Toxicological Profile for Chlorobenzene

October 2020
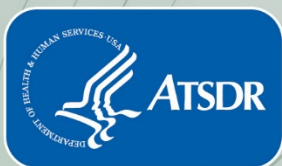
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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

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.

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 due to associated acute, intermediate, and chronic exposures;

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

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

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. 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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed 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.

VERSION HISTORY

Date	Description
October 2020	Final toxicological profile released
December 2019	Draft for public comment profile released
August 2013	Addendum to the toxicological profile released
December 1990	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers
were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response,
Compensation, and Liability Act, as amended.

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

Chlorobenzene (C_6H_5Cl; CAS Number 108-90-7) is used as a solvent and as a chemical intermediate in industry, a portion of which is lost to the environment in water and air discharges. Chlorobenzene adsorbs moderately to soil and is biodegraded comparatively rapidly.

The most likely sources of potential exposure of the general population to chlorobenzene are from breathing air, drinking water, or eating food contaminated with chlorobenzene. However, chlorobenzene has been detected in only very small quantities in air, water, and limited food sources. In a study of urban volatile organic compound (VOC) concentrations in the United States between 1996 and 1997, the highest levels of chlorobenzene were <1 ppbv (<4.6 µg/m^3) at 13 monitoring stations (Mohamed et al. 2002). The potential for toxic exposure to chlorobenzene via the water supply may be somewhat limited by the relatively low solubility of chlorobenzene in water, as evidenced by the fact that environmental levels of chlorobenzene in groundwater and surface water are generally in the low ppb range (e.g., Van Wijk et al. 2004; USGS 2006).

According to the results of the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Surveys conducted between 2003 and 2016, blood levels in the general public were undetectable at a limit of detection (LOD) of 0.011 ng/mL (CDC 2019).

1.2 SUMMARY OF HEALTH EFFECTS

- Available data, mostly from animal studies, identify the liver, kidney, and nervous system as principal targets of chlorobenzene, as illustrated in Figures 1-1 and 1-2 for inhalation and oral exposure, respectively.
- Results from oral studies in rats and mice indicate that the immunological system may be a target of chlorobenzene toxicity; however, tests of immune function in chlorobenzene-treated animals have not been performed.
- Results from limited animal studies suggest possible chlorobenzene-induced hematological effects.
- It is not clear whether chlorobenzene may cause cancer in humans.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Chlorobenzene

Concentration (ppm)   **Effects in Animals**

5,850

Acute: Clinical signs of neurotoxicity

2,990

Acute: Clinical signs of ocular irritation

450-550

Acute: Death
Intermediate: Death, degeneration of testicular germinal epithelium

150

Intermediate: Increased liver weight, hepatocellular hypertrophy, renal lesions
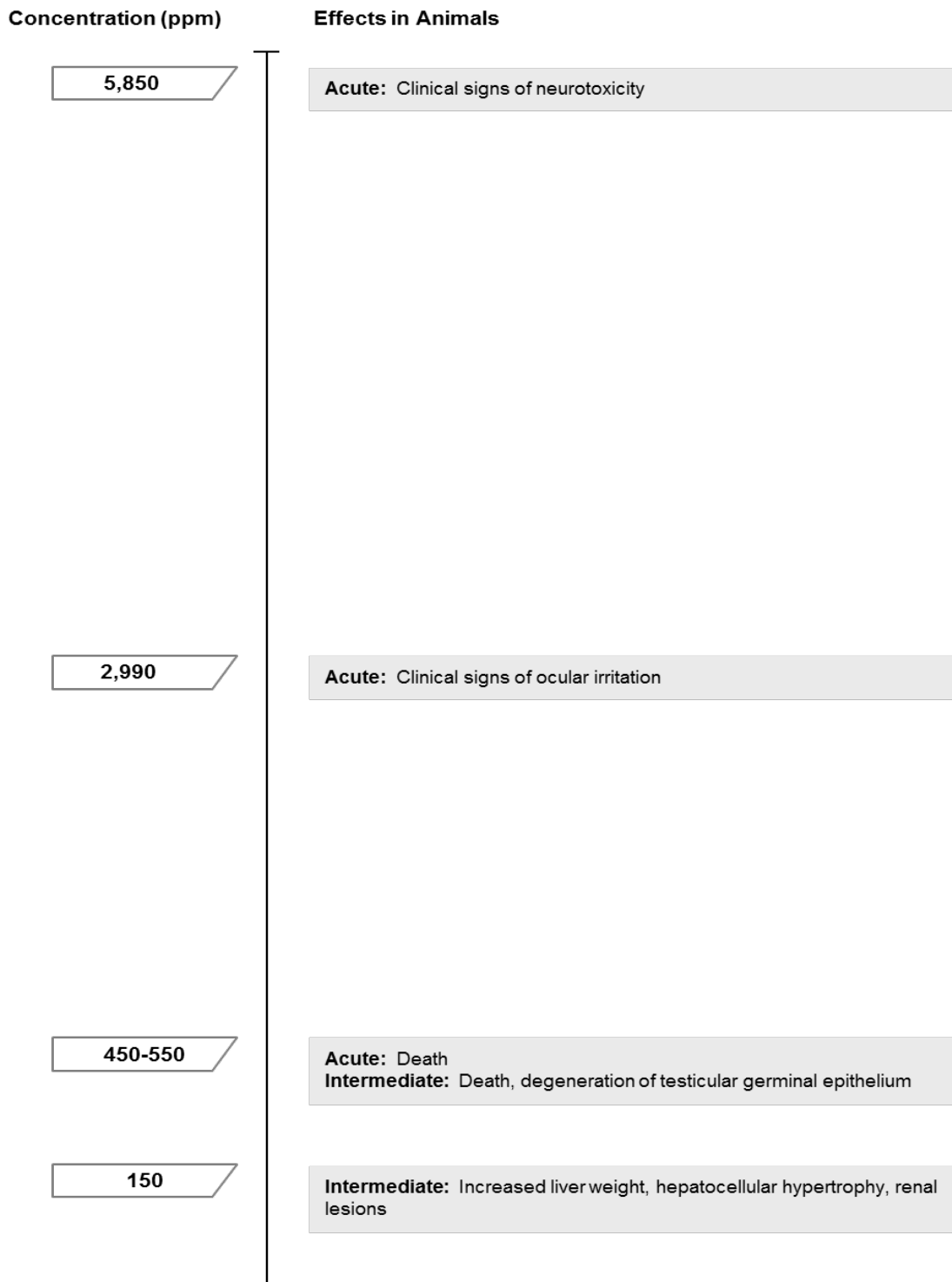
Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Chlorobenzene

Dose (mg/kg/day)   Effects in Animals

1,000   Acute: Death, clinical signs of neurotoxicity

250-280   Intermediate: Death, depressed body weight, increased kidney weight, histopathologic kidney lesions, lymphoid depletion/necrosis, hematological changes

120-125   Intermediate: Increased liver weight, histopathologic liver lesions
Chronic: Decreased survival, neoplastic liver nodules

55   Intermediate: Increased liver weight, histopathologic liver lesions

0.07 mg/kg/day ● Intermediate MRL

1. RELEVANCE TO PUBLIC HEALTH

Hematological Effects. Limited animal data suggest that chlorobenzene may exert adverse effects on red blood cell (RBC) parameters (NIOSH 1977) and cause leukopenia and lymphocytosis (Zub 1978). Decreases in hematocrit, hemoglobin, and/or RBC counts and changes in white blood cell (WBC) counts were noted in dogs administered chlorobenzene orally for 13 weeks (Monsanto Co. 1967a).

Hepatic Effects. Available information regarding the potential for chlorobenzene-induced hepatic effects in humans is limited to a single case report of severe liver necrosis in a suicidal male with a daily alcohol consumption of 200 g (Babany et al. 1991; Reygagne et al. 1992). The liver was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure; effects included increased liver weight and histopathologic liver lesions (e.g., hepatocellular hypertrophy, vacuolation, degeneration/necrosis, bile duct hyperplasia) (Monsanto Co. 1967a, 1967b; Nair et al. 1987; NTP 1985).

Renal Effects. The kidney was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure; effects included increased kidney weight and histopathologic kidney lesions (e.g., tubular dilatation, interstitial nephritis, degeneration/focal necrosis of proximal tubules, foci of regenerative epithelium) (Monsanto Co. 1967a; Nair et al. 1987; NTP 1985).

Immunological Effects. Results from 13-week studies of orally-exposed rats and mice suggest that chlorobenzene may affect the immune system; effects observed included myeloid and/or lymphoid depletion in bone marrow, spleen, and/or thymus (NTP 1985). However, no data were located regarding testing of immune function in animals exposed to chlorobenzene.

Neurological Effects. Case reports of humans demonstrated that chlorobenzene caused disturbances of the central nervous system, but there were no reports of changes in the structure of the brain or other parts of the nervous system. Neurological effects (e.g., headaches, dizziness, sleepiness) were observed in humans who inhaled vapors of chlorobenzene in the workplace for up to 2 years (Rozenbaum et al. 1947). However, quantitative exposure data were not available. Acute inhalation data from animals confirm the neurotoxicity of chlorobenzene at high exposure concentrations (Rozenbaum et al. 1947).

Cancer. No studies were found regarding the carcinogenicity of chlorobenzene in humans. In a chronic bioassay in animals, chlorobenzene (up to 120 mg/kg/day) did not produce increased tumor incidences in mice of either sex or in female rats (NTP 1985). High-dose (120 mg/kg/day) male rats exhibited statistically significantly increased incidence of neoplastic liver nodules. Based on available information from animal carcinogenicity studies and genotoxicity evaluations, the U.S. Environmental Protection

Agency (EPA) (IRIS 2003) assigned chlorobenzene to group D (not classifiable as to human carcinogenicity).

1.3   MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, available data have identified the liver and kidney as sensitive targets of chlorobenzene toxicity following inhalation exposure. No inhalation MRLs were derived for chlorobenzene due to insufficient data (see Appendix A). As presented in Figure 1-4, available data have identified the liver and kidney as sensitive targets of chlorobenzene toxicity following oral exposure. The oral database was considered adequate for derivation of an intermediate-duration oral MRL for chlorobenzene. The MRL value is summarized in Table 1-1 and discussed in detail in Appendix A. The database was not considered adequate for derivation of acute- or chronic-duration oral MRLs (see Appendix A).

Figure 1-3. Summary of Sensitive Targets of Chlorobenzene – Inhalation

The liver and kidney are the most sensitive targets of chlorobenzene inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.
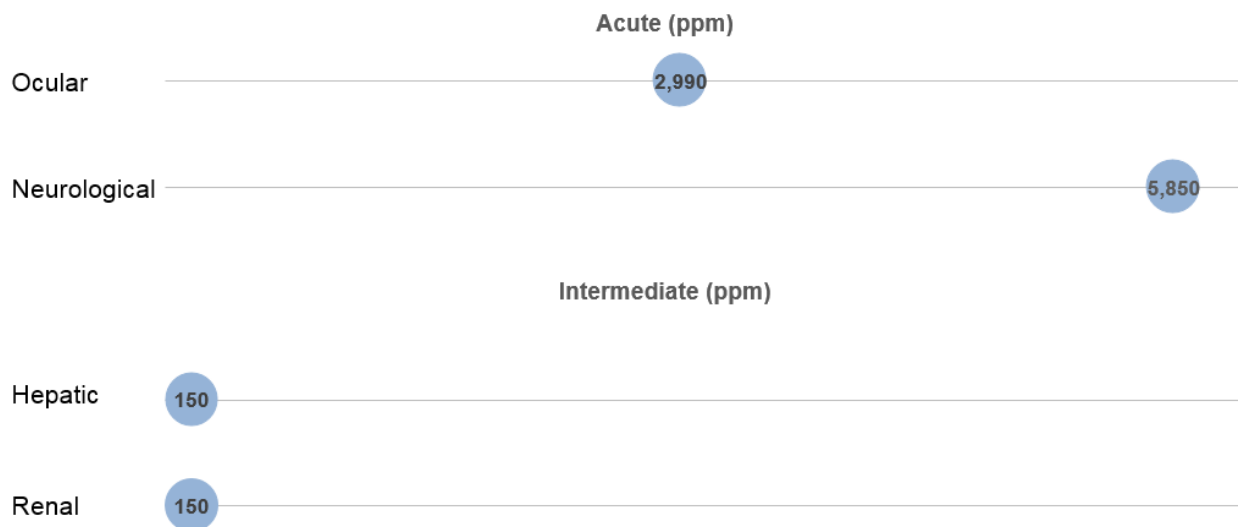
Figure 1-4. Summary of Sensitive Targets of Chlorobenzene – Oral

The liver is the most sensitive target of chlorobenzene oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

Acute (mg/kg/day)

Neurological ⸻⸻⸻⸻⸻⸻⸻⸻⸻⸻⸻⸻⸻⸻ 1,000

Intermediate (mg/kg/day)

Hepatic ⸺ 55

Renal ⸺⸺ 250

Immunological ⸺⸺ 250

Hematological ⸺⸺ 280
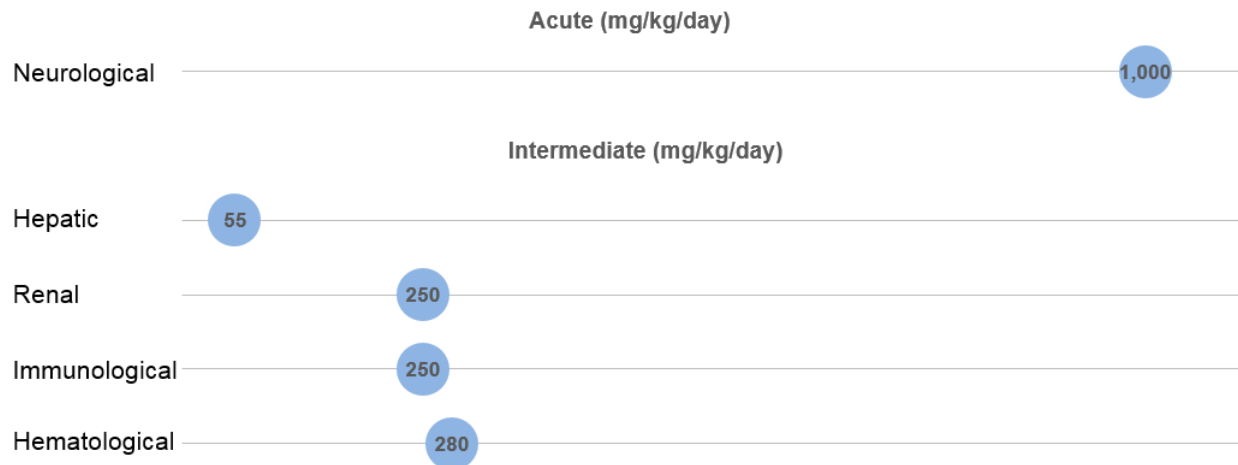
Table 1-1. Minimal Risk Levels (MRLs) for Chlorobenzene[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.07	Bile duct hyperplasia	$BMDL_{10}$: 9.59 mg/kg ($BMDL_{ADJ}$: 6.85)	UF: 100	Monsanto Co. 1967a
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

ADJ = duration-adjusted; $BMDL_{10}$ = 95% lower confidence limit on the benchmark dose with a benchmark response of 10% of extra risk; UF = uncertainty factor

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 chlorobenzene. 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 chlorobenzene, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; no dose-response dermal data were identified for chlorobenzene.

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 or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure to chlorobenzene associated with cancer (Cancer Effect Levels, CELs) 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.

Human data regarding the potential health effects of chlorobenzene exposure are essentially limited to reports of clinical signs of neurotoxicity among occupationally-exposed workers and among volunteers exposed by inhalation.

As illustrated in Figure 2-1, available animal data suggest the following sensitive targets of chlorobenzene toxicity:

- **Hepatic endpoint:** Inhalation or oral exposure of animals to chlorobenzene resulted in hepatic effects such as liver weight increases and dose-related increased incidence and severity of histopathologic liver effects such as hepatocellular hypertrophy and degenerative and regenerative liver lesions.

- **Renal endpoint:** Inhalation or oral exposure of animals to chlorobenzene resulted in renal effects such as increased kidney weight and dose-related increased incidence and severity of histopathologic kidney effects such as tubular dilatation, interstitial nephritis, and degenerative and regenerative kidney lesions.

- **Neurotoxicity endpoint:** Occupational and voluntary inhalation exposure to chlorobenzene has been associated with clinical signs of neurotoxicity such as numbness, cyanosis, muscle spasms, drowsiness, headache, ocular pain, and sore throat. Neurotoxic signs in animals exposed to chlorobenzene by inhalation or gavage include ataxia, decreased activity, salivation, prostration, and narcosis.

- **Immunological endpoint:** Lymphoid depletion/necrosis in thymus and/or spleen, and myeloid depletion in bone marrow were reported among rats and/or mice in 13-week gavage studies.

2. HEALTH EFFECTS

Figure 2-1. Overview of the Number of Studies Examining Chlorobenzene Health Effects

Most studies examined the potential body weight, hepatic, and renal effects of chlorobenzene
The majority of the studies examined inhalation or oral exposure in animals; limited data were identified for humans (counts represent the number of studies examining endpoint)
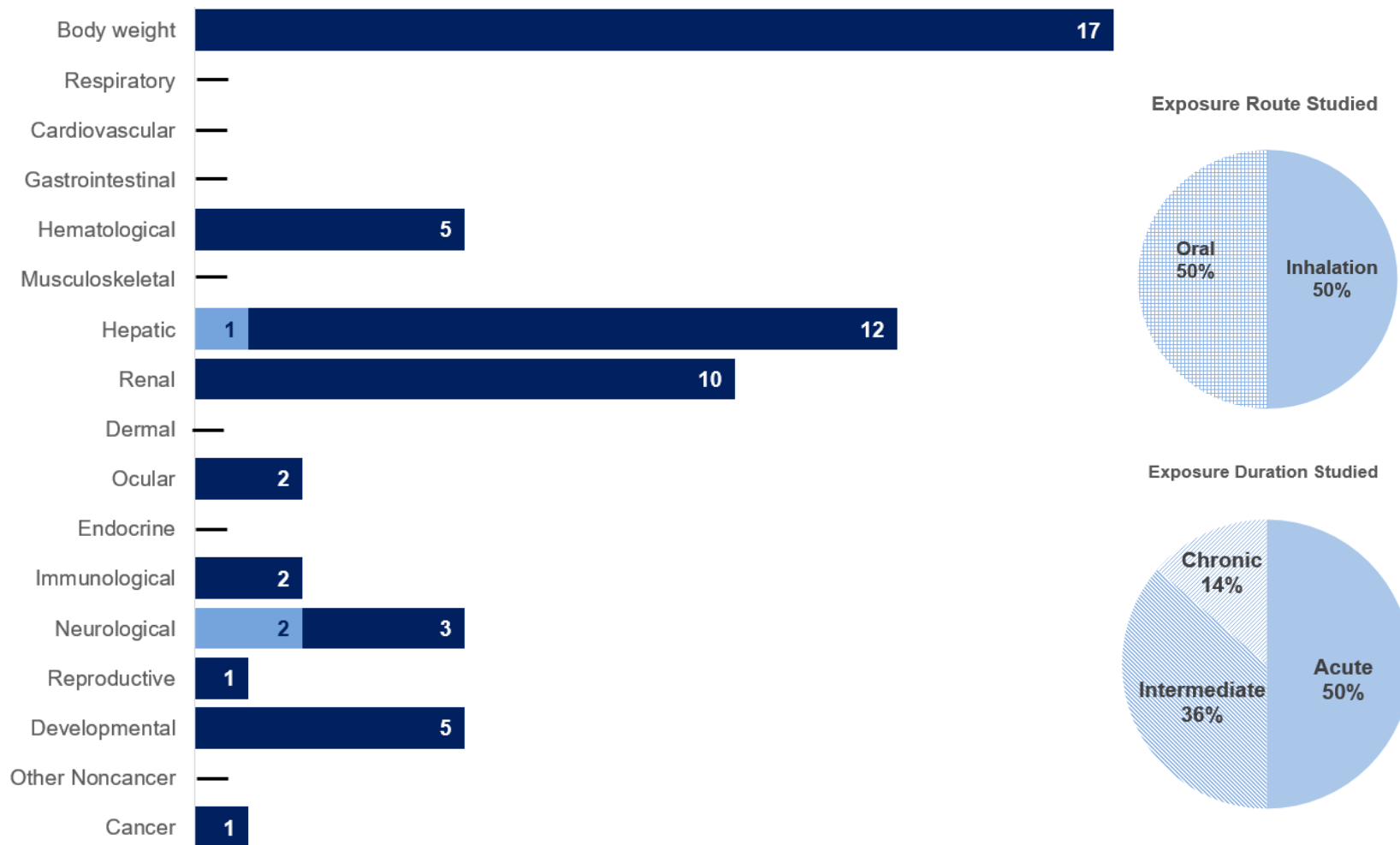
*Includes studies discussed in Chapter 2. A total of 22 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Chlorobenzene – 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	Rat (Sprague-Dawley) 5 M, 5 F	30 minutes	2,990, 5,850, 7,970	BW, CS, GN, HP, LE, OW	Bd wt	7,970			
					Hepatic	7,970			
					Renal	7,970			
					Ocular		2,990		Squinting, lacrimation
					Neuro	2,990		5,850	Ataxia, narcosis
Shell Oil Co. 1991									
2	Mouse	2 hours		LE	Death			4,300	100% mortality
Rozenbaum et al. 1947									
3	Rabbit	2 hours		LE	Death			537	
Rozenbaum et al. 1947									
4	Rat (Fischer 344) 32–33 F	GDs 6–15 6 hours/day	0, 75, 210, 590	BW, DX, FI, FX, LE, MX, OW, TG, WI	Bd wt	590			
					Develop	590			
John et al. 1984									
5	Rabbit (New Zealand white) 30 F	GDs 6–18 6 hours/day	0, 75, 210, 590	BW, DX, FI, FX, LE, MX, OW, TG, WI	Bd wt	590			
					Develop	590			
John et al. 1984									
6	Rabbit (New Zealand white) 30 F	GDs 6–18 6 hours/day	0, 10, 30, 75, 590	BW, DX, FI, FX, LE, MX, OW, TG, WI	Bd wt	590			
					Develop	590			
John et al. 1984									

Table 2-1. Levels of Significant Exposure to Chlorobenzene – 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
7	Guinea pig (Hartley albino) 5 M, 5 F	30 minutes	2,990, 5,850, 7,970	BW, CS, GN, HP, LE, OW	Bd wt	7,970			
					Hepatic	7,970			
					Renal	7,970			
					Ocular		2,990		Squinting, lacrimation
					Neuro	2,990		5,850	Salivation, narcosis
Shell Oil Co. 1991									
INTERMEDIATE EXPOSURE									
8	Rat (Sprague-Dawley) 30 M, 30 F	2 generations 18–20 weeks per generation 6 hours/day	9, 50, 150, 450	BW, CS, FI, DX, GN, HP, LE, OF, OW	Bd wt	450			
					Hepatic	50 M 450 F	150 M		Increased mean relative liver weight, increased incidence of hepatocellular hypertrophy in parental males
					Renal	50 M 450 F	150 M		Renal lesions including chronic interstitial nephritis and foci of regenerative epithelium in parental males
					Repro	150 M 450 F	450 M		Increased incidence of degeneration of testicular germinal epithelium in the absence of apparent effects on fertility
					Develop	450			
Nair et al. 1987 (data also reported in CMA 1986)									
9	Rat (Sprague-Dawley) 32 M	Up to 24 weeks 5 days/week 7 hours/day	0, 75, 250	BC, BW, CS, EA, FI, GN, HE, HP, LE, OF, OW	Bd wt	250			
					Hemato	250			
					Hepatic	250			
NIOSH 1977									
10	Mouse (Swiss) 5 M, 5 F	3 weeks 7 hours/day	0, 543	BW, CS, HE, LE	Death			543	5/10 mice died
Zub 1978									

2. HEALTH EFFECTS

Table 2-1. Levels of Significant Exposure to Chlorobenzene – 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
11	Rabbit (NS) 32 M	Up to 24 weeks 5 days/week 7 hours/day	0, 75, 250	BC, BW, CS, EA, FI, GN, HE, HP, LE, OF, OW	Bd wt	250			
					Hemato	250			
					Hepatic	250			
NIOSH 1977									
12	Dog (beagle) 6 M, 6 F	6 months 5 days/week 6 hours/day	0, 173.8, 349.8, 453.2	BC, BW, CS, EA, FI, GN, HE, HP, LE, OF, UR	Bd wt	453.2			
					Hemato	453.2			
					Hepatic	453.2			
					Renal	453.2			
Monsanto Co. 1980									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

BC = serum (blood) chemistry; Bd wt or BW = body weight; CS = clinical signs; EA = enzyme activity; Develop = developmental; DX = developmental toxicity; F = female(s); FI = food intake; FX = fetal toxicity; GD = gestation day(s); GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; TG = teratogenicity; UR = urinalysis; WI = water intake

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Chlorobenzene – Inhalation
Acute (≤14 days)

Death	Bd Wt	Hepatic	Renal	Ocular	Neuro	Develop

M-Mouse   o Animal - NOAEL
R-Rat
H-Rabbit   ◑ Animal - Less Serious LOAEL
G-Guinea Pig   ● Animal - Serious LOAEL

Figure 2-2. Levels of Significant Exposure to Chlorobenzene – Inhalation
Intermediate (15-364 days)

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Chlorobenzene – 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 (F344/N) 5 M, 5 F	Once (GO)	250, 500, 1,000, 2,000, 4,000	CS, LE	Death			4,000	3/5 males and 4/5 females died
					Neuro	2,000		4,000	Prostration
NTP 1985 (data also reported in Kluwe et al. 1985)									
2	Rat (albino) 22 F	GDs 6–15 1 time/day (GO)	0, 100, 300	BW, CS, DX, FX, LE, MX, TG	Bd wt	300			
					Develop	300			
Monsanto Co. 1977									
3	Rat (F344/N) 5 M, 5 F	14 days 1 time/day (GO)	0, 125, 250, 500, 1,000, 2,000	BW, CS, GN, LE	Death			1,000	5/5 males and 5/5 females died
					Bd wt	500			
					Neuro	500		1,000	Prostration
NTP 1985 (data also reported in Kluwe et al. 1985)									
4	Mouse (B6C3F1) 5 M, 5 F	Once (GO)	250, 500, 1,000, 2,000, 4,000	CS, LE	Death			1,000 M 2,000 F	5/5 males died 5/5 females died
NTP 1985 (data also reported in Kluwe et al. 1985)									
5	Mouse (B6C3F1) 5 M, 5 F	14 days 1 time/day (GO)	0, 30, 60, 125, 250, 500	BW, CS, GN, LE	Bd wt	500			
NTP 1985 (data also reported in Kluwe et al. 1985)									

Table 2-2. Levels of Significant Exposure to Chlorobenzene – 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
INTERMEDIATE EXPOSURE									
6	Rat (F344/N) 10 M, 10 F	13 weeks 5 days/week 1 time/day (GO)	0, 60, 125, 250, 500, 750	BC, BW, CS, GN, HE, HP, LE, OW, UR	Death			500	4/10 males and 3/10 females died
					Bd wt	125 M 250 F	250 M 500 F		12% lower mean final body weight
					Hepatic	125 M 60 F	250 M 125 F	750 M, F	Males: 24% increased mean relative liver weight at 250 mg/kg/day; hepatic degeneration/necrosis at 750 mg/kg/day Females: 19% increased mean relative liver weight at 125 mg/kg/day; hepatic degeneration/necrosis at 750 mg/kg/day
					Renal	250	500	750 F	13–15% increased mean relative kidney weight at 500 mg/kg/day; renal necrosis/degeneration in females at 750 mg/kg/day
					Immuno	500	750		Myeloid depletion in bone marrow, lymphoid depletion in spleen
NTP 1985 (data also reported in Kluwe et al. 1985)									
7	Rat (albino) 18 M, 18 F	3 months 1 time/day (GO)	Controls (untreated), 12.5, 50, 100, 250	BC, BW, CS, FI, GN, HE, HP, LE, OF, OW, UR	Bd wt	250			
					Hemato	250			
					Hepatic	100	250		27–29% increased liver weight
					Renal	100	250		13–14% increased kidney weight
Monsanto Co. 1967b									

Table 2-2. Levels of Significant Exposure to Chlorobenzene – 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
8	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 1 time/day (GO)	0, 60, 125, 250, 500, 750	BC, BW, CS, GN, HE, HP, LE, OW, UR	Death			250	5/9 males and 4/10 females died
					Bd wt	125 M 250 F	250 M 500 F		15–20% lower mean final body weight at lethal dose levels
					Hepatic	60 M 125 F	125 M	250 M, F	At 125 mg/kg/day: 14% increased mean relative liver weight in males At 250 mg/kg/day: 29–35% increased mean relative liver weight and hepatic necrosis/degeneration
					Renal	125		250	Renal necrosis/degeneration
					Immuno	125		250	Males: lymphoid depletion/necrosis in thymus and spleen; myeloid depletion in bone marrow Females: lymphoid depletion/necrosis in spleen
NTP 1985 (data also reported in Kluwe et al. 1985)									
9	Dog (beagle) 4 M, 4 F	13 weeks 5 days/week 1 time/day (C)	0, 28, 55, 280	BC, BW, CS, FI, GN, HE, HP, LE, OF, OW, UR	Death			280	2/4 dogs of each sex died
					Bd wt	55		280	Emaciation, weight loss at lethal dose
					Hemato	55	280		Males: decreased hematocrit, hemoglobin, RBCs; increased lymphocytes Females: decreased hemoglobin, RBCs, total WBCs

Table 2-2. Levels of Significant Exposure to Chlorobenzene – 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	28[b] M 55 F	55 M	280	At 55 mg/kg/day: 22% increased liver weight in males; bile duct hyperplasia (2/4) males At 280 mg/kg/day: increased liver weight (56% in males, 77% in females); degenerative liver lesions in most males and females (BMDL$_{10}$ of 9.59 mg/kg)
					Renal	55		280	Increased kidney weight (62% in males, 87% in females); degenerative kidney lesions in most males and females
Monsanto Co. 1967a									
CHRONIC EXPOSURE									
10	Rat (F344/N) 50 M, 50 F	103 weeks 5 days/week 1 time/day (GO)	0, 60, 120	BW, CS, GN, HP, LE	Death			120	Decreased survival
					Bd wt	120			
					Hepatic	120			
					Renal	120			
					Cancer			120	CEL: neoplastic liver nodules
NTP 1985 (data also reported in Kluwe et al. 1985)									

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Chlorobenzene – 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
11	Mouse (B6C3F1) 50 M, 50 F	103 weeks 5 days/week 1 time/day (GO)	Males: 0, 30, 60 Females: 0, 60,120	BW, CS, GN, HP, LE	Bd wt	60 M 120 F			
					Hepatic	60 M 120 F			
					Renal	60 M 120 F			

NTP 1985 (data also reported in Kluwe et al. 1985)

[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-duration oral MRL of 0.07 mg/kg/day; based on a BMDL$_{10}$ of 9.59 mg/kg, adjusted to continuous duration exposure (BMDL$_{ADJ}$ of 6.85 mg/kg/day) and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

BC = serum (blood) chemistry; Bd wt or BW = body weight; (C) = capsule; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); FI = food intake; FX = fetal toxicity; (GO) = gavage in oil; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; OF = organ function; OW = organ weight; RBC = red blood cell; TG = teratogenicity; UR = urinalysis; WBC = white blood cell

Figure 2-3. Levels of Significant Exposure to Chlorobenzene – Oral
Acute (≤14 days)
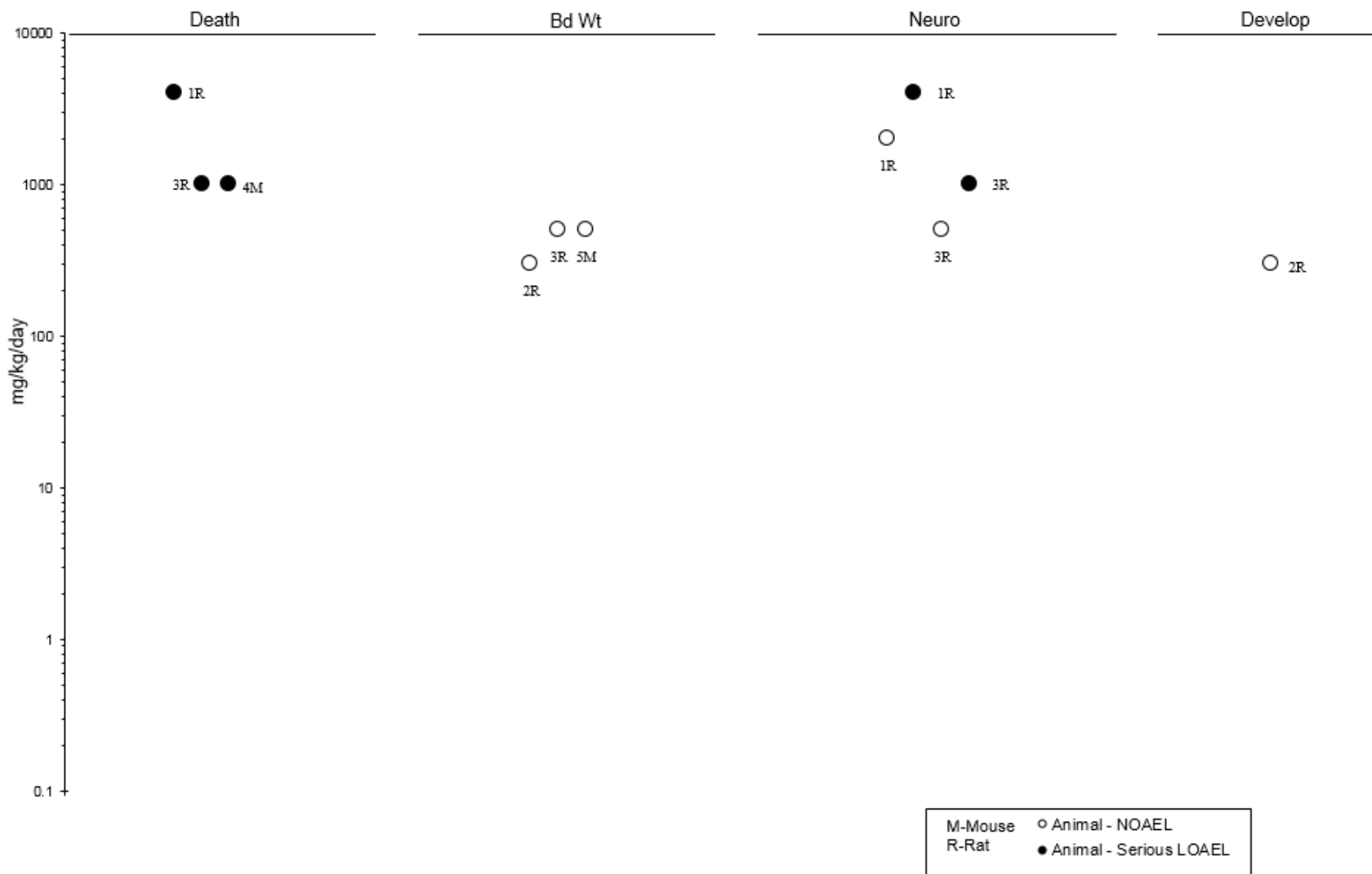
2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Chlorobenzene – Oral
Intermediate (15-364 days)
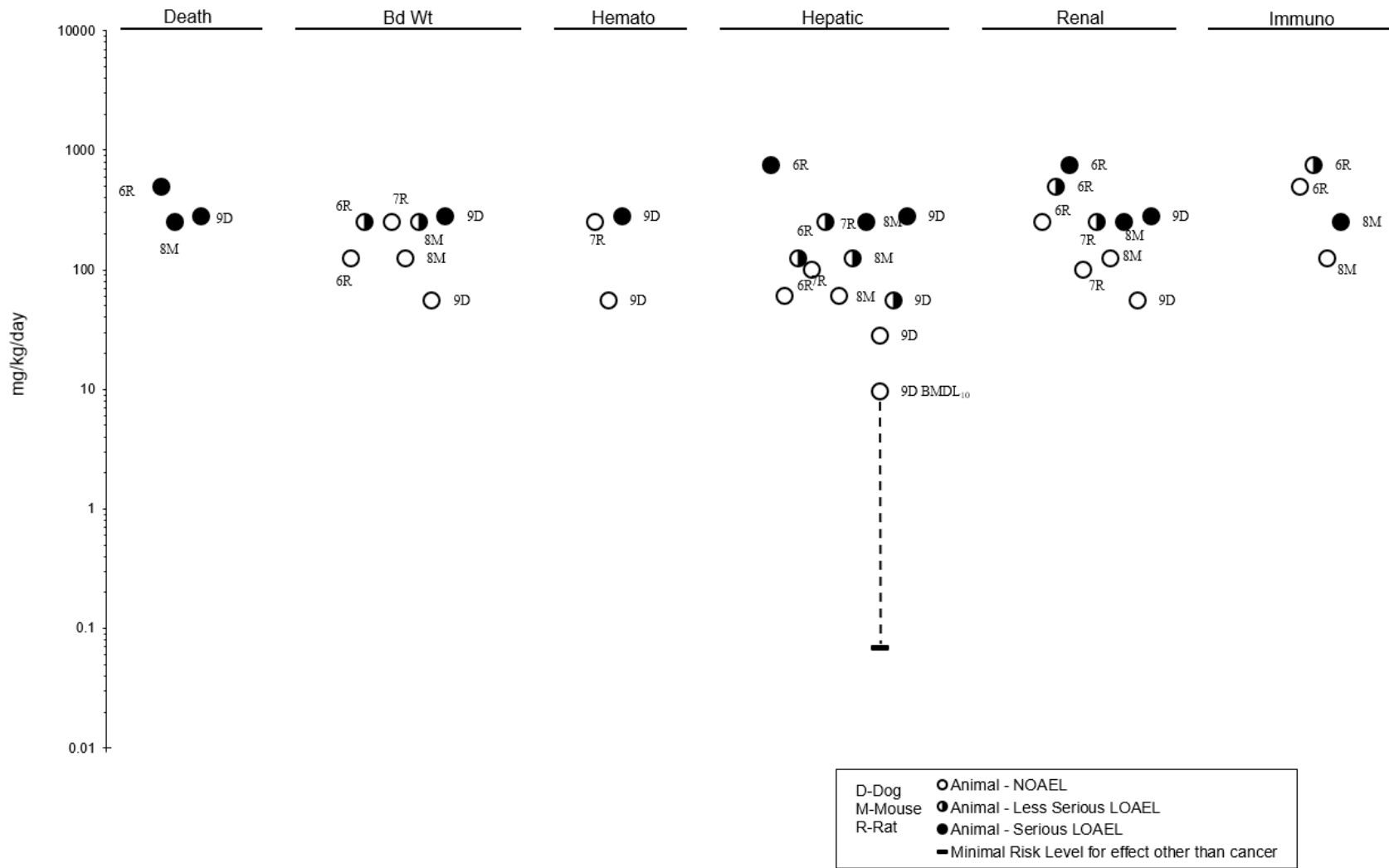
2. HEALTH EFFECTS

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

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.
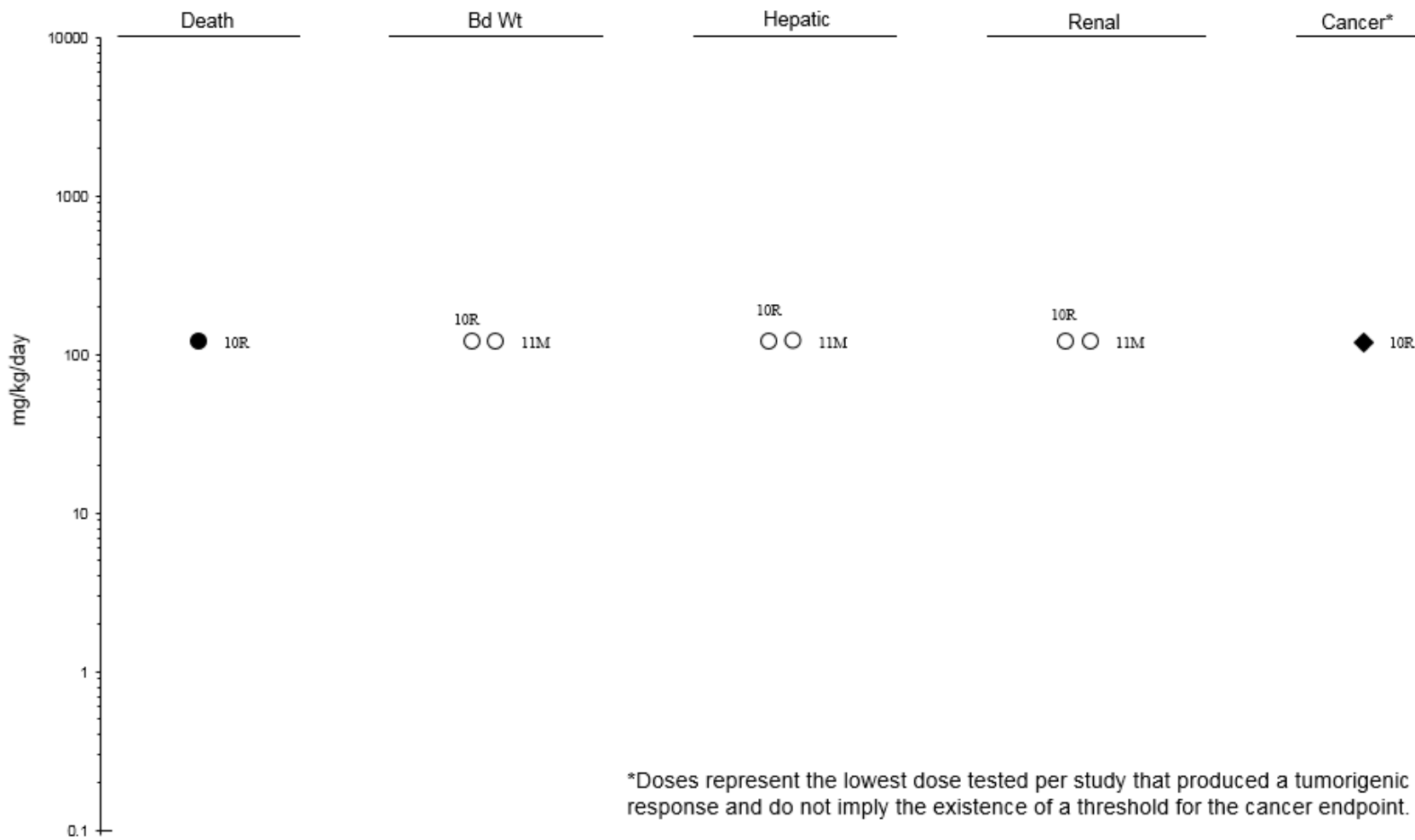
M-Mouse   o Animal - NOAEL
R-Rat   ● Animal - Serious LOAEL
              ◆ Animal - Cancer Effect Level

2.2   DEATH

There have been no documented human deaths from chlorobenzene exposure.

The acute lethality of chlorobenzene is relatively low in animals. Single exposure of mice to chlorobenzene vapor at 4,300 ppm for 2 hours resulted in 100% mortality (Rozenbaum et al. 1947). Rabbits died 2 weeks after a 2-hour inhalation exposure at approximately 537 ppm (Rozenbaum et al. 1947). In a 3-week study of mice exposed to chlorobenzene vapor for 7 hours/day at 543 ppm, death was reported in 5/10 mice (Zub 1978). Death occurred in 3/5 male and 4/5 female rats within 2–3 days following a single gavage dose at 4,000 mg/kg; similar exposure of mice resulted in 100% mortality of males at 1,000 mg/kg and females at 2,000 mg/kg (NTP 1985). In a 14-day repeated-dose study of rats, gavage exposure at doses ≥1,000 mg/kg resulted in 100% lethality (NTP 1985). In 13-week repeated-dose studies, survival was reduced in male and female rats gavaged at doses ≥500 and male and female mice gavaged at doses ≥250 mg/kg/day (NTP 1985). In a 13-week oral study of dogs, ingestion of chlorobenzene at 280 mg/kg/day resulted in death of 2/4 dogs of each sex (Monsanto Co. 1967a). In a 2-year oral rat study, survival of males at 120 mg/kg/day was significantly lower than that of vehicle controls (NTP 1985).

2.3   BODY WEIGHT

No exposure-related effects on body weight were observed in laboratory animals repeatedly exposed to chlorobenzene vapor at concentrations as high as 250–590 ppm (NIOSH 1977; John et al. 1984; Monsanto Co. 1980; Nair et al. 1987). In a 13-week gavage study, chlorobenzene exposure of male and female rats and mice at 250 mg/kg/day (males) and 500 mg/kg/day (females) resulted in 12–20% depressed mean final body weight (NTP 1985). Dogs, which were exposed for 13 weeks to chlorobenzene by daily capsule, exhibited emaciation and weight loss at a lethal dose of 280 mg/kg/day (Monsanto Co. 1967a).

2.4   RESPIRATORY

Available information regarding chlorobenzene-induced respiratory effects is limited to observations of nose rubbing behavior among guinea pigs exposed to chlorobenzene vapor for 30 minutes at a concentration as low as 2,990 ppm (Shell Oil Co. 1991).

Chlorobenzene has been used as a model VOC in several *in vitro* studies to investigate possible mechanisms of lung inflammation (Feltens et al. 2010; Fischäder et al. 2008; Lehmann et al. 2008; Röder-Stolinski et al. 2008).

2.5   CARDIOVASCULAR

No studies were located regarding cardiovascular effects in humans or laboratory animals exposed to chlorobenzene.

2.6   GASTROINTESTINAL

No studies were located regarding gastrointestinal effects in humans or laboratory animals exposed to chlorobenzene.

2.7   HEMATOLOGICAL

Information regarding the potential for inhaled chlorobenzene to cause hematological effects is limited. In studies of rats and rabbits exposed to chlorobenzene vapor for 7 hours/day, 5 days/week, for up to 24 weeks at concentrations of 75 or 250 ppm, NIOSH (1977) reported exposure concentration-related effects on RBC parameters (primarily an increase in reticulocyte count). Other hematological parameters (RBC count, hemoglobins, hematocrit, and WBC count) were variable and were comparable to controls at the end of the test. Zub (1978) reported slight leukopenia and lymphocytosis in mice exposed to chlorobenzene for 7 hours/day for 3 months at 21.7 ppm, and similar effects in mice similarly exposed for up to 3 weeks at 543 ppm (Zub 1978). However, limited details in the study report and lack of supportive evidence from other animal studies preclude meaningful evaluation of chlorobenzene-induced hematological effects following inhalation exposure. Monsanto Co. (1967a) reported changes in selected blood parameters in dogs receiving chlorobenzene in daily capsule at 280 mg/kg/day for 13 weeks. High-dose males exhibited decreases in hematocrit, hemoglobin, and RBCs, and increased lymphocytes; high-dose females exhibited decreased in hemoglobin, RBCs, and total WBCs.

2.8   MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans or laboratory animals exposed to chlorobenzene.

2.9   HEPATIC

Available information regarding the potential for chlorobenzene to cause adverse liver effects in humans is limited to a single case report in which ingestion of 140 mL of 90% chlorobenzene by a suicidal 40-year-old, 58-kg, male with a daily alcohol intake of 200 g resulted in severe liver necrosis (Babany et al. 1991; Reygagne et al. 1992). Although daily alcohol consumption was estimated at approximately 200 g, the patient had no history of chronic liver disease. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels on the third day after chlorobenzene ingestion were 345 and 201 times, respectively, the upper limit of normal. Liver biopsy revealed centrilobular and mediolobular necrosis.

Results from animal studies identify the liver as a target of chlorobenzene toxicity. In a 2-generation inhalation study of rats, repeated inhalation exposure to chlorobenzene vapor at 150 ppm resulted in statistically significantly increased mean relative liver weight and increased incidence of hepatocellular hypertrophy of parental males (incidence data not included in the study report) (Nair et al. 1987). In several studies that employed repeated gavage exposure to chlorobenzene for up to 3 months, increased liver weight was reported in rats at doses as low as 100–250 mg/kg/day (Monsanto Co. 1967b; NTP 1985), mice at 125 mg/kg/day (NTP 1985), and male dogs at 55 mg/kg/day (Monsanto Co. 1967a). Two of four male dogs treated at 55 mg/kg/day exhibited bile duct hyperplasia (a lesion not observed in control dogs); bile duct hyperplasia was noted in 4/4 male and 3/4 female dogs dosed at 280 mg/kg/day (Monsanto Co. 1967a). Hepatic degeneration/necrosis were observed in rats treated at 750 mg/kg/day and mice treated at 250 mg/kg/day (NTP 1985). There were no apparent exposure-related hepatic effects among rats or mice administered chlorobenzene by gavage for up to 2 years at doses as high as 60–120 mg/kg/day (NTP 1985).

2.10   RENAL

Available animal data implicate the kidney as a target of chlorobenzene toxicity. Nair et al. (1987) reported tubular dilatation with eosinophilic material, interstitial nephritis, and foci of regenerative epithelium in 2 generations of parental male rats exposed to chlorobenzene vapor at concentrations ≥150 ppm. In 3-month repeated-dose gavage studies of rats and mice (NTP 1985), increased kidney weight was observed at doses ≥500 mg/kg/day. Histopathologic kidney lesions (degeneration/focal necrosis of the proximal tubules) were observed in rats at 750 mg/kg/day and in mice at doses ≥250 mg/kg/day (NTP 1985). Kidney lesions (e.g., tubule dilatation, epithelial degeneration, vacuolation) were observed in dogs treated with chlorobenzene in capsules for 13 weeks at 280 mg/kg/day (Monsanto

Co. 1967a). There were no indications of exposure-related kidney effects in rats or mice administered chlorobenzene by gavage for up to 2 years at doses as high as 60–120 mg/kg/day (NTP 1985).

2.11 DERMAL

Limited information was located regarding chlorobenzene-induced dermal effects. There were no signs of dermal sensitization in a guinea pig dermal sensitization assay in which chlorobenzene was applied via intradermal injection (induction at 1% chlorobenzene), followed by topical induction of a 50% solution and two challenge dermal applications of a 25% solution (Miles Inc. 1984).

2.12 OCULAR

Limited information was located regarding chlorobenzene-induced ocular effects. Lacrimation and squinting behavior was observed among rats and guinea pigs exposed to chlorobenzene vapor for 30 minutes at concentrations ≥2,990 ppm (Shell Oil Co. 1991). Mild to moderate corneal opacity, iritis, redness, chemosis, and discharge were among the effects observed in the eyes of rabbits following ocular instillation of chlorobenzene (Zeneca Specialties 1982).

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans or laboratory animals exposed to chlorobenzene.

2.14 IMMUNOLOGICAL

Histological studies in mice and rats suggest that chlorobenzene has immunotoxic properties. In a 13-week oral study of rats, gavage exposure at 750 mg/kg/day resulted in myeloid depletion in bone marrow and lymphoid depletion in the spleen (NTP 1985). Similar exposure of mice at doses ≥250 mg/kg/day resulted in lymphoid depletion/necrosis in the thymus and spleen and myeloid depletion in bone marrow of males and lymphoid depletion/necrosis in the spleen of females (NTP 1985). Since no human data were located regarding immunotoxic effects and no animal studies that evaluated immune function are available, firm conclusions cannot be made concerning the potential for chlorobenzene to affect the immune system in humans.

2.15 NEUROLOGICAL

Chlorobenzene affects the central nervous system. Humans occupationally exposed to chlorobenzene intermittently for up to 2 years displayed signs of neurotoxicity including numbness, cyanosis (from depression of respiratory center), hyperesthesia, and muscle spasms (Rozenbaum et al. 1947). Specific exposure levels and histopathologic data were not provided in the study report. When four volunteers were exposed via inhalation to 60.2 ppm chlorobenzene for 7 hours during a study of urinary metabolites in exposed workers, all complained of disagreeable odor and drowsiness, three complained of headache, two of throbbing pain in eyes, and one of sore throat (Ogata et al. 1991). A test of critical flicker fusion frequency was also conducted. The critical flicker fusion rate is the frequency at which an intermittent light stimulus is perceived as continuous; the test is used to evaluate the rate of perceptual temporal processing capacity. The mean flicker-fusion value declined 3.1 cycles/second in exposed subjects, compared to controls (Ogata et al. 1991).

Neurological effects of chlorobenzene have also been reported in animals following inhalation. Acute inhalation exposure produced muscle spasms followed by narcosis in rabbits exposed to 1,090 ppm chlorobenzene for >2 hours (Rozenbaum et al. 1947). Ataxia and narcosis were observed in rats exposed to chlorobenzene vapor for 30 minutes at concentrations ≥5,850 ppm; most rats displayed these effects within 25 minutes following initiation of exposure, but they recovered rapidly after removal from the test chamber (Shell Oil Co. 1991). At an exposure concentration of 7,970 ppm, tremors were observed as well. In addition to the narcotic effects observed in the rats, similarly-exposed guinea pigs also exhibited salivation at 7,970 ppm.

There is a paucity of data on the effects of chlorobenzene in humans following oral exposure. A 2-year-old male swallowed 5–10 cc of a stain remover, which consisted almost entirely of chlorobenzene. He became unconscious, did not respond to skin stimuli, showed muscle spasms, and became cyanotic. The odor of chlorobenzene could be detected in his urine and exhaled air; however, the child recovered uneventfully (Reich 1934).

Available information regarding the potential for chlorobenzene to cause neurological effects following oral exposure in laboratory animals is limited to findings of decreased activity and prostration among rats administered chlorobenzene by gavage once at 4,000 mg/kg/day or repeatedly for 14 days at 1,000 mg/kg/day; these doses were also lethal (NTP 1985).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans exposed to chlorobenzene.

Limited information is available regarding the potential for chlorobenzene-induced reproductive effects in laboratory animals. In a two-generation study of rats intermittently exposed to chlorobenzene vapor from at least 10 weeks prior to mating through lactation of their progeny, increased incidences of degenerative testicular changes were observed in males of both generations (6/30 versus 1/30 among controls; p=0.051) exposed at 450 ppm (Nair et al. 1987). The toxicological significance of this finding is unclear because mean mating, pregnancy, and male fertility indices for both F0 and F1 generations were comparable for all groups.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans exposed to chlorobenzene.

Limited information is available regarding the potential for chlorobenzene-induced developmental effects in laboratory animals. No indications of chlorobenzene exposure-related developmental effects were observed in studies of rats and rabbits exposed to chlorobenzene vapor for 6 hours/day at concentrations as high as 590 ppm during gestation days 6–15 (rats) or 6–18 (rabbits) (John et al. 1984). No indications of exposure-related developmental effects were observed in a study of rats administered chlorobenzene by daily gavage at doses up to 300 mg/kg/day during gestation days 6–15 (Monsanto Co. 1977).

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects.

2.19 CANCER

In a chronic oral bioassay in rats and mice (NTP 1985), there was no evidence for carcinogenicity in either sex of mice or in female rats administered chlorobenzene in corn oil by gavage at dose levels up to 120 mg/kg/day. Increased tumor frequencies were not seen in female rats or in male or female mice. Male rats showed a significant (p<0.05) increase in the incidence of neoplastic nodules of the liver in the 120 mg/kg/day dose group, but no increases were found at lower doses. While progression from nodules to carcinomas is a well-characterized phenomenon, existing data are inadequate to characterize the

carcinogenic potential of chlorobenzene in humans. EPA (IRIS 2003) assigned chlorobenzene to class D (not classifiable as to human carcinogenicity), based on lack of human data, inadequate animal data, and predominantly negative genetic toxicity data in bacterial, yeast, and mouse lymphoma cells.

2.20 GENOTOXICITY

No studies were located regarding the genotoxic effects of chlorobenzene in humans. The potential genotoxicity of chlorobenzene has been evaluated in several *in vivo* studies (Table 2-3) and a greater number of *in vitro* assays (Table 2-4). Collectively, the results indicate that chlorobenzene is not likely to act as a mutagen; however, *in vivo* results indicate that chlorobenzene may induce other genotoxic effects. However, as shown in Figure 3-1, chlorobenzene undergoes CYP450 catalyzed oxidation to form the 3,4- and 2,3-epoxides of chlorobenzene. Both epoxides can be formed in liver and lung (and other tissues such as kidney and adrenal cortex) and are capable of covalently binding to deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins.

Table 2-3. Genotoxicity of Chlorobenzene *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila:			
Male germ cells (airborne exposure)	Sex-linked recessive lethal mutations	–	Bioassay Systems Corp. 1982
Mammalian cells:			
Rat bone marrow (intraperitoneal injection)	Chromosomal aberrations	+	Siddiqui et al. 2006
Mouse bone marrow (intraperitoneal injection)	Chromosomal aberrations	+	Mohtashumipur et al. 1987
Rat bone marrow (intraperitoneal injection)	Micronuclei	+	Siddiqui et al. 2006
Mouse bone marrow (intraperitoneal injection)	Micronuclei	+	Mohtashumipur et al. 1987
Mouse bone marrow (intraperitoneal injection)	Micronuclei	–	Shelby and Witt 1995
Mouse bone marrow (intraperitoneal injection)	Micronuclei	–	Shelby et al. 1993
Mouse peripheral lymphocytes (intraperitoneal injection)	DNA damage	+	Vaghef and Hellman 1995
Mouse bone marrow (intraperitoneal injection)	DNA damage	–	Vaghef and Hellman 1995

+ = positive result; – = negative result; DNA = deoxyribonucleic acid

Table 2-4. Genotoxicity of Chlorobenzene *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	E.I. DuPont 1977
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Haworth et al. 1983; NTP 1985
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	Monsanto Co. 1976a, 1976b
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	Shimizu et al. 1983
Saccharomyces cerevisiae D4	Gene mutation	–	–	Monsanto Co. 1976a, 1976b
Eukaryotic organisms:				
Aspergillus nidulans	Gene mutation	–	No data	Prasad 1970
Mammalian cells:				
Mouse L5178Y lymphoma cells	Gene mutation	+	+/–	McGregor et al. 1988
Mouse L5178Y lymphoma cells	Gene mutation	–	–	Monsanto Co. 1976c
Rat liver epithelial cells	Cell transformation	No data	+	Shimada et al. 1983
Rat hepatocytes	DNA repair	No data	–	Shimada et al. 1983
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Bioassay Systems Corp. 1982
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Loveday et al. 1989
Chinese hamster ovary cells	Sister chromatid exchange	–	+	Loveday et al. 1989

+ = positive result; – = negative result; +/– = inconclusive results; DNA = deoxyribonucleic acid

Chlorobenzene did not induce sex-linked recessive lethal mutations in male *Drosophila* germ cells (Bioassay Systems Corp. 1982). Chlorobenzene induced chromosomal aberrations and micronuclei in bone marrow cells in two assays that employed intraperitoneal injection of chlorobenzene into rats and mice (Mohtashumipur et al. 1987; Siddiqui et al. 2006), but did not induce micronuclei in mouse bone marrow cells in other similarly-designed studies (Shelby and Witt 1995; Shelby et al. 1993). Vaghef and Hellman (1995) reported DNA damage in peripheral lymphocytes from mice following intraperitoneal

injection of chlorobenzene for 3 days at 750 mg/kg/day, but no evidence of DNA damage to bone marrow cells.

Chlorobenzene did not induce gene mutations either in the presence or absence of exogenous metabolic activation in bacterial assays that employed multiple strains of *Salmonella typhimurium* (E.I. DuPont 1977; Haworth et al. 1983 [also reported in NTP 1985]; Monsanto Co. 1976a, 1976c; Shimizu et al. 1983) or the D4 strain of *Saccharomyces cerevisiae* (Monsanto Co. 1976a, 1976b). Chlorobenzene did not induce gene mutations in the fungus *Aspergillus nidulans* in the presence of exogenous metabolic activation (Prasad 1970). Positive results for chlorobenzene-induced gene mutations in mouse L5178Y lymphoma cells in the presence and absence of exogenous metabolic activation were obtained in one study (McGregor et al. 1988), but not in another study (Monsanto Co. 1976c). Chlorobenzene induced cell transformation in rat liver epithelial cells, but did not induce DNA repair in rat hepatocytes (Shimada et al. 1983). In Chinese hamster ovary cells, negative results were obtained for chromosomal aberrations in the presence and absence of exogenous metabolic activation (Bioassay Systems Corp. 1982; Loveday et al. 1989), but positive results were obtained for sister chromatic exchange in the absence of exogenous metabolic activation (Loveday et al. 1989).

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

3.1   TOXICOKINETICS

- Chlorobenzene is readily absorbed from the respiratory and gastrointestinal tracts.

- Chlorobenzene is widely distributed in the blood, but may accumulate to some extent in adipose tissue due to its lipophilicity.

- Most chlorobenzene is metabolized via a chlorobenzene 3,4-epoxide pathway to ultimate urinary glucuronide or sulfate conjugates.

- Urinary excretion of chlorobenzene metabolites is the major route of excretion.

3.1.1   Absorption

Limited information was located regarding absorption of inhaled chlorobenzene. Absorption from the respiratory tract of two workers exposed to airborne chlorobenzene concentrations in the range of 0.5–0.84 ppm was estimated to have been 70% (Ogata and Shimada 1983). In other human studies that involved occupational exposure to chlorobenzene, the detection of chlorobenzene metabolites in blood and urine provides unquantified demonstration that chlorobenzene is absorbed from the respiratory tract (Knecht and Woitowitz 2000; Kumagai and Matsunaga 1994; Kusters and Lauwerys 1990; Ogata et al. 1991; Yoshida et al. 1986). Rats were reported to readily absorb ^{14}C-labeled chlorobenzene at airborne concentrations up to 700 ppm (Sullivan et al. 1983). Shimada (1981, 1988) evaluated distribution and urinary excretion of chlorobenzene and its metabolites in laboratory animals exposed to chlorobenzene by inhalation, thus demonstrating that inhaled chlorobenzene is absorbed.

Chlorobenzene is readily absorbed from the gastrointestinal tract. Ogata and Shimada (1983) reported at least 31% absorption of chlorobenzene orally administered to a single volunteer. In the same study, rats administered chlorobenzene absorbed at least 18% of the administered dose. Lindsay Smith et al. (1972) administered [^{14}C]chlorobenzene to two rabbits orally at approximately 500 mg/rabbit, twice per day for 4 days and measured radioactivity in urine and feces of both rabbits and tissues of one rabbit. Recovered radioactivity was 19.6% in the urine, 1.05–1.55% in the feces, and 0.05% in tissues; thus, approximately 20% of the administered dose was absorbed. The absorption of orally-administered chlorobenzene from the gastrointestinal tract was demonstrated in a variety of oral animal studies that were designed to evaluate chlorobenzene metabolites in urine (e.g., Azouz et al. 1952; Gillham and Young 1968; Krewet et al. 1989; Parke and Williams 1953; Lindsay Smith et al. 1950, 1972; Spencer and Williams 1950).

3.1.2   Distribution

Limited information was located regarding distribution of absorbed chlorobenzene in humans. Knecht and Woitowitz (2000) exposed eight volunteers to Germany's maximum workplace concentration (MAK) of 10 ppm chlorobenzene 8 hours/day for 5 days. There was no apparent tendency for chlorobenzene or its metabolites to accumulate in blood or urine with prolonged exposure. Blood levels reached a steady state (mean, 197.0±9.7 µg/L) after the first hour of exposure. The mean concentration of chlorobenzene in blood in five subjects exposed during physical exercise (75 W, 10 minutes/hour on a bicycle) was 217 µg/L. The mean chlorobenzene blood concentrations were 133 µg/L in two subjects exposed during mild exercise (50 W, 10 minutes/hour on a bicycle) and 78 µg/L in one subject exposed while at rest.

Studies in laboratory animals indicate that chlorobenzene is widely distributed and may accumulate in adipose tissue (Shimada 1988; Sullivan et al. 1983). Accumulation in adipose tissue is related to the lipophilicity of chlorobenzene and likely depends on the species-specific lipid distribution in various organs.

3.1.3   Metabolism

A proposed metabolic pathway of chlorobenzene (Chadwick et al. 1984) is shown in Figure 3-1. The numbers 1–16 in Figure 3-1 correspond to the numbers in the following text that presents the various metabolic processes.

According to the proposed metabolic pathway, chlorobenzene undergoes CYP450 catalyzed oxidation to form chemically-reactive chlorobenzene 3,4-epoxide (1), relatively nontoxic chlorobenzene 2,3-epoxide (2) to a lesser extent, and 3 chlorophenol (3). Both epoxides can be formed in liver and lung (and other tissues such as kidney and adrenal cortex) and are capable of covalently binding to DNA, RNA, and proteins. The chlorobenzene epoxides can be further metabolized by three separate pathways. One pathway for 3,4- and 2,3-chlorobenzene epoxides involves the GSH transferase-catalyzed formation of glutathione conjugates of 4-chlorophenyl (4) and 2-chlorophenyl (5), respectively, followed by conversion to mercapturic acid derivatives. Another metabolic pathway for the 3,4- and 2,3-epoxides is the enzymatic (epoxide hydrase) conversion to 3,4-dihydro-3,4-dihydroxychlorobenzene (6 and 7, respectively) which is enzymatically converted to chlorocatechol (8) or chlorophenol (9). Both chlorocatechol and chlorophenol can form glucuronide and sulfate conjugates (10 and 11, respectively).

Figure 3-1. Mammalian Metabolism of Chlorobenzene to Phenols, Dihydrodiols, Catechols, and Glutathione Conjugates
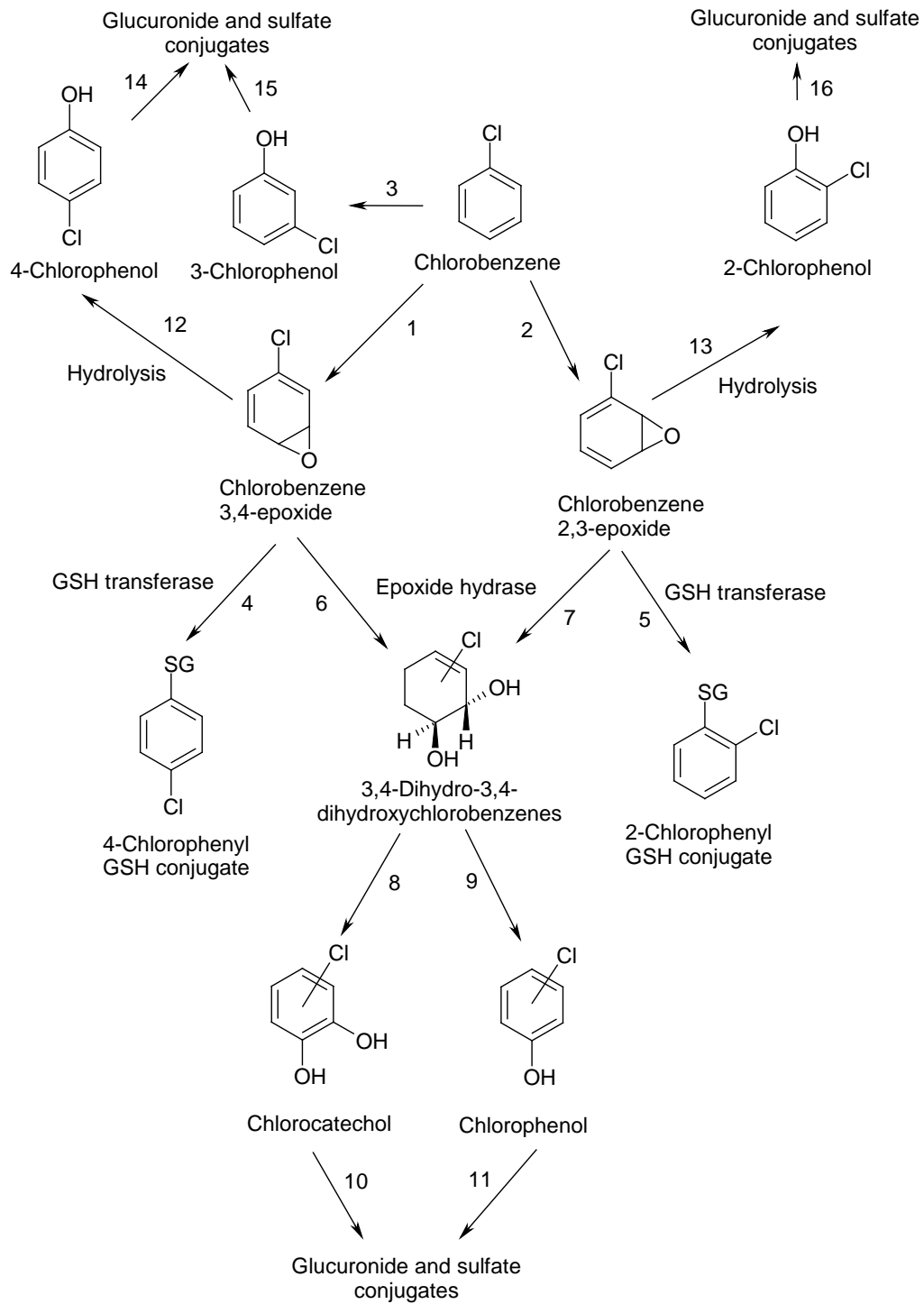
Source: Chadwick et al. 1984; reprinted from Pesticide Biochemistry and Physiology 21:148-161 (1984) with permission from Elsevier.

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

The 3,4- and 2-3-epoxides can also undergo hydrolysis to form 4-chlorophenol (12) and 2-chlorophenol (13), respectively. The chlorophenols (4-chlorophenol, 3-chlorophenol, and 2-chlorophenol) can form glucuronide and sulfate conjugates (14, 15, and 16, respectively).

Chlorobenzene metabolites that have been detected in the urine of a variety of animal species include 2-, 3-, and 4-chlorophenyl-mercapturic acid, chlorophenols and chlorocatechols and their glucuronide and sulfate conjugates, and 3,4-dihydro-3,4-dihydroxychlorobenzene. Chlorocatechol and 2-chlorophenyl-mercapturic acid were detected in the urine of humans who received chlorobenzene orally or by inhalation (Ogata and Shimada 1983). Chlorobenzene metabolites that have been detected in the urine of chlorobenzene-exposed humans include 4-chlorocatechol, 4-chlorophenol, and 2-chlorophenyl-mercapturic acid (Kusters and Lauwerys 1990; Ogata and Shimada 1983; Ogata et al. 1991; Yoshida et al. 1986).

Cytochrome P-450 2E1 is the main enzyme involved in the oxidation of chlorobenzene in mice, rats, and humans. Cytochrome P-450 3A also appears to play a role in the generation of reactive metabolites in mice, rats, and humans. It is important to note, however, that, compared to mice and rats, the rate of metabolism of chlorobenzene to soluble metabolites is higher in humans, and the formation of covalently bound products is lower (Nedelcheva et al. 1998). In addition, there is up to a 10-fold difference in the rate of metabolism of chlorobenzene in different human livers. There are also significant species and sex differences in the metabolism of chlorobenzene with markedly higher rates of oxidation in male mice than in male rats and female mice.

Co-treatment of rats with chlorobenzene and an epoxide hydrase inhibitor (cyclohexane oxide) resulted in decreases in chlorobenzene metabolism and its necrotic toxicity on the liver, suggesting that the metabolism of chlorobenzene is partially responsible for its liver toxicity (Oesch et al. 1973).

3.1.4   Excretion

Knecht and Woitowitz (2000) exposed eight volunteers to Germany's MAK of 10 ppm chlorobenzene 8 hours/day for 5 days. Half-lives of elimination of chlorobenzene from blood were 53 minutes in the first hour after cessation of exposure and 150 minutes thereafter. The major urinary metabolite of chlorobenzene was 4-chlorocatechol (74%), with the remainder comprised of chlorophenol isomers of which 4-chlorophenol (13%) was the most abundant. Urinary 4-chlorophenol was useful as a biomarker

of exposure due to its half-life of approximately 12 hours. The elimination half-life of urinary 4-chlorocatechol was 6.4 hours (Knecht and Woitowitz 2000).

Ogata and Shimada (1983) reported that in two workers exposed by inhalation to 0.84 and 0.5 ppm of chlorobenzene, the excretion of 4-chlorophenylmercapturic acid was markedly lower than that of 4-chlorocatechol. Ogata and Shimada (1983) also assayed the urinary metabolites of chlorobenzene of a 57-year-old male volunteer given an oral dose of 0.3 mmol/kg of chlorobenzene. Two urinary metabolites, 4-chlorophenylmercapturic acid and 4-chlorocatechol, were detected. As in the case of inhalation exposure, the excretion of 4-chlorophenylmercapturic acid was reported to be markedly lower than that of 4-chlorocatechol. However, the ratio of mercapturic-acid to 4-chlorocatechol in the urine of human subject receiving oral chlorobenzene was similar to that of the two workers inhaling chlorobenzene.

Linear correlations between urinary 4-chlorocatechol excretion and airborne exposure of workers to chlorobenzene were established by Yoshida et al. (1986) after monitoring end-of-shift urinary metabolites in healthy male workers in two chemical factories where chlorobenzene was used as a solvent. The primary urinary metabolites were 4-chlorocatechol (mean 76.9%) and 4-chlorophenol (mean 12.4%). In factories A and B, average chlorobenzene concentrations in air were 3.16 ppm (range 1.72–5.78 ppm) and 3.14 ppm (range 2.68–3.68 ppm), respectively. These levels of exposure in factories A and B corresponded, respectively, to mean 4-chlorocatechol levels of 0.362 µmoles/mg creatinine (range 0.166–0.787 µmoles/mg creatinine) and 0.482 µmoles/mg creatinine (range 0.354–0.655 µmoles/mg creatinine) in urine (Yoshida et al. 1986).

Assessing 44 maintenance workers in a diphenylmethane 4,4'-diisocyanate plant for chlorobenzene exposure, Kusters and Lauwerys (1990) also found that the main urinary metabolites at the end of shift were 4-chlorophenol and 4-chlorocatechol, with the latter being 3 times more abundant than the former. The time-weighted average exposure to chlorobenzene in air (mean 1.2 ppm, range 0.05–106 ppm) was less than the current German MAK value of 10 ppm established in 1995. More than 80% of the metabolites were eliminated within 16 hours after the end of exposure, and there was no tendency for an increase in concentration during the working week.

Ogata et al. (1991) reported that, in order of abundance, the main urinary metabolites of chlorobenzene in exposed workers were 4-chlorocatechol and 2-chlorophenylmercapturic acid. The concentrations of chlorobenzene in blood and metabolites in urine (e.g., 4-chlorocatechol, approximately 26% of exposure)

were both proportional to the concentration of chlorobenzene in air. The molar ratio of urinary chlorocatechol to inhaled chlorobenzene was estimated to be approximately 26%, and the mean slope of regression line for chlorobenzene in air versus blood was 4.6±1.15 µg/L for 1 ppm chlorobenzene. The measured biological half-time of 4-chlorocatechol was 2.9 hours.

Rats were exposed to ^{14}C-chlorobenzene vapor at concentrations of 100, 400, and 700 ppm for 8 hours (Sullivan et al. 1983). The plasma concentration-time profile for chlorobenzene on cessation of exposure, as estimated by respiratory elimination of radioactivity, indicated a two-compartment elimination. Increase in exposure by a factor of 7 (100–700 ppm) increased the total uptake of radioactivity by a factor of about 13. This increase in body burden was associated with a decrease in total body clearance, as indicated by an approximate 4-fold increase in the half-life of the central compartment. The proportion of the dose excreted via the lungs (which may be presumed to be largely, if not entirely, unchanged chlorobenzene) increased nonlinearly and the proportion eliminated by hepatic metabolism decreased. Increase in the dose of chlorobenzene was associated with a decrease in the proportion cleared as the mercapturic acid derivative. Of interest, the half-life of chlorobenzene was shorter at the 700 ppm exposure level when the animals were subjected to repeated exposure daily for 5 days, as compared with that of the single 700 ppm exposure animals, raising the possibility of induction of metabolic clearance. In agreement with this possibility, the proportion cleared by metabolism in the multi-exposed animals was increased, and the proportion excreted unchanged via the lung was decreased, as compared with the 700 ppm-single exposure animals.

In the repeated-dose oral study of rabbits administered [^{14}C]chlorobenzene (Lindsay Smith et al. 1972), total recovery of radioactivity from the urine was approximately 20% of the administered dose. The contributions of the various metabolites in the urine were 33.88% for ethereal sulfates, 33.57% for glucuronides, 23.8% for mercapturic acids, 4.17% for diphenols, 2.84% for monophenols, and 0.57% for 3,4-dihydro-3,4-dihydroxychlorobenzene. It was concluded that the remaining radiolabel was excreted in the expired air. The major urinary metabolites were 4-chlorophenylmercapturic acid and conjugates of 4-chlorocatechol. Other identified urinary metabolites included quinol, 3-chlorocatechol, and 2- and 3-chlorophenylmercapturic acid. Ogata and Shimada (1983) reported that the primary urinary metabolite in rats was 4-chlorophenylmercapturic acid and that 4-chlorocatechol was a minor metabolite.

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.

Thrall et al. (2004) developed a rat PBPK model for chlorobenzene in air using metabolic data derived from groups of F344 male rats exposed to chlorobenzene levels ranging from 82 to 6,750 ppm in air. Physiological values (e.g., breathing rate, organ volumes, etc.) were taken from the literature, and partition coefficients were determined from *in vitro* experiments with rat tissues and blood samples. The finished model was evaluated by using it to predict the chlorobenzene levels in exhaled breath of rats exposed by corn oil gavage (127 mg/kg) or intraperitoneal injection (131 mg/kg).

A PBPK model was developed to estimate the amount of 19 different VOCs that a nursing infant would receive from its occupationally-exposed mother (Fisher et al. 1997). In a simulation of a lactating woman exposed to the threshold limit value (TLV) concentration of chlorobenzene in air at the workplace, the amount of chlorobenzene transferred to a nursing infant from mother's milk was calculated to be 0.229 mg for a 10-kg infant.

3.1.6   Animal-to-Human Extrapolations

A number of differences between humans and various laboratory animal species preclude meaningful extrapolation from animals to humans. Compared to mice and rats, the rate of metabolism of chlorobenzene to soluble metabolites is higher in humans, and the formation of covalently bound products is lower (Nedelcheva et al. 1998). In addition, there is up to a 10-fold difference in the rate of metabolism of chlorobenzene in different human livers. There are also significant species and sex differences in the metabolism of chlorobenzene with markedly higher rates of oxidation in male mice than in male rats and female mice.

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 chlorobenzene are discussed in Section 5.7, Populations with Potentially High Exposures.

No information was located regarding potential differences in susceptibility to chlorobenzene.

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 chlorobenzene 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 chlorobenzene 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 by chlorobenzene 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

Levels of chlorobenzene and its metabolites have been measured in blood, urine, and exhaled air. Levels of 0.05–17 mg/L in the blood and 25–120 µg/L in the urine were detected in samples from residents living near a former toxic chemical dump, while trace amounts were found in exhaled air (Barkley et al. 1980). Yoshida et al. (1986) demonstrated linear correlations between urinary 4-chlorocatechol excretion and airborne exposure of workers to chlorobenzene. These authors suggested that the former might be an effective biomarker of exposure in humans.

Kumagai and Matsunaga (1994, 1995) also found that the major urinary metabolites of chlorobenzene in humans, including 4-chlorocatechol (especially) and 4-chlorophenol, are good biomarkers of recent exposure in workers. The slopes of the regression line for urinary metabolite concentration versus inhalation exposure concentration do appear to vary somewhat between studies, probably because of differences in workloads (active versus at rest) and patterns of exposure (acute versus chronic). Nevertheless, controlled chamber studies with workers have demonstrated that the concentrations of both major urinary metabolites of chlorobenzene correlate well with workers' 8-hour time-weighted average exposure to chlorobenzene and reflect variations in workplace exposure to chlorobenzene (Kumagai and Matsunaga 1995).

In an occupational study by Knecht and Woitowitz (2000), the major urinary metabolite of chlorobenzene was 4-chlorocatechol (74%). The remainder consisted of chlorophenol isomers of which 4-chlorophenol (13%) was the most abundant. In spite of its being <20% as abundant as 4-chlorocatechol, urinary 4-chlorophenol was still considered to be potentially useful as a biomarker of exposure due to its longer half-life (approximately 12 hours). The elimination half-life of urinary 4-chlorocatechol was 6.4 hours.

3.3.2   Biomarkers of Effect

There are no known biomarkers of effect that are specific to chlorobenzene exposure.

3.4   INTERACTIONS WITH OTHER CHEMICALS

In an attempt to identify the proposed epoxide intermediate of chlorobenzene, Oesch et al. (1973) co-administered the epoxide hydrase inhibitor, cyclohexane oxide, together with chlorobenzene to rats. Instead of increasing the toxicity of chlorobenzene as expected, through the inhibition of epoxide hydrase, cyclohexane oxide actually decreased the metabolism of chlorobenzene and its necrotic toxicity on the liver, suggesting that the metabolism of chlorobenzene is partially responsible for its liver toxicity.
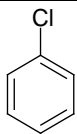
In a mechanistic rat study, a chlorobenzene oral dose of 0.04 mL/180 g (approximately 246 mg/kg) caused extensive liver necrosis in rats pretreated with phenobarbital, but little or none in rats that were that were not pretreated with phenobarbital (Brodie et al. 1971). In another study, the severity of chlorobenzene-induced necrosis was decreased by pretreatment with the microsomal enzyme inhibitor, SKF 525A. The authors concluded that reactive metabolites of chlorobenzene that were formed in the liver may have subsequently reacted with tissue macromolecules (Brodie et al. 1971).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1   CHEMICAL IDENTITY

Data pertaining to the chemical identity of chlorobenzene are listed in Table 4-1.

Table 4-1. Chemical Identity of Chlorobenzene

Characteristic	Information	Reference
Chemical name	Chlorobenzene	NLM 2020
Synonym(s) and registered trade name(s)	Monochlorobenzene; Benzene chloride; Phenylchloride; MCB; Chlorobenzol; Caswell no. 183A	NLM 2020
Chemical formula	C_6H_5Cl	NLM 2020
Chemical structure		NLM 2020
CAS Registry Number	108-90-7	NLM 2020

CAS = Chemical Abstracts Service

4.2   PHYSICAL AND CHEMICAL PROPERTIES

The odor threshold for chlorobenzene in humans has been reported to be as low as 0.21 ppm or 0.97 mg/m^3 (Leonardos et al. 1969). However, others have reported its "almond-like odor" to be "barely perceptible" at 60 ppm (Von Burg 1981; Willhite and Book 1990). The physical and chemical properties of chlorobenzene are presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of Chlorobenzene

Property	Information	Reference
Molecular weight	112.56	Weast 1985
Color	Colorless	Verschueren 1983
Physical state	Liquid	Verschueren 1983
Melting point	-45.6°C	Weast 1985
Boiling point	132°C	Weast 1985
Density at 20°C	1.1058	Weast 1985
Odor	Aromatic, almond-like	Sax and Lewis 1987

Table 4-2. Physical and Chemical Properties of Chlorobenzene

Property	Information	Reference
Odor threshold:	Conflicting data	Leonardos et al. 1969
Water	0.050 mg/L	Verschueren 1983
Air	1–8 mg/m^3	Verschueren 1983
Solubility:		
Water at 20°C	500 mg/L	Verschueren 1983
Organic solvents	Soluble in alcohol, ether, benzene	Weast 1985
Partition coefficients:		
Log K_{ow}	2.84	Verschueren 1983
Log K_{oc}	2.52	EPA 1982
Vapor pressure at 20°C	8.8 mmHg	Verschueren 1983
Henry's law constant at 25°C	3.58×10^{-3} atm-m^3/mol	EPA 1982
Autoignition temperature	637°C	Sax and Lewis 1987
Flashpoint	29.4°C	Sax and Lewis 1987
Flammability limits	1.8–9.6%	Sax and Lewis 1987
Conversion factors	1 ppm=4.7 mg/m^3 1 mg/m^3=0.22 ppm	Verschueren 1983
Explosive limits	1.3-11 vol% in air)	NIOSH 2015

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chlorobenzene has been identified in at least 491 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which chlorobenzene has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 490 are located within the United States, and 1 is located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Chlorobenzene Contamination
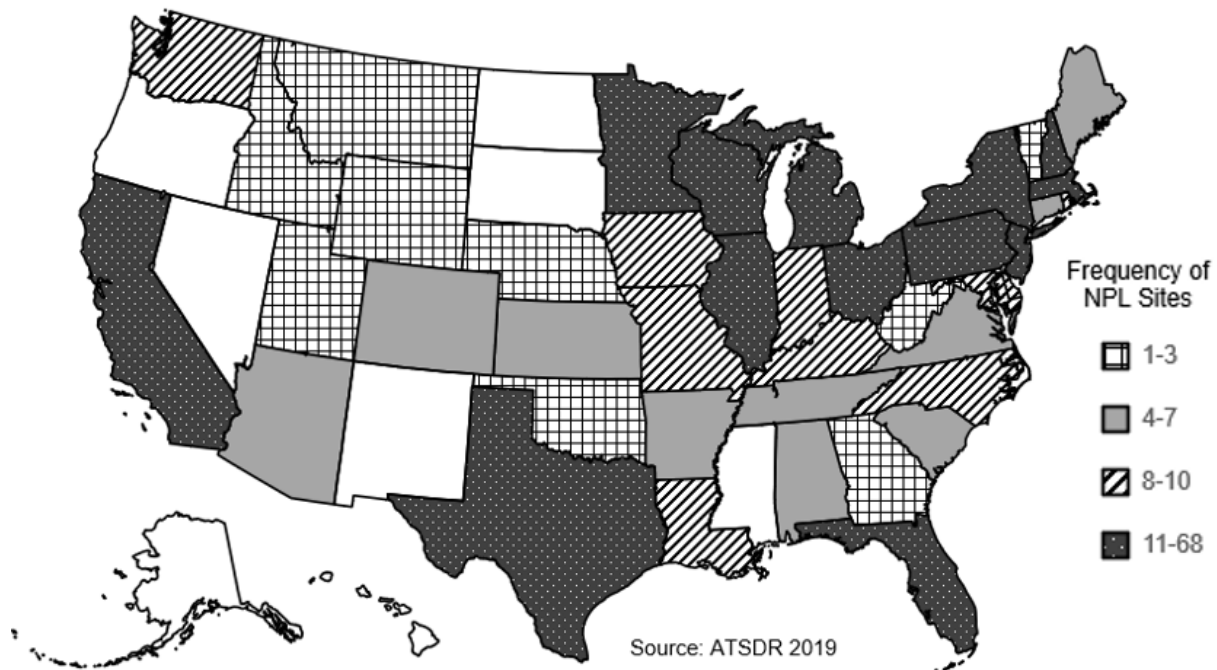
Source: ATSDR 2019

- The most likely sources of potential exposure of the general population to chlorobenzene are from breathing air, drinking water, or eating food that contains chlorobenzene.

- Chlorobenzene has been detected in only very small quantities in air, water, and limited food sources.

- Chlorobenzene degrades rapidly in air, water, and soil; it is not expected to bioconcentrate.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Production of chlorobenzene in the United States declined by nearly 60%, from the peak production volume of 274,000,000 kg in 1960 to 112,000,000 kg in 1987. This decline is attributed primarily to the replacement of chlorobenzene by cumene in phenol production and the cessation of DDT production in the United States. In addition, pesticide production using chlorobenzene as an intermediate has declined and no major new uses have been found for chlorobenzene in recent years. Therefore, the decline in chlorobenzene production is expected to continue (EPA 1980a; Hughes et al. 1983; USITC 1988).

In the 1980s, chlorobenzene was produced by three United States chemical companies: Monsanto Chemical Company, Sauget, Illinois; PPG Industries, Inc., Natrium, West Virginia; and Standard Chlorine Chemical Co., Inc., Delaware City, Delaware. Production capacity for chlorobenzene at these plants remained constant after 1985, although it appeared that actual production declined slightly after 1985 (Hughes et al. 1983; SRI 1985, 1986, 1987, 1988; USITC 1988).

Chlorobenzene is produced commercially by the chlorination of benzene in the presence of a catalyst (e.g., ferric chloride, aluminum chloride, or stannic chloride). This process yields a mixture of chlorobenzene, dichlorobenzenes, and higher analogs, which are distilled and crystallized to obtain pure products (EPA 1985; Hughes et al. 1983).

The Hazardous Substance Data Bank (HSDB) listed the following figures for U.S. production capacity (in lbs/year): 368 million in 1990; 371 million in 1993; 370 million in 1996; 358 million in 1999; and 205 million in 2004; and 52.7 million in 2014 (NLM 2020). Table 5-1 summarizes information on U.S. companies that manufactured or used chlorobenzene in 2018 (TRI18 2020).

Table 5-1. Facilities that Produce, Process, or Use Chlorobenzene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	10,000	99,999	6, 7
AR	4	100	999,999	7, 12
CA	1	100,000	999,999	7, 11
CO	1	10,000	99,999	6, 10

Table 5-1. Facilities that Produce, Process, or Use Chlorobenzene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
GA	1	1,000,000	9,999,999	1, 2, 3, 6, 11
IA	2	100,000	999,999	7, 10
IL	1	1,000	9,999	12
IN	3	100	99,999	9, 12, 14
KS	3	100	999	12
KY	3	10,000	999,999	1, 3, 6, 7, 9
LA	10	0	9,999,999	1, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
MI	3	0	999,999	1, 5, 6, 10, 11, 13, 14
MO	3	1,000	99,999	10, 12
NE	1	100,000	999,999	9, 12
NY	2	100	99,999	10, 12
OH	6	1,000	9,999,999	9, 10, 12, 14
PA	1	1,000	9,999	12
SC	1	0	0	0
TN	2	10,000	99,999	1, 5, 6, 10, 13
TX	16	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
UT	1	100,000	999,999	12
WI	3	0	999,999	6, 7, 12

[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: TRI18 2020 (Data are from 2018)

5.2.2   Import/Export

Import and export data for chlorobenzene are not readily available. Estimates indicated that both imports
and exports were negligible in the late 1970s and early 1980s (Hughes et al. 1983).

From 2002 to 2003, U.S. exports of chlorobenzene declined from 3.5 million to 1.5 million pounds
annually. Imports remained negligible during that time period (NLM 2020; Kirschner 2004).

Current data regarding import and export of chlorobenzene were not located.

5.2.3   Use

Historically, the primary uses of chlorobenzene were as a solvent for pesticide formulations, diisocyanate
manufacture, degreasing automobile parts, and for the production of nitrochlorobenzene and diphenyl
oxide. Solvent uses accounted for about 37% of chlorobenzene consumption in the United States in 1981,
nitrochlorobenzene production for 33%, and diphenyl oxide and phenylphenol production for 16% of
consumption. Chlorobenzene has also been used in silicone resin production and as an intermediate in the
synthesis of other halogenated organics, including DDT (Hughes et al. 1983). Recent data regarding
chlorobenzene uses were not located.

5.2.4   Disposal

Because chlorobenzene is listed as a hazardous substance, disposal of waste chlorobenzene is controlled
by a number of federal regulations. Spent solvent wastes, which may include chlorobenzene, are
prohibited from land disposal, except under specific conditions. Land disposal restrictions (treatment
standards) are proposed for other wastes containing chlorobenzene. Wastes containing chlorobenzene
may be disposed of by liquid injection, rotary kiln, or fluidized bed incineration (EPA 1988, 1989). Since
chlorobenzene is a volatile compound and is used extensively as a solvent, large quantities are released to
the air. Some estimates indicate that 30–50% of the annual production of chlorobenzene is released to the
atmosphere, while <0.1% is found in wastewater and <1% is disposed of on land (EPA 1985).

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 546,112 pounds (~248 metric tons) of chlorobenzene to the atmosphere from
69 domestic manufacturing and processing facilities in 2018, accounted for about 77.94% of the estimated
total environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are
summarized in Table 5-2.

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

							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
AL	1	10	0	0	0	0	10	0	10
AR	4	780	0	0	14	76	780	90	870
CA	1	324	0	0	0	0	324	0	324
CO	1	32	0	0	0	0	32	0	32
GA	1	61,167	0	0	4,564	0	61,167	4,564	65,731
IL	1	1	0	0	13	0	1	13	14
IN	3	164	0	0	580	0	164	580	744
IA	2	800	0	0	0	0	800	0	800
KS	3	1	0	0	0	0	1	0	1
KY	3	533	9	0	0	0	542	0	542
LA	10	206,072	250	130,000	241	207	336,322	448	336,770
MI	3	930	25	0	9	0	955	9	964
MO	3	281	0	0	0	643	281	643	924
NE	1	10	0	0	12	0	10	12	22
NY	2	65	1	0	0	0	65	1	67
OH	6	236,342	360	0	5,683	0	236,452	5,932	242,384
PA	1	64	0	0	0	0	64	0	64
SC	1	0	0	0	0	0	0	0	0
TN	2	422	74	0	20	0	516	0	516
TX	16	30,170	42	9	11,638	85	41,544	400	41,944
UT	1	3	0	0	0	0	3	0	3

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

							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
WI	3	7,942	0	0	0	0	7,942	0	7,942
Total	69	546,112	762	130,009	22,773	1,011	687,974	12,694	700,668

Reported amounts released in pounds per year[b]

[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, wastewater 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: TRI18 2020 (Data are from 2018)

5.3.2 Water

Estimated releases of 762 pounds (~0.35 metric tons) of chlorobenzene to surface water from 69 domestic manufacturing and processing facilities in 2018, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are summarized in Table 5-2.

The principal source of chlorobenzene in water is release from chemical manufacturing facilities. Dow Chemical Company estimated that 0.1% of its annual production entered waters (EPA 1980b). EPA (1979) found chlorobenzene in 6/63 industrial effluent in concentrations up to 100 µg/L. Based on 1,338 samples collected from about 1980 to 1983, the medium concentration of chlorobenzene in waste effluent was <3 ppb and was detected in 54 samples. The total amount released to the environment was not reported (Staples et al. 1985). Chlorobenzene has been detected in both surface and groundwater samples at hazardous waste sites.

5.3.3   Soil

Estimated releases of 22,773 pounds (~10.3 metric tons) of chlorobenzene to soil from 69 domestic
manufacturing and processing facilities in 2018, accounted for about 0.03% of the estimated total
environmental releases from facilities required to report to the TRI (TRI18 2020). Estimated releases of
130,009 pounds (~55 metric tons) of chlorobenzene via underground injection from 69 domestic
manufacturing and processing facilities in 2018, accounted for about 18.56% of the estimated total
environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are
summarized in Table 5-2.

5.4   ENVIRONMENTAL FATE

5.4.1   Transport and Partitioning

The air, undoubtedly, plays a large role in the environmental transport and degradation of chlorobenzene,
although studies addressing this aspect were not found. Chlorobenzene is volatile and has only moderate
solubility in water (500 mg/L). Chlorobenzene was observed to evaporate (>99%) from an unaerated
aqueous solution in 72 hours (Garrison and Hill 1972). Chlorobenzene is considered sufficiently volatile
and toxic to pose inhalation risk via vapor intrusion from soil and groundwater (EPA 2018a).

5.4.2   Transformation and Degradation

Under hypoxic conditions in groundwater, shifts in the bacterial community may occur as a result of
syntrophic interactions rather than competitive interactions, facilitating the degradation of chlorobenzene
(Kiesel et al. 2007). Syntrophy occurs when one organism lives off the product of another organism,
rather than the organism itself.

Air.   Physical constants for chlorobenzene, especially its vapor pressure and water solubility, indicate
that the air is an important, and perhaps the dominant, medium for the transport and transformation of
chlorobenzene. As an aromatic molecule with strong ultraviolet-absorption, chlorobenzene has a half-life
of 20–40 hours under simulated atmospheric conditions (Dilling et al. 1976). This appears to be
confirmed by the large difference between chlorobenzene measurements in urban air (3,000 ng/m^3
[0.66 ppb]) and in rural air (not detected) in 1982 (EPA 1983).

Water.   Biodegradation in a wastewater inoculum was studied by Tabak et al. (1981). Among 57 environmental pollutants tested, chlorobenzene at 5 mg/L (5 ppm) was among the more rapidly biodegraded substances, with 89% degradation in a week and 100% after adaptation. Biodegradation is therefore a major degradation process in oxygenated waters, while evaporation will play an additional role in surface waters.

Few data are available from the field, but evaporation, hydrolysis, and microbial degradation, in that order, are likely to be the major fates of chlorobenzene discharged to water.

Bioconcentration of chlorobenzene does not appear to be a significant process in aquatic environments. However, bioconcentration factors for chlorobenzene do increase somewhat in phytoplankton as temperature increases between 4.5 and 27.6°C (Koelmans and Sanchez 1994).

Oxygen appears to be required for the initial activation of chlorobenzene and the fission of the aromatic ring, although it can be partially replaced by nitrate (Nestler et al. 2007).

Metabolic dechlorination of chlorobenzenes seems to proceed fastest under methanogenic conditions (Adrian and Görisch 2002; Ramanand et al. 1993). While the negative changes in Gibbs free energy associated with all 20 possible dechlorination reactions of chlorobenzenes are large enough to be coupled to adenine triphosphate (ATP) generation, not all of those reactions have been observed in laboratory systems, and the extent to which any of them occurs in nature remains unknown (Adrian and Görisch 2002).

The potential for anaerobic degradation has also been studied in contaminated groundwater plumes, where oxygen levels are generally lower than they are outside the plume. In a study of three North Central Florida landfills, Hallbourg et al. (1992) found that due to the high water table, anaerobic degradation predominated. In a contaminated aquifer in Bitterfeld, Germany, the decreases of chlorobenzene concentrations at the horizontal fringes of the plume and at shallower depths were accompanied by changes in isotopic composition (i.e., enrichment in ^{13}C) that suggested the *in situ* anaerobic degradation of chlorobenzene was occurring, albeit slowly (Kaschl et al. 2005). Since the known aerobic pathway initiated by dioxygenases in chlorobenzene-degrading strains (*Ralstonia* sp. DSM 8910, *Acidovorax facilis* UFZ B517, *Rhodococcus erythropolis* UFZ B528, and *Pseudomonas verinii* UFZ B547) did not result in isotopic fractionation, it was concluded that a novel anaerobic pathway resulting in isotopic fractionation was the predominant process of chlorobenzene degradation in this

aquifer. Chlorobenzene contamination of this aquifer was the likely result of its proximity to a site where lindane had been formerly produced; chlorobenzene was measured at up to 30 ppm. The anaerobic microbial degradation of $[^{13}C_6]$-chlorobenzene was confirmed by Nijenhuis et al. (2007). In a constructed wetland designed to treat contaminated groundwater, Braeckevelt et al. (2007a) observed an isotope shift that was higher than expected for aerobic chlorobenzene degradation and concluded that an anaerobic degradation pathway must be making a significant contribution to the overall degradation. Natural attenuation of ^{13}C-labeled chlorobenzene in this constructed wetland was indicated by: (1) detection of ^{13}C-labeled (i.e., reductively dechlorinated) benzene; (2) incorporation of chlorobenzene-derived radiolabel (^{13}C) into bacterial fatty acids; and (3) a systematic correlation between decreasing chlorobenzene concentration and significant enrichment in ^{13}C with increasing distance from the source of contamination (Braeckevelt et al. 2007b).

Sediment and Soil.   Biodegradation of chlorobenzene is rapid, leaving no detectable residues after 1 or 2 weeks. Adaptation is also rapid (Tabak et al. 1981).

Evaporation and microbial degradation, in that order, are likely to be the major fates of chlorobenzene in soils. However, very few data are available from the field. Most relevant information comes from laboratory studies on amended soils and strains of soil bacteria isolated from contaminated water, soil, or sediments.

Under aerobic conditions, all 15 volatile and semivolatile organic compounds (including chlorobenzene) in a soil-applied mixture disappeared rapidly during a 7-day observation period due to abiotic factors (Anderson et al. 1991). Feidieker et al. (1995) documented the aerobic degradation of chlorobenzene with mixed bacterial cultures. Complete metabolism of chlorinated benzenes is not a feature that is generally found in aerobic bacteria. However, at chlorobenzene-contaminated sites, indigenous bacteria populations appear able to evolve the capacity for natural attenuation of chlorobenzene (Van der Meer et al. 1998). *Pseudomonas putida* MST that was previously isolated in the presence of α-methylstyrene was shown to regioselectively hydroxylate chlorobenzene to 3-chlorocatechol, and 2- and 4-chlorophenol to 3- and 4-chlorocatechol, respectively (Bestetti et al. 1992). Inoculation of a soil slurry with *Pseudomonas aeruginosa* (105 microbes/g soil) led to rapid and complete degradation of 0.8 mM chlorobenzene within 30 hours (Brunsbach and Reineke 1994). Indigenous soil microbes also degraded chlorobenzene, but the higher chlorobenzenes persisted.

Chlorobenzene contamination of soil stimulates the growth of indigenous, chlorobenzene metabolizing bacteria. The latter may even out-compete inoculated strains of *Pseudomonas* (Nishino et al. 1994).

In an *in vitro* study, Nowak et al. (1996) demonstrated the total reductive dechlorination of chlorobenzenes by a methanogenic culture enriched from Saale River sediment. Dechlorination of chlorobenzene to benzene was also observed in these cultures. However, the amount of benzene formed was extremely low and the reaction occurred only in the presence of higher chlorinated benzenes (Nowak et al. 1996). Presumably, this was a co-metabolic process (i.e., one in which the metabolism of chlorobenzene occurred without benefit to the organism), but was co-incident with the metabolism of the substrate on which the microbe actually depended for energy production. Such reactions are useful in bioremediation because they can proceed at concentrations far below those required to support the organism (Hazen 2009).

As previously documented in the field for pesticides and other contaminants, the residue of chlorobenzene in soil that is not volatilized or metabolized tends to bind more tightly to soil with time, a phenomenon known as "aging" (Sharer et al. 2003). As a result, degradation occurs at lower rates and to a lesser extent, even though chlorobenzene-degrading bacteria still have access to sorbed chlorobenzene in aged wetland soils (Lee et al. 2009).

The reductive dechlorination of chlorobenzenes in an anaerobic estuarine sediment followed first-order reaction kinetics, with rate constants ranging from 0.0016 to 0.0389 day^{-1} or half-lives between 17 and 433 days (Kochany and Boltob 1992; Masunaga et al. 1996). From the detected intermediates, it was apparent that the removal of chlorine atoms occurred at all possible positions on the aromatic ring, but removal followed a thermodynamically favored order (i.e., a chlorine atom flanked on both sides by another > one of two adjacent chlorine atoms > a chlorine with no adjacent chlorine atoms) (e.g., the dechlorination of chlorobenzene) (Masunaga et al. 1996).

Other Media. No studies on the transformation or degradation of chlorobenzene in food or other media were located.

5.5   LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chlorobenzene depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens.

Concentrations of chlorobenzene 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 chlorobenzene 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	0.47 ppt	Krost et al. 1982
Drinking water	0.01 µg/L (ppb)	NEMI 2019
Surface water and groundwater	0.003 µg/L (ppb)	NEMI 2019
Soil	0.003 µg/L (ppb)	NEMI 2019
Sediment	0.002 ng/mL (ppb)	Wolska et al. 2003
Whole blood	0.011 ng/mL (ppb)	CDC 2018

[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 Chlorobenzene

Media	Low	High	For more information
Outdoor air (ppbv)	<0.05	0.50	Section 5.5.1
Surface water (ppb)	<0.01	10	Section 5.5.2
Ground water (ppb)	<1	<5	Section 5.5.2
Drinking water (ppb)	No data		Section 5.5.2
Food (ppb)	<2	13	Section 5.5.4
Soil (ppb)		<5 (median value)	Section 5.5.3

Detections of chlorobenzene in air, water, and soil at NPL sites are summarized in Table 5-5.

Table 5-5. Chlorobenzene 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)	38	73.5	23.4	215	127
Soil (ppb)	1,550	1,780	84.9	92	64
Air (ppbv)	1.92	2.66	35.2	28	19

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). 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

Air samples at 56 localities in the United States in 1982 showed mean chlorobenzene concentrations of 0.24 ppb (EPA 1983). The highest concentration measured concentrations were in urban and suburban areas; the median concentration in these areas were 0.33 ppb. Chlorobenzene was not detectable in rural and remote areas. The median concentration at the sites of production was 0.03 ppb. EPA (1981) measured average concentrations of chlorobenzene of 0.309, 0.240, and 0.290 ppb in Houston, Texas, St. Louis, Missouri, and Denver, Colorado, respectively, with a calculated residence time of 13 days. Data collected from three urban sites in New Jersey from 1981 to 1982 contained mean chlorobenzene concentrations of ranging from 0.07 to 0.22 ppb (Harkov et al. 1987). A study of New Jersey waste sites found similar air levels of chlorobenzene (mean values of 0.05–0.80 ppb) (Harkov et al. 1985). However, air levels found by another study performed for the EPA (1978) were an order of magnitude lower, with only the air over a waste site approaching the mean urban concentrations reported above.

Ambient air outside homes of "Old Love Canal" (Niagara Falls, New York) contained chlorobenzene ranging from not detectable at four sites to traces at four sites and 120 ng/m^3 (0.026 ppb) at one site (Barkley et al. 1980). Corresponding indoor air concentrations of chlorobenzene were not detected at six sites and ranged from 60–600 ng/m^3 (0.0013–0.13 ppb) at the remaining three sites (Barkley et al. 1980). In an air sampling study in West Virginia (Cohen et al. 1989), chlorobenzene was not detected in outdoor air samples; however, corresponding indoor air concentrations of chlorobenzene were reported at mean, median, and maximum values of 16.5, 5.62, and 72.22 µg/m^3, respectively (3.62, 1.23, and 15.8 ppb), in 63% of homes evaluated.

5.5.2   Water

Historically, chlorobenzene was found in U.S. rivers at levels up to and exceeding 10 µg/L (10 ppb) (EPA 1976; Sheldon and Hites 1978). Private wells near a hazardous waste site contained as much as 41 µg/L (41 ppb) (Clark et al. 1982) and tap water at Love Canal contained concentrations ranging from 10 to 60 ng/L (0.01–0.06 ppb) (Barkley et al. 1980). Of 2,401 groundwater samples from domestic wells and 1,096 samples from public wells in a survey in the United States, >90% of the chlorobenzene concentrations were <1 ppb and none were as high as 5 ppb (USGS 2006).

Chlorobenzene was not detected in thousands of surface water and groundwater samples collected across the United States from 2016 to 2020 (WQP 2020). The highest concentration of chlorobenzene in landfill leachate samples collected during this time period was 6.09 ppb (WQP 2020). Chlorobenzene was not found in the limited number of storm water samples reported (WQP 2020).

A risk assessment on chlorobenzene for the marine environment (the North Sea area) was conducted in which "risk" was indicated by the ratio of predicted environmental concentration (PEC) to the predicted no-effect concentration (PNEC) (set to 32 µg/L [ppb]) for the marine aquatic environment (Van Wijk et al. 2004). Since monitoring data indicated that chlorobenzene in surface waters was below the detection limits of 0.1, 0.2, and 0.5 µg/L (ppb), the worst-case PEC was assumed to be 0.5 µg/L (ppb), yielding a PEC/PNEC of at least 60, without even taking into account dilution of chlorobenzene-containing surface waters in the sea. The authors concluded that chlorobenzene is not a toxic, persistent, or bioaccumulating substance, and that current use of the compound posed no unacceptable risk to the aquatic environment (Van Wijk et al. 2004).

5.5.3   Sediment and Soil

Staples et al. (1985) reported that the median concentration of chlorobenzene in the United States was estimated to be <5 ppb dry sediments. In more than 3,000 sediment data points compiled from Storage and Retrieval (STORET) Data Warehouse and the National Water Information System (NWIS), chlorobenzene was not detected in over 82%, was reported at less than the detection limit in about 18%, and was found above the detection limit in about 0.4% (WQP 2020).

5.5.4   Other Media

A national survey of the United States indicated that chlorobenzene was below detection limits in milk supplies (Schaum et al. 2003). VOCs were analyzed in 70 food types over a 5-year period, of the 41 types reported, chlorobenzene was identified in nine (cheddar cheese, chocolate cake with frosting, carbonated cola beverage, chocolate chip cookies, sour cream, French fries, cheese and pepperoni pizza, sugar cookies, cake doughnuts with icing) at concentrations ranging from 2 to 13 ppb (Fleming-Jones and Smith 2003).

5.6   GENERAL POPULATION EXPOSURE

Chlorobenzene was found in 96% of human adipose tissue samples from all regions of the United States at levels ranging from 1 to 9 ng/g (EPA 1986). At Love Canal, Niagara Falls, chlorobenzene was detected in the breath of one of nine people evaluated for exposure and in the urine of six of nine persons at concentrations ranging from 20 to 120 ng/L (Barkley et al. 1980).

Personal sampling at chemical companies (NIOSH 1981) indicated that chlorobenzene levels, measured at up to 4 ppm in workplace air did not exceed the American Conference of Governmental Industrial Hygienists (ACGIH) and Occupational Safety and Health Administration (OSHA) permissible limit of 75 ppm.

According to the results of the National Health and Nutrition Examination Survey (NHANES), chlorobenzene was undetectable in blood samples of every age group, gender, race, and ethnicity studied in the survey years between 2003 and 2016 (CDC 2019). The detection limit was 0.011 ng/mL.

Vapor intrusion may also be a potential source of chlorobenzene exposure, as vapor intrusion has been observed for several VOCs with similar properties. EPA's compilation of six studies of background indoor air concentrations found a 0–8% detection rate for chlorobenzene in 1,050 U.S. resident samples between 1997 and 2004 (EPA 2011). The background medians ranged from <0.01 to <0.92 $\mu g/m^3$ and the maximum values ranged from 0.04 to 9.7 $\mu g/m^3$. ATSDR extracted environmental data from 135 ATSDR reports evaluating the vapor intrusion pathway at 121 sites published between 1994 and 2009 (Burk and Zarus 2013). The levels of chlorobenzene did not exceed comparisons values (concentrations used by ATSDR to identify contaminants requiring further evaluation).

Chlorobenzene in water is expected to volatilize; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information, along with human activity patterns, is used to calculate a daily time-weighted average exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov.

5.7   POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational settings provide the greatest potential for high exposures to chlorobenzene. Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1980 to 1983, indicated that 18,050 workers, including 3,881 women, in 912 plants spanning 35 occupations were potentially exposed to chlorobenzene in the workplace (NIOSH 2018a). Since chlorobenzene is a volatile compound and is used extensively as a solvent, large quantities may be released to the workplace air. Other populations that might be exposed include persons living near industrial facilities where chlorobenzene emissions are not properly controlled.

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 chlorobenzene 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 chlorobenzene.

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 chlorobenzene 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 chlorobenzene. 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.

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 Chlorobenzene By Route and Endpoint*

Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined inhalation or oral exposure in animals; limited data were identified for humans (counts represent studies examining endpoint)

	Inhalation Studies	Oral Studies	Dermal Studies
Body weight	9	8	—
Respiratory	—	—	—
Cardiovascular	—	—	—
Gastrointestinal	—	—	—
Hematological	3	2	—
Musculoskeletal	—	—	—
Hepatic	6	1 6	—
Renal	4	6	—
Dermal	—	—	—
Ocular	2	—	—
Endocrine	—	—	—
Immunological	—	2	—
Neurological	2 2	1	—
Reproductive	1	—	—
Developmental	4	1	—
Other Noncancer	—	—	—
Cancer	—	1	—

*Includes studies discussed in Chapter 2; many studies examined more than one endpoint. The number of studies include those finding no effect. No dermal studies in humans or animals were located.

6. ADEQUACY OF THE DATABASE

Acute-Duration MRLs. No information is available on the health effects of acute-duration exposure of humans to chlorobenzene by any route of exposure. Limited studies that evaluated the health effects of acute-duration inhalation or oral exposure to chlorobenzene found adverse effects only at exposure levels that also caused lethality (Monsanto Co. 1977; NTP 1985; Rozenbaum et al. 1947; Shell Oil Co. 1991). Since data on health effects in humans are not available and animal data are mostly limited to lethality, data are not sufficient to derive acute-duration MRLs. Further studies would be useful to identify target tissues and threshold levels for health effects that may exist.

Intermediate-Duration MRLs. No studies are available in humans on the health effects of intermediate-duration exposure to chlorobenzene by any route. Available animal studies identify the nervous system, liver, and kidneys as targets of chlorobenzene toxicity. Oral data were considered adequate to derive an intermediate-duration oral MRL for chlorobenzene. Additional animal studies could be designed to provide useful information to serve as the basis for deriving an intermediate-duration inhalation MRL for chlorobenzene.

Chronic-Duration MRLs. Limited studies are available on the health effects in humans chronically exposed to chlorobenzene via inhalation and suggest that the nervous system is a target tissue. Specific exposure data were not provided. No information is available on effects of chlorobenzene in humans following chronic oral exposure. No information is available regarding health effects of chlorobenzene in animals following chronic-duration inhalation exposure. One 2-year oral toxicity and carcinogenicity study of rats gavaged with chlorobenzene at 60 or 120 mg/kg/day reported decreased survival and increased incidences of neoplastic liver lesions at 120 mg/kg/day in the absence of other signs of exposure-related adverse effects (NTP 1985). There were no signs of adverse effects in mice similarly treated at 30 or 60 mg/kg/day (males) or 60 or 120 mg/kg/day (females) (NTP 1985). No nonlethal or nonneoplastic effects were observed in rats or mice following chronic-duration oral exposures at doses resulting in adverse nonneoplastic effects in animals following intermediate-duration exposures. Results from intermediate-duration oral exposure to chlorobenzene indicate that dogs are more sensitive than rats or mice to chlorobenzene-induced adverse liver and kidney effects. The absence of chronic-duration oral data for dogs precludes derivation of a chronic-duration oral MRL for chlorobenzene. A well-designed chronic-duration oral study in dogs could potentially serve as the basis for deriving a chronic-duration oral MRL for chlorobenzene.

Health Effects.

Hematological Effects. No data were located regarding the potential for chlorobenzene-induced renal effects in humans. Limited animal data are available. One study reported concentration-related effects on RBC parameters (primarily an increase in reticulocyte count) in rats and rabbits repeatedly exposed to chlorobenzene by inhalation (NIOSH 1977). Slight leukopenia and lymphocytosis were reported in mice repeatedly exposed by inhalation; however, limited details were included in the study report (Zub 1978). Additional studies could be designed to evaluate hematological effects in animals exposed to chlorobenzene.

Hepatic Effects. Available information regarding the potential for chlorobenzene-induced hepatic effects in humans is limited to a single case report (Babany et al. 1991; Reygagne et al. 1992). The liver was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure (Monsanto Co. 1967a, 1967b; Nair et al. 1987; NTP 1985). No further animal studies are considered necessary.

Renal Effects. No data were located regarding the potential for chlorobenzene-induced renal effects in humans. The kidney was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure (Monsanto Co. 1967a; Nair et al. 1987; NTP 1985). No further animal studies are considered necessary.

Immunotoxicity. No data were located regarding the potential immunotoxicity of chlorobenzene in humans. Histological examination of organs and tissues of the immunological system in orally-treated rats and mice resulted in some evidence for the immunotoxicity of chlorobenzene (NTP 1985). Immune function tests would provide a better assessment of potential immunotoxic effects.

Neurotoxicity. Limited data in humans indicate that exposure to chlorobenzene via inhalation and oral exposures can result in effects on the nervous system. Results from one acute-duration (30-minute exposure) inhalation study of rats and guinea pigs demonstrate the neurotoxicity of inhaled chlorobenzene at very high concentrations ($\geq$2,990 ppm) (Shell Oil Co. 1991). Oral studies in animals could be designed to evaluate the potential neurotoxicity of chlorobenzene by this exposure route. However, it is not likely that oral exposure to chlorobenzene would cause neurological effects at environmentally-relevant exposure levels.

Reproductive Toxicity. No studies were located regarding the potential reproductive toxicity of chlorobenzene in humans. In a 2-generation oral toxicity study of rats (Nair et al. 1987), chlorobenzene gavage exposure of parental males for 18–20 weeks at 450 mg/kg/day resulted in increased incidence of testicular germinal epithelial degeneration, but no evidence of impaired reproductive function. There was no evidence of adverse reproductive effects among chlorobenzene-treated parental females of either generation at doses as high as 450 mg/kg/day. Additional animal studies (including another animal species) could provide additional information regarding the potential for chlorobenzene-induced reproductive effects.

Developmental Toxicity. No data were located regarding the potential developmental toxicity of chlorobenzene in humans. Chlorobenzene did not affect the developing fetus following inhalation exposure of rats or rabbits (John et al. 1984) or oral exposure of rats (Monsanto Co. 1977). Additional studies, particularly in other species, could provide useful information for evaluating the potential of chlorobenzene to induce developmental effects in humans.

Cancer. No studies were found in humans regarding the carcinogenicity of chlorobenzene. Epidemiological studies would be useful to assess potential risk to people who may be occupationally exposed to chlorobenzene or people who live near hazardous waste sites where chlorobenzene may be present. There was no evidence for carcinogenicity in male or female mice or in female rats following oral exposure to chlorobenzene. However, an increased incidence of neoplastic liver nodules was observed in male rats. Based on available information from animal carcinogenicity studies and genotoxicity evaluations, EPA (IRIS 2003) assigned chlorobenzene to group D (not classifiable as to human carcinogenicity). An additional animal study could be designed to further assess the potential carcinogenicity of chlorobenzene. Although available human and animal data have not provided convincing evidence regarding the carcinogenicity of chlorobenzene, additional mechanistic studies should be designed to evaluate possible genotoxic mechanisms of carcinogenicity because chlorobenzene metabolism results in the formation of epoxides that can react with DNA, RNA, and proteins. Any *in vitro* assays should be performed using human microsomes due to interspecies differences in chlorobenzene metabolism.

Epidemiology and Human Dosimetry Studies. No epidemiological studies have been conducted to evaluate the adverse health effects of chlorobenzene. Existing studies are limited to case reports of

occupational exposures in which the nervous system was identified as a target tissue following chronic inhalation of chlorobenzene. Reliable exposure data were not reported. Additional studies that provide quantitative exposure data would be useful in evaluating potential noncancer and cancer risk in humans exposed to chlorobenzene.

Biomarkers of Exposure and Effect. Parent chlorobenzene and metabolites can be detected in biological tissues and fluids. However, existing methods may not be useful for evaluating the general population as opposed to industrial situations where preexposure levels are established prior to known chlorobenzene exposure. The overall reliability of these biomarkers are further reduced since data are not available on the half-life of chlorobenzene in various biological media.

Central nervous system injury is a common effect associated with exposure to chlorobenzene vapor in humans. Studies in animals suggest that chlorobenzene can also result in damage to the liver and kidneys. Since similar effects occur with exposure to other chemicals, additional studies are needed to identify more specific biomarkers by which to monitor populations living near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of chlorobenzene have not been evaluated to any great extent in humans. Limited studies suggest that chlorobenzene can be absorbed following inhalation and oral exposures, but no data were located regarding absorption following dermal exposure. Based on absorption characteristics of benzene and the high lipid solubility of chlorobenzene, absorption may be significant depending on conditions. Additional studies are needed to determine absorption rates following exposure by all routes.

Data are also sparse on the distribution of chlorobenzene. No information is available regarding distribution of chlorobenzene in humans by inhalation, oral, or dermal exposure. Limited animal data suggest preferential distribution to adipose tissue in rats via inhalation. The kidneys and liver also showed significant amounts of chlorobenzene and rats that received multiple doses exhibited higher tissue burdens than rats exposed only once.

The metabolic transformation of chlorobenzene has been evaluated in humans and animals. Principal metabolites have been determined, but quantities and ratios differ among species. Additional studies would be useful to determine if these differences affect the toxicity of chlorobenzene.

There are limited data on the excretion of chlorobenzene. In humans exposed via the inhalation and oral routes, chlorobenzene and its metabolites were detected in urine and there were differences in excretion patterns via the two routes. Chlorobenzene and its metabolites were also detected in exhaled air of rats following inhalation and in exhaled air and urine of rabbits after oral exposure. The urinary metabolite profile appeared to be dose dependent and there were changes in excretion patterns due to multiple versus single exposures. No data on excretion following dermal exposure are available. Additional studies would be useful in determining the significance of these differences with regard to risk associated with different routes of exposure.

Comparative Toxicokinetics. Although existing studies regarding toxicokinetics of chlorobenzene in humans are limited, available data provide some understanding of the absorption, metabolism, and excretion following inhalation and oral exposures. Since studies on distribution of chlorobenzene are lacking, quantitative data correlating human exposure and tissue accumulation would be useful. In animals, quantitative data on absorption, distribution, metabolism, and excretion are very limited in extent and quality. Additional studies using a variety of species and including PBPK modeling would be useful in determining the most suitable animal model for assessing human risk.

Children's Susceptibility. No data were located to suggest age-related differences in susceptibility to chlorobenzene toxicity. Studies are needed to assess the susceptibility of children to chlorobenzene toxicity and to evaluate potential differences in sensitive endpoints.

Physical and Chemical Properties. Physical and chemical properties of chlorobenzene have been adequately evaluated.

Production, Import/Export, Use, Release, and Disposal. Data indicate that chlorobenzene production has declined dramatically over the past two decades, but current quantitative data on use (especially solvent uses) and disposal practices would be helpful in evaluating the effect of current industrial practices on environmental levels of chlorobenzene.

Environmental Fate. Information on biodegradation in soil under aerobic conditions exists, but degradation products were not identified. Anaerobic biodegradation, as might occur in river bottoms and in Superfund sites, has not been studied and would be valuable. Emissions from waste lagoons have been modelled and measured in bench-top experiments and are measured as part of many Superfund Remedial Investigation/Feasibility studies, but those were not located.

Bioavailability from Environmental Media. Chlorobenzene is absorbed primarily following inhalation of contaminated air. There is also some potential for exposure from water and soil. Chlorobenzene has been detected at low levels in surface water, groundwater, drinking water, and food. Since chlorobenzene binds tightly to soil particles, skin contact with, or ingestion of, contaminated soil may be an important source of exposure, particularly in children living near hazardous waste sites. Additional studies would be useful to determine if soil-bound chlorobenzene is bioavailable. There is also potential for inhalation exposure via vapor intrusion from soil and groundwater and during showering.

Food Chain Bioaccumulation. No information is available regarding biomagnification within aquatic or terrestrial food chains. Additional studies would be useful in assessing potential for human exposure to chlorobenzene.

Exposure Levels in Environmental Media. There are studies on concentrations of chlorobenzene in air and water, but many of the samples measured had low levels or did not have detectable levels. Additional studies using more sensitive analytical methods would be useful for measuring low levels of chlorobenzene in environmental media.

Exposure Levels in Humans. Chlorobenzene can be measured in blood, urine, and exhaled air. A survey of the general population (NHANES) did not find detectable levels of chlorobenzene in blood samples. Chlorobenzene is used in various occupational settings; however, there are limited biomonitoring data of populations potentially exposed to high levels of chlorobenzene. Additional studies are needed to evaluate occupational populations.

Exposures of Children. No data were located to suggest age-related differences in potential exposure to children. Studies are needed to evaluate potential exposure risks that are unique to children.

Analytical Methods. As noted previously, many environmental samples have undetectable levels of chlorobenzene. Additional studies to evaluate analytical methods with lower detection limits would be useful.

6.3   Ongoing Studies

No ongoing studies were identified in the National Institutes of Health (NIH) RePORTER (2020) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding chlorobenzene 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 referring to 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 chlorobenzene.

Table 7-1. Regulations and Guidelines Applicable to Chlorobenzene

Agency	Description	Information	Reference
Air			
EPA	RfC	Not evaluated	IRIS 2003
	Provisional Peer Reviewed Toxicity Value		EPA 2006
	Provisional chronic RfC	$5x10^{-2}$ mg/m^3 (0.01 ppm)	
	Provisional subchronic RfC	$5x10^{-1}$ mg/m^3 (0.1 ppm)	
WHO	Air quality guidelines	Not listed	WHO 2010
Water & Food			
EPA	Drinking water standards and health advisories		EPA 2018b
	1-Day health advisory (10-kg child)	4 mg/L	
	10-Day health advisory (10-kg child)	4 mg/L	
	DWEL	0.7 mg/L	
	Lifetime health advisory	0.1 mg/L	
	10^{-4} Cancer risk	No data	
	National primary drinking water regulations		EPA 2009
	MCL	0.1 mg/L	
	PHG	0.1 mg/L	
	RfD	$2x10^{-2}$ mg/kg/day	EPA 2018b; IRIS 2003
	Provisional Peer Reviewed Toxicity Value		EPA 2006
	Provisional subchronic RfD	$7x10^{-2}$ mg/kg/day	
WHO	Drinking water quality guidelines	Guideline value not established	WHO 2017
FDA	Substances Added to Food[a]	Not listed	FDA 2020
	Allowable level in bottled water	0.1 mg/L	FDA 2017

Table 7-1. Regulations and Guidelines Applicable to Chlorobenzene

Agency	Description	Information	Reference
Cancer			
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	D[b]	IRIS 2003
IARC	Carcinogenicity classification	No data	IARC 2020
Occupational			
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	75 ppm (350 mg/m^3)	OSHA 2019a, 2019b, 2019c
NIOSH	REL (up to 10-hour TWA)	No data[c]	NIOSH 2019
	IDLH	1,000 ppm	NIOSH 1994
Emergency Criteria			
EPA	AEGLs-air		EPA 2018c
	AEGL 1[d]		
	10-minute	10 ppm	
	30-minute	10 ppm	
	60-minute	10 ppm	
	4-hour	10 ppm	
	8-hour	10 ppm	
	AEGL 2[d]		
	10-minute	430 ppm	
	30-minute	300 ppm	
	60-minute	150 ppm	
	4-hour	150 ppm	
	8-hour	150 ppm	
	AEGL 3[d]		
	10-minute	1,100 ppm	
	30-minute	800 ppm	
	60-minute	400 ppm	
	4-hour	400 ppm	
	8-hour	400 ppm	
DOE	PACs-air		DOE 2018a
	PAC-1[e]	10 ppm	
	PAC-2[e]	150 ppm	
	PAC-3[e]	400 ppm	

[b]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group D: not classifiable as to human carcinogenicity.
[c]After reviewing available published literature, NIOSH provided comments to OSHA on August 1, 1988, regarding the "Proposed Rule on Air Contaminants" (29 CFR 1910, Docket No. H-020). In these comments, NIOSH questioned whether proposed PELs for certain chemicals including chlorobenzene (TWA 75 ppm) were adequate to protect workers from recognized health hazards (NIOSH 2018b).

7. REGULATIONS AND GUIDELINES

Table 7-1. Regulations and Guidelines Applicable to Chlorobenzene

Agency	Description	Information	Reference

[d]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018d).
[e]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; 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; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MCL = maximum contaminant level; 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; PHG = public health goal; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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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 Office of Innovation and Analytics, Toxicology Section, 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 Office of Innovation and Analytics, Toxicology Section, 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***:** Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: Available information regarding adverse effects following acute-duration inhalation exposure to chlorobenzene is limited to evaluations of lethality (Rozenbaum et al. 1947), developmental toxicity studies of rats and rabbits in which no adverse effects were observed at exposure concentrations as high as 590 ppm (John et al. 1984), and a study that evaluated effects of a single 30-minute exposure at 2,990–7,970 ppm (Shell Oil Co. 1991).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: Available information regarding the effects of intermediate-duration inhalation exposure to chlorobenzene is limited. Chlorobenzene exposure-related liver effects (increased liver weight and increased incidence of hepatocellular hypertrophy) and kidney effects (renal lesions including chronic interstitial nephritis and foci of regenerative epithelium) were reported for two generations of parental male (but not female) rats repeatedly exposed to chlorobenzene vapor at 150 ppm (NOAEL of 50 ppm) for 18–20 weeks (Nair et al. 1987). NIOSH (1977) reported significantly increased relative liver and kidney weights 31 and 13%, respectively, greater than controls) among rats (but not rabbits) repeatedly exposed to chlorobenzene vapor for up to 24 weeks at 250 ppm; however, there were no increased incidences of exposure-related histopathological liver or kidney lesions. Similar exposure of rabbits resulted in no significant changes in liver or kidney weight and no evidence of exposure-related increased incidence of histopathological liver or kidney lesions. No effects on liver or kidney were noted among dogs repeatedly exposed to chlorobenzene vapor at concentrations as high as 453.2 ppm for up to 6 months (Monsanto Co. 1980). No data were located to support the findings of liver and kidney effects in the 2-generation study of rats (Nair et al. 1987) at exposure levels as low as 150 ppm. No intermediate-duration inhalation MRL was derived for chlorobenzene because intermediate-duration inhalation studies of rats and rabbits (NIOSH 1977) and dogs (Monsanto Co. 1980) did not identify effects on liver or kidney at exposure levels approximately 2–3 times higher than the LOAEL of 150 ppm for parental male rats of the 2-generation study (Nair et al. 1987).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

*Chemical Name***:**   Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No exposure-response human or animal data are available for the chronic-duration inhalation exposure to chlorobenzene.

Agency Contacts (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

*Chemical Name***:**   Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: Limited studies that evaluated the effects of acute-duration oral exposure to chlorobenzene found adverse effects only at doses that also caused lethality (Monsanto Co. 1977; NTP 1985).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL   0.07 mg/kg/day
Critical Effect: Hepatic effect; bile duct hyperplasia
Reference: Monsanto Co. 1967a
Point of Departure: $BMDL_{10}$ of 9.59 mg/kg ($BMDL_{ADJ}$ of 6.85 mg/kg/day)
Uncertainty Factor: 100
LSE Graph Key: 9
Species: Dog

MRL Summary: An intermediate-duration oral MRL of 0.07 mg/kg/day was derived for chlorobenzene based on dose-related hepatic changes (bile duct hyperplasia) in dogs treated orally (via capsule) with chlorobenzene 5 days/week for 13 weeks (Monsanto Co. 1967a). The MRL is based on a $BMDL_{10}$ of 9.59 mg/kg, which was adjusted to continuous duration exposure to a $BMDL_{ADJ}$ of 6.85 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). 1967a

Selection of the Critical Effect: There are no intermediate-duration oral studies in humans. Several intermediate-duration oral studies are available for rats or mice treated with chlorobenzene by gavage (Monsanto Co. 1967b; NTP 1985) or dogs treated via capsule (Monsanto Co. 1967a). NOAELs and LOAELs identified in these studies are summarized in Table A-1. The effects observed at the lowest LOAEL (55 mg/kg/day for liver and kidney effects in dogs) were considered to represent the critical effects for deriving an intermediate-duration oral MRL for chlorobenzene.

Table A-1. Intermediate-Duration Oral NOAELs and LOAELs for Chlorobenzene

Species (dosing)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight				
Rat (GO, 5 days/week)	125	250	12% lower mean final body weight in males	NTP 1985
Mouse (GO, 5 days/week)	125	250	15–20% lower mean final body weight	NTP 1985
Dog (C, 5 days/week)	55	280	Emaciation, weight loss at lethal dose	Monsanto Co.1967a
Rat (GO, 7 days/week)	250			Monsanto Co. 1967b
Hematological				
Dog (C, 5 days/week)	55	280	Low hemogram, increased numbers of immature WBCs	Monsanto Co. 1967a
Rat (GO, 7 days/week)	250			Monsanto Co. 1967b

Table A-1. Intermediate-Duration Oral NOAELs and LOAELs for Chlorobenzene

Species (dosing)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic				
Dog (C, 5 days/week)	28	55	22% increased liver weight, bile duct hyperplasia (2/4 males)	Monsanto Co. 1967a
Rat (GO, 5 days/week)	60	125	19% increased liver weight in females (LOAEL of 250 mg/kg in males)	NTP 1985
Mouse (GO, 5 days/week)	60	125	14% increased liver weight in males	NTP 1985
		250	Hepatic necrosis/degeneration in males and females	
Rat (GO, 7 days/week)	100	250	27–29% increased mean relative liver weight	Monsanto Co. 1967b
Renal				
Rat (GO)	100	250	13–14% increased kidney weight	Monsanto Co. 1967b
Mouse (GO, 5 days/week)	125	250	Renal necrosis/degeneration	NTP 1985
Dog (C, 5 days/week)	55	280	Increased kidney weight; tubule dilatation, vacuolation, epithelial degeneration	Monsanto Co. 1967a
Rat (GO, 5 days/week)	250	500	13–15% increased kidney weight	NTP 1985
Immunological				
Mouse (GO, 5 days/week)	125	250	Lymphoid depletion/necrosis in thymus and spleen; myeloid depletion in bone marrow in males; lymphoid depletion/necrosis in spleen in females	NTP 1985
Rat (GO, 5 days/week)	500	750	Myeloid depletion in bone marrow, lymphoid depletion in spleen	NTP 1985

C = capsule administration; GO = gavage in oil; LOAEL = lowest-observed-adverse-effect-level; NOAEL = no-observed-adverse-effect level; WBC = white blood cell

Selection of the Principal Study: The study of Monsanto Co. (1967a) was selected as the principal study for deriving an intermediate-duration oral MRL for chlorobenzene because it identified the lowest LOAEL of 55 mg/kg/day for increases in liver and kidney weight and increased incidences of histopathologic liver and kidney lesions in chlorobenzene-treated dogs (see Table A-1).

Summary of the Principal Study:

Monsanto Co. 1967a. 13-Week oral administration- dogs. Monochlorobenzene final report. Monsanto Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0200587. 877800212. 8DHQ10780212.

Groups of beagle dogs (4/sex/group) were treated with chlorobenzene orally (in capsule) at 0, 0.025, 0.05, or 0.25 mL/kg/day (0, 28, 55, and 280 mg/kg/day, respectively, based on a density of 1.1058 g/mL for chlorobenzene), 5 days/week for 13 weeks. Dogs were monitored for survival, clinical signs, food intake,

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and body weight. At study initiation and 1 and 3 months, blood was collected for clinical chemistry and hematology and urine was collected for urinalysis. At death or terminal sacrifice, all animals were subjected to gross pathological examination; organ or tissues weighed included heart, liver, spleen, kidneys, testes, thyroid, and adrenals. Selected tissues were processed for histopathologic examination.

All dogs in control, 28, and 55 mg/kg/day groups survived to terminal sacrifice. Four of eight dogs dosed at 280 mg/kg/day died or were sacrificed moribund (between weeks 3 and 5). Decedents exhibited decreased appetite, decreased activity, anorexia, and body weight loss. There were no clear signs of exposure-related body weight effects at 28 and 55 mg/kg/day dose levels. Other effects observed at 280 mg/kg/day included liver and kidney effects (56–77% increased mean relative liver weight, 62–87% increased mean relative kidney weight, increased incidences of pathologic liver and kidney lesions), increased adrenal weight, alterations in selected hematological parameters (low hemogram, increased numbers of immature WBCs), increases in selected serum chemistry parameters (low blood sugar; increased alkaline phosphatase, ALT, total bilirubin, and total cholesterol), increased urinary acetone and bilirubin, and death. The small numbers of animals (4/sex/group) limit the power to determine dose levels resulting in statistically significant changes in liver and kidney lesion incidences. However, as shown in Table A-2, the high-dose level (280 mg/kg/day) is an adverse effect level for liver effects in males (87% increased mean relative liver weight and centrilobular degeneration and bile duct hyperplasia in 4/4 high-dose males; no incidences in controls) and females (62% increased mean relative liver weight and centrilobular degeneration in 3/4 high-dose females; no incidences in controls). Bile duct hyperplasia was noted in 2/4 male dogs and 1/4 female dogs in the 55 mg/kg/day dose group (4/4 males and 3/4 females in the 280 mg/kg/day dose group, compared to no incidences among control or 28 mg/kg/day groups of males or females). The incidences of bile duct hyperplasia in the 55 mg/kg/day group of male dogs is considered to represent a LOAEL for chlorobenzene-induced liver effects. Furthermore, after combining sexes, the bile duct hyperplasia exhibited a dose-response characteristic (incidences of 3/8 and 7/8 at 55 and 280 mg/kg/day, respectively). The 28 mg/kg/day dose level is considered a NOAEL for liver effects and the 280 mg/kg/day dose level is considered a serious LOAEL for multiple degenerative liver effects (e.g., centrilobular degeneration, vacuolation, bile duct hyperplasia). As shown in Table A-3, the 280 mg/kg/day dose level represents a LOAEL for increased incidences of kidney lesions (e.g., significantly increased incidences of tubule dilatation, vacuolation, epithelial degeneration in combined sexes). The smaller number and nature of the reported histopathologic kidney lesions at the low- and mid-dose levels (28 and 55 mg/kg/day) and/or lack of dose-response characteristics suggest that the mid-dose (55 mg/kg/day) represents a NOAEL for kidney effects.

Table A-2. Liver Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

	Chlorobenzene dose (mg/kg)							
	0		28		55		280	
Effect	Male	Female	Male	Female	Male	Female	Male	Female
Parenchymal irregularity			3/4 (1)		2/4 (1)	3/4 (1)		
Chronic hepatitis		1/4 (1)						
Portal fibrosis			1/4 (1)		1/4 (1)			
Stromal infiltration		1/4 (1)			2/4 (1)	1/4 (1)		

Table A-2. Liver Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

Effect	Chlorobenzene dose (mg/kg)							
	0		28		55		280	
	Male	Female	Male	Female	Male	Female	Male	Female
Focal leukocyte infiltration			2/4 (1)		1/4 (1)			
Pigment deposition				1/4 (1)			1/4 (1)	2/4 (1–2)
Extramedullary blood production	1/4 (1)	1/4 (1)						
Centrilobular degeneration							4/4[b] (3)	4/4[b] (1–3)
Vacuolation						1/4 (1)	3/4 (2–4)	3/4 (1–3)
Bile duct hyperplasia				2/4 (1)		1/4 (1)	4/4[b] (+/0–4)	3/4 (1)
Cytologic changes				1/4 (1)			2/4 (2–3)	2/4 (1–2)
Cloudy swelling				2/4 (1–3)		1/4 (1)		
Cholangitis							1/4 (2)	1/4 (1)
Bile stasis							2/4 (1–3)	2/4 (3)

[a]Numbers in parentheses denote relative severity of lesion (4 represents highest degree of severity).
[b]Significantly different from control incidence ($p < 0.05$).

Source: Monsanto Co. 1967a

Table A-3. Kidney Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

Effect	Chlorobenzene dose (mg/kg)							
	0		28		55		280	
	Male	Female	Male	Female	Male	Female	Male	Female
Pelvic epithelial irregularity		1/4 (2)	2/4 (1–2)					
Terminal proximal tubule swelling	3/4 (2)		3/4 (1–3)		3/4 (3)		1/4 (3)	1/4 (1)
Terminal proximal tubule vacuolation			1/4 (1)					2/4 (4)

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Table A-3. Kidney Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

| | Chlorobenzene dose (mg/kg) | | | | | | | |
| | 0 | | 28 | | 55 | | 280 | |
Effect	Male	Female	Male	Female	Male	Female	Male	Female
Tubule dilatation					1/4 (1)	1/4 (1)	2/4 (1–2)	2/4 (2)
Tubule epithelial degeneration					1/4 (1)		1/4 (2)	3/4 (1–3)
Proximal convoluted tubule swelling							1/4 (1)	1/4 (1)
Proximal convoluted tubule vacuolation						1/4 (1)	1/4 (1)	3/4 (2–3)
Glomerular swelling							1/4 (2)	
Glomerulosclerosis	1/4 (1)	1/4 (1)		4/4 (1)	1/4 (1)	3/4 (1)	1/4 (1)	
Chronic pyelitis		2/4 (2–3)	1/4 (1)			1/4 (2)		
Intraluminal foreign matter								1/4 (1)
Epithelial pigment deposition							2/4 (2–3)	1/4 (+/0)

[a]Numbers in parentheses denote relative severity of lesion (4 represents highest degree of severity).

Source: Monsanto Co. 1967a

Selection of the Point of Departure: Among available rat, mouse, and dog studies that employed intermediate-duration oral exposure, the lowest LOAEL is 55 mg/kg/day for liver effects in the dogs; the corresponding NOAEL is 28 mg/kg/day. Because the study employed only four dogs/sex/group, results for each sex were combined for each reported liver lesion type. The dataset for bile duct hyperplasia for combined sexes (see Table A-4) was considered adequate for benchmark dose (BMD) analysis. The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.12) using the extra risk option. A benchmark response (BMR) of 10% over the control incidence was used. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve.

Table A-4. Dataset for Benchmark Dose Analysis of Bile Duct Hyperplasia Incidences in Male and Female Dogs Administered Chlorobenzene in Capsule for 13 Weeks[a]

| | Chlorobenzene dose (mg/kg/day) | | | |
	Control	28	55	280
Males	0/4	0/4	2/4 (1)	4/4[b]
Females	0/4	0/4	1/4 (1)	3/4 (1)

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Table A-4. Dataset for Benchmark Dose Analysis of Bile Duct Hyperplasia Incidences in Male and Female Dogs Administered Chlorobenzene in Capsule for 13 Weeks[a]

	Chlorobenzene dose (mg/kg/day)			
	Control	28	55	280
Males and females (combined)	0/8	0/8	3/8 (1)	7/8[b] (+/0–4)

[a]Numbers in parentheses denote relative severity of lesion (4 represents highest degree of severity).
[b]Significantly different from control incidence (p<0.05).

Source: Monsanto Co. 1967a

The model predictions are presented in Table A-5. Among all models providing adequate fit to the data, the lowest BMDL (Multistage 1-degree model) was selected as the point of departure because the difference between the BMDLs estimated from these models was >3-fold.

Table A-5. Results from BMD Analysis of Bile Duct Hyperplasia Incidence in Male and Female Dogs Administered Chlorobenzene in Capsule 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)

					Scaled residuals[b]	
Model	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	p-Value[a]	AIC	Dose near BMD	Control group
Dichotomous Hill	47.04	20.44	0.959	22.62	3.00×10^{-3}	-3.49×10^{-4}
Gamma[c]	29.15	10.37	0.182	25.05	-9.13×10^{-1}	-3.49×10^{-4}
Log-Logistic[d]	31.35	11.08	0.507	22.57	-8.40×10^{-1}	-3.49×10^{-4}
Multistage Degree 3[e]	23.07	9.96	0.165	25.43	-1.05	-3.49×10^{-4}
Multistage Degree 2[e]	23.07	9.96	0.165	25.43	-1.05	-3.55×10^{-4}
Multistage Degree 1[e,f]	**16.41**	**9.59**	**0.593**	**21.81**	**-1.26**	**-3.49×10^{-4}**
Weibull[c]	26.73	10.20	0.176	25.20	-9.73×10^{-1}	-3.71×10^{-4}
Logistic	54.72	30.85	0.118	25.77	1.61	-7.80×10^{-1}
Log-Probit	32.93	12.70	0.523	22.41	-7.74×10^{-1}	-3.49×10^{-4}
Probit	52.18	31.71	0.123	25.55	1.64	-7.21×10^{-1}

[a]Values <0.1 fail to meet adequate fit
[b]Scaled residuals for dose group near the BMD and for the control dose group
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Recommended 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 (1-degree Multistage).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% relative deviation from control)

BMD modeling was also conducted on selected kidney lesion data (tubule dilatation, tubule epithelial degeneration, and proximal convoluted tubule vacuolation) for combined sexes (see Table A-6) because they exhibited some evidence of dose-response characteristics and statistically significantly increased incidences for these lesions were observed at the highest dose (280 mg/kg/day). Each dataset was fit to all available dichotomous models in EPA's BMDS (version 3.1.2) using the BMD approach described for the liver lesion data above.

Table A-6. Dataset for Benchmark Dose Analysis of Selected Kidney Lesion in Male and Female Dogs Administered Chlorobenzene in Capsule in 13 Weeks

	Chlorobenzene dose (mg/kg)			
	Control	28	55	280
Tubule dilatation				
Males	0/4	0/4	1/4	2/4
Females	0/4	0/4	1/4	2/4
Males and females combined	0/8	0/8	2/8	4/8[a]
Tubule epithelial degeneration				
Males	0/4	0/4	1/4	1/4
Females	0/4	0/4	0/4	3/4
Males and females combined	0/8	0/8	1/8	4/8[a]
Proximal convoluted tubule vacuolation				
Males	0/4	0/4	0/4	1/4
Females	0/4	0/4	1/4	3/4
Males and females combined	0/8	0/8	1/8	4/8[a]

[a]Significantly different from control incidence (p<0.05).

All models provided adequate fit to each dataset for kidney lesions. The model results for tubule dilatation are presented in Table A-7. Most models provided adequate fit to the incidence data. The estimated BMDLs varied by greater than 3-fold, thus, the model with the lowest BMDL was selected (Log-Logistic model). The model for tubule dilatation estimated a BMD_{10} of 37.71 mg/kg and $BMDL_{10}$ of 14.07 mg/kg. The incidence data for proximal convoluted tubule vacuolation and tubule epithelial degeneration were the same. The results of the BMD modeling for these two endpoints are presented in Table A-8. All models provided adequate fit and the Log-Probit model was selected because it had the lowest BMDL value. This model estimated a BMD_{10} of 61.67 mg/kg and $BMDL_{10}$ of 13.99 mg/kg.

Table A-7. Results from BMD Analysis of Renal Tubule Dilatation Incidence in Male and Female Dogs Administered Chlorobenzene in Capsule 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)

Model	BMD_{10}[a] (mg/kg)	$BMDL_{10}$[a] (mg/kg)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Dichotomous Hill	48.55	16.15	0.999	24.09	3.92×10^{-3}	-3.49×10^{-4}
Gamma[d]	38.94	21.00	0.682	24.03	-7.93×10^{-1}	-3.49×10^{-4}
Log-Logistic[e,f]	**37.71**	**14.07**	**0.511**	**25.91**	**-7.94×10^{-1}**	**-3.49×10^{-4}**
Multistage Degree 3[g]	38.94	21.00	0.682	24.03	-7.93×10^{-1}	-3.49×10^{-4}
Multistage Degree 2[g]	38.94	21.00	0.682	24.03	-7.93×10^{-1}	-3.49×10^{-4}
Multistage Degree 1[g]	38.94	21.00	0.682	24.03	-7.93×10^{-1}	-3.49×10^{-4}
Weibull[d]	38.94	21.00	0.682	24.03	-7.93×10^{-1}	-3.49×10^{-4}
Logistic	104.66	63.17	0.190	27.86	1.48	-6.94×10^{-1}
Log-Probit			0.531	25.77	-7.40×10^{-1}	-3.49×10^{-4}
Probit	95.50	58.90	0.199	27.70	1.47	-6.54×10^{-1}

[a]BMD and BMDL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Recommended model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL was selected (Log-Logistic).
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% relative deviation from control)

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Table A-8. Results from BMD Analysis of Renal Proximal Tubule Vacuolation and Tubule Epithelial Degeneration Incidences in Male and Female Dogs Administered Chlorobenzene in Capsule 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)

Model	$BMD_{10}{}^a$ (mg/kg)	$BMDL_{10}{}^a$ (mg/kg)	p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Control group
Dichotomous Hill	53.67	20.27	1.000	21.12	8.67×10^{-4}	-3.49×10^{-4}
Gamma[d]	65.97	25.36	0.480	23.83	4.88×10^{-1}	-3.55×10^{-4}
Log-Logistic[e]	63.81	19.73	0.497	23.80	4.51×10^{-1}	-3.56×10^{-4}
Multistage Degree 3[f]	67.37	25.06	0.461	23.94	4.74×10^{-1}	-3.52×10^{-4}
Multistage Degree 2[f]	67.37	25.06	0.762	21.94	4.74×10^{-1}	-3.49×10^{-4}
Multistage Degree 1[f]	47.59	24.41	0.904	20.17	9.19×10^{-2}	-3.49×10^{-4}
Weibull[d]	66.14	25.28	0.476	23.86	4.80×10^{-1}	-3.49×10^{-4}
Logistic	127.20	75.54	0.497	22.78	9.37×10^{-1}	-4.60×10^{-1}
Log-Probit[g]	**61.67**	**13.99**	**0.534**	**23.68**	**4.23×10^{-1}**	**-8.93×10^{-3}**
Probit	114.82	69.29	0.522	22.65	9.10×10^{-1}	-4.21×10^{-1}

[a]BMD and BMDL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL was selected (Log-Probit).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% relative deviation from control)

A comparison of the BMD values for the liver and kidney endpoint was made:

- BMD_{10} of 16.41 mg/kg for bile duct hyperplasia ($BMDL_{10}$ of 9.59 mg/kg),
- BMD_{10} of 37.71 mg/kg for renal tubular dilation ($BMDL_{10}$ of 14.07 mg/kg), and
- BMD_{10} of 61.67 mg/kg for proximal convoluted tubule vacuolation and tubule epithelial degeneration ($BMDL_{10}$ of 13.99 mg/kg)

The bile duct hyperplasia had the lowest BMD_{10} and was selected as the critical effect. The $BMDL_{10}$ of 9.59 mg/kg for this endpoint was selected as the POD for the MRL. This $BMDL_{10}$ was estimated using the 1-degree Multistage model, which is presented in Figure A-1.

Figure A-1. Fit of 1-Degree Multistage Model for Bile Duct Hyperplasia in Male and Female Dogs Administered Chlorobenzene 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)
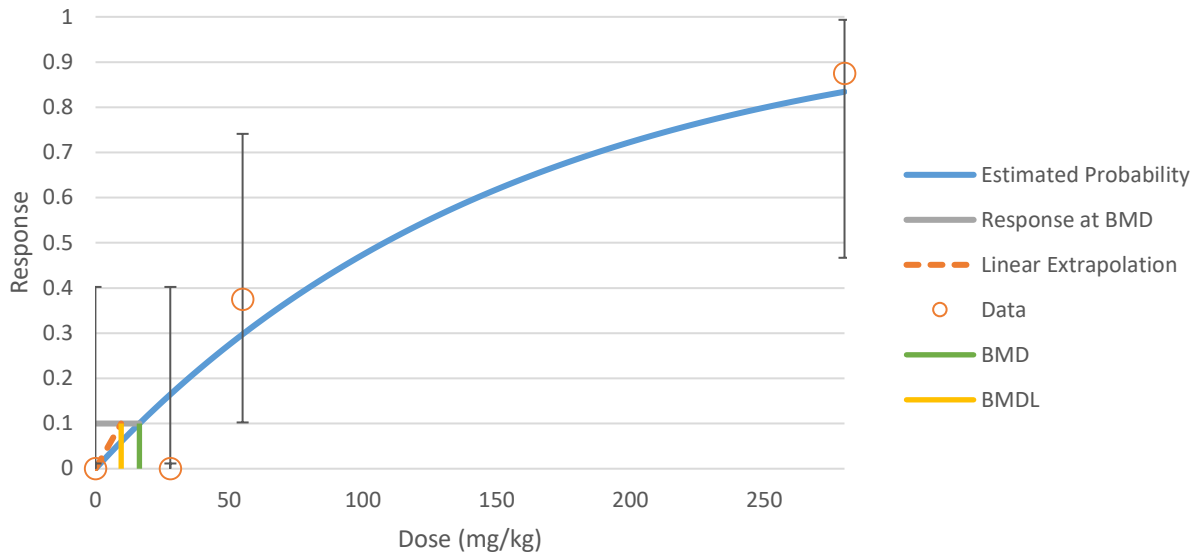
Intermittent Exposure: The $BMDL_{10}$ of 9.59 mg/kg/day was adjusted for intermittent exposure (5 days/7 days) resulting in adjusted value of 6.85 mg/kg/day.

$$BMDL_{ADJ} = 9.59 \text{ mg/kg x (5 days/7 days)} = 6.85 \text{ mg/kg/day}$$

Uncertainty Factor: The $BMDL_{ADJ}$ was divided by a total uncertainty factor (UF) of 100:

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

$$MRL = BMDL_{ADJ} \div UFs$$
$$6.85 \text{ mg/kg/day} \div (10 \text{ x } 10) = 0.0685 \text{ mg/kg/day} \approx 0.07 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support: As shown in Table A-1, liver and kidney effects were observed in rats and mice treated orally with chlorobenzene for intermediate-duration periods (Monsanto Co. 1967b; NTP 1985).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

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MINIMAL RISK LEVEL (MRL) WORKSHEET

*Chemical Name***:**   Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: One 2-year oral toxicity and carcinogenicity study of rats gavaged with chlorobenzene at 60 or 120 mg/kg/day reported decreased survival and increased incidences of neoplastic liver lesions at 120 mg/kg/day in the absence of other signs of exposure-related adverse effects (NTP 1985). There were no signs of adverse effects in mice similarly treated at 30 or 60 mg/kg/day (males) or 60 or 120 mg/kg/day (females) (NTP 1985). No nonlethal and nonneoplastic effects were observed in the rats or mice following chronic-duration oral exposures at doses resulting in adverse nonneoplastic effects in animals following intermediate-duration exposures. Therefore, no chronic-duration oral MRL was derived for chlorobenzene.

Agency Contacts (Chemical Managers): Breanna Alman, MPH

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLOROBENZENE

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 chlorobenzene.

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, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for chlorobenzene. 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 chlorobenzene 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 chlorobenzene 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

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

Other noncancer effects
Cancer

Toxicokinetics
   Absorption
   Distribution
   Metabolism
   Excretion
   PBPK models
Biomarkers
   Biomarkers of exposure
   Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
   Releases to the environment
      Air
      Water
      Soil
   Environmental fate
      Transport and partitioning
      Transformation and degradation
   Environmental monitoring
      Air
      Water
      Sediment and soil
      Other media
   Biomonitoring
      General populations
      Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for chlorobenzene released for public comment in 2019; thus, the literature search was restricted to studies published between April 2016 and April 2020. The following main databases were searched in April 2020:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

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

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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 chlorobenzene 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	
04/2020	((108-90-7[rn] OR "chlorobenzene"[nm]) OR (("Benzene chloride"[tw] OR "Benzene, chloro-"[tw] OR "Chlorbenzene"[tw] OR "Chlorbenzol"[tw] OR "Chlorobenzene"[tw] OR "Chlorobenzene, mono-"[tw] OR "Chlorobenzine"[tw] OR "Chlorobenzol"[tw] OR "I P Carrier T 40"[tw] OR "IP Carrier T 40"[tw] OR "Monochlorbenzene"[tw] OR "Monochlorobenzene"[tw] OR "Monochlorobenzenes"[tw] OR "Phenyl chloride"[tw] OR "Tetrosin SP"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR chlorobenzenes/ai OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR toxicokinetics[mh:noexp] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])))) OR (("Benzene chloride"[tw] OR "Benzene, chloro-"[tw] OR "Chlorbenzene"[tw] OR "Chlorbenzol"[tw] OR "Chlorobenzene"[tw] OR "Chlorobenzene, mono-"[tw] OR "Chlorobenzine"[tw] OR "Chlorobenzol"[tw] OR "I P Carrier T 40"[tw] OR "IP Carrier T 40"[tw] OR "Monochlorbenzene"[tw] OR "Monochlorobenzene"[tw] OR "Monochlorobenzenes"[tw] OR "Phenyl chloride"[tw] OR "Tetrosin SP"[tw]) NOT medline[sb])) AND (2017/04/01:3000[mhda] OR 2017/04/01:3000[crdt] OR 2017/04/01:3000[edat] OR 2016/04/01:3000[dp])
NTRL	
04/2020	"Benzene chloride" OR "Benzene, chloro-" OR "Chlorbenzene" OR "Chlorbenzol" OR "Chlorobenzene" OR "Chlorobenzene, mono-" OR "Chlorobenzine" OR "Chlorobenzol" OR "I P Carrier T 40" OR "IP Carrier T 40" OR "Monochlorbenzene" OR "Monochlorobenzene" OR "Monochlorobenzenes" OR "Phenyl chloride" OR "Tetrosin SP"
Toxcenter	
04/2020	FILE 'TOXCENTER' ENTERED AT 09:15:35 ON 29 APR 2020 L1 9299 SEA FILE=TOXCENTER 108-90-7

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
	L2 7919 SEA FILE=TOXCENTER L1 NOT PATENT/DT
	L3 510 SEA FILE=TOXCENTER L2 AND ED>=20170401
	L4 717 SEA FILE=TOXCENTER L2 AND PY>2015
	L5 741 SEA FILE=TOXCENTER L3 OR L4
	ACT TOXQUERY/Q

	L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE 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 OR L30
	L32 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?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L36 QUE L34 OR L35

	L37 242 SEA FILE=TOXCENTER L5 AND L36
	L38 7 SEA FILE=TOXCENTER L37 AND MEDLINE/FS
	L39 235 SEA FILE=TOXCENTER L37 NOT MEDLINE/FS
	L40 236 DUP REM L38 L39 (6 DUPLICATES REMOVED) ANSWERS '1-236' FROM FILE TOXCENTER
	L*** DEL 7 S L37 AND MEDLINE/FS
	L*** DEL 7 S L37 AND MEDLINE/FS
	L41 7 SEA FILE=TOXCENTER L40
	L*** DEL 235 S L37 NOT MEDLINE/FS
	L*** DEL 235 S L37 NOT MEDLINE/FS
	L42 229 SEA FILE=TOXCENTER L40
	L43 229 SEA FILE=TOXCENTER (L41 OR L42) NOT MEDLINE/FS D SCAN L43

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
04/2020	Compounds searched: 108-90-7
NTP	
04/2020	108-90-7 "Benzene chloride" "Chlorobenzene" "Monochlorobenzene" "Phenyl chloride" "Benzene, chloro-" "Chlorbenzene" "Chlorbenzol" "Chlorobenzene, mono-" "Chlorobenzine" "Chlorobenzol" "I P Carrier T 40" "IP Carrier T 40" "Monochlorbenzene" "Monochlorobenzenes" "Tetrosin SP"
NIH RePORTER	
05/2020	Search Criteria: Text Search: "Benzene chloride" OR "Benzene, chloro-" OR "Chlorbenzene" OR "Chlorbenzol" OR "Chlorobenzene" OR "Chlorobenzene, mono-"

Table B-3. Strategies to Augment the Literature Search	
Source	Query and number screened when available
	OR "Chlorobenzine" OR "Chlorobenzol" OR "I P Carrier T 40" OR "IP Carrier T 40" OR "Monochlorbenzene" OR "Monochlorobenzene" OR "Monochlorobenzenes" OR "Phenyl chloride" OR "Tetrosin SP" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:
- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 486
- Number of records identified from other strategies: 38
- Total number of records to undergo literature screening: 524

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on chlorobenzene:

- 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: 524
- Number of studies considered relevant and moved to the next step: 39

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: 39
- Number of studies cited in the pre-public draft of the toxicological profile: 127
- Total number of studies cited in the profile: 164

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

Figure B-1. April 2020 Literature Search Results and Screen for Chlorobenzene
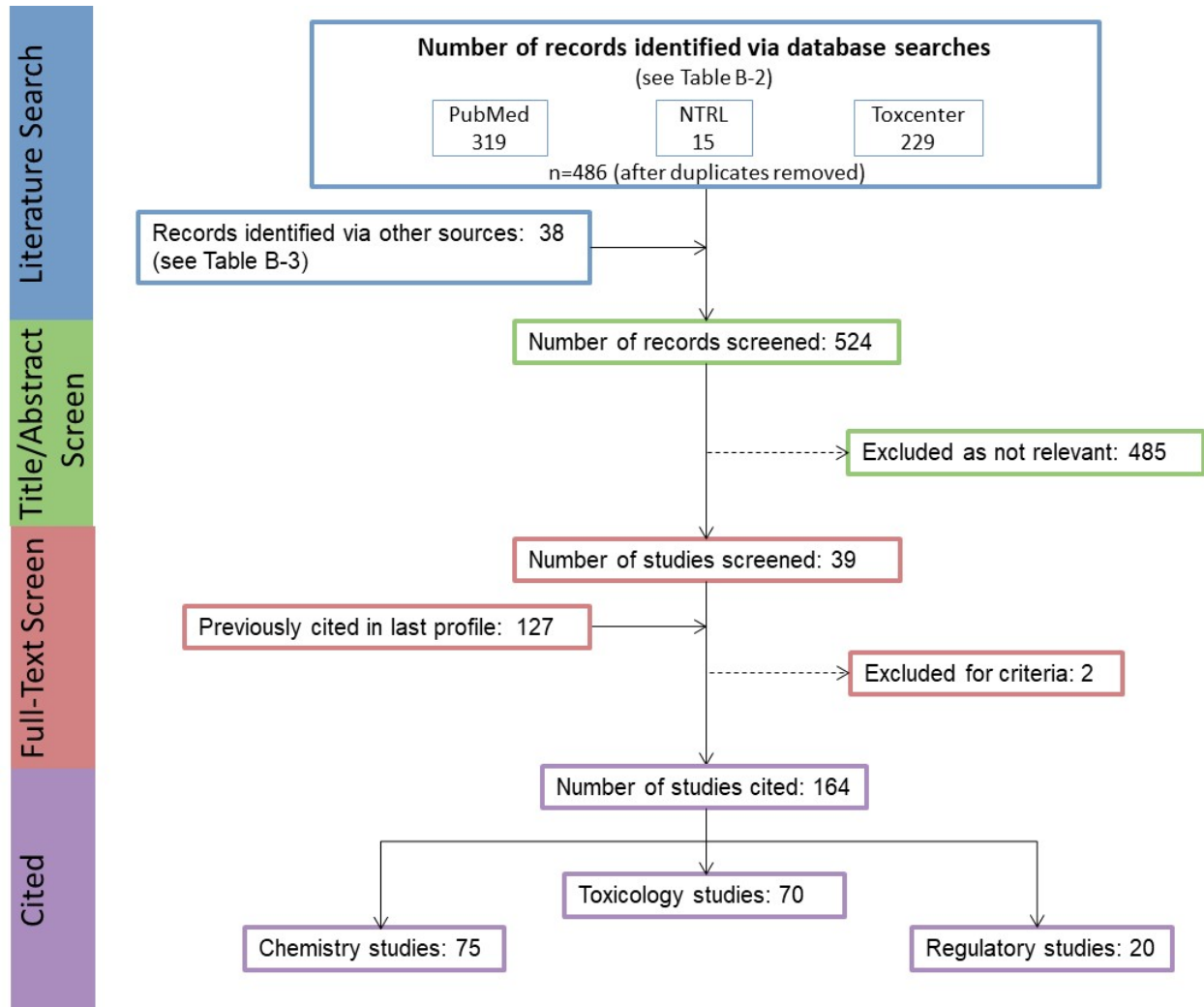
APPENDIX C. USER'S GUIDE

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 [1]

Figure key[a]	Species (strain) No./group [4]	Exposure parameters [5]	Doses (mg/kg/day)	Parameters monitored [6]	Endpoint [7]	NOAEL (mg/kg/day) [8]	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day) [9]	Effect
[2] CHRONIC EXPOSURE									
51 [3]	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
[10] 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.
[11] [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the BMDL05 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 BMDL10 of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral
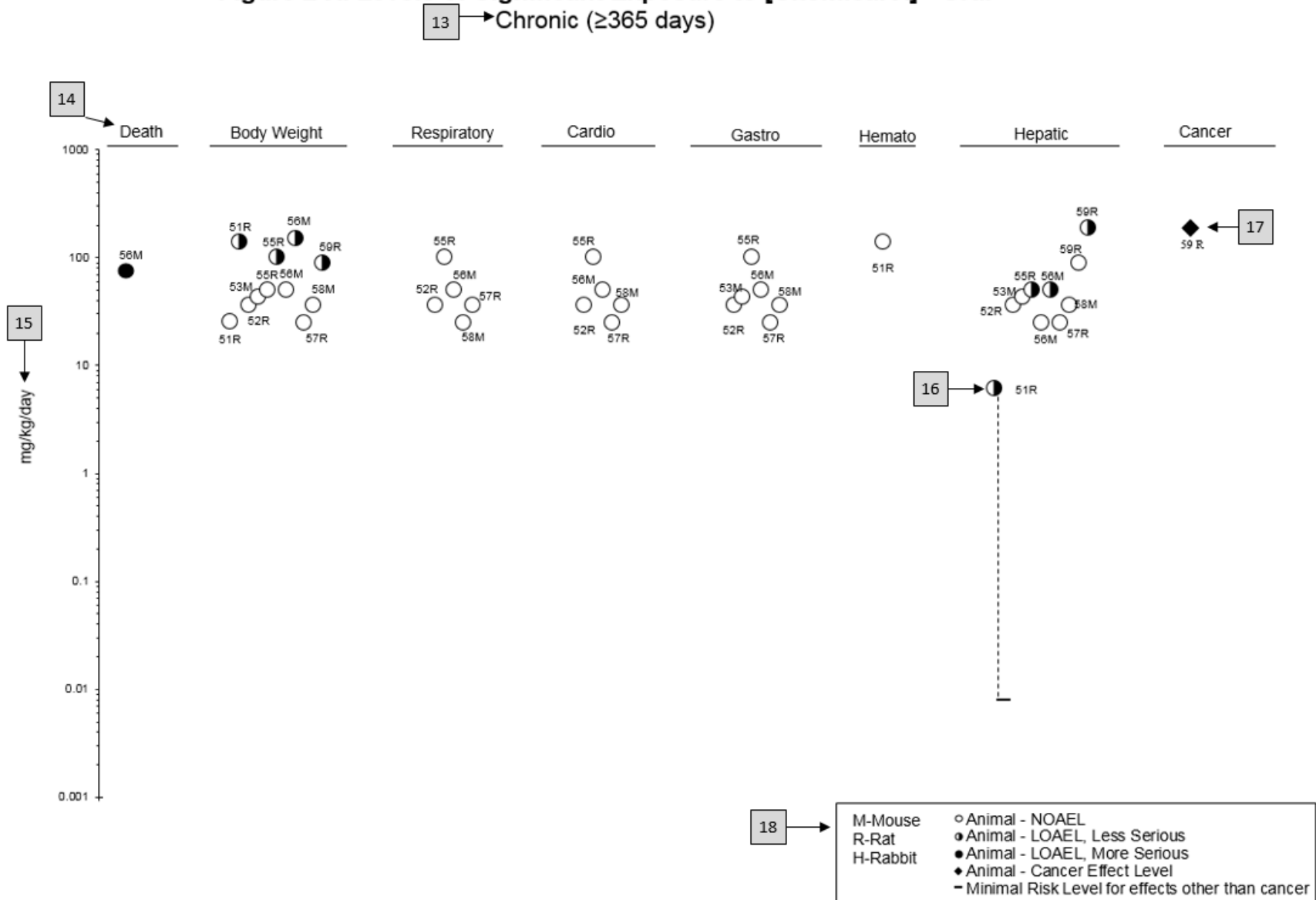
APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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).

APPENDIX D

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.

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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.

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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
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

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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

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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