.

- Approximately 80% of an oral dose is absorbed through the gastrointestinal tract. No absorption data are available for inhalation or dermal routes although absorption is presumed based on remote toxicity.
- Absorbed 1,2,3-trichloropropane is widely distributed throughout the body.
- 1,2,3-Trichloropropane is rapidly and extensively metabolized. It likely undergoes cytochrome P450-catalyzed dehalogenation reactions.
- 1,2,3-Trichloropropane and its metabolites are excreted via urine, feces, and exhaled breath. It is excreted within 2 days of a single exposure.

3.1.1 Absorption

No quantitative information was located regarding absorption of 1,2,3-trichloropropane following inhalation exposure; however, since liver and hematological toxicity has been reported in animals exposed by the inhalation route (Johannsen et al. 1988; Miller et al. 1986a), it can be concluded that absorption occurs to some extent. The results of studies performed in rats indicate that near complete absorption (>80%) from the gastrointestinal tract occurs within the first day following oral exposure (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984). As with inhalation exposure, dermal absorption can be implied based on the lethality study conducted by Smyth et al. (1962) in which the dermal application site was protected by an impervious membrane.

3.1.2 Distribution

Muscle, blood, liver, skin, and adipose tissue contained the largest amounts of 1,2,3-trichloropropane following oral exposure in rats (Sipes et al. 1982). Retention in all tissues was low, however, as elimination of 1,2,3-trichloropropane-derived radioactivity from tissues was nearly complete (>97%) within 8 days after oral exposure in rats (Sipes et al. 1982). Another study found that 6 hours after receiving a gavage dose of radiolabeled 1,2,3-trichloropropane, the highest concentrations of radioactivity were found in the gastrointestinal tract (in decreasing concentration: forestomach, glandular stomach,

small intestine, large intestine), adipose, kidney, and liver (Mahmood et al. 1991). After 60 hours, the highest concentrations were found in the liver, kidneys, and forestomach. In mice, the highest concentrations were found in the forestomach, liver, and kidney 60 hours post-dosing (Mahmood et al. 1991). The 1,2,3-trichloropropane remaining in the forestomach, liver, and kidney was non-extractable metabolites, suggesting that it was covalently bound to tissue macromolecules.

Distribution studies of intravenously injected 1,2,3-trichloropropane in rats have provided a quantitative description of the distribution kinetics from which predictions can be made regarding other routes of exposure (Sipes et al. 1982; Volp et al. 1984). Intravenously injected 1,2,3-trichloropropane rapidly distributes to many tissues. The major sites of accumulation are liver, kidney, small and large intestine, adipose tissue, muscle, and skin. Peak concentrations are achieved within l–2 hours after intravenous injection. Elimination of 1,2,3-trichloropropane from tissues in the rat is also rapid and a two-phase process (Volp et al. 1984). Elimination half-times for >90% of the 1,2,3-trichloropropane in tissues ranged from 20 minutes in kidney to 2 hours in adipose tissue (first phase). A small fraction of the 1,2,3-trichloropropane in these tissues (<10%) was eliminated more slowly, with half-times ranging from 23 to 45 hours (second phase). Elimination of total radioactivity from the tissues after intravenous injection of radiolabeled 1,2,3-trichloropropane (phase one half-times between 2 and 5 hours, phase two half-times between 87 and 182 hours) is slower than elimination of parent 1,2,3-trichloropropane. This suggests that metabolites of 1,2,3-trichloropropane are eliminated slower than the parent compound. Based on the results of studies in the rat, it can be concluded that 1,2,3-trichloropropane absorbed by any route is likely to be widely distributed in the body. Most of the 1,2,3-trichloropropane that enters tissues is eliminated within hours to days.

3.1.3 Metabolism

Gavage administered or intravenously injected 1,2,3-trichloropropane is extensively metabolized within hours in rats. Metabolic products in rats include carbon dioxide, which is expired, and numerous metabolites that are excreted in urine and enter the bile to be excreted in feces or absorbed in the intestines (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984). Many of the metabolites of 1,2,3-trichloropropane that are formed in the rat have not been identified; based on the metabolic pathways that have been identified for other halogenated alkanes, dehalogenation products, glutathione conjugates, and their subsequent metabolites, mercapturic acids, can be anticipated. Chloroalkanes such as 1,2,3-trichloropropane undergo dehalogenation reactions catalyzed by cytochrome P450 (Ivanetich et al. 1978; Salmon et al. 1981; Van Dyke et al. 1971). Depending on the reaction mechanism, highly

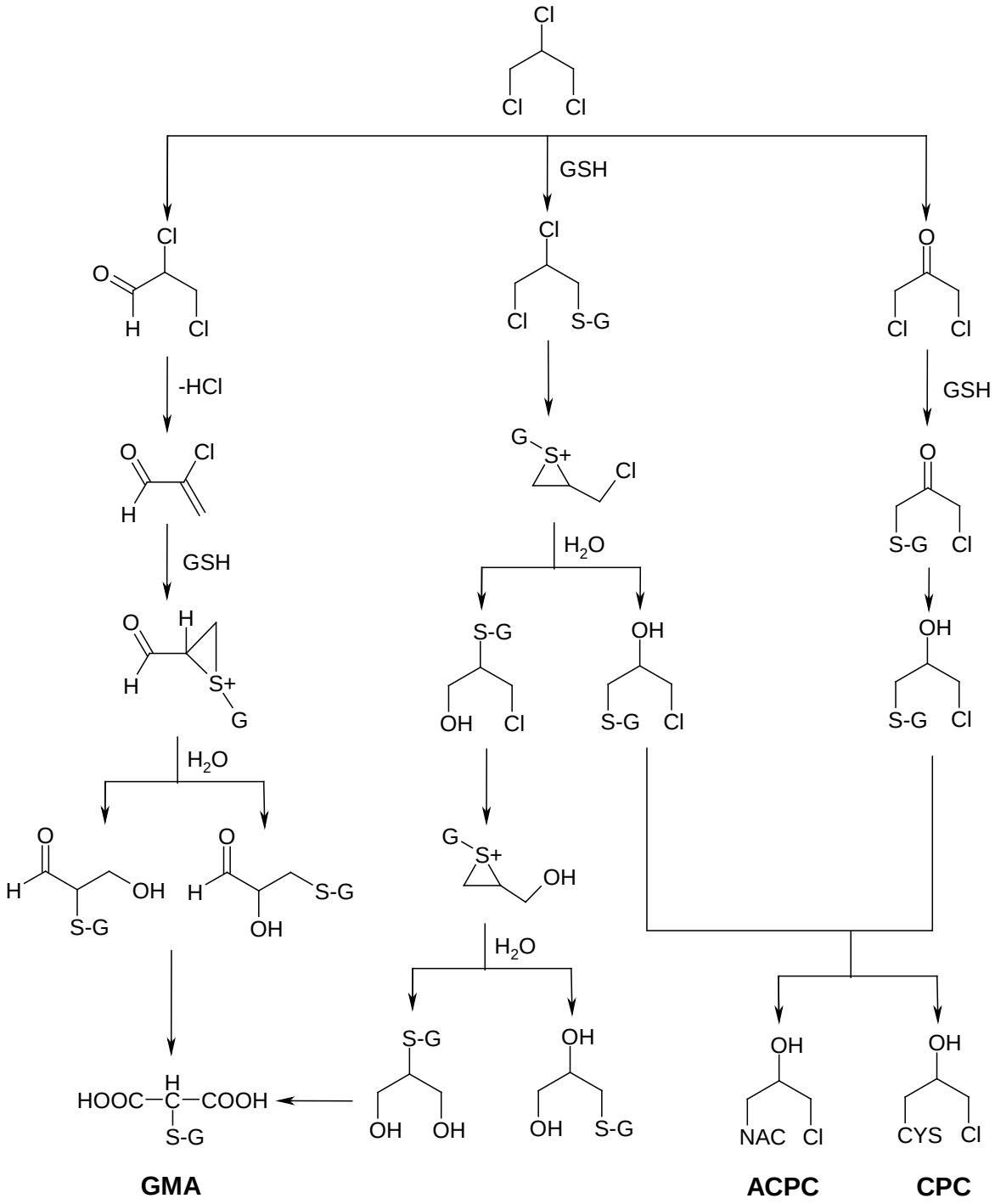
reactive intermediates (e.g., radicals) can be formed from these reactions, leading to protein and DNA adducts or lipid peroxidation. Conjugation with glutathione could result in formation of sulfur mustard-like compounds that are potential alkylating agents.

Mahmood et al. (1991) proposed three possible metabolic pathways for 1,2,3-trichloropropane, which involve cytochrome P450 metabolism or glutathione conjugation. The possible pathways are summarized below and illustrated in Figure 3-1:

1. Nucleophilic displacement of chlorine at the C1 or C2 position, possibly by glutathione transferase, to form a β-chlorothio ether. Displacement of the β-chlorine could result in the formation of a reactive episulfonium ion. The episulfonium ion could react with water to form glutathione conjugates at the C1 or C2 position.
    a. Cleavage of the glutathione conjugate at the C2 position could ultimately result in the formation of N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine (ACPC) or S-(3-chloro-2-hydroxypropyl)-L-cysteine (CPC).
    b. The episulfonium ion could also react with water at the C1 position to form another episulfonium ion. The second episulfonium ion could react with water at the C3 position to form a 1,3-dihydroxypropyl glutathione conjugate which could oxidize to form 2-(S-glutathionyl)malonic acid (GMA).
2. Oxidation of 1,2,3-trichloropropane at the C2 position, possibly by cytochrome P450, would result in the formation of 1,3-dichloroacetone. 1,3-Dichloroacetone could undergo chlorine displacement by glutathione and reduction of the keto group to form ACPC and CPC.
3. Oxidation of 1,2,3-trichloropropane at the C1 position, possibly by cytochrome P450, to form the α-chlorohydrin, 2,3-dichloropropanal. Loss of HCl from 2,3-dichlorpropanal would form chloroacrolein, which could react with glutathione to form an episulfonium ion. The episulfonium ion could react with water at the C3 position to form GMA after oxidation of the C2 and C3 atoms to carboxylic acids.

The results of an *in vitro* study (Weber and Sipes 1992) in rat hepatic microsomes suggest two similar possible metabolic pathways for 1,2,3-trichloropropane: oxidation at the C2 position to form the unstable compound *gem*-chlorohydrin, which is dehalogenated to form 1,3-dichloroacetone and oxidation at the C1 position to form *gem*-chlorohydrin, which is dehalogenated to form 2,3-dichloropropanal, which is subsequently reduced to 2,3-dichloropropanol.

Figure 3-1. Possible Metabolic Pathways for the Formation of ACPC, CPC, and GMA from 1,2,3-Trichloropropane



ACPC = N-Acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine; CPC = S-(3-chloro-2-hydroxypropyl)-L-cysteine; GMA = 2-(S-glutathionyl)malonic acid

Source: Mahmood et al. 1991

3.1.4 Excretion

Studies conducted with rats showed that 1,2,3-trichloropropane and its metabolites were excreted in urine, feces, and exhaled breath after oral exposure (Sipes et al. 1982). Excretion was nearly complete (95–96%) within 2 days. Most of the dose was excreted in the urine and feces (up to 56 and 25%, respectively), with the remainder in the breath. Mahmood et al. (1991) demonstrated that ≥90% of the radioactivity was excreted 60 hours following a gavage dose of radiolabeled 1,2,3-trichloropropane in rats and mice. Urine was the primary route of excretion, accounting for 50–57% of the dose in rats and 65% of the dose in mice. In the urine, the radiolabel was primarily found in the form of *N*-acetyl-*S*-(3-chloro-2-hydroxypropl)-L-cysteine. Excretion as carbon dioxide or in the feces accounted for 20 and 20% of the radiolabel, respectively, in rats and 20 and 15% of the label, respectively, in mice. Comparison of excretion data from rats and mice suggest that at a given dose, male mice appear to eliminate 1,2,3-trichloropropane faster and retain less radioactivity than male (or female) rats (Mahmood et al. 1991).

Studies of the excretion of intravenously injected 1,2,3-trichloropropane in rats have provided a quantitative description of the excretion kinetics from which predictions can be made about other routes of exposure (Sipes et al. 1982; Volp et al. 1984). Excretion of intravenously injected 1,2,3-trichloropropane and metabolites is nearly complete within 2 days. Unchanged 1,2,3-trichloropropane and its major metabolite, carbon dioxide, are expired in exhaled breath. Nonvolatile metabolites are excreted in the urine. Extensive biliary excretion of nonvolatile metabolites also occurs, resulting in fecal excretion as well as reabsorption of metabolites from the gastrointestinal tract. Based on the results of studies in rats, exhaled breath, urine, and feces are likely to be significant routes of excretion of absorbed 1,2,3-trichloropropane and its metabolites in humans.

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

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

Volp et al. (1984) developed a PBPK model in male rats to investigate the time course of 1,2,3-trichloropropane is tissues. The flow-limited model consisted of seven compartments: blood, liver, kidney, fat, muscle, skin, and remaining distribution volume. The model, with some adjustments of pharmacokinetic parameters, predicted the concentration versus time curves for the selected tissues.

3.1.6 Animal-to-Human Extrapolations

The limited available toxicokinetic data do not allow for an assessment of potential species differences. Most of the toxicity studies were conducted in rats; two studies tested rats and mice, which allow for a comparison across species. In an 11-day inhalation study, Miller et al. (1986a) found similar targets of toxicity, but differences in sensitivity between rats and mice. In rats, exposure to 3 ppm resulted in thickening of the nasal olfactory epithelium. In mice, 3 ppm was a NOAEL for nasal effects; at 10 ppm, nasal olfactory inflammation was observed. Similar findings were observed in intermediate- and chronic-duration studies (NTP 1993). In rats, increases in liver weight were observed at ≥16 mg/kg (5 days/week) and hepatocellular necrosis and bile duct hyperplasia were observed at 125 ppm. In contrast, increases in liver weight was not observed in mice at doses lower than 125 ppm and hepatocellular necrosis was observed at 250 ppm. Chronic-duration exposure resulted in differences in the types of effects (e.g., bile duct hyperplasia in rats and hepatocellular necrosis in mice) and sensitivity. Collectively, these studies suggest species differences in the toxicity of 1,2,3-trichloropropane. There are insufficient data to assess whether rats or mice would be a better model for human toxicity. In the absence of these data, it was assumed that the most sensitive species would be appropriate for MRL derivation.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to 1,2,3-trichloropropane are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited data on the susceptibility of children to the toxicity of 1,2,3-trichloropropane; in the absence of data to the contrary, it is assumed that it would be the same as in adults. The developmental toxicity of 1,2,3-trichloropropane has not been thoroughly investigated. A 2-generation study found decreases in fertility in F1 mice (NTP 1990); however, it is not known if this was due to impaired development of the reproductive system as similar effects were observed in the P0 animals.

No populations with unusual susceptibility to health effects of 1,2,3-trichloropropane have been identified. The respiratory tract, blood, liver, and kidneys are principal targets of 1,2,3-trichloropropane in animals (see Section 2.4). It is therefore possible that people with chronic respiratory, liver, or kidney disease, or possibly people with compromised pulmonary, hepatic, or renal function (e.g., alcoholics), might be unusually susceptible to 1,2,3-trichloropropane.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers 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). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,2,3-trichloropropane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,2,3-trichloropropane from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused 1,2,3-trichloropropane are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Biomarkers of exposure to 1,2,3-trichloropropane cannot be identified because information on levels of 1,2,3-trichloropropane or its metabolites in human tissues, fluids, or excreta or information on effects specific for 1,2,3-trichloropropane is not available. Studies with rats indicate that excretion of 1,2,3-trichloropropane in the breath or urine may be sufficient for monitoring purposes (see Section 3.1.4).

3.3.2 Biomarkers of Effect

Effects in humans that are specifically attributable to 1,2,3-trichloropropane exposure are not known. Principal targets of 1,2,3-trichloropropane in animals are the respiratory tract, blood, liver, and kidneys. One study with rats suggests that alterations of serum enzymes (e.g., decreased serum pseudocholinesterase activity) and anemia might be useful biomarkers for hepatic and hematologic effects, respectively, of 1,2,3-trichloropropane. Insufficient data exist, however, to determine whether 1,2,3-trichloropropane is likely to cause anemia in humans, and substances other than 1,2,3-trichloropropane could also cause similar hematologic and hepatic effects.

3.4 INTERACTIONS WITH OTHER CHEMICALS

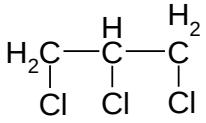
Rats were exposed by inhalation to 500 ppm trichloropropane and 1,000 ppm dichloropropane alone and in combination for 4 hours (Drew et al. 1978). Activities of liver-associated serum enzymes (serum glutamicoxaloacetic transaminase, serum glutamic-pyruvic transaminase, ornithine carbamyl transferase) were increased 24–48 hours following exposure to each chemical alone. The combined exposure resulted in higher enzyme activities than with either chemical alone, but the increases were less than additive.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of 1,2,3-trichloropropane are listed in Table 4-1.

Table 4-1. Chemical Identity of 1,2,3-Trichloropropane

Characteristic	Information	Reference
Chemical name	1,2,3-Trichloropropane	CAS 1989
Synonym(s) and registered trade name(s)	Allyl trichloride; glycerol trichlorohydrin; trichlorohydrin	CAS 1989
Chemical formula	$C_3H_5Cl_3$	CAS 1989
Chemical structure		
CAS Registry Number	96-18-4	CAS 1989

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,2,3-trichloropropane are presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of 1,2,3-Trichloropropane

Property	Information	Reference
Molecular weight	147.43	Weast 1985
Color	Colorless	Hawley 1981
Physical state	Liquid	Hawley 1981
Melting point	-14.7°C	Williams 1949
Boiling point	156.8°C	Ruddick et al. 1986
Density at 20 °C	1.3888 g/cm^2	Ruddick et al. 1986
Odor	Strong, acrid; trichloroethylene-like; “sweet smelling”	HSDB 1989; McNeill 1979; Ruth 1986
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20 °C	1,750 mg/L	Ruddick et al. 1986
Organic solvents	Soluble in ethyl alcohol and higher alcohols, chloroform and other chlorinated hydrocarbons, ethyl ether, benzene	Weast 1985; Williams 1949
Partition coefficients:		
Log K_{ow}	1.98	EPA 1988b
Log K_{oc}[a]	1.99 (estimated)	Lyman et al. 1982
Bioconcentration factor[b]	9.2 (estimated)	Lyman et al. 1982
Vapor pressure at 20°C	3.1 mmHg	Mackay et al. 1982
Henry's law constant at 25°C	3.17x10^{-4} atm-m^3/mol (calculated)	Lyman et al. 1982
Autoignition temperature	304°C (580°F)	Hawley 1981
Flashpoint		
Open cup	82.2°C	Hawley 1981
Open cup	78.9°C	Williams 1949
Closed cup	73.3°C	Williams 1949
Flammability limits	No data	
Conversion factors	1 ppm (v/v)x6.03 =mg/m^2 1 mg/m^{3}x0.166 = ppm (v/v)	
Explosive limits	No data	

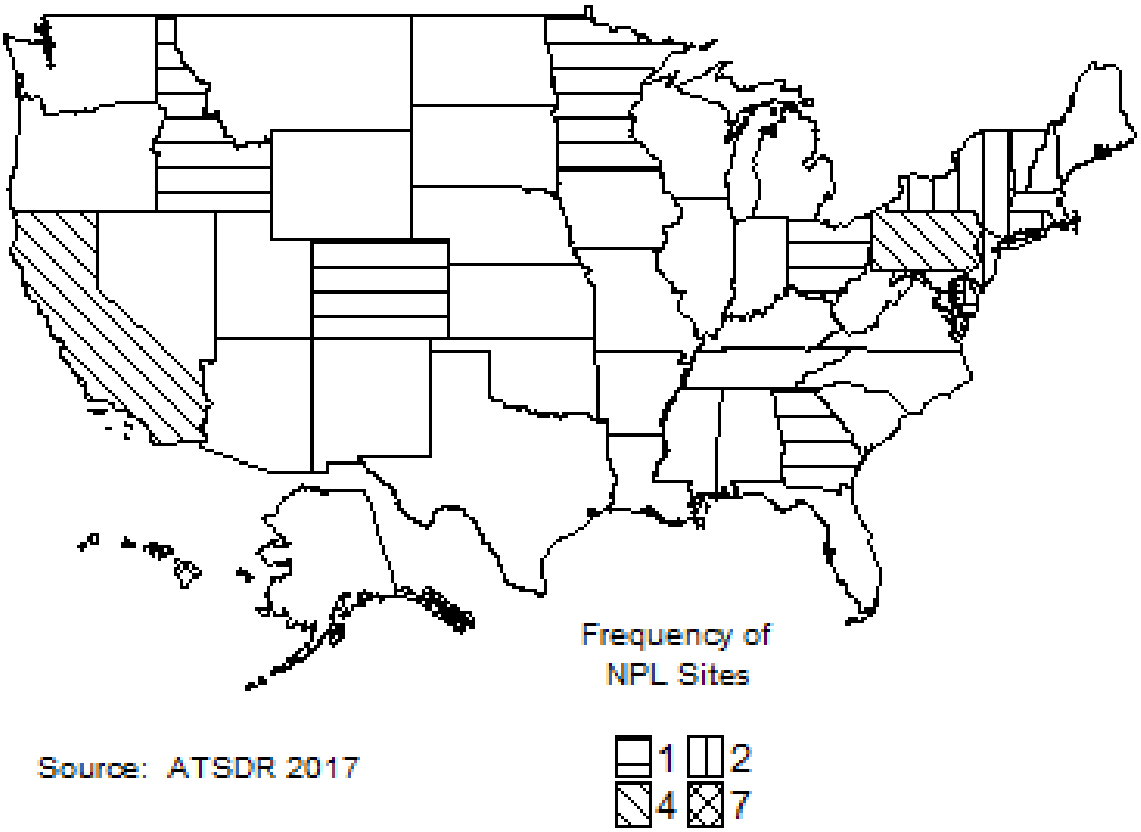
[a]Calculated from water solubility using equation 4-7 (Lyman et al. 1982).
[b]Calculated from log K_{ow} using equation 5-2 (Lyman et al. 1982).

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2,3-Trichloropropane has been identified in at least 25 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 1,2,3-trichloropropane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 25 are located within the United States.

Figure 5-1. Number of NPL Sites with 1,2,3-Trichloropropane Contamination



- The most likely route of exposure for the general population is through ingestion of contaminated water. Additional exposure may occur through the inhalation of contaminated air, especially for those who live near facilities that manufacture or use 1,2,3-trichloropropane or at treatment or disposal facilities.

- Releases to the environment are likely to occur as a result of its manufacture, formulation, and use as a solvent and extractive agent, paint- and varnish-remover, cleaning and degreasing agent, cleaning and maintenance reagent, and chemical intermediate.

- In ambient air, the primary removal process is expected to be the vapor phase reaction with photochemically generated hydroxyl radicals. In surface waters, the primary removal process is likely to be volatilization. In soil, the primary removal processes are volatilization from near-surface soil and leaching to groundwater. Aerobic biodegradation is probably a slow process in natural waters and soil.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Recent data regarding production volumes for 1,2,3-trichloropropane are not available. The estimated 1977 production volume for the chemical ranged from 21 to 110 million pounds (EPA 1989b). Manufacturers of 1,2,3-trichloropropane in 1989 included Dow Chemical U.S.A., Freeport, Texas, and Shell Oil Company, Deer Park, Texas (SRI 1989). In 1977, two additional manufacturing locations were Dow Chemical U.S.A., a major producer in Midland, Michigan, and Columbia Organic Chemicals Co., a minor producer in Columbia, South Carolina (EPA 1989b). 1,2,3-Trichloropropane can be produced via the chlorination of propylene (Hawley 1981). Other reported methods for producing 1,2,3-trichloro-propane include the addition of chlorine to allyl chloride, reaction of thionyl chloride with glycerol, and the reaction of phosphorus pentachloride with either 1,3- or 2,3-dichloropropanol (NIOSH 1981; Williams 1949). 1,2,3-Trichloropropane also may be produced in potentially significant amounts as a byproduct of processes primarily used to produce other chemicals, including dichloropropene (a soil fumigant and nematocide), propylene chlorohydrin, propylene oxide, dichlorohydrin, and glycerol (Baier et al. 1987; NIOSH 1981). Technical-grade 1,2,3-trichloropropane reportedly varies between 97.5 and 99.4% purity (Alberti 1982; NTP 1983a). The material tested by the NTP (1983a) contains the following impurities: 0.066% water, 0.14% unspecified chlorohexene, two unspecified chlorohexadienes (0.24 and 0.13%), and total acidity of 48 ppm (as HCl). Table 5-1 summarizes information on U.S. companies that reported the manufactured or used 1,2,3-trichloropropane in 2016 (TRI16 2017).

5.2.2 Import/Export

No data concerning the import or export of 1,2,3-trichloropropane were located.

Table 5-1. Facilities that Produce, Process, or Use 1,2,3-Trichloropropane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
LA	2	0	9,999,999	1, 5, 6, 12, 13, 14
TX	4	1,000	999,999	1, 4, 5, 6, 12, 13

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

5.2.3 Use

1,2,3-Trichloropropane has, in the past, been used mainly as a solvent and extractive agent. No current information is available that indicates that the compound is still used for these purposes today. It dissolves a variety of resins, oils, waxes, and other materials while having a low solubility in water (Williams 1949). Common uses have included use as a paint- and varnish remover, a cleaning and degreasing agent, and a cleaning and maintenance reagent (Hawley 1981; NIOSH 1981). It is used as a chemical intermediate; for example, in the production of polysulfone liquid polymers and dichloropropene, synthesis of hexafluoropropylene, and as a crosslinking agent in the synthesis of polysulfides (Baier et al. 1987; Ellerstein and Bertozzi 1982; Gangal 1980; HSDB 1989). No data were found concerning the approximate amounts currently used for particular purposes.

5.2.4 Disposal

1,2,3-Trichloropropane has been identified as a hazardous waste by the EPA, and the disposal of this compound is regulated under the Resource Conservation and Recovery Act (RCRA). Specific information regarding the federal regulations of land disposal of 1,2,3-trichloropropane is available (EPA 1988a). 1,2,3-Trichloropropane can be disposed of via atomization in a suitable incinerator equipped with appropriate effluent gas scrubbers (HSDB 1989). In case of accidental spills, the chemical may be disposed of by absorption onto vermiculite, dry sand, earth, or similar material followed by disposal in a secured landfill (HSDB 1989); however, land disposal may no longer be allowed by the disposal regulations discussed above. Significant removal of 1,2,3-trichloropropane from waste water and sewage

may be accomplished through the use of activated sludge treatment processes (Matsui et al. 1975). No data were found concerning the approximate amounts disposed by the various methods.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 2,717 pounds (~1.23 metric tons) of 1,2,3-trichloropropane to the atmosphere from 6 domestic manufacturing and processing facilities in 2016, accounted for about 53.9% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

Data on releases of 1,2,3-trichloropropane to the atmosphere are lacking. Based on the few data available, current releases to the air are expected to be relatively small. Minor releases may have occurred as exhaust, stack, and fugitive emissions from its manufacture, formulation, and use as a solvent (HSDB 1989). 1,2,3-Trichloropropane may have been released in the past into the air as a result of its use as a paint and varnish remover, a degreasing agent, and a cleaning and maintenance reagent (Hawley 1981; NIOSH 1981). No information was found that indicates that 1,2,3-trichloropropane is still used for these purposes today. Very small amounts may be released during its use as a chemical intermediate and as a result of its formation during the synthesis of other organic chemicals. Volatilization from contaminated surface waters, effluent waters, and near surface soils may also be minor atmospheric

sources of this compound. This includes volatilization from identified and unidentified hazardous waste dumps that contain 1,2,3-trichloropropane and from farmland treated with 1,2,3-trichloropropane-contaminated fumigants and nematocides (no information is available to determine whether or not the soil fumigants and nematocides currently manufactured contain 1,2,3-trichloropropane). Small amounts may be released to the air during treatment of water containing 1,2,3-trichloropropane, because some of the chemical may be removed via evaporative stripping from the water.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2,3-Trichloropropane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
LA	2	1,554	0	0	0	0	1,554	0	1,554
TX	4	1,163	2,218	0	105	0	3,384	102	3,486
Total	6	2,717	2,218	0	105	0	4,938	102	5,040

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

5.3.2 Water

Estimated releases of 2,218 pounds (~1 metric ton) of 1,2,3-trichloropropane to surface water from 6 domestic manufacturing and processing facilities in 2016, accounted for about 44% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

Data on the release of 1,2,3-trichloropropane to environmental waters are lacking. Based on the few data available, current releases to environmental waters are expected to be relatively small. Releases to surface water may have occurred through runoff of waste water from hazardous waste sites containing 1,2,3-trichloropropane and runoff from farmland treated with certain soil fumigants and nematocides that contain 1,2,3-trichloropropane. Releases to surface and groundwater may have occurred as a result of the improper disposal of 1,2,3-trichloropropane-containing industrial wastes or wastes from its use in paint- and varnish-removers, cleaning and degreasing agents, and maintenance reagents. Releases to groundwater may have occurred as a result of the chemical leaching through soil at waste sites and agricultural soil treated with fumigants that contain the chemical. Small amounts of the chemical may have entered surface waters as a result of washout from 1,2,3-trichloropropane-contaminated air; however, some of the 1,2,3-trichloropropane removed from the atmosphere by washout is likely to have re-entered the atmosphere by volatilization.

5.3.3 Soil

Estimated releases of 105 pounds (~0.05 metric tons) of 1,2,3-trichloropropane to soils from 6 domestic manufacturing and processing facilities in 2016, accounted for about 2.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). No 1,2,3-trichloropropane was released via underground injection (TRI16 2017). These releases are summarized in Table 5-2.

Data on releases of 1,2,3-trichloropropane to soils are sparse, which makes a quantitative estimation of the magnitude of such releases impossible. However, releases to soils are expected to be relatively small based upon the available data. Releases to farmland soil have occurred as a result of the use of certain soil fumigants and nematocides known to contain 1,2,3-trichloropropane as an impurity. No current information is available, however, that indicates that these soil fumigants and nematocides still contain 1,2,3-trichloropropane. Releases of the chemical to soil may have occurred as a result of disposal of 1,2,3-trichloropropane-containing sewage sludge from municipal sewage treatment plants (Jacobs and Zabik 1983). Very small amounts of the chemical may be brought to the surface of the earth as a result of washout from 1,2,3-trichloropropane-containing air; however, much of the 1,2,3-trichloropropane removed from the atmosphere by washout may re-enter the atmosphere by volatilization from near-surface soil. Land disposal of wastes from its use in paint and varnish removers, cleaning and degreasing agents, and cleaning and maintenance reagents may have released 1,2,3-trichloropropane to soil.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

No experimental or predictive data were located in the literature regarding the transport of 1,2,3-trichloropropane in the atmosphere. 1,2,3-Trichloropropane is expected to exist in the atmosphere predominantly in the vapor phase, based on its vapor pressure (Table 4-2) (Eisenreich et al. 1981; MacKay et al. 1982). The speculation that substantial amounts of 1,2,3-trichloropropane are not likely to be present in the particulate phase indicates that dry deposition to the earth's surface will not be an important removal process. Based upon its low water solubility and moderate vapor pressure (Table 4-2), very small amounts of 1,2,3-trichloropropane present in air may be removed by wet deposition; however, much of the 1,2,3-trichloropropane removed from the atmosphere by washout is likely to re-enter the atmosphere by volatilization. Based upon an estimated soil organic carbon partition coefficient (K_{oc}) of 98 (calculated from water solubility) (Lyman et al. 1982; Riddick et al. 1986), 1,2,3-trichloropropane is expected to display high mobility in soil (Swann et al. 1983); therefore, it has the potential to leach into groundwater. This predicted mobility is confirmed by the detection of 1,2,3-trichloropropane in groundwater from various locations. The vapor pressure of 1,2,3-trichloropropane (3.1 mmHg at 25°C) (MacKay et al. 1982) and the calculated Henry's law constant (3.17×10^{-4} atm-m^3/mol at 25°C) (Lyman et al. 1982) suggest that volatilization from either dry or moist soil to the atmosphere will be a significant environmental process. 1,2,3-Trichloropropane in surface water is expected to volatilize rapidly to the atmosphere. An experimental half-life of 56.1 minutes has been measured for evaporation of 1,2,3-trichloropropane from a 1 ppm solution, with a depth of 6.5 cm, stirred with a shallow pitch propeller at 200 rpm at 25°C under still air (<0.2 mph air currents) (Dilling 1977). Using the Henry's law constant, a half-life of 6.9 hours was calculated for evaporation from a model river 1 m deep, flowing at 1 m/second, with a wind velocity of 3 m/second, and neglecting adsorption to sediment (Lyman et al. 1982). A volatilization half-life of 3.5 days from a model pond can be estimated (EPA 1985). 1,2,3-Trichloropropane is not expected to significantly adsorb to sediment and suspended organic matter based upon the estimated K_{oc} of 98 (calculated from water solubility) (Lyman et al. 1982; Riddick et al. 1986). It is also not expected to significantly bioconcentrate in fish and aquatic organisms based upon an estimated bioconcentration factor (BCF) of 9.2 (calculated from log octanol-water partition coefficient (K_{ow}) (EPA 1988b; Lyman et al. 1982). No data were located to indicate a potential for 1,2,3-trichloropropane to biomagnify from lower to higher trophic states of the food chain, but based upon the estimated BCF, this is not likely.

5.4.2 Transformation and Degradation

Air. The primary degradation process for 1,2,3-trichloropropane in the atmosphere is expected to occur via gas-phase reaction with photochemically produced hydroxyl radicals. The rate constant for this process is an estimated 1.0475×10^{-12} cm^3/molecule-second (Atkinson 1987). This corresponds to a half-life of 15.3 days at an estimated atmospheric concentration of 5×10^5 hydroxyl radicals/cm^3. Direct photolysis of 1,2,3-trichloropropane is not expected to occur in the atmosphere because the chemical lacks a chromophore that absorbs light at environmentally significant wavelengths (>290 nm) (Silverstein et al. 1974).

Water. Degradation of 1,2,3-trichloropropane in natural waters is expected to be a slow process. The chemical should volatilize from surface waters before significant degradation can occur. Hydrolysis of 1,2,3-trichloropropane in natural waters is not expected to be a significant removal process. The measured neutral and base hydrolysis rate constants at 25°C are 1.8×10^{-6} $hour^{-l}$ and 9.9×10^{-4} M^{-1} $hour^{-l}$, respectively (EPA 1988c). These rate constants correspond to a hydrolysis half-life of 44 years over a pH range of 5–9. Direct photolysis of 1,2,3-trichloropropane is not expected to occur in environmental waters because the chemical lacks a chromophore that absorbs light at environmentally significant wavelengths (>290 nm) (Silverstein et al. 1974).

No studies were located regarding the biodegradation of 1,2,3-trichloropropane in natural waters. An aqueous screening study with activated sewage sludge has indicated that 1,2,3-trichloropropane can be removed by biological treatment processes and that at least part of the removal was due to volatilization. However, this study cannot be used to predict the biodegradability of this compound under natural conditions. Other authors have observed that halogenated hydrocarbons, in general, and especially those with multiple chlorine substitution, such as 1,1,2-trichloroethane and 1,1,2,2-tetrachloroethane, are recalcitrant towards biodegradation (Kawasaki 1980; Tabak et al. 1981). No data concerning the potential for anaerobic aqueous biodegradation of 1,2,3-trichloropropane were found.

Sediment and Soil. No data specifically regarding the degradation of 1,2,3-trichloropropane in soil were found. However, it has been observed that 1,2-dichloropropane will not significantly biodegrade in soil (Roberts and Stoydin 1976). Therefore, 1,2,3-trichloropropane is expected to be even less biodegradable because it contains an additional chlorine. The rate of 1,2,3-trichloropropane loss from soil due to biodegradation may not be significant when compared with its loss by volatilization and leaching from soil. 1,2,3-Trichloropropane will be lost from the soil by evaporation (from both moist and dry

near-surface soil) and by leaching to groundwater before 1,2,3-trichloropropane will hydrolyze in soil. Direct photolysis on the surface of soil will not occur.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,2,3-trichloropropane depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,2,3-trichloropropane in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,2,3-trichloropropane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-3 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-4.

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.3 mg/sample	NIOSH 1987
Drinking water	0.03 µg/L	EPA 1986a; Ho 1989
Surface water and groundwater	No data	E{PA 1986b
Soil	No data	Lopez-Avila et al. 1987

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-4. Summary of Environmental Levels of 1,2,3-Trichloropropane

Media	Low	High	For more information
Outdoor air (ppbv)		No monitoring data identified	
Indoor air (ppbv)		No monitoring data identified	
Surface water (ppb)		No monitoring data identified	
Ground water (ppb)	0.1 µg/L	5.0 µg/L	Section 5.5.2
Drinking water (ppb)		No monitoring data identified	
Food (ppb)		No monitoring data identified	
Soil	0.2 ppb	2 ppb	See Section 5.5.3

Detections of 1,2,3-trichloropropane in air, water, and soil at NPL sites are summarized in Table 5-5.

Table 5-5. 1,2,3-Trichloropropane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	0.8	7.2	283,000	11	8
Soil (ppb)	12,500,000	79,100	3,430,000	2	1

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

No data were located regarding the detection of 1,2,3-trichloropropane in ambient air in the United States. Therefore, no estimate of U.S. atmospheric levels of the chemical, including background levels, is possible.

5.5.2 Water

Limited data are available regarding the detection of 1,2,3-trichloropropane in environmental waters. It has been detected by one of the sampling techniques at <0.2 μg/L in drinking water from the Carrollton Water Plant in New Orleans, Louisiana, sampled during August, 1974; however, since two of the three sampling techniques failed to detect the compound, the significance of this detection is in question (Keith et al. 1976). 1,2,3-Trichloropropane has been qualitatively detected in the drinking water of Cincinnati, Ohio, sampled during 1978 (EPA 1984), and Ames, Iowa, on an unspecified date (EPA 1987). Data from the EPA STORET database indicate that 1,2,3-trichloropropane was found in 39% of 941 samples of groundwater at a median concentration of 0.69 μg/L, at an average concentration of 1.0 μg/L, and a range of trace (below unspecified detection limit) to 2.5 μg/L (STORET 1989). It has been found at concentrations ranging from 0.1 to 5.0 μg/L in groundwater samples from California and Hawaii during small- and large-scale retrospective studies of farmlands possibly treated with fumigants and nematocides that contained 1,2,3-trichloropropane as an impurity (Cohen et al. 1986, 1987). The locations that had 1,2,3-trichloropropane-contaminated wells included the island of Oahu, Hawaii, and the Central Valley of California. Typical concentrations ranged from 0.2 to 2 μg/L. 1,2,3-Trichloropropane was found in water from nine of nine wells in Oahu, Hawaii, sampled in 1983 and 1984 at maximum concentrations ranging

from 0.30 to 2.8 µg/L (Oki and Giambelluca 1987). The wells had been closed previously to drinking water use due to contamination with other halogenated hydrocarbons. 1,2,3-Trichloropropane has been detected in groundwater from 2 of 10 sites in an agricultural community in Suffolk County, New York, at concentrations of 6 and 10 µg /L (Lykins and Baier 1985).

1,2,3-Trichloropropane was qualitatively found in 1 of 30 water samples from the Delaware, Schuylkill, and Lehigh Rivers, taken February 17–20, 1976 (DeWalle and Chian 1978). 1,2,3-Trichloropropane was qualitatively found in water from Narragansett Bay, Rhode Island, sampled during the summers of 1979 and 1980, and the winters of 1980 and 1981 (Wakeham et al. 1983). Some samples reportedly contained significant levels of the chemical. The chemical was qualitatively detected in effluent from an advanced waste treatment plant in Lake Tahoe, California, in 1974 (EPA 1984).

5.5.3 Sediment and Soil

Limited data are available regarding the detection of 1,2,3-trichloropropane in soil samples. It has been found in soil samples from California and Hawaii during small- and large-scale retrospective studies at levels typically ranging from 0.2 to 2 ppb (Cohen et al. 1987). It was found at least 10 feet down in the soil profiles in Hawaii. 1,2,3-Trichloropropane may be present in these soils as a result of the use of dichloropropene (a soil fumigant and nematocide). 1,2,3-Trichloropropane is used in the preparation of this nematocide and is an impurity in the formulation of it (Baier et al. 1987).

5.5.4 Other Media

1,2,3-Trichloropropane has been qualitatively identified as a component of ethylene dichloride-tar, a tarlike, oily waste byproduct of vinyl chloride production that had been disposed of by dumping into the sea (Jensen et al. 1975). The chemical has been found in the volatile products from the thermal oxidative degradation of the flame-retardant plasticizer, tris(dichloropropy1) phosphate (Christos et al. 1977). No information was found that indicated that 1,2,3-trichloropropane has been found in food. Because of the lack of recent comprehensive monitoring data, the average daily intake of 1,2,3-trichloropropane and the relative significance of each source of exposure cannot be determined.

5.6 GENERAL POPULATION EXPOSURE

There are not enough measured data to assess the general population's exposure to this compound. The paucity of data may be the result of either a lack of 1,2,3-trichloropropane contamination in the

environment or a lack of studies that attempt to identify and quantify the compound in the environment using sufficiently sensitive techniques. Based upon the few data available, the estimated transport and partitioning properties of the compound, and information on production and use, the following estimations concerning exposure can be made. A small part of the population may be exposed to very low levels of 1,2,3-trichloropropane through the ingestion of contaminated drinking water. Exposure to very low levels of 1,2,3-trichloropropane also may occur through the inhalation of contaminated air; however, no monitoring data regarding the presence of 1,2,3-trichloropropane in the atmosphere in the United States were located. General exposure to air containing low levels may occur near chemical manufacturing facilities that produce 1,2,3-trichloropropane and certain other chemicals, near 1,2,3-trichloropropane-containing hazardous waste dumps, and farmlands treated with fumigants and nematocides that contain 1,2,3-trichloropropane. No current information is available, however, that indicates that 1,2,3-trichloropropane is still present in soil fumigant formulations, and commercial manufacturing processes generally occur in closed and tightly sealed systems (NIOSH 1981). Inhalation and dermal exposure may occur during the use of 1,2,3-trichloropropane as a solvent and extractive agent, in paint and varnish removers, in cleaning and degreasing agents, and in cleaning and maintenance reagents, although there is no current information that indicates that the compound is still used for these purposes (Hawley 1981; NIOSH 1981). No data regarding the detection of 1,2,3-trichloropropane in humans in the United States were located.

According to the NOES conducted by NIOSH from 1981 to 1983, 492 workers (of which 9 were women) were potentially exposed to 1,2,3-trichloropropane in the workplace in 1980 (NIOSH 1989); however, no report of actual measured exposure levels in any occupational situation in the United States was located. The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals therein. This survey provides only an estimate of the number of workers potentially exposed to chemicals in the workplace. Occupational exposure to 1,2,3-trichloropropane is expected to be higher in facilities where the chemical or products containing the chemical are used than in facilities that produce 1,2,3-trichloropropane either directly or as a byproduct, since the commercial manufacturing processes generally occur in closed and tightly sealed systems (NIOSH 1981). Furthermore, exposure may result from procedures that require direct handling of the material; these include purification, formulation of products, sampling and quality control, packaging and storage, leakage of equipment, startup and shutdown procedures, maintenance, cleanup, spills, and other plant emergencies (NIOSH 1981).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Data regarding the presence of 1,2,3-trichloropropane in the environment are lacking, which prevents the thorough assessment of the potential for high exposure in various populations. Populations with potentially high exposure to 1,2,3-trichloropropane will generally include those that may be exposed to environmental contamination over long periods of time. These may include populations exposed to low levels of 1,2,3-trichloropropane via inhalation of contaminated air at or near both identified and unidentified 1,2,3-trichloropropane-containing waste disposal sites and landfills. Children playing in and around these sites may also be dermally exposed to soil containing 1,2,3-trichloropropane, although any 1,2,3-trichloropropane in surface soil would be expected to volatilize or leach through the soil. Persons whose drinking water is derived from 1,2,3-trichloropropane-contaminated groundwater or surface water for a long period of time may be exposed to relatively high levels of 1,2,3-trichloropropane. Workers involved in the manufacture or use of 1,2,3-trichloropropane or 1,2,3-trichloropropane-containing products may have the highest potential for exposure to 1,2,3-trichloropropane. Potentially high general population exposure may occur during the use of 1,2,3-trichloropropane-containing products, such as paint and varnish removers and cleaners, especially when they are used in poorly ventilated areas such as in the cleaning of reactors. Exposure through the manufacture or use of 1,2,3-trichloropropane-containing products may not be significant, however, since current manufacturing processes generally occur in closed and tightly sealed systems (NIOSH 1981) and no current information indicates that 1,2,3-trichloropropane is still used for those purposes listed.

CHAPTER 6. 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 1,2,3-trichloropropane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of 1,2,3-trichloropropane.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2,3-trichloropropane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,2,3-trichloropropane. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

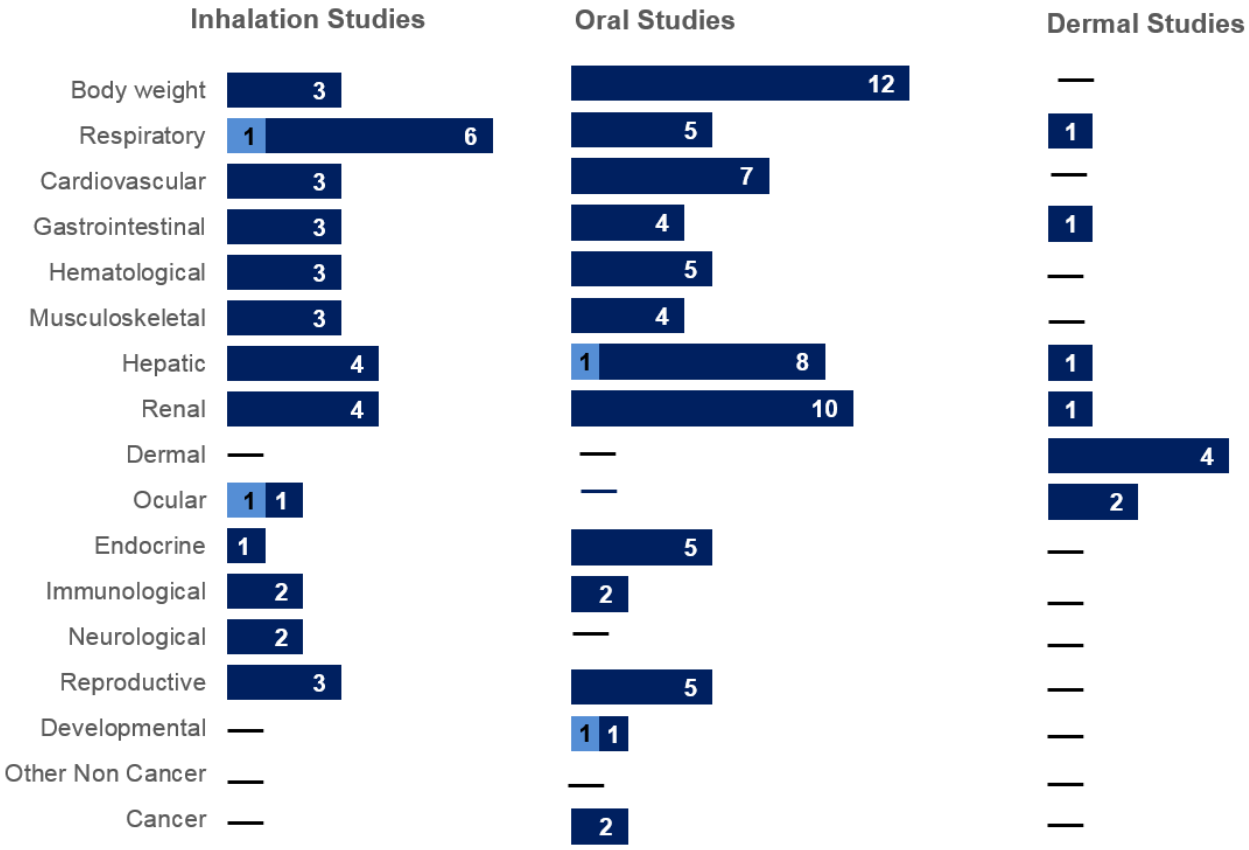
As illustrated in Figure 6-1, most of the data on the toxicity of 1,2,3-trichloropropane come from studies in experimental animals. The most commonly examined endpoints were liver, body weight, respiratory, and kidneys. Information of the toxicity of 1,2,3-trichloropropane in humans is limited to three studies, one being a case report. Approximately half of the experimental animal studies involved oral exposure; the remaining studies were equally split between inhalation and dermal/ocular exposure routes.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on 1,2,3-Trichloropropane By Route and Endpoint*

Potential hepatic, respiratory, body weight, and renal effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

Acute-Duration MRLs. The available acute inhalation database was considered adequate for derivation of a provisional MRL. Although several studies have evaluated the acute oral toxicity of 1,2,3-trichloropropane, the database was not considered adequate for derivation of an MRL. Several limitations were identified, including the lack of support for categorizing the increase in liver weight observed in the Merrick et al. (1991) study as adverse and support for the observed cardiovascular lesions (Merrick et al. 1991). Additionally studies that included examination of the liver and heart would provide valuable information for identifying critical effects and establishing dose-response relationships.

Intermediate-Duration MRLs. Several studies have evaluated the intermediate-duration toxicity of inhaled 1,2,3-trichloropropane in experimental animals (Johannsen et al. 1988); several adverse effects were identified including peribronchial hyperplasia, hepatocellular hypertrophy, and splenic extramedullary hematopoiesis. However, derivation of an MRL based on these endpoints resulted in a value that was about 10 times higher than the acute-duration inhalation MRL. One limitation of the intermediate-duration database is the lack of a study examining the nasal cavity, which was the most sensitive effect following acute exposure. Intermediate-duration studies examining a wide range of endpoints, particularly the nasal cavity, would be useful for identifying the most sensitive effect and derivation of an MRL. The oral exposure database was considered adequate for derivation of an oral MRL.

Chronic-Duration MRLs. No chronic-duration inhalation studies were identified for 1,2,3-trichloropropane, precluding the derivation of an MRL. Chronic-duration studies examining a wide range of endpoints, particularly the nasal cavity, which was the most sensitive target following acute-duration exposure, would be useful for identifying the most sensitive effect, establishing concentration-response relationships and derivation of an MRL. The chronic-duration oral database was considered adequate for deriving a provisional MRL.

Health Effects.

Respiratory. Acute inhalation studies have identified the nasal olfactory epithelium as a sensitive target of 1,2,3-trichloropropane toxicity in rats and mice (Miller et al. 1986a, 1986b). Nasal effects have also been observed in following oral exposure (NTP 1993). However, nasal effects have not been examined in longer-term inhalation studies. Longer-term studies examining the nasal cavity would allow for a better understanding of the toxicity of inhaled 1,2,3-trichloropropane.

Cardiovascular. Inflammation, degeneration, and necrosis have been observed in rats following acute and intermediate oral exposure (Merrick et al. 1991). However, other investigators have not reported adverse effects in rats administered similar or higher doses. Additional studies are needed to support this finding.

Immune. Effects such as lymphoid depletion and decreased weight of the spleen of rats and mice exposed orally and by inhalation to near-lethal levels of 1,2,3-trichloropropane for several weeks could have immunological significance (Johannsen et al. 1988; Merrick et al. 1991; NTP 1993). However, these effects could also be secondary to the observed decreases in body weight. Limited evidence from one study suggests that 1,2,3-trichloropropane may be a weak dermal sensitizer in guinea pigs (Clark 1977). Studies examining immune function are needed to evaluate the potential immunotoxicity of 1,2,3-trichloropropane.

Developmental. There were no effects on growth or viability of offspring of rats exposed by inhalation to low concentrations of 1,2,3-trichloropropane prior to mating and during gestation, (Johannsen et al. 1988). In a 2-generation study, decreases in reproductive function was observed in F1 rats (NTP 1990). Both studies were of limited scope. Given the genotoxicity of 1,2,3-trichloropropane, there is potential for developmental effects. Single and 2-generation studies examining a wide range of endpoints are needed; the developmental studies should also include neurological and cognitive endpoints.

Carcinogenicity. Although animal studies provide evidence of the carcinogenicity of 1,2,3-trichloropropane, very little information is available on the mechanisms of action for carcinogenicity and the causative agent. Mechanistic studies would provide valuable information to the understanding of the carcinogenic potential in humans.

Epidemiology and Human Dosimetry Studies. A small number of human studies have been examined the toxicity 1,2,3-trichloropropane (Brender et al. 2014; Han 2010; Silverman et al. 1946). Only one of these provided exposure data (Silverman et al. 1946), but only examined sensory responses. Studies of populations exposed to 1,2,3-trichloropropane could provide information on whether rodents are good models for human toxicity.

Biomarkers of Exposure and Effect. There are no known biomarkers of exposure for 1,2,3-trichloropropane in humans. Studies with rats suggest that respiratory or urinary excretion of 1,2,3-trichloropropane may be sufficient for monitoring purposes (Sipes et al. 1982). Additional studies could help determine the feasibility of using 1,2,3-trichloropropane in the breath or urine as a biomarker of exposure.

There are no known biomarkers of effects for 1,2,3-trichloropropane in humans. One study with rats (NTP 1993) suggests that anemia and alterations of serum enzymes (e.g., decreased serum pseudocholinesterase activity) might be sensitive biomarkers for hematologic and hepatic effects of 1,2,3-trichloropropane, respectively. Additional animal studies or examination of humans with known exposure to 1,2,3-trichloropropane are needed to identify potential biomarkers of exposure, especially biomarkers that would be indicative of subclinical alterations.

Absorption, Distribution, Metabolism, and Excretion. There is limited information on absorption and excretion of single oral doses of 1,2,3-trichloropropane in rats (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984), but no data are available on the toxicokinetics of 1,2,3-trichloropropane in animals after inhalation or dermal exposure. Tissue distribution, metabolism, and excretion of intravenously injected 1,2,3-trichloropropane also have been investigated in rats (Volp et al. 1984). A PBPK model describing tissue distribution and excretion was developed using data from this intravenous study. A more complete oral study in animals, as well as animal studies using inhalation and dermal exposure, could provide necessary data (e.g., absorption kinetics) for expanding the model to include inhalation, oral, and dermal exposure and verifying the model. It might then be possible to use the model to predict the pharmacokinetics of 1,2,3-trichloropropane in humans exposed by these routes. Studies with several dose levels and exposure durations would allow more accurate comparison between routes (e.g., assessment of relative rates and extent of absorption, distribution, metabolism, and excretion) as well as detection of saturation effects.

Comparative Toxicokinetics. The toxicokinetics of 1,2,3-trichloropropane have been studied only in rats by the oral and intravenous routes (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984). A PBPK model has been proposed based on the intravenous data. Studies in other species would be useful for verifying predictions made from the model about other species, including humans.

Children's Susceptibility. No information is available on children's susceptibility; additionally, there are limited developmental toxicity studies (see Health Effects section). Studies examining immature animals may provide valuable information on the potential increased sensitivity of children.

Physical and Chemical Properties. Physical and chemical property data are essential for estimating the transport and partitioning of a chemical in the environment. Many of the physical and chemical properties of 1,2,3-trichloropropane are available (Table 4-2) (Hawley 1981; HSDB 1989; Mackay et al. 1982; McNeill 1979; Riddick et al. 1986; Ruth 1986; Weast 1985; Williams 1949). However, only estimated values are listed for the log K_{ow}, K_{oc}, and BCF (Lyman et al. 1982). Since the log K_{ow} was used to estimate the K_{oc} and BCF, an experimentally determined log K_{ow} would lead to less uncertainty in those estimated properties. Experimentally determined values would clarify the reliability of these data, although the techniques used for the estimations appear to be accurate.

Production, Import/Export, Use, Release, and Disposal. Data regarding the production methods for 1,2,3-trichloropropane are available (Bauer et al. 1987; Hawley 1981; NIOSH 1981; SRI 1989; Williams 1949); however, data regarding current production, import, and export volumes, and use patterns are lacking. We do know that the chemical is currently produced (SRI 1989), but not in what quantities or whether future production levels will increase. We do not know if the chemical is widely used in the home, the environment, or in the workplace, but it does not appear that such widespread use is likely. It has not been found in food, although foods may not have been tested for its presence. Use, release, and disposal information is useful for determining where environmental exposure to 1,2,3-trichloropropane may be high, and may help in estimating whether exposure is likely, and may therefore help to determine whether further toxicological studies are warranted. General data are available regarding the methods of disposal of 1,2,3-trichloropropane (HSDB 1989; Matsui et al. 1975), but information concerning the efficiencies of these methods, as well as the amount disposed of by each method, is lacking. Specific disposal information, obtainable by polling industries or industry organizations, may be useful for determining environmental burden and potential concentrations where environmental exposures may be high. Rules and regulations governing land disposal of 1,2,3-trichloropropane are known (EPA 1988a).

Environmental Fate. The environmental fate of 1,2,3-trichloropropane remains unclear due to a lack of experimental data. We do not know where the chemical partitions in the environment. However, based upon estimated physical properties (Lyman et al. 1982), the chemical is expected to partition into the atmosphere and groundwater (Swann et al. 1983). It has been shown that the chemical leaches

through soil (Cohen et al. 1986, 1987; Lykins and Baier 1985; Oki and Giamelluca 1987; STORET 1989). It is estimated that it can volatilize, through near-surface soil and water to the atmosphere (EPA 1985; Lyman et al. 1982). Nothing definitive is known about the biodegradability of the compound. The rate constant for reaction with hydroxyl radicals in the atmosphere is an estimated value (Atkinson 1987), as are significant partition coefficient values used in predicting the environmental fate of the compound (EPA 1988b). Experimental data in these areas would aid in assessing the ultimate environmental fate of 1,2,3-trichloropropane, which would, in turn, aid in assessing its background levels in the environment and levels of human exposure.

Bioavailability from Environmental Media. Studies have shown that 1,2,3-trichloropropane is absorbed through the lungs, gastrointestinal tract, and skin of animals (Alpert 1982; Clark 1977; Johannsen et al. 1988; Sipes et al. 1982; Union Carbide 1958; Volp et al. 1984). This indicates that it may be absorbed through the inhalation of contaminated air, ingestion of contaminated water, food, and soil, and through dermal contact. The amount of 1,2,3-trichloropropane that is bioavailable from each route is not well documented, and no data were found for humans. Data on the bioavailability of 1,2,3-trichloropropane would be helpful in assessing the importance of environmental exposure levels.

Food Chain Bioaccumulation. The estimated BCF for 1,2,3-trichloropropane (EPA 1988b; Lyman et al. 1982) indicates that this compound would not significantly bioconcentrate in plants, aquatic organisms, or animals. No experimental data were found to support this conclusion. Information was unavailable on the biomagnification of 1,2,3-trichloropropane in food chains. Additional information on bioconcentration by plants, aquatic organisms, and animals and biomagnification in terrestrial and aquatic food chains could be helpful because it might help to indicate whether the chemical biomagnifies in food chains and thereby poses a potential for significant exposure. Biomagnification is not likely, however, based upon the estimated BCF.

Exposure Levels in Environmental Media. Limited data were available regarding the levels of 1,2,3-trichloropropane in the environment (Baier et al. 1987; Cohen et al. 1986, 1987; Dewalle and Chian 1978; EPA 1984, 1987; Jacobs and Zabik 1983; Keith et al. 1976; Lykins and Baier 1985; Oki and Giambelluca 1987; STORET 1989; Wakeham et al. 1983). Information on exposure to 1,2,3-trichloropropane from environmental media would be useful, especially from drinking water derived from groundwater downgradient from 1,2,3-trichloropropane-containing hazardous waste disposal sites and other contaminated surface waters, air near facilities that make or use products containing the compound,

and soil at waste disposal sites. Data concerning the presence of 1,2,3-trichloropropane in foods would also be useful in assessing potential exposure.

Exposure Levels in Humans. No data have been found that indicate that 1,2,3-trichloropropane has been found in human samples of blood, urine, fat, or breast milk. Furthermore, no biomarkers of exposure or effect have been identified. Data on both workplace exposure and ambient environmental exposure are sparse and outdated (NIOSH 1981, 1989). A detailed, recent database of exposure would be helpful in determining the current exposure levels, thus allowing estimation of the average daily dose associated with various scenarios such as living near a hazardous waste disposal site, drinking contaminated drinking water, or working in a contaminated workplace. This database of exposure may be very useful if current use patterns, for which information is not available, warrant it.

Exposures of Children. No monitoring data were identified for children. General population monitoring studies should include children to allow for an assessment of potential differences in exposure of children and adults.

Analytical Methods. Analytical methods for determining 1,2,3-trichloropropane in contaminated air, water, soil, liquid and solid waste, sewage sludge, and citrus fruits are available (EPA 1986a, 1986b; Ho 1989; Lopez-Avila et al. 1987; NIOSH 1987; Tonogai et al. 1986). No methods were found for the determination of 1,2,3-trichloropropane in sediments. Most of the methods used for environmental samples, however, did not report detection limits, recovery, accuracy, or precision for 1,2,3-trichloropropane. Knowledge of these factors, as well as the development of alternative methods of analysis, would help in estimating the potential for human exposure to 1,2,3-trichloropropane. No information was found regarding degradation products of 1,2,3-trichloropropane. Consequently, no comment regarding the availability of analytical methods for determining degradation products can be made.

There are methods for analyzing 1,2,3-trichloropropane in most of the biological matrices for the rat, although important information such as detection limits and recoveries was not reported (Sipes et al. 1982). These methods may be sufficient for the analysis of human biological matrices.

6.3 Ongoing Studies

No ongoing studies were identified for 1,2,3-trichloropropane.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding 1,2,3-trichloropropane in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs which are substance specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for 1,2,3-trichloropropane.

Table 7-1. Regulations and Guidelines Applicable to 1,2,3-Trichloropropane

Agency	Description	Information	Reference
	Air		
EPA	RfC	$3x10^{-4}$ mg/m^3 [a]	IRIS 2009
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water health advisories		EPA 2012
	1-Day (10-kg child)	0.6 mg/L	
	10-Day (10-kg child)	0.6 mg/L	
	DWEL	0.1 mg/L	
	National primary drinking water regulations	No data	EPA 2009a
	RfD	$4x10^{-3}$ mg/kg-day[b]	IRIS 2009
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	EAFUS	No data[c]	FDA 2013
	Cancer		
ACGIH	Carcinogenicity classification	A2[d,e]	ACGIH 2015, 2016
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen[f]	NTP 2016
EPA	Carcinogenicity classification	Likely to be carcinogenic to humans[g]	IRIS 2009
IARC	Carcinogenicity classification	Group 2A[h]	IARC 2017
	Occupational		
ACGIH	TLV	0.005 ppm	ACGIH 2016
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	50 ppm (300 mg/m^3)	OSHA 2016a, 2016b, 2016c
NIOSH	REL (up to 10-hour TWA)	10 ppm (60 mg/m^3)[i,j]	NIOSH 2014, 2016
	IDLH	100 ppm[i,k]	

Table 7-1. Regulations and Guidelines Applicable to 1,2,3-Trichloropropane

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
AIHA	ERPGs	No data	AIHA 2015
DOE	PACs-air		DOE 2016a
	PAC-1[l]	0.015 ppm	
	PAC-2[l]	170 ppm	
	PAC-3[l]	1000 ppm	

[a]Based on peribronchial lymphoid hyperplasia in male rats.
[b]Based on increased absolute liver weight in male rats.
[c]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[d]A2: suspected human carcinogen.
[e]Based on studies in rats and mice that found a wide range of tumors in both sexes following oral exposure, and on mechanistic studies that found the mechanism of tumor induction to involve interaction with genetic material.
[f]Based on sufficient evidence of carcinogenicity from studies in experimental animals.
[g]Based on a statistically significant and dose-related increase in the formation of multiple tumors in both sexes of two species in a chronic oral bioassay.
[h]Group 2A: probably carcinogenic to humans.
[i]Potential occupational carcinogen.
[j]Skin designation indicates the potential for dermal absorption.
[k]Based on acute inhalation toxicity data in humans.
[l]Definitions of PAC terminology are available from U.S. DOE (2016b).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health concentrations; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, 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 MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
CAS Numbers: 96-18-4
Date: May 2019
Profile Status: Final, Draft for Public Comment
Route: Inhalation
Duration: Acute
Provisional MRL: 0.001 ppm
Critical Effect: Decreased thickness of nasal olfactory epithelium
Reference: Miller et al. 1986b
Point of Departure: $NOAEL_{HEC}$ of 0.03 ppm
Uncertainty Factor: 30
LSE Graph Key: 5
Species: Rat

MRL Summary: A provisional acute-duration inhalation MRL of 0.001 ppm was derived for 1,2,3-trichloropropane based on decreased thickness of the nasal olfactory epithelium of rats exposed 6 hours/day for 9 days over an 11-day period (Miller et al. 1986b). The MRL is based on a $NOAEL_{HEC}$ of 0.03 ppm and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: A small number of studies have evaluated the toxicity of 1,2,3-trichloropropane following acute-duration inhalation exposure. In humans, a 15-minute exposure to 100 ppm 1,2,3-trichloropropane resulted in eye and throat irritation (Silverman et al. 1946). Acute inhalation studies in experimental animals (rats and mice) identify the respiratory tract and liver as the most sensitive targets of 1,2,3-trichloropropane toxicity; a summary of relevant NOAEL and LOAEL values for respiratory and hepatic effects is presented in Table A-1. The respiratory effects consisted of ***decreases*** in the thickness of nasal olfactory epithelium at the lowest adverse effect levels (3 ppm in rats and 10 ppm in mice) (Miller et al. 1986b), degeneration and inflammation of olfactory epithelium at 13 ppm in rats (Miller et al. 1986a), subacute inflammation of olfactory epithelium at 40 ppm in mice (Miller et al. 1986b), and multifocal fibrosis of nasal submucosa at 132 ppm in rats (Miller et all. 1986a). The Miller et al. (1986a) rat study demonstrated that the severity of the nasal lesions increased with concentration; the degeneration of olfactory epithelium was graded as slight at 13 ppm, moderate at 40 ppm, and severe at 132 ppm. The liver effects consisted of increases in liver weights in rats exposed to ≥40 ppm (Miller et al. 1986a) and mice exposed to 132 ppm (Miller et al. 1986a), very slight individual cell hepatocellular necrosis in male rats exposed to 132 ppm (Miller et al. 1986a), and very slight hepatocellular vacuolization at 132 ppm in mice (Miller et al. (1986a). Other acute-duration studies have primarily focused on lethality (Gushow and Quast 1984; Johannsen et al. 1988; Smyth et al. 1965; Union Carbide 1958). Based on the available data, the nasal olfactory epithelium appears to be the most sensitive target of toxicity following acute-duration inhalation exposure.

Table A-1. Summary of Relevant LOAEL Values Following Acute Inhalation Exposure to 1,2,3-Trichloropropane

Species	Exposure	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Nasal effects					
F344 rat	6 hours/day 5 days/week 2 weeks		13	Degeneration and inflammation of nasal olfactory epithelium	Miller et al. 1986a
F344 rat	6 hours/day 5 days/week 2 weeks	1	3	Decreased thickness of olfactory epithelium	Miller et al. 1986b
B6C3F1 mouse	6 hours/day 5 days/week 2 weeks		13	Decreased thickness of olfactory epithelium	Miller et al. 1986a
B6C3F1 mouse	6 hours/day 5 days/week 2 weeks	3	10	Nasal olfactory inflammation	Miller et al. 1986b
Hepatic effects					
F344 rat	6 hours/day 5 days/week 2 weeks	40	132	Very slight hepatocellular necrosis	Miller et al. 1986a
B6C3F1 mouse	6 hours/day 5 days/week 2 weeks	40	132	Hepatocellular vacuolization	Miller et al. 1986a

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: Based on a comparison of NOAEL and LOAEL values and the observed effects, rats appear to be more sensitive than mice to 1,2,3-trichloropropane-induced nasal toxicity. The Miller et al. (1986b) rat study, which identified a NOAEL of 1 ppm and LOAEL of 3 ppm, was selected as the principal study.

Summary of the Principal Study:

Miller RR, Quast JF, Momany-Pfruender JJ. 1986b. 1,2,3-Trichloropropane: 2-Week vapor inhalation study to determine the no-adverse-effect level in rats and mice. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D.

Groups of five male and five female Fischer 344 rats were exposed to 0, 1, 3, or 10 ppm 1,2,3-trichloropropane 6 hours/day, 5 days/week for 9 exposures in an 11-day period. The following parameters were used to assess toxicity: observations after each exposure period, body weight measurements prior to 1st, 3rd, 5th, and 7th exposure, urinalysis (bilirubin, glucose, ketones, occult blood, pH, protein, urobilinogen, and specific gravity), organ weights (brain, heart, liver, kidneys, thymus, and testes), gross necropsy of major tissues and organs, and histopathological examination of nasal tissue.

There were no deaths or alterations in body weight gain, or urinalysis, or organ weights. A very slight decrease in olfactory epithelial thickness was observed in 10/10 rats exposed to 3 ppm, but was not observed in controls or other groups of exposed rats. Very slight olfactory epithelial degeneration was observed in 10/10 rats at 10 ppm and in 0/10 control rats. Very slight multifocal, bilateral subacute inflammation of olfactory epithelium was observed in 6/10, 4/10, 2/10, and 10/10 rats in the 0, 1, 3, and 10 ppm groups, respectively. No alterations were observed during the gross necropsy.

Selection of the Point of Departure for the MRL: The NOAEL/LOAEL approach was used to select the point of departure (POD) for the MRL. The incidence data for olfactory epithelial alterations were not considered suitable for benchmark dose (BMD) modeling due to the lack of concentration-response data, 0% incidence in controls and 1 ppm groups and 100% in the 3 ppm group. Thus, the NOAEL of 1 ppm was selected as the POD for the MRL.

Intermittent Exposure: The NOAEL of 1 ppm was adjusted for intermittent exposure as follows: 1 ppm x 6 hours/24 hours x 9 exposures/11 days = 0.20 ppm.

Human Equivalent Concentration: The $NOAEL_{ADJ}$ of 0.20 ppm was converted to a human equivalent concentration (HEC) of 0.03 ppm using the following equation: $NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ET}$, where $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) for the extrathoracic region. Extrathoracic regional gas doses were calculated for each species as follows: V_E (minute volume) ÷ SA_{ET} (surface area of the extrathoracic region); where V_E = 138 mL/minute (calculated using the average body weight for males and females, 0.181 k) and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ET}$
$NOAEL_{HEC} = 0.20 \text{ ppm} \times (138 \text{ mL/minute} \div 15 \text{ cm}^2)/(13{,}800 \text{ mL/minute} \div 200 \text{ cm}^2)$
$NOAEL_{HEC} = 0.20 \text{ ppm} \times 0.133$
$NOAEL_{HEC} = 0.03 \text{ ppm}$

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

MRL = $NOAEL_{HEC}$ ÷ UFs
0.03 ppm ÷ (3 x 10) = 0.001 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Although the principal study only included histological examination of the nasal cavity, a companion study (Miller et al. 1986a) examined a wide range of endpoints and demonstrated that the olfactory epithelium was the most sensitive target of toxicity.

Agency Contact (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
CAS Numbers: 96-18-4
Date: September 1993
March 2017—Update literature search
Profile Status: Final, Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: The available intermediate inhalation data were not considered adequate for derivation of an intermediate-duration inhalation MRL for 1,2,3-trichloropropane.

Rationale for Not Deriving an MRL: An intermediate-duration inhalation MRL was not derived for 1,2,3-trichloropropane because derivation of an MRL based on the available intermediate studies resulted in an MRL that was higher than the acute-duration inhalation MRL and the only available study did not examine nasal tissue (the most sensitive target following acute exposure).

Reliable information on the intermediate-duration toxicity of 1,2,3-trichlorochloropropane is limited to a series of studies in rats conducted by Johannsen et al. (1988). These studies identified several sensitive targets of toxicity including the respiratory tract, liver, and the hematological system. In a 4-week preliminary study (6 hours/day, 5 days/week), increases in liver weight were observed at ≥95 ppm; the study did not include histological examinations. In a more extensive 13-week study (6 hours/day, 5 days/week), exposure to 4.5 ppm resulted in peribronchial lymphoid hyperplasia, midzonal hepatocellular hypertrophy, and extramedullary hematopoiesis in the spleen. At 15 ppm, decreases in body weight gain and excessive lacrimation were observed. No adverse effects were observed at the two lowest test concentrations (0.05 and 1.54 ppm). It is noted that the Johannsen et al. (1988) study did not include examination of nasal tissue, which was the most sensitive target of toxicity following acute inhalation exposure. In a reproductive/developmental toxicity study, no alterations in mating, fertility, histopathology of reproductive tissues, gestation length, number of live births, litter size at birth or postnatal days 4–21, birth weight, pup body weight, or pup survival through postnatal day 21 were observed in male and female rats exposed to concentrations as high as 15 ppm for a 10-week pre-mating period, 30–40-day mating period, and gestation days 0–14.

Based on the available data, an MRL could be derived based on the lung, liver, and spleen effects observed in rats exposed to ≥4.5 ppm; the NOAEL for these effects is 1.54 ppm. Adjusting the NOAEL concentration for intermittent exposure results in a $NOAEL_{ADJ}$ of 0.275 ppm. A $NOAEL_{HEC}$ of 0.275 ppm is calculated by multiplying the $NOAEL_{ADJ}$ by an extra-respiratory regional gas dose ratio (RGDR) of 1. Because blood:gas partition coefficients are not available for rats or humans, the default ratio of 1 was used for the $RGDR_{ER}$. It is noted that the peribronchial lymphoid hyperplasia observed in the lungs was not considered a portal-of-entry effect since the effect occurred in lymphoid tissue rather than lung tissue. Dividing the $NOAEL_{HEC}$ POD of 0.275 ppm by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) results in a candidate MRL of 0.009 ppm. This value is higher than the acute-duration inhalation MRL of 0.001 ppm based on nasal lesions observed in rats exposed to 1,2,3-trichloropropane for 11 exposures (Miller et al. 1986b). Thus, an intermediate-duration inhalation MRL was not derived for 1,2,3-trichloropropane.

Agency Contact (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
CAS Numbers: 96-18-4
Date: September 1993
March 2017—Update literature search
Profile Status: Final, Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: The available chronic inhalation data were not considered adequate for derivation of chronic-duration inhalation MRL for 1,2,3-trichloropropane.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified for 1,2,3-trichloropropane.

Agency Contact (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
CAS Numbers: 96-18-4
Date: September 1993
March 2017—Update literature search
Profile Status: Final, Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: The available acute oral data were not considered adequate for derivation of an acute-duration oral MRL for 1,2,3-trichloropropane.

Rationale for Not Deriving an MRL: A small number of studies have examined the toxicity of 1,2,3-trichloropropane following acute oral exposure. Increases in mortality were observed at ≥150 mg/kg (Alpert 1983; NTP 1993; Smyth et al. 1962). The most sensitive effect identified in the available database was an increase in relative liver weights observed in rats administered via gavage ≥29.5 mg/kg/day for 10 days (Merrick et al. 1991). At 118 mg/kg/day, decreases in body weight gain; myocardial inflammation, degeneration, and necrosis; and thymic atrophy were observed in rats administered 1,2,3-trichloropropane via gavage for 10 days (Merrick et al. 1991). Two studies examining reproductive effects in male rats did not find increases in the incidence of histological alterations 60 mg/kg/day for 10 days (Dix 1979) or 80 mg/kg/day for 5 days (Saito-Suzuki et al. 1982) or dominant lethality at 80 mg/kg/day (Saito-Suzuki et al. 1982).

Although the available acute-duration studies identified several effects, the database was not considered suitable for MRL derivation. The increase in liver weight was considered a LOAEL based on intermediate and chronic studies that reported histological alterations in the liver. However, no significant increases in liver lesions were observed in the Merrick et al. (1991) study, although centrilobular hepatic necrosis was observed in 3/20 animals at 118 mg/kg/day. Heart lesions were observed in acute- and intermediate-duration studies conducted by Merrick et al. (1991), but no cardiovascular effects have been observed in other acute, intermediate, or chronic oral studies; this endpoint was not considered suitable for MRL derivation due to the lack of corroborative data. Interpretation of the thymic atrophy observed at 118 mg/kg/day is difficult given that a 22–25% decrease in body weight gain was also observed at this dose level.

Agency Contact (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
CAS Numbers: 96-18-4
Date: May 2019
Profile Status: Final, Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.06 mg/kg/day
Critical Effect: Increased absolute liver weight, decreased hemoglobin, decreased erythrocytes
Reference: NTP 1993
Point of Departure: NOAEL of 5.7 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 9
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.06 mg/kg/day was derived for 1,2,3-trichloro-propane based on increased absolute liver weight, decreased hemoglobin levels, and decreased erythrocyte levels observed in female rats administered via gavage 1,2,3-trichloropropane 5 days/week for 17 weeks (NTP 1993). The MRL is based on a duration-adjusted NOAEL of 5.7 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Four studies have evaluated the intermediate-duration oral toxicity of 1,2,3-trichloropropane. These studies have identified a number of targets of toxicity: body weight, respiratory tract, heart, forestomach, hematological system, liver, kidney, and reproductive/ developmental systems. The NOAEL and LOAEL values for these effects are summarized in Table A-2.

Based on a comparison of the lowest LOAEL values for each endpoint, the liver appears to be one of the most sensitive targets of toxicity. At gavage doses ≥11 mg/kg/day, >10% increases in absolute liver weight were observed in rats (NTP 1993); a similar LOAEL of 14.7 mg/kg/day was identified in another rat gavage study (Merrick et al. 1991). An increase in liver weight was also observed in mice administered ≥89 mg/kg/day (NTP 1993). Serum clinical chemistry alterations have also been observed at lower doses; decreases in pseudocholinesterase levels, likely due to decreased synthesis in the liver, were observed at ≥5.7 mg/kg/day (NTP 1993) and increases in serum total bilirubin and alanine aminotransferase were observed at ≥58.9 mg/kg/day (NTP 1993). At higher doses, hepatocellular necrosis was observed in rats and mice administered 89 and 179 mg/kg/day, respectively (NTP 1993), and anisokaryosis and fatty vacuolation was observed in rats at 113 mg/kg/day (Villeneuve et al. 1985). Additionally, bile duct hyperplasia was observed in rats at 58.9 mg/kg/day (Merrick et al. 1991), 89 mg/kg/day (NTP 1993), and 149 mg/kg/day (Villeneuve et al. 1985).

The lowest LOAEL for hematological effects is also 11 mg/kg/day identified in the NTP (1993) rat study. The hematological effects consisted of decreases in hematocrit, hemoglobin, and erythrocyte levels in female rats. NTP noted that the observed anemia was nonregenerative and possibly associated with depressed erythropoiesis. No hematological effects were observed in a 13-week rat drinking water study (Villenueve et al. 1985) or in a 17-week gavage mouse study (NTP 1993).

Table A-2. Summary of NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,2,3-Trichloropropane

Species	Exposure	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight effects					
Sprague-Dawley rat	30 days (GO)	14.7	58.9	14–20% decrease in body weight gain	Merrick et al. 1991
F344 rat	17 weeks, 5 days/week (GO)	23[a]	45[a]	11% decreases in body weight gain in males (females at 89 mg/kg/day)	NTP 1993
Sprague-Dawley rat	13 weeks (W)	17	113	Reduced body weight gain	Villeneuve et al. 1985
B6C3F1 mouse	17 weeks, 5 days/week (GO)	179[a]		No effect on body weight gain	NTP 1993
Respiratory effects					
F344 rat	17 weeks, 5 days/week (GO)	45[a]	89[a]	Necrosis in nasal turbinates	NTP 1993
B6C3F1 mouse	17 weeks, 5 days/week (GO)	23[a]	45[a]	Regeneration of bronchiolar epithelium in the lungs in females (males at ≥89 mg/kg/day)	NTP 1993
Cardiovascular effects					
Sprague-Dawley rat	30 days (GO)	14.7	58.9	Myocardial inflammation, degeneration, and necrosis	Merrick et al. 1991
F344 rat	17 weeks, 5 days/week (GO)	89[a]		No histological alterations	NTP 1993
Sprague-Dawley rat	13 weeks (W)	113		No histological alterations	Villeneuve et al. 1985

Table A-2. Summary of NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,2,3-Trichloropropane

Species	Exposure	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
B6C3F1 mouse	17 weeks, 5 days/week (GO)	179[a]		No histological alterations	NTP 1993
Gastrointestinal effects					
F344 rat	17 weeks, 5 days/week (GO)	89[a]		No histological alterations	NTP 1993
B6C3F1 mouse	17 weeks, 5 days/week (GO)	23[a]	45[a]	Hyperkeratosis and acanthosis of forestomach	NTP 1993
Hematological effects					
F344 rat	17 weeks, 5 days/week (GO)	5.7[a]	11[a]	Decreases in hematocrit, hemoglobin, and erythrocyte levels after 8 and 17 weeks	NTP 1993
Sprague-Dawley rat	13 weeks (W)	113		No hematological alterations	Villeneuve et al. 1985
B6C3F1 mouse	17 weeks, 5 days/week (GO)	179[a]		No hematological alterations	NTP 1993
Hepatic effects					
Sprague-Dawley rat	30 days (GO)	7.4	14.7	Increased relative liver weight	Merrick et al. 1991
		14.7	58.9	Bile duct hyperplasia	
F344 rat	17 weeks, 5 days/week (GO)	5.7[a]	11[a]	Increased absolute liver weight	NTP 1993
			89[a]	Hepatocellular necrosis and hemorrhage, bile duct hyperplasia	

Table A-2. Summary of NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,2,3-Trichloropropane

Species	Exposure	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Sprague-Dawley rat	13 weeks (W)	17	113	Anisokaryosis, accentuated zonation and fatty vacuolation	Villeneuve et al. 1985
			149	Biliary hyperplasia (females only)	
B6C3F1 mouse	17 weeks, 5 days/week (GO)	45[a]	89[a]	Increased liver weights	NTP 1993
			179[a]	Focal hepatocellular necrosis	
Renal effects					
F344 rat	17 weeks, 5 days/week (GO)	11[a]	23[a]	Increased absolute and relative liver weight in males	NTP 1993
			45[a]	Regenerative hyperplasia after 8 weeks of exposure; not observed after 17 weeks of exposure	
Sprague-Dawley rat	13 weeks (W)	17	113	Eosinophilic inclusions, pyknosis, nuclear displacement, fine glomerular adhesions, interstitial reactions, and histologic proteinuria	Villeneuve et al. 1985
B6C3F1 mouse	17 weeks, 5 days/week (GO)		179[a]	Multifocal tubular necrosis in animals dying early	NTP 1993
Reproductive/developmental effects					
Swiss mice	98 days (GO)	30	60	Decreased number of live pups per litter	NTP 1990
		120		No alterations in epididymal sperm motility, count, or morphology or estrous cycle length	
			120	Ovarian amyloidosis	

Table A-2. Summary of NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,2,3-Trichloropropane

Species	Exposure	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Swiss mice	Prenatal exposure, post weaning, mating, and gestation exposure	60	120	Decreases in mating, fertility, and pregnancy indices	NTP 1990

[a]Adminstered doses of 8, 16, 32, 63, 125, or 250 mg/kg were adjusted for intermittent exposure (5 days/week) resulting in continuous doses of 5.7, 11, 23, 45, 89, and 179 mg/kg/day.

GO = gavage in oil; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; W = drinking water administration

At the next highest LOAEL of 23 mg/kg/day, increases in kidney weights were observed in male rats (NTP 1992); the adversity of this finding is supported by histological alterations in the kidney observed at ≥45 mg/kg/day (NTP 1993; Villeneuve et al. 1985). Other effects that have been observed in rats and mice at higher LOAELs included decreases in body weight gain (lowest LOAEL of 45 mg/kg/day) (Merrick et al. 1991; NTP 1993; Villeneuve et al. 1985), regeneration of bronchiolar epithelium (45 mg/kg/day) (NTP 1993), hyperkeratosis and acanthosis of the forestomach, myocardial inflammation, degeneration, and necrosis (58.9 mg/kg/day) (Merrick et al. 1991), decreases in reproductive function (60 mg/kg/day) (NTP 1990), and necrosis in nasal turbinates (89 mg/kg/day) (NTP 1993).

Selection of the Principal Study: NTP (1993) was selected as the principal study because it identified the lowest LOAEL (11 mg/kg/day) for liver and hematological effects.

Summary of the Principal Study:

NTP. 1993. Toxicology and carcinogenesis studies of 1,2,3-trichloropropane (CAS No. 96-18-4) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program Tech Rep Ser 384.

Groups of 20 male and 20 female F344/N rats were administered 8, 16, 32, 63, 125, or 250 mg/kg 1,2,3-trichloropropane in corn oil 5 days/week for 17 weeks; a vehicle control group consisted of 30 males and 30 females. After 8 weeks of exposure, 10 rats/sex/group were sacrificed. The following parameters were used to assess toxicity: weekly clinical observations, weekly body weights, organ weights (brain, epididymis, heart, kidney, liver, lung, testis, thymus), urinalysis, hematology, serum clinical chemistry, and histopathology of major tissues and organs (control and 125 mg/kg groups and other groups as needed).

- ***Death.*** Deaths were observed in all male and female rats in the 250 mg/kg group by week 5 and 2, respectively, and in 1/10 males and 4/10 females at 125 mg/kg. The cause of death in the 250 mg/kg group was kidney or hepatic toxicity. There was no mortality at lower doses.
- ***Body weight.*** Body weight gain was reduced in males at 63 mg/kg (11% lower than controls) and in males (21%) and females (24%) at 125 mg/kg. Food consumption markedly reduced at 250 mg/kg prior to death.
- ***Respiratory.*** There was a significant increase in relative lung after 17 weeks in males at 125 mg/kg. Epithelial necrosis and attenuation of epithelial lining of the dorsal portion of nasal turbinates was observed at 125 mg/kg; in females, the lesions were observed after 8 and 17 weeks of exposure.
- ***Hematological.*** Significant decreases in hematocrit, hemoglobin, and erythrocyte levels were observed at 63 and 125 mg/kg after 17 weeks of exposure; decreases in hemoglobin levels were also observed in females at 16 and 32 mg/kg. After 8 weeks of exposure, decreases in hematocrit, hemoglobin, and erythrocyte levels were observed at ≥16 mg/kg and hematocrit and erythrocyte levels were decreased in females at 8 mg/kg.
- ***Hepatic.*** After 8 weeks of exposure, significant increases were observed in total bilirubin at ≥63 mg/kg, ALT in females at ≥63 mg/kg, aspartate aminotransferase (AST) in females at ≥125 mg/kg, lactic dehydrogenase (LDH) at ≥63 mg/kg in females and 125 mg/kg in males, and sorbitol dehydrogenase (SDH) at 125 mg/kg. Pseudocholinesterase levels were significantly decreased in males 32 and 125 mg/kg after 8 weeks and ≥32 mg/kg in males at 17 weeks, and ≥8 mg/kg in females at 8 and 17 weeks. The investigators suggested that the decrease in pseudocholinesterase levels suggest a decrease in synthesis due to hepatocellular damage. Significant increases in absolute liver weight was observed in males after 17 weeks of exposure at ≥8 mg/kg and in females at ≥16 mg/kg; the increases in absolute liver weight in the males did not appear to be dose-related. Significantly increased relative liver weights were observed at ≥32 mg/kg in males and ≥16 mg/kg in females. In the liver, necrosis, hemorrhage, and bile duct

hyperplasia were observed in females at 125 mg/kg after 8 or 17 weeks of exposure; degeneration and hemorrhage were observed in males at 250 mg/kg after 8 weeks of exposure. There were no treatment-related effects in lower dose groups after 17 weeks.

- ***Renal.*** Blood urea nitrogen (BUN) levels were decreased in females at 16, 63, and 125 mg/kg after 8 weeks of exposure and in males at 125 mg/kg and females at ≥32 mg/kg after 17 weeks. Absolute and relative kidney weights were increased ($p<0.05$) after 17 weeks at ≥32 mg/kg in males and at ≥63 mg/kg in females. Renal regenerative hyperplasia was observed at ≥63 mg/kg after 8 weeks of exposure and at 125 mg/kg after 17 weeks of exposure in males; necrosis and karyomegaly (males only) were also observed at 250 mg/kg after 8 weeks of exposure.
- ***Other Effects.*** The investigators noted that thymic lymphoid depletion, hypocellularity of sternal bone marrow, splenic atrophy, uterine hypoplasia, adrenal cortical cell vacuolation, and myocardial chronic inflammation occurred less frequently in animals dying during the study; however, incidence data were not provided and NOAEL and LOAEL values could not be identified for these effects.

Selection of the Point of Departure for the MRL: The lowest LOAEL identified in the NTP (1993) rat study was 11 mg/kg/day. At this dose level, increases in absolute liver weight in females, increases in relative liver weight, decreases in hemoglobin levels in females, and decreases in erythrocyte counts in females were observed. BMD modeling was attempted for these endpoints; the results of the modeling are presented in the Benchmark Dose Modeling section. None of the BMD models provided adequate fit to the absolute liver weight data; thus, the highest dose associated with a <10% increase in absolute liver weight (11 mg/kg/day) was selected as the POD. The hemoglobin and erythrocyte doses also did not provide adequate fit with any of the BMD models and the NOAEL values were used as PODs for these effects.

Four PODs were considered for the MRL:

- NOAEL of 8 mg/kg (5.7 mg/kg/day) for absolute liver weight increases in female rats
- $BMDL_{RD10}$ of 15.74 mg/kg (11 mg/kg/day) for relative liver weight increases in female rats
- NOAEL of 8 mg/kg (5.7 mg/kg/day) for decreases in hemoglobin levels in female rats
- NOAEL of 8 mg/kg (5.7 mg/kg/day) for decreases in erythrocyte levels in female rats

The NOAEL value of 5.7 mg/kg/day for increases in absolute liver weight and decreases in hemoglobin and erythrocyte levels was selected as the basis of the MRL since this value is lower than the $BMDL_{RD10}$ for increases in relative liver weight.

Intermittent Exposure: The NOAEL of 8 mg/kg was adjusted for intermittent exposure (5 days/7 days) resulting in an adjusted $BMDL_{RD10}$ of 5.7 mg/kg/day.

Uncertainty Factor: The adjusted NOAEL was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = NOAEL÷ UFs
5.7 mg/kg/day ÷ (10 x 10) = 0.06 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Similar liver and erythrocyte effects have been observed in rats administered 1,2,3-trichloropropane for 15 months (NTP 1993).

Benchmark Dose Modeling: The absolute and relative liver weights in females, hemoglobin levels in females, and erythrocyte levels in females were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.6.0). The following procedure for fitting continuous data was used: the simplest model (linear) was first applied to the data while assuming constant variance; if the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark dose response (BMR). Among all of the models providing adequate fit to the data, the lowest BMDL (the lower limit of a one-sided 95% CI on the BMD) was selected as a reasonably conservative POD when differences between the BMDLs estimated from these models are >2–3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. A BMR of 10% change from the control was used for liver weights and 1 standard deviation change relative to controls was used for hemoglobin and erythrocyte levels.

The model predictions for the relative liver weight in females are presented in Table A-3 and the fit of the selected model is presented in Figure A-1. The available BMD models did not provide adequate fit for absolute liver weights in females, hemoglobin levels in females, or erythrocyte levels in females; dropping the highest and second highest dose levels did not sufficiently improve the fit of the models.

Table A-3. Model Predictions for 1,2,3-Trichloropropane, Increased Relative Liver Weight in Female Rats for 17 weeks (NTP 1993)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{RD10} (mg/kg)	$BMDL_{RD10}$ (mg/kg)
All Doses									
Constant variance									
Linear[d]	<0.0001	<0.0001	0.00	1.02	0.78	-2.82	177.25	12.38	11.14
Nonconstant variance									
Exponential (model 2)[e]	18.12	0.70	0.16	1.20	-0.92	1.20	141.63	18.12	16.57
Exponential (model 3)[e]	20.97	0.70	0.11	1.43	-0.52	1.43	143.12	20.97	16.71
Exponential (model 4)[e]	15.44	0.70	0.01	0.75	0.78	2.19	149.56	15.44	13.43
Exponential (model 5)[e]	23.54	0.70	0.01	1.66	-0.36	1.66	148.15	23.54	15.85
Hill[e]	23.57	0.70	0.01	1.66	-0.36	1.66	148.19	23.57	15.81
Linear[d]	15.44	0.70	0.01	0.75	0.78	2.19	147.56	15.44	13.43
Polynomial (2-degree)[d]	21.83	0.70	0.12	1.46	-0.34	1.46	142.81	21.83	16.75

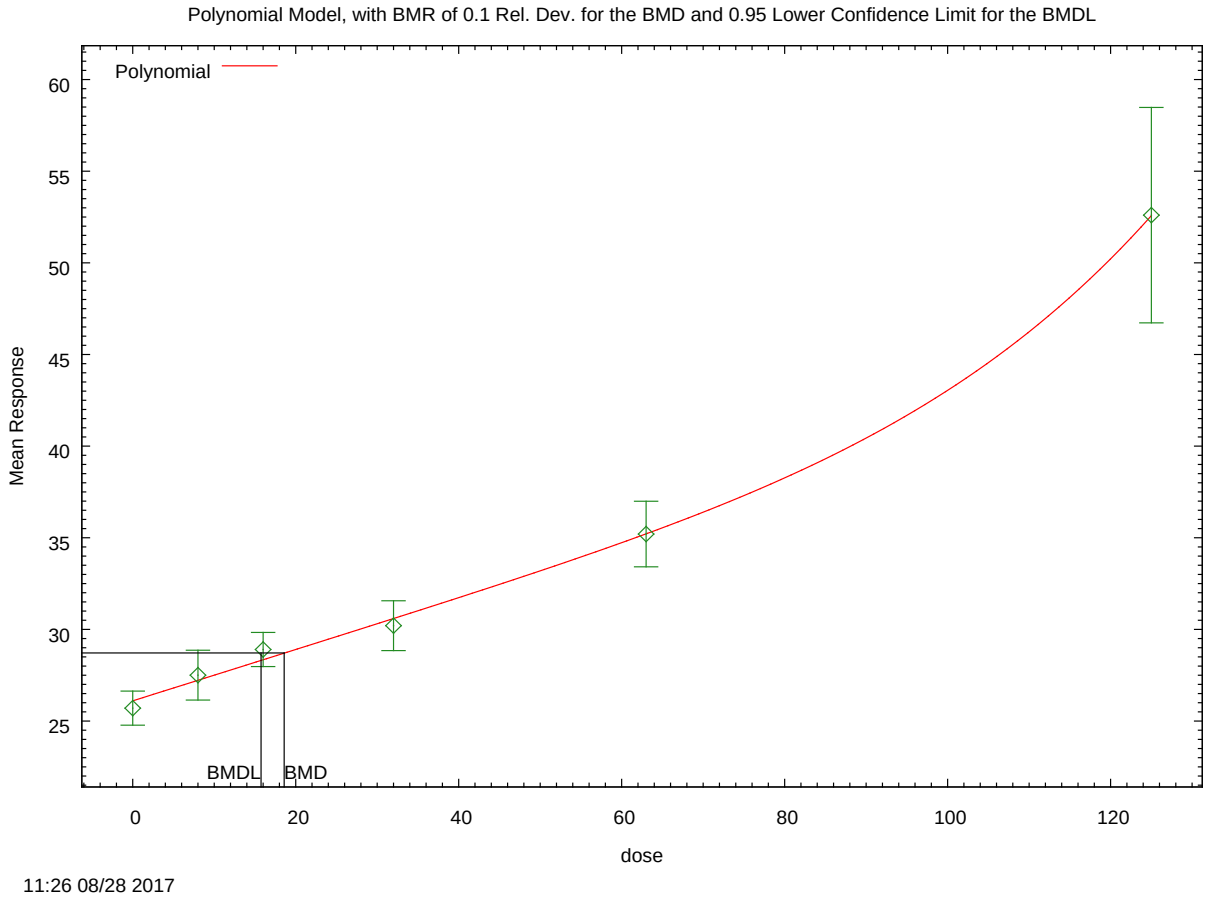
Table A-3. Model Predictions for 1,2,3-Trichloropropane, Increased Relative Liver Weight in Female Rats for 17 weeks (NTP 1993)

Model	Test for	Variance	Mean	Scaled residuals[c]			AIC	BMD_{RD10}	$BMDL_{RD10}$
Polynomial (3-degree)[d]	20.27	0.70	0.30	1.25	-0.41	1.25	140.66	20.27	16.46
Polynomial (4-degree)[d]	19.14	0.70	0.38	1.13	-0.57	1.13	140.05	19.14	16.00
Polynomial (5-degree)[d,f]	***18.58***	***0.70***	***0.41***	***1.07***	***-0.69***	***1.07***	***139.90***	***18.58***	***15.74***
Power[d]	23.54	0.70	0.03	1.66	-0.36	1.66	146.15	23.54	15.85

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be positive.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not provide adequate fit to the variance data but nonconstant variance did. With nonconstant variance model applied, the Exponential 2 and 3 and Polynomial models 2–5 provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Polynomial 5-degree).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed); RD = relative deviation

Figure A-1. Fit of 5th Degree Polynomial Model to Data on Relative Liver Weight in Female Rats Administered 1,2,3-Trichloropropane for 17 Weeks (NTP 1993)



Agency Contact (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
CAS Numbers: 96-18-4
Date: May 2019
Profile Status: Final, Draft for Public Comment
Route: Oral
Duration: Chronic
Provisional MRL: 0.005 mg/kg/day
Critical Effect: Bile duct hyperplasia
Reference: NTP 1993
Point of Departure: $BMDL_{10}$ of 0.47 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 14
Species: Rat

MRL Summary: A provisional chronic-duration oral MRL of 0.005 mg/kg/day was derived for 1,2,3-trichloropropane based on an increased incidence of bile duct hyperplasia in male rats administered gavage doses 5 days/week for 15 months (NTP 1993). The MRL is based on an adjusted $BMDL_{10}$ of 0.47 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: The oral toxicity of 1,2,3-trichloropropane following chronic-duration exposure has been investigated in rats and mice (NTP 1993). The rats and mice were administered via gavage 1,2,3-trichloropropane in corn oil 5 days/week for up to 2 years. Decreased survival was observed in rats administered 10 or 30 mg/kg and a decrease in body weight gain (15%) was observed in females at 30 mg/kg. A number of non-neoplastic and neoplastic alterations were observed. Neoplastic lesions were observed at ≥3 mg/kg and included squamous cell papillomas or carcinomas in the forestomach and adenomas of the pancreas at ≥3 mg/kg; squamous cell papillomas or carcinomas in oral mucosa, adenoma in renal tubules, adenoma or carcinoma of the clitoral gland, and adenocarcinoma of the mammary gland (females only) at ≥10 mg/kg; and adenoma or carcinoma in preputial gland and carcinoma in Zymbal's gland (females only) at 30 mg/kg. Non-neoplastic target tissues included esophagus, tongue, hematopoietic tissues, liver and bile duct, kidney, pancreas, and testes; however, some of observed lesions were considered precancerous or were secondary to cancerous lesions. A summary of the effects and NOAEL and LOAEL values for the non-neoplastic lesions is presented in Table A-4. NTP (1993) considered the hematological effects to likely be due to depressed hematopoiesis or by blood loss from neoplasms in the forestomach or oral mucosa. NTP (1993) noted that hyperplasia observed in the pancreas was part of the morphological continuum to adenoma to adenocarcinoma, and focal hyperplasia in the kidney and renal adenomas constituted a morphological continuum. The bile duct and nephropathy effects do not appear to be associated with carcinogenicity and were considered as possible critical effects for the MRL.

Table A-4. Summary of the Results of the NTP (1993) Chronic-Duration Rat Study[a]

	NOAEL (mg/kg)	LOAEL (mg/kg)	Effect
Body weight	3	10	15% decrease in body weight gain in females
Gastrointestinal	3	10	Hyperkeratosis of esophagus Acute inflammation of tongue in females (males at 30 mg/kg)
Hematological	3	10	Hematopoietic cell proliferation in spleen at ≥10 mg/kg Decreased hemoglobin, increased leukocytes, increased segmented neutrophils (measured after 15 months) at 30 mg/kg
Hepatic	3	10	Increased liver weight at ≥10 mg/kg Bile duct hyperplasia in males at 10 mg/kg at 15 months, 30 mg/kg at 2 years
Renal	3	10	Renal tubular hyperplasia and increased severity of nephropathy (males only)
Endocrine		3	Focal hyperplasia of pancreatic acini
Reproductive	10	30	Interstitial cell hyperplasia in testes

[a]Rats were administered 1,2,3-trichloropropane 5 days/week for up to 2 years.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

A summary of the hepatic and renal effects observed in the NTP (1993) study are presented in Table A-5. These data clearly demonstrate a LOAEL of 10 mg/kg for increases in the incidences of bile duct hyperplasia in male rats and an increased severity of nephropathy in male rats. The increases in absolute liver and kidney weights in male rats administered 3 mg/kg were considered minimally adverse because the liver and kidney are target tissues and the increases in organ weight may be representative of early-stage adverse effects.

Table A-5. Summary of Hepatic and Renal Effects Observed in Rats Administered 1,2,3-Trichloropropane for 2 Years (NTP 1993)

	Dose (mg/kg, 5 days/week)			
	0	3	10	30
Hepatic effects				
Serum alanine aminotransferase (IU/L)				
Males	99	91 (-8.1%)[a]	90 (-9.1%)	68 (-31%)[b]
Females	58	57 (-1.7%)	65 (12%)	66 (14%)

Table A-5. Summary of Hepatic and Renal Effects Observed in Rats Administered 1,2,3-Trichloropropane for 2 Years (NTP 1993)

	Dose (mg/kg, 5 days/week)			
	0	3	10	30
Absolute liver weight at 15 months (g)				
Males	14.27	15.63[b] (9.5%)	16.8[b] (17.7%)	18.23[b] (27.7%)
Females	7.79	8.87[b] (13.9%)	9.00[b] (15.5%)	10.4[b] (33.5%)
Relative liver weight at 15 months (mg organ weight/g body weight)				
Males	31.2	33.1 (6.1%)	36[b] (15.4%)	39.8[b] (27.6%)
Females	30.8	30.9 (0.32%)	34.6[b] (12.3%)	43.2[b] (40.3%)
Bile duct hyperplasia at 15 months				
Males	1/10	2/10	5/10[c]	8/10[c]
Females	0/10	0/10	1/8	3/8
Bile duct hyperplasia at 2 years				
Males	0/50	0/50	1/49	12/52[c]
Females	0/50	0/49	0/52	2/52
Renal effects				
Absolute kidney weight at 15 months (g)				
Males	1.35	1.46[b] (8.1%)	1.51[b] (11.8%)	1.75[b] (29.6%)
Females	0.786	0.839 (6.7%)	0.869[b] (10.6%)	0.971[b] (23.5%)
Relative kidney weight at 15 months (mg organ weight/g body weight)				
Males	2.96	3.09 (4.4%)	3.25[b] (9.8%)	3.82[b] (29.0%)
Females	3.08	2.93 (-4.9%)	3.34[b] (8.4%)	4.04[b] (31.2%)
Nephropathy at 2 years				
Males	48/50 (2.0)[d]	50/50 (2.0)	48/49 (2.6)	52/52 (2.4)
Females	18/50	21/47	17/52	5/51

[a]Percent differences from controls.
[b]Significantly different (p≤0.05) from controls.
[c]Significantly different (p≤0.05) from controls; Fisher Exact Test performed by ATSDR.
[d]Mean severity score; 1=minimal (<25% renal tubules involved), 2=mild (25–50% involvement), 3=moderate (50–75% involvement) and 4=marked (>75% involvement).

The toxicity of 1,2,3-trichloropropane appears to differ in mice, as compared to rats. A decrease in survival was observed in mice administered ≥6 mg/kg 5 days/week for 2 years (NTP 1993); a 12–18% decrease in body weight gain was observed at 60 mg/kg. Non-neoplastic effects observed in mice included bronchiole hyperplasia at 60 mg/kg and hepatocellular necrosis at 60 mg/kg. Squamous cell hyperplasia was also observed in the forestomach, but this was part of the continuum to forestomach adenocarcinomas. Likewise, the hematopoietic cell proliferation observed in the spleen at ≥6 mg/kg may have been due to bleeding from the forestomach tumors. Increases in the incidence of neoplastic lesions

were observed at all dose levels: squamous cell papilloma or carcinoma in the forestomach and hepatocellular adenoma or carcinoma in males at ≥6 mg/kg; harderian gland adenoma in males at ≥20 mg/kg; squamous cell papilloma or carcinoma in oral mucosa in females, harderian gland adenoma in females, and uterine stromal polyps and endometrial adenoma or adenocarcinoma at 60 mg/kg. The lowest LOAEL for an effect unrelated to carcinogenicity is 60 mg/kg for increases in bronchiole hyperplasia and hepatocellular necrosis.

Selection of the Principal Study: The NTP (1993) rat gavage study was selected as the principal study because it identified the lowest LOAELs for non-carcinogenic effects.

Summary of the Principal Study:

NTP. 1993. Toxicology and carcinogenesis studies of 1,2,3-trichloropropane (CAS No. 96-18-4) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program Tech Rep Ser 384.

Groups of 60 male and 60 female F344/N rats were administered 0, 3, 10, or 30 mg/kg 1,2,3-trichloropropane in corn oil by gavage 5 days/week for 2 years. Due to high mortality, rats in the 30 mg/kg groups were terminated after 77 (males) or 67 (females) weeks of exposure. After 15 months of exposure, 10 animals/sex/group were sacrificed. Parameters used to assess toxicity included twice daily clinical observations, body weights (weekly for 13 weeks and monthly thereafter), organ weights (brain, liver, kidney; evaluated at 15 months), hematological and serum clinical chemistry indices (evaluated at 15 months), and histopathology of major tissues and organs.

Significant decreases in survival were observed in rats at 10 and 30 mg/kg; mean survival days were 596 and 465 days in the 10 mg/kg males and females, respectively, and 580 and 366 days in the 30 mg/kg males and females, respectively, compared to 647 and 649 days in control males and females, respectively. No compound-related clinical signs were observed. Small decreases in body weight gain (<5%) were observed at 30 mg/kg in males; in females, body weight in the last year of the study was 15% lower than controls. In rats dying early, emaciation, lethargy, diarrhea, dyspnea, and tissue masses were observed; most of these signs were attributed to neoplasms of the oral mucosa or forestomach. Increases in absolute liver weights were observed at ≥3 mg/kg; relative liver weights were observed at ≥10 mg/kg. Increases in absolute kidney weights were observed at ≥3 mg/kg in males and ≥10 mg/kg in females; increases in relative kidney weights were observed at ≥10 mg/kg. Decreased hemoglobin levels were observed at 30 mg/kg; increases in leukocytes and segmented neutrophils were also observed at this dose level. Hematopoietic cell proliferation was observed at 10 and 30 mg/kg. Histological alterations were observed in the oral mucosa (pharynx and tongue), forestomach, pancreas, liver, kidney, preputial gland, clitoral gland, mammary gland, Zymbal's gland, and intestines. Acute inflammation was observed in the tongue of male rats treated with 30 mg/kg and female rats at 10 mg/kg. Oral mucosal lesions consisted of squamous cell papillomas or carcinomas at 10 mg/kg (37 and 54% in males and females, respectively) and 30 mg/kg (77 and 62% in males and females, respectively); but not at 3 mg/kg (8 and 12% in males and females, respectively) or controls (2 and 2% in males and females, respectively). Hyperkeratosis of the esophagus was observed in males at 30 mg/kg and females at ≥10 mg/kg. Squamous cell papillomas or carcinomas were also observed in the forestomach at 3 (20 and 33% in males and females, respectively), 10 mg/kg (40 and 63% in males and females, respectively), and 30 mg/kg (83 and 37% in males and females, respectively); no tumors were observed in controls. Increases in the incidence of forestomach tumors were also observed in the 10 and 30 mg/kg groups after 15 months of exposure. In the pancreas, focal hyperplasia of pancreatic acini was observed at ≥3 mg/kg/day (56, 92, 94, and 92% in males at 0, 3, 10, or 30 mg/kg and 10, 29, 46, and 17% in females) and adenomas were observed in males at ≥3 mg/kg (10, 42, 73, 56% in males and 0, 0, 4, 0% in females); the investigators noted that there was a morphologic continuum from the acinar hyperplasia to adenomas. Bile duct hyperplasia was observed in males at 10 and 30 mg/kg after 15 months and at 30 mg/kg after 2 years. Renal tubular hyperplasia in

males at ≥10 mg/kg and females at 30 mg/kg; an increase in nephropathy was observed in males at 10 or 30 mg/kg, although the incidence was similar to controls (98–100% compared to 96% in controls). The mean severity scores were 2.0, 2.0, 2.6, and 2.4 in the 0, 3, 10, and 30 mg/kg groups, respectively. An increase in the incidence of adenomas in the kidneys was observed in males at 10 and 30 mg/kg; an increased incidence was also observed in the 30 mg/kg group after 15 months of exposure. Significant increases in the incidence of adenoma or carcinoma were observed in the preputial gland at 30 mg/kg and in the clitoral gland at ≥10 mg/kg. In females, increases in the incidence of adenocarcinomas of the mammary gland were observed at 10 and 30 mg/kg. An increased incidence on Zymbal's gland carcinoma was observed in females at 30 mg/kg. Adenomatous polyps or adenocarcinomas were observed in the 30 mg/kg group; although the incidence was not statistically higher than controls, the investigators considered them to be treatment-related given the rarity of the lesion in historical controls and the decreased survival in rats in this group. In the testes, interstitial cell hyperplasia was observed at 30 mg/kg.

Selection of the Point of Departure for the MRL: Exposure data for several endpoints were considered as the POD for the MRL: increases in absolute liver weight at 15 months, bile duct hyperplasia at 15 months, increases in absolute kidney weight at 15 months, and increases in the severity of nephropathy in male rats at 2 years. The 15-month data were used for liver and kidney weights because organ weights were not assessed at 2 years; 15-month incidence data for bile duct hyperplasia were used because the LOAEL was lower than after 2 years of exposure. BMD modeling was attempted for the increases in absolute liver and kidney weights and for bile duct hyperplasia; the results of the modeling is presented in the Benchmark Dose Modeling section. Because only mean severity scores were reported for nephropathy, the data was not suitable for BMD modeling.

Four PODs were considered for the MRL:

- BMD_{RD10} of 3.77 mg/kg for absolute liver weight increases in male rats
- BMD_{RD10} of 11.22 mg/kg for absolute kidney weight increases in male rats
- BMD_{10} of 2.56 mg/kg for increases in incidence of bile duct hyperplasia in male rats at 15 months
- NOAEL of 3 mg/kg for increases in severity of nephropathy in male rats

The $BMDL_{10}$ of 0.66 mg/kg, which is associated with the lowest POD of 2.56 mg/kg, was selected as the basis of the MRL.

Intermittent Exposure: The $BMDL_{10}$ of 0.66 mg/kg was adjusted for intermittent exposure (5 days/7 days) resulting in adjusted value of 0.47 mg/kg/day.

Uncertainty Factor: The adjusted $BMDL_{10}$ was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

$$MRL = BMDL_{10} \div UFs$$
$$0.47 \text{ mg/kg/day} \div (10 \times 10) = 0.005 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Identification of the liver and kidney as sensitive targets of toxicity is supported by intermediate-duration oral studies, which also found increases in liver and kidney weights, bile duct hyperplasia, and regenerative tubular hyperplasia in rats exposed for up to 17 weeks (NTP 1993).

Benchmark Dose Modeling: The absolute liver and kidney weight were fit to all available continuous models in EPA's BMDS (version 2.6.0). The following procedure for fitting continuous data was used:

the simplest model (linear) was first applied to the data while assuming constant variance; if the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Incidence data for bile duct hyperplasia at 15 months were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option. For the continuous and dichotomous models, adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (the lower limit of a one-sided 95% CI on the BMD) was selected as a reasonably conservative POD when differences between the BMDLs estimated from these models are >2–3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. For the continuous models in which the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. For the liver and kidney datasets, a BMR of 10% change from the control was used; a BMR of 10% was used for the bile duct hyperplasia incidence data.

The model predictions for the liver weight, kidney weight, and bile duct hyperplasia are presented in Tables A-6, A-7, and A-8 and the fit of the selected models are presented in Figures A-2, A-3, and A-4.

Table A-6. Model Predictions for 1,2,3-Trichloropropane, Increased Absolute Liver Weights in Male Rats at 15 Months (NTP 1993)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{RD10} (mg/kg)	$BMDL_{RD10}$ (mg/kg)
Constant variance									
Exponential (model 2)[d]	<0.0001	0.78	0.03	1.58	-0.57	-1.73	68.70	NA	NA
Exponential (model 3)[d]	<0.0001	0.78	0.03	1.58	-0.57	-1.73	68.70	NA	NA
Exponential (model 4)[d]	<0.0001	0.78	0.51	0.50	-0.34	0.50	64.32	4.33	2.17
Exponential (model 5)[d]	<0.0001	0.78	0.51	0.50	-0.34	0.50	64.32	4.33	2.17
Hill[d,e]	***<0.0001***	***0.78***	***0.68***	***0.28***	***-0.27***	***0.28***	***64.06***	***3.77***	***1.60***
Linear[f]	<0.0001	0.78	0.05	1.48	-0.63	-1.61	68.03	NA	NA
Polynomial (2-degree)[f]	<0.0001	0.78	0.05	1.48	-0.63	-1.61	68.03	NA	NA
Polynomial (3-degree)[f]	<0.0001	0.78	0.05	1.48	-0.63	-1.61	68.03	NA	NA

Table A-6. Model Predictions for 1,2,3-Trichloropropane, Increased Absolute Liver Weights in Male Rats at 15 Months (NTP 1993)

Model	Test for	Variance	Mean	Scaled residuals[c]			AIC	BMD_{RD10}	$BMDL_{RD10}$
Power[d]	<0.0001	0.78	0.05	1.48	-0.63	-1.61	68.03	NA	NA

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model provided adequate fit to variance data. With constant variance model applied, the only models that provided adequate fit to the means were the Exponential 4 and 5 models (the Exponential 5 converged on to the Exponential 4) and the Hill model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Hill).
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable; model did not provide adequate fit; RD = relative deviation

Figure A-2. Fit of Exponential 2 Model to Data on Absolute Liver Weight in Male Rats Administered 1,2,3-Trichloropropane for 15 Months (NTP 1993)

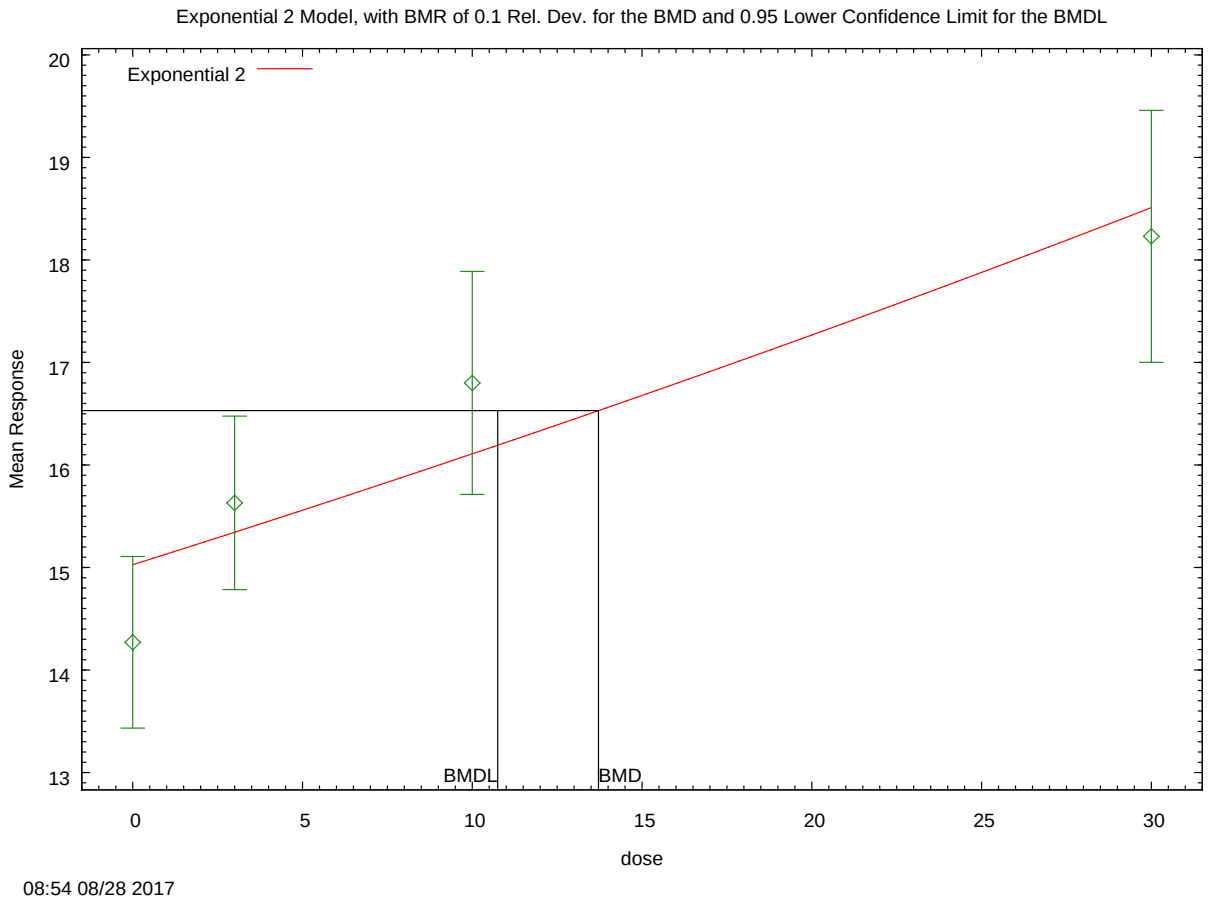


Table A-7. Model Predictions for 1,2,3-Trichloropropane, Increased Absolute Kidney Weights in Male Rats at 15 Months (NTP 1993)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c]			AIC	BMD_{RD10} (mg/kg/day)	$BMDL_{RD10}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Exponential (model 2)[d]	<0.0001	0.40	0.27	0.21	-0.16	-1.14	-123.27	12.21	10.09
Exponential (model 3)[d]	<0.0001	0.40	0.27	0.21	-0.16	-1.14	-123.27	12.21	10.09
Exponential (model 4)[d]	<0.0001	0.40	0.17	1.08	-0.49	1.08	-121.98	8.77	4.62
Exponential (model 5)[d]	<0.0001	0.40	0.17	1.08	-0.49	1.08	-121.98	8.77	4.62
Hill[d]	<0.0001	0.40	0.17	1.07	-0.52	1.07	-122.01	8.61	4.12
Linear[e,f]	***<0.0001***	***0.40***	***0.32***	***0.04***	***-0.14***	***1.09***	***-123.57***	***11.22***	***9.02***
Polynomial (2-degree)[e]	<0.0001	0.40	0.32	0.04	-0.14	1.09	-123.57	11.22	9.02
Polynomial (3-degree)[e]	<0.0001	0.40	0.32	0.04	-0.14	1.09	-123.57	11.22	9.02
Power[d]	<0.0001	0.40	0.32	0.04	-0.14	1.09	-123.57	11.22	9.02

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance model provided adequate fit to variance data. With constant variance model applied, all models provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Linear; the polynomial and power models converged onto the linear model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; RD = relative deviation

Figure A-3. Fit of Exponential 2 Model to Data on Absolute Kidney Weight in Male Rats Administered 1,2,3-Trichloropropane for 15 Months (NTP 1993)

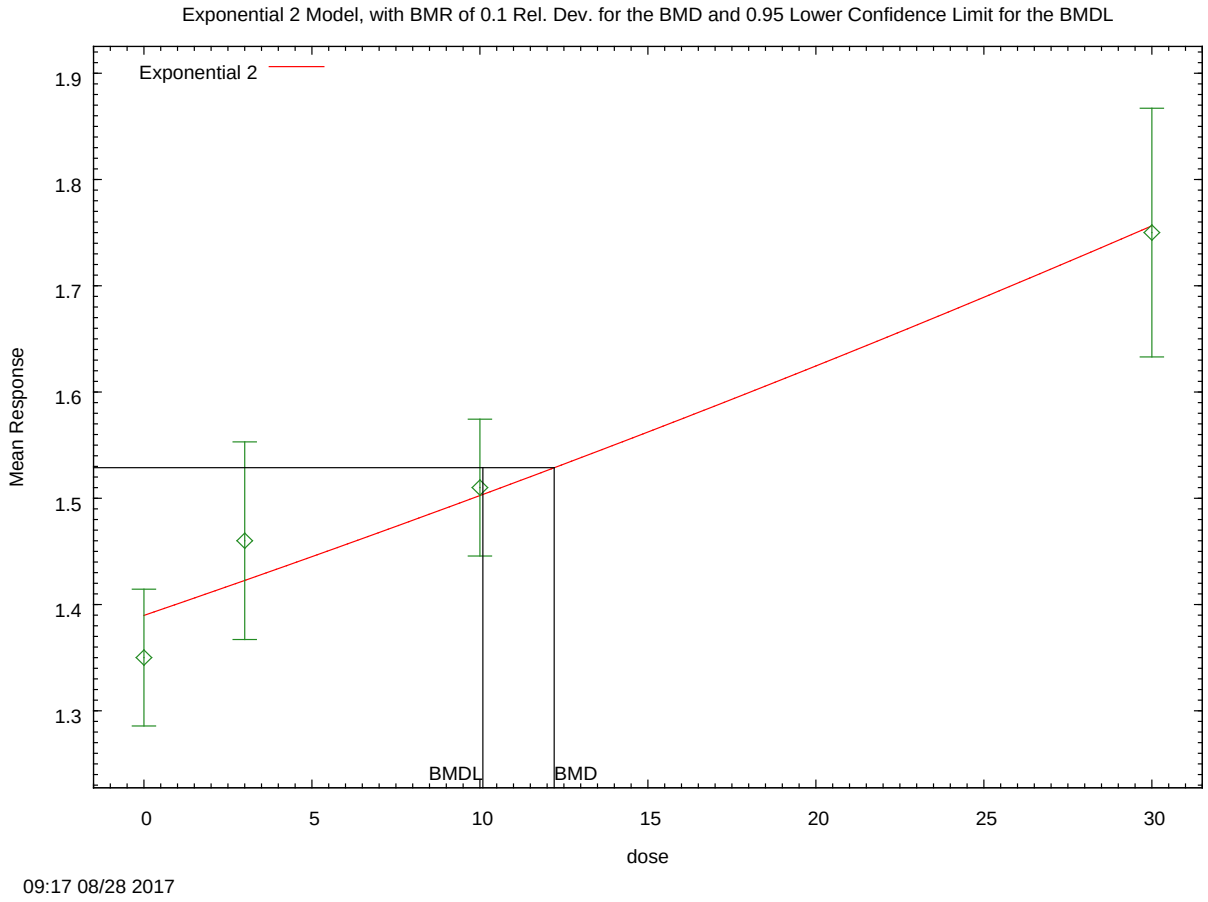


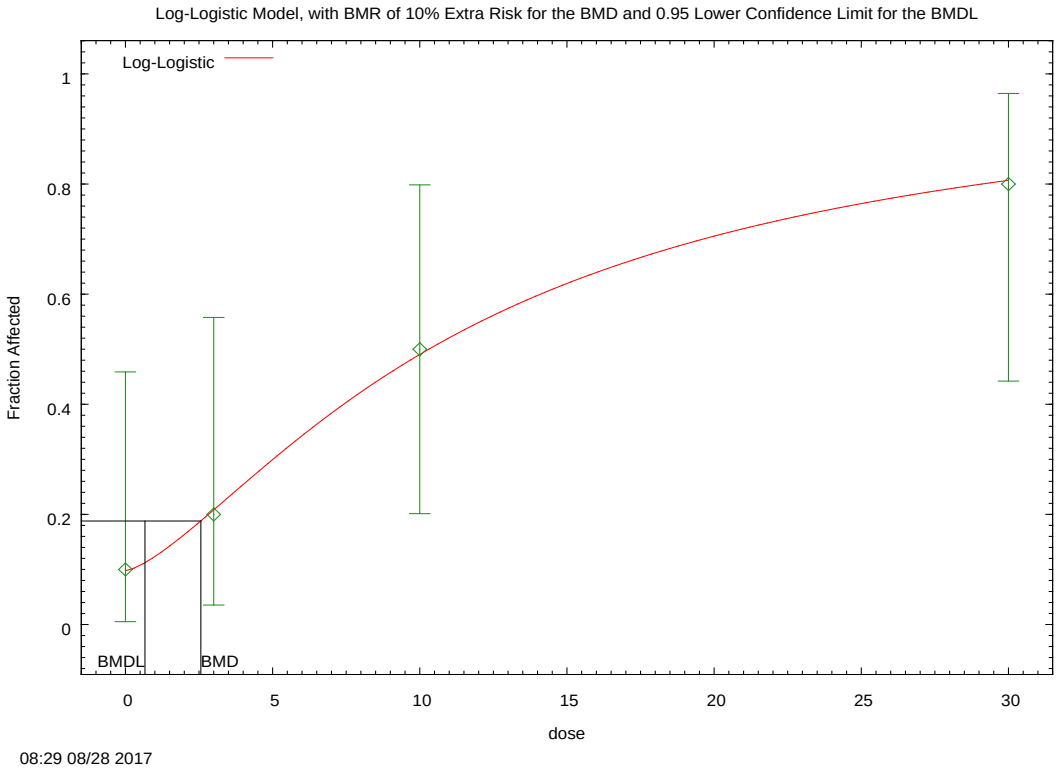
Table A-8. Model Predictions for 1,2,3-Trichloropropane, Incidence of Bile Duct Hyperplasia in Male Rats at 15 Months (NTP 1993)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)
Gamma[c]	1	0.1	0.75	0.05	-0.19	0.24	46.49	2.05	1.21
Logistic	2	1.15	0.56	-0.14	0.82	0.82	45.54	4.68	3.02
LogLogistic[d,e]	***1***	***0.01***	***0.92***	***0.02***	***-0.06***	***0.07***	***46.39***	***2.56***	***0.66***
LogProbit[d]	2	0.13	0.94	0.16	0.15	-0.24	44.51	3.50	2.03
Multistage (1-degree)[f]	2	0.1	0.95	0.05	-0.20	0.23	44.49	2.01	1.21
Multistage (2-degree)[f]	2	0.1	0.95	0.05	-0.20	0.23	44.49	2.01	1.21
Multistage (3-degree)[f]	2	0.1	0.95	0.05	-0.20	0.23	44.49	2.01	1.21
Probit	2	1.11	0.57	-0.12	0.84	0.84	45.50	4.54	3.09
Weibull[c]	2	0.1	0.95	0.05	-0.20	0.23	44.49	2.01	1.21

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL was selected.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom

Figure A-4. Fit of Gamma Model to Data on Bile Duct Hyperplasia in Male Rats Administered 1,2,3-Trichloropropane for 15 Months (NTP 1993)



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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,2,3-TRICHLOROPROPANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2,3-trichloropropane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, and chemical interactions data for 1,2,3-trichloropropane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,2,3-trichloropropane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,2,3-trichloropropane are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for 1,2,3-trichloropropane (ATSDR 1992), thus, the literature search was restricted to studies published between January 1990 to March 2017. The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for 1,2,3-trichloropropane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance priority list (SPL) resource page, and other items as needed. Regulations applicable to 1,2,3-trichloropropane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	(("1,2,3-Trichloropropane"[tw] OR "Allyl trichloride"[tw] OR "Glycerol trichlorohydrin"[tw] OR "Glyceryl trichlorohydrin"[tw] OR "Trichlorohydrin"[tw] OR "Trichloropropane"[tw]) AND

Table B-2. Database Query Strings

Database search date	Query string
	(1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[crdat] OR 1990/01/01 : 3000[edat])) OR (("1,2,3-trichloropropane"[supplementary concept] OR 96-18-4[rn] OR 3MJ7QCK0Z0[rn] OR "1,2,3-trichloropropane"[nm]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[mhda]))
Toxline	
03/2017	("1 2 3-trichloropropane" OR "allyl trichloride" OR "glycerol trichlorohydrin" OR "glyceryl trichlorohydrin" OR "trichlorohydrin" OR "trichloropropane" OR 96-18-4 [rn]) AND 1990:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	FILE 'TOXCENTER' ENTERED AT 14:44:17 ON 21 MAR 2017 L1 797 SEA 96-18-4 L2 754 SEA L1 NOT TSCATS/FS L3 717 SEA L2 NOT PATENT/DT L4 577 SEA L3 AND PY>=1990 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR

Table B-2. Database Query Strings

Database search date	Query string
	DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 372 SEA L4 AND L37
	L39 34 SEA L38 AND MEDLINE/FS
	L40 18 SEA L38 AND BIOSIS/FS
	L41 293 SEA L38 AND CAPLUS/FS
	L42 27 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L43 329 DUP REM L39 L40 L42 L41 (43 DUPLICATES REMOVED)
	L*** DEL 34 S L38 AND MEDLINE/FS
	L*** DEL 34 S L38 AND MEDLINE/FS
	L44 34 SEA L43
	L*** DEL 18 S L38 AND BIOSIS/FS
	L*** DEL 18 S L38 AND BIOSIS/FS
	L45 11 SEA L43
	L*** DEL 293 S L38 AND CAPLUS/FS
	L*** DEL 293 S L38 AND CAPLUS/FS
	L46 264 SEA L43

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 27 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 27 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 20 SEA L43 L48 295 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 96-18-4
NTP	
03/2017	96-18-4 1,2,3-Trichloropropane
NIH RePORTER	
06/2017	Text Search: "1,2,3-Trichloropropane" OR "Allyl trichloride" OR "Glycerol trichlorohydrin" OR "Glyceryl trichlorohydrin" OR "Trichlorohydrin" OR "Trichloropropane" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 473
- Number of records identified from other strategies: 32
- Total number of records to undergo literature screening: 505

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,2,3-trichloropropane:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

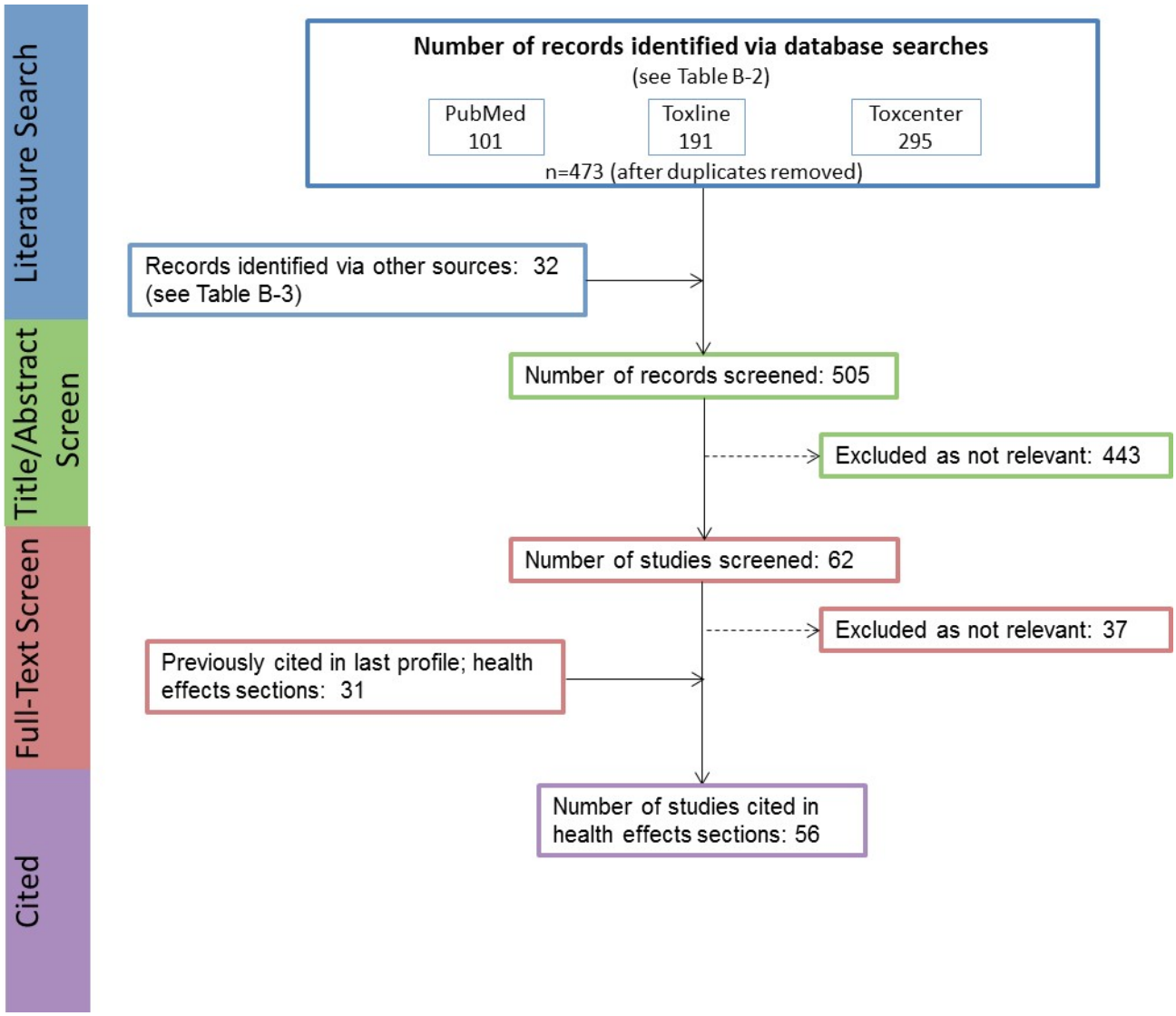
- Number of titles and abstracts screened: 505
- Number of studies considered relevant and moved to the next step: 62

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 62
- Number of studies cited in the health effects sections of the existing toxicological profile (September, 1992): 31
- Total number of studies cited in the health effects sections of the updated profile: 56

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. March 2017 Literature Search Results and Screen for 1,2,3-Trichloropropane



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, 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 endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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 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 that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. 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 and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used 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 tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(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 figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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 chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

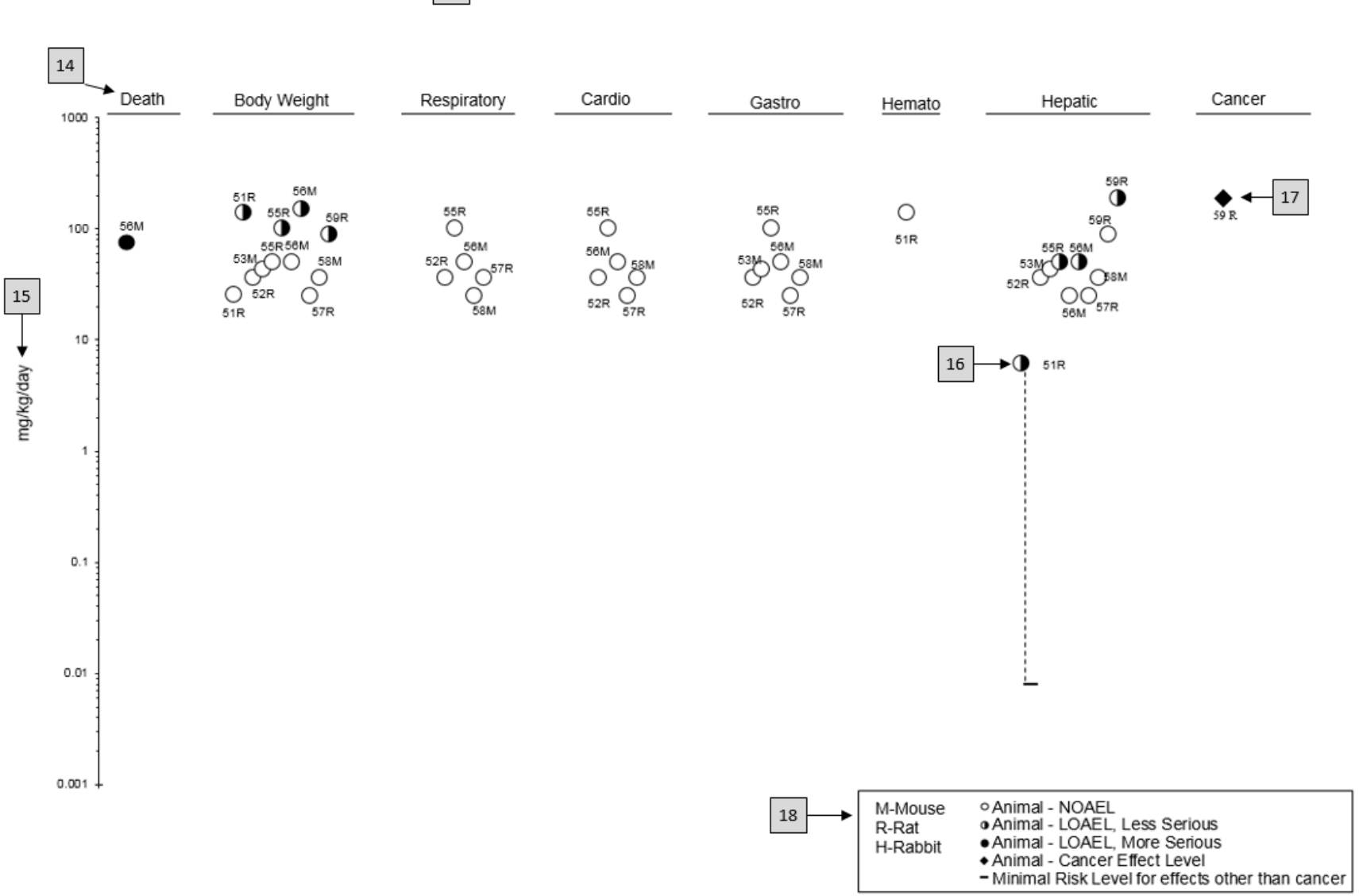
APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

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

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
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

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result