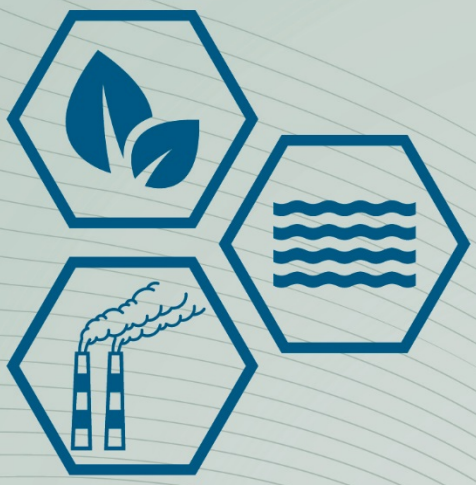


Toxicological Profile for Chlordane

February 2018

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

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.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*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
May 1994	Final toxicological profile released
December 2013	Addendum to the toxicological profile released
February 2018	Update of data in Chapters 2 and 3, and 7

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Jennifer Przybyla, Ph.D.

ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

David W. Wohlers, Ph.D.

SRC, Inc., North Syracuse, NY

CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for Chlordane* was released in 1994, and an Addendum to this profile was released in 2013. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2 and 3 were revised to reflect the most current health effects data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

Chlordane is a man-made substance that was used as a pesticide in the United States from 1948 to 1988. Technical chlordane (CAS Number 12789-03-6) is a mixture of >140 related chemicals; major components are *trans*-chlordane and *cis*-chlordane (60–85% of technical chlordane); other components include chlordene, heptachlor, and *cis*- and *trans*-nonachlor. Technical chlordane is the major focus of this toxicological profile for chlordane. Chlordane is a thick liquid ranging from colorless to amber; it may have no smell or a mild, irritating smell. Chlordane does not dissolve in water.

Prior to 1978, chlordane was used as a pesticide on agricultural crops, lawns, and gardens, and as a fumigating agent. From 1983 until 1988 chlordane's only approved use was to control termites in homes. EPA canceled all uses for chlordane in 1988 because of concerns over cancer risk, evidence of human exposure and build up in body fat, persistence in the environment, and danger to wildlife.

In soil, chlordane attaches strongly to particles in upper layers where it may remain as long as 20 years; chlordane in soil is not likely to enter groundwater. Most chlordane in surface soil is lost by evaporating into air. In water, chlordane attaches strongly to sediment and particles in the water column. Chlordane does not break down rapidly in air and accumulates in fish, birds, and mammals. Therefore, chlordane and its breakdown products may be detected in most humans.

The most likely source of exposure of the general population to chlordane was from living in homes that were treated with chlordane for termites. The next most likely source was from eating chlordane-contaminated food. Because chlordane uses were banned in 1988, it is not likely that current populations would be exposed to chlordane levels high enough to cause adverse health effects. However, there may be potential for exposure to chlordane by individuals living near storage or disposal sites.

1.2 SUMMARY OF HEALTH EFFECTS

Animal studies identify hepatic, developmental, and hematological endpoints as most sensitive to chlordane toxicity. For each exposure duration, the lowest adverse effect level for each of these endpoints and others is identified in Figures 1-1 and 1-2. Oral studies in mice have consistently reported chlordane-induced liver tumors. Available data are inconclusive regarding the carcinogenicity of chlordane in humans.

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

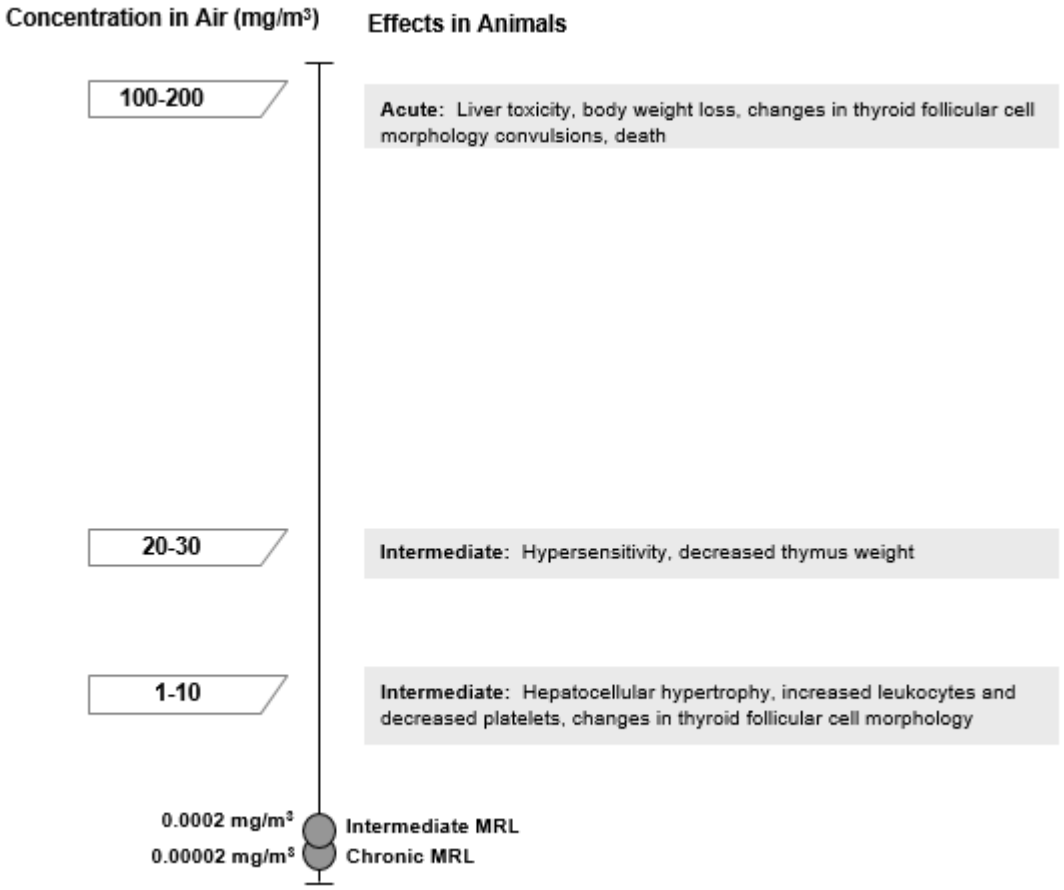
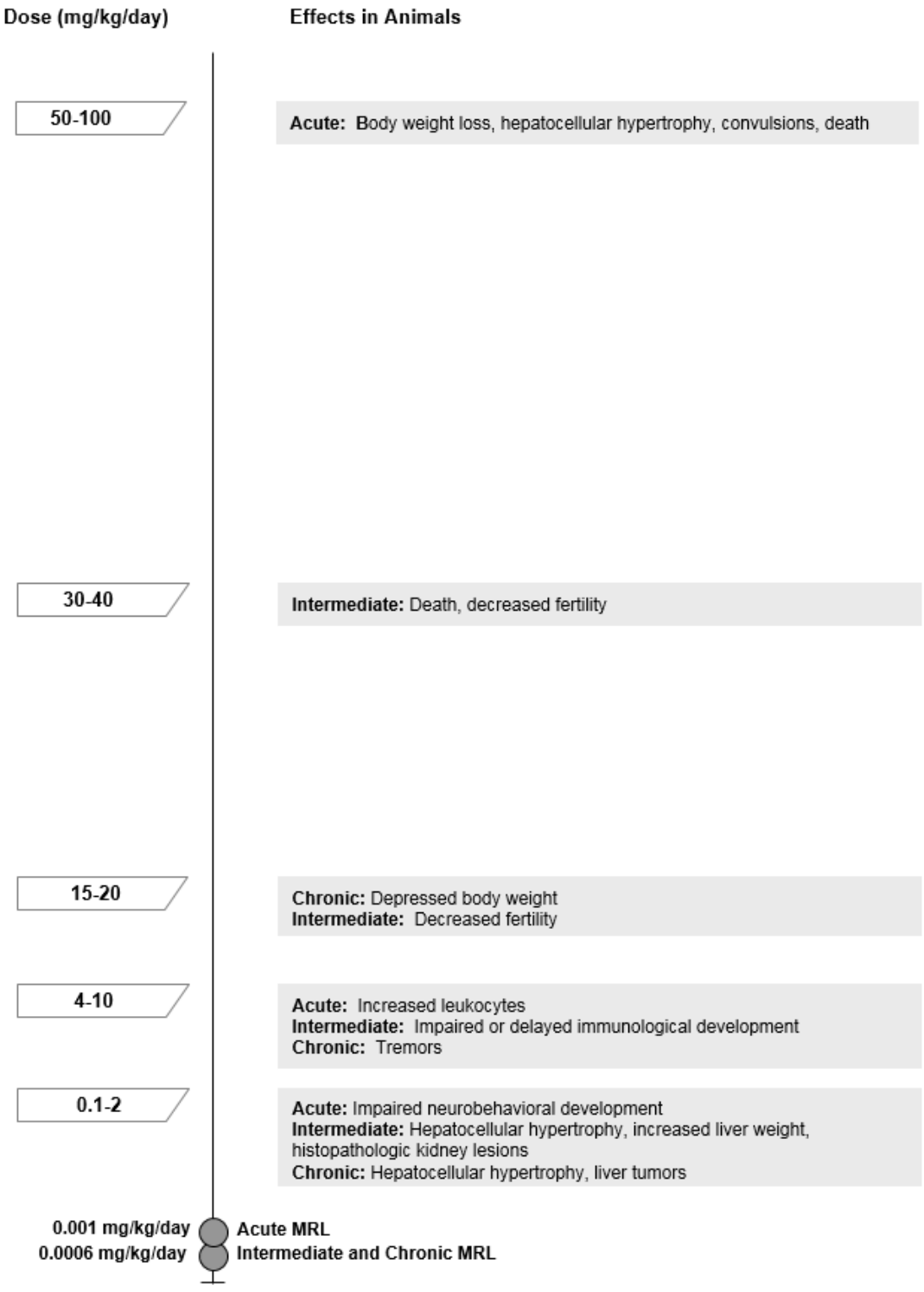


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Chlordane



Hematological Effects. One inhalation study in rats reported chlordane exposure-related increased leukocyte count and decreased platelets in female (but not male) rats intermittently exposed for 90 days at 1 and 10 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). One oral study in mice reported increased leukocyte count following single gavage dosing of chlordane at 8 mg/kg/day (Johnson et al. 1986).

Hepatic Effects. Chlordane-induced hepatic effects have been observed in one series of animal studies that employed inhalation exposure (EPA 1987f; Khasawinah et al. 1989) and in numerous studies that employed oral exposure (Ambrose et al. 1953a; Bondy et al. 2000; EPA 1985a; Kacew and Singhal 1973; Khasawinah and Grutsch 1989a, 1989b; Mahon et al. 1978; Malarkey et al. 1995; Ogata and Izushi 1991; Ortega et al. 1957; Truhaut et al. 1974, 1975). Effects ranged from increased liver weight and hepatocellular to degenerative histopathologic effects. Nonneoplastic liver effects were observed at inhalation exposure levels as low as 1 mg/m^3 and at oral doses as low as 0.1 mg/kg/day. Chlordane-induced neoplastic liver lesion data are discussed in the cancer section below.

Neurological Effects. Neurotoxicity is a consistent and predictable finding in humans (Aldrich and Holmes 1969; Balistreri et al. 1973; Barnes 1967; Curley and Garrettson 1969; Dadey and Kammer 1953; EPA 1980a, 1986d; Harrington et al. 1978; Kilburn and Thornton 1995; Lensky and Evans 1952; Menconi et al. 1988; NIOSH 1984a; Olanoff et al. 1983) and animals (Drummond et al. 1983; Frings and O'Tousa 1950; Hrdina et al. 1974; Ingle 1952; Khasawinah et al. 1989; NCI 1977; Stohlman et al. 1950) exposed to chlordane. In the human studies, clinical signs and symptoms included migraines, convulsion, and seizures following inhalation, oral, or dermal routes of exposure. In the animal studies, convulsions and seizures were consistent findings after inhalation, oral, and dermal routes of exposure to chlordane (Ambrose et al. 1953a; EPA 1987f; Hrdina et al. 1974; Ingle 1953; Khasawinah et al. 1989; NCI 1977).

Developmental Effects. Limited information is available regarding potential for chlordane-induced developmental effects in human (Fenster et al. 2006; Gladen et al. 2003; Trabert et al. 2012). Available oral animal data suggest that subtle behavioral and immunological effects occur in developing mice (Al-Hachim and Al-Baker 1973; Barnett et al. 1985a, 1985b, 1990a, 1990b; Chernoff and Kavlock 1982; Cranmer et al. 1984; Menna et al. 1985; Spyker-Cranmer et al. 1982; Theus et al. 1992; Usami et al. 1986). Adverse neurobehavioral effects have been shown to occur in the offspring of mice receiving chlordane orally during gestation at a dose of 1 mg/kg/day ((Al-Hakim and Al-Baker 1973).

Cancer. Most epidemiological studies found no significant association between occupational exposure to chlordane (Brown 1992; Ditraglia et al. 1981; MacMahon et al. 1988; Shindell and Ulrich 1986; Wang and MacMahon 1979a, 1979b; Woods and Polissar 1989) or serum levels of chlordane and/or chlordane

constituents or metabolites and risk of cancer (Demers et al. 2000; Falck et al. 1992; Gammon et al. 2002; Hardell et al. 2006b; Ward et al. 2000; Weiderpass et al. 2000; Wolff et al. 2000). However, some studies reported significant associations between serum levels of chlordane and/or chlordane constituents or metabolites and risk of cancer of the male reproductive tract (Hardell et al. 2003, 2006a; McGlynn et al. 2008), non-Hodgkin's lymphoma (Hardell et al. 1996; Quintana et al. 2004; Spinelli et al. 2007), and pancreatic cancer (Hardell et al. 2007). One population-based case-control study found a significant association between self-reported chlordane use and risk of rectal cancer (Purdue et al. 2006). One registry-based case-control study reported a significant association between chlordane usage in pesticide application and risk of breast cancer diagnosed between 1988 and 1994 (Mills and Yang 2005). However, these studies are limited by lack of control for confounding variables and concurrent exposures, lack of exposure levels and route information, small sample size, and/or low incidences. Chronic oral exposure studies in mice have found increases in neoplastic tumors in the liver (EPA 1985a; Epstein 1976; IRDC 1973; Khasawinah and Grutsch 1989b; Malarkey et al. 1995; NCI 1977).

The U.S. Department of Health and Human Services has not classified chlordane as to its carcinogenicity (NTP 2016). EPA categorized it as a probable human carcinogen (Group B2) (IRIS 2002). The International Agency for Research on Cancer categorized it as possibly carcinogenic to humans (Group 2B) (IARC 2001, 2017). The cancer classifications are based on sufficient evidence of carcinogenicity in animal studies and inadequate evidence in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figures 1-3 and 1-4, available data suggest that hepatic, hematological, and developmental endpoints are the most sensitive targets of chlordane toxicity. Inhalation and oral MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Chlordane -- Inhalation

Hepatic and hematological endpoints are the most sensitive targets of chlordane.
Numbers in circles are the lowest LOAELs (ppm) for all health effects in animals; no exposure-response data were identified for humans.

Figure 1-4. Summary of Sensitive Targets of Chlordane -- Oral

Hepatic and developmental endpoints are the most sensitive targets of chlordane.
Numbers in circles are the lowest LOAELs (mg/kg/day) for all health effects in animals; no reliable dose response data were available for humans.

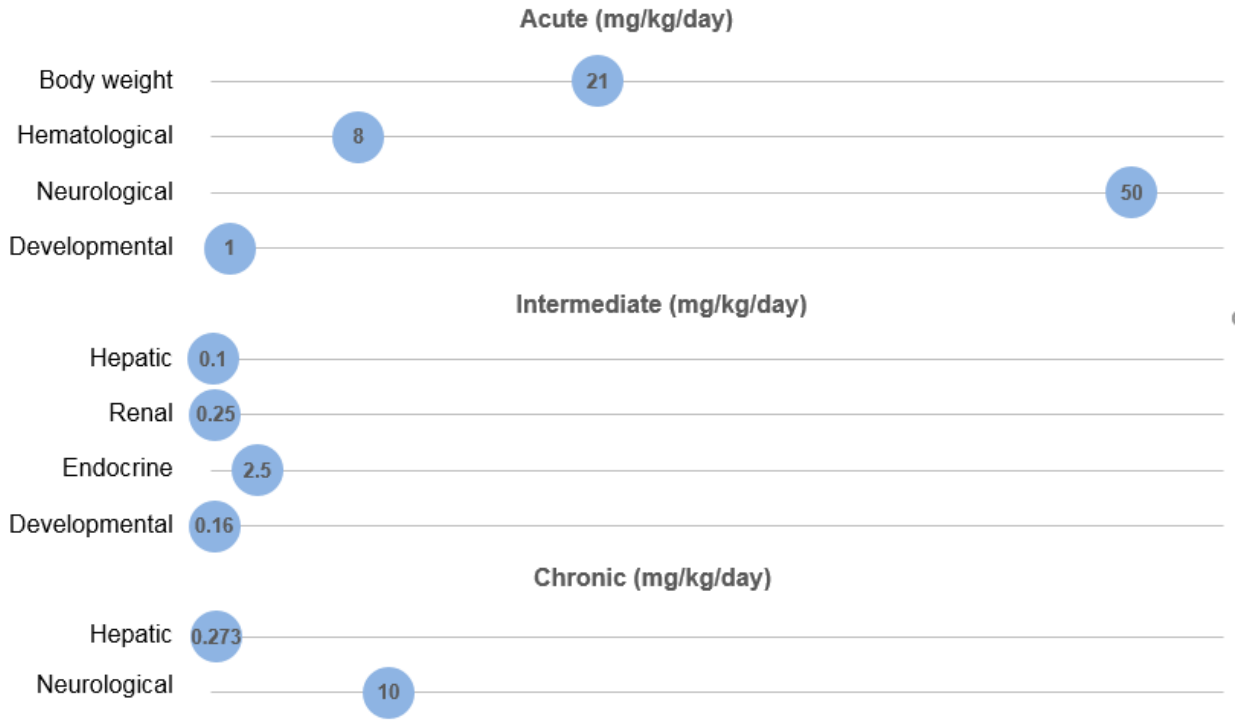


Table 1-1. Minimal Risk Levels (MRLs) for Chlordane Technical[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (mg/m^3)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.0002	Hepatocellular hypertrophy	0.024 ($NOAEL_{ADJ}$)[b]	100	EPA 1987f; Khasawinah et al. 1989
Chronic	0.00002	Hepatocellular hypertrophy	0.024 ($NOAEL_{ADJ}$)[b]	1,000	EPA 1987f; Khasawinah et al. 1989
Oral exposure (mg/kg/day)					
Acute	0.001	Neurodevelopmental effects	1 (LOAEL)	1,000	Al-Hachim and Al-Baker 1973
Intermediate	0.0006	Hepatocellular hypertrophy	0.055 (NOAEL)	100	EPA 1985a; Khasawinah and Grutsch 1989a
Chronic	0.0006	Hepatocellular hypertrophy	0.055 (NOAEL)	100	EPA 1985a; Khasawinah and Grutsch 1989a; Velsicol Chemical Co. 1983a

[a]See Appendix A for additional information.
[b]Rat NOAEL of 0.1 mg/m^3 adjusted for intermittent exposure 5 days/7 days and 8 hours/24 hours = 0.024 mg/m^3.

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

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of chlordane. 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.

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 chlordane, 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. Animal dermal studies are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the

Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether 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 associated with cancer (Cancer Effect Levels, CELs) of chlordane 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.

As illustrated in Figure 2-1, human studies predominantly evaluated neurological and cancer endpoints. Available human and animal data suggest the following sensitive targets of chlordane toxicity:

- Hepatic endpoint: Inhalation and oral exposure of animals resulted in liver weight increases and histopathologic effects including hepatocellular hypertrophy and dose-related incidence and severity of degenerative and regenerative liver lesions.

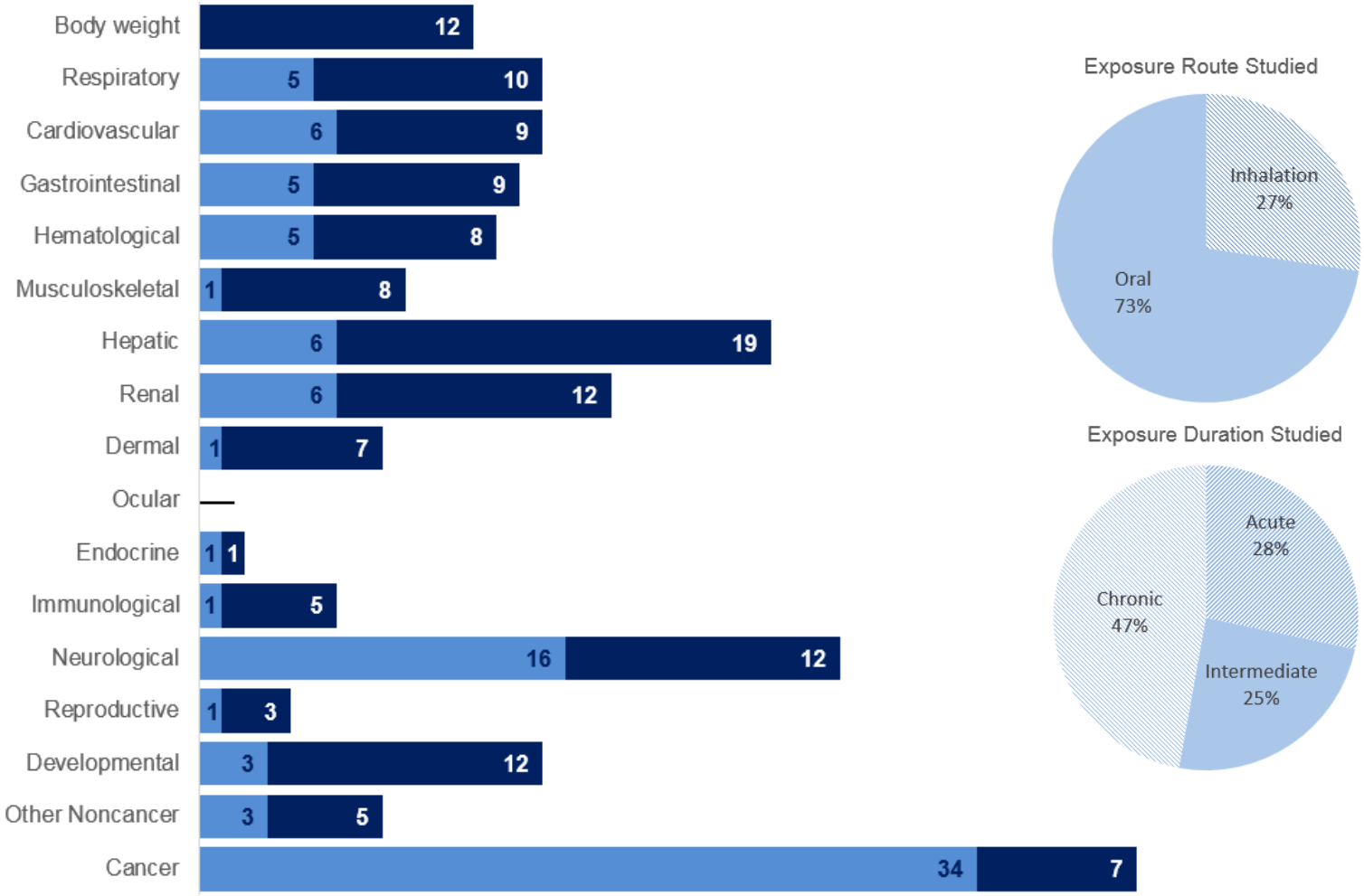
- Neurological endpoint: Central nervous system effects including headache, dizziness, muscle tremors, and convulsions have been reported in humans exposed by inhalation following its former use as a pesticide and following ingestion of chlordane-containing substances. Effects such as tremors and convulsions were observed in laboratory animals following relatively high level inhalation or oral exposure to chlordane.

- Developmental endpoint: Limited human data have not provided reliable associations between chlordane exposure and developmental outcomes. However, results from oral animal studies suggest that pre- and postnatal exposure may adversely affect neurobehavioral development and the immune system; one study reported chlordane treatment-related decreased postnatal survival.

- Hematological endpoint: Limited human data have not provided associations between chlordane exposure and hematological effects. One 90-day inhalation study of rats reported 8% increased leukocyte count and 26% decreased platelets in females (but not males) intermittently exposed at a concentration as low as 1 mg/m^3. One oral study in mice reported increased leukocyte count following single gavage dosing of chlordane at 8 mg/kg/day. However, these effects have not been substantiated in other animal studies.

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

Most studies examined the potential hepatic, renal, neurological, and cancer effects of chlordane
More studies evaluated health effects in **animals** than **humans**, **except for neurological and cancer endpoints**
(counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 106 studies include those finding no effect. Most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Chlordane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effect
ACUTE EXPOSURE									
1	Rat (Wistar) 10 M, 10 F	Up to 28 days 5 days/week 8 hours/day	0, 5.8, 28.2, 154, 413		Death			154	Terminated after 11 exposures due to deaths by day 5; at 413 mg/m^3, terminated after 3 exposures
					Bd Wt		154		Unspecified body weight loss
					Resp	154		413	Epithelial degeneration and cellular debris in bronchi and alveoli
					Hemato	154			
					Hepatic		154	413	Increased blood ALT, AST, SGDH, bile acids, cholesterol, liver enlargement and discoloration, centrilobular hepatocyte enlargement; effects were more severe at 413 mg/m^3
					Neuro			154	Abnormal respiratory movements, salivation, convulsions
					Other noncancer		154		Increased height of thyroid follicular cells

EPA 1987f; Khasawinah et al. 1989; Chlordane technical

Table 2-1. Levels of Significant Exposure to Chlordane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effect
INTERMEDIATE EXPOSURE									
2	Rat (Wistar) 10 M, 10 F	28 days 5 days/week 8 hours/day	0, 5.8, 28.2		Resp	28.2			
					Cardio	28.2			
					Gastro	28.2			
					Hemato	28.2			
					Musc/skel	28.2			
					Hepatic	5.8	28.2		Centrilobular hepatocellular hypertrophy; decreased blood glucose, increased blood total protein, albumin, and globulin
					Renal	28.2			
					Dermal	28.2			
					Immuno	5.8	28.2		Decreased thymus weight in females
					Neuro	5.8	28.2		Hypersensitivity to touch in females
					Other noncancer	5.8	28.2		Increased heighted of follicular epithelium of thyroid

EPA 1987f; Khasawinah et al. 1989; Chlordane technical

Table 2-1. Levels of Significant Exposure to Chlordane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effect
3	Rat (Wistar) 15 M, 15 F	90 days 5 days/week 8 hours/day	0, 0.1, 1.0, 10		Resp	10			
					Cardio	10			
					Gastro	10			
					Hemato	0.1	1		8% increased leukocytes, 26% decreased platelets in females
					Musc/skel	10			
					Hepatic	0.1[b,c]	1		Centrilobular hypertrophy, hepatocellular vacuolization, increased P-450, decreased albumin, decreased albumin/ globulin ratio
					Renal	10			
					Dermal	10			
					Other noncancer	1	10		Increased height of follicular cells of the thyroid in males
EPA 1987f; Khasawinah et al. 1989; Chlordane technical									
4	Monkey (cyno-molgus) 6 M, 6 F	90 days 5 days/week 8 hours/day	0, 0.1, 1.0, 10		Resp	10			
					Cardio	10			
					Gastro	10			
					Hemato	10			
					Musc/skel	10			
					Hepatic	10			
					Renal	10			
					Dermal	10			
					Other noncancer	10			
EPA 1987f; Khasawinah et al. 1989; Chlordane technical									

Table 2-1. Levels of Significant Exposure to Chlordane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effect
CHRONIC EXPOSURE									
5	Human	1–15 years 8 hours/day 5 days/week			Resp	0.0017			
					Cardio	0.0017			
					Gastro	0.0017			
					Hemato	0.0017			
					Hepatic	0.0017			
					Renal	0.0017			
					Other noncancer	0.0017			

Fishbein et al. 1964

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.0002 mg/m^3; concentration adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 to extrapolate from animals to humans and 10 for human variability).
[c]The NOAEL of 0.1 mg/m^3 for hepatic effects identified in an intermediate-duration study (EPA 1987f; Khasawinah et al. 1989) was used to derive a chronic-duration inhalation MRL of 0.00002 mg/m^3; the concentration was adjusted for an intermittent exposure and divided by an uncertainty factor of 1,000 (10 to extrapolate from intermediate duration to chronic duration exposure, 10 to extrapolate from animals to humans, and 10 for human variability).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; F = female(s); Gastro = gastrointestinal; Hemato = hematological; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; Resp = respiratory; SGDH = serum glutamic dehydrogenase

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

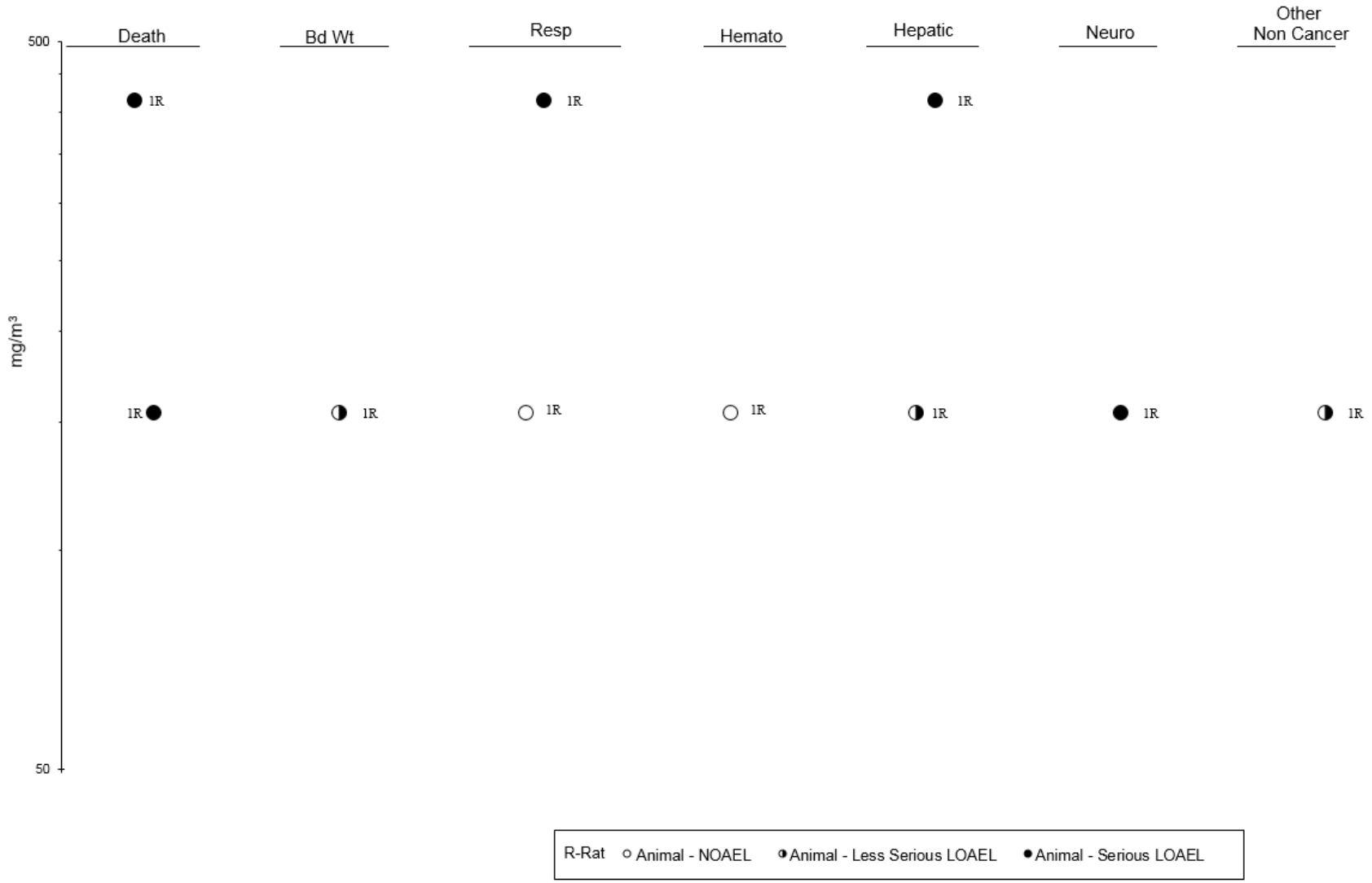


Figure 2-2. Levels of Significant Exposure to Chlordane – Inhalation
Intermediate (15-364 days)

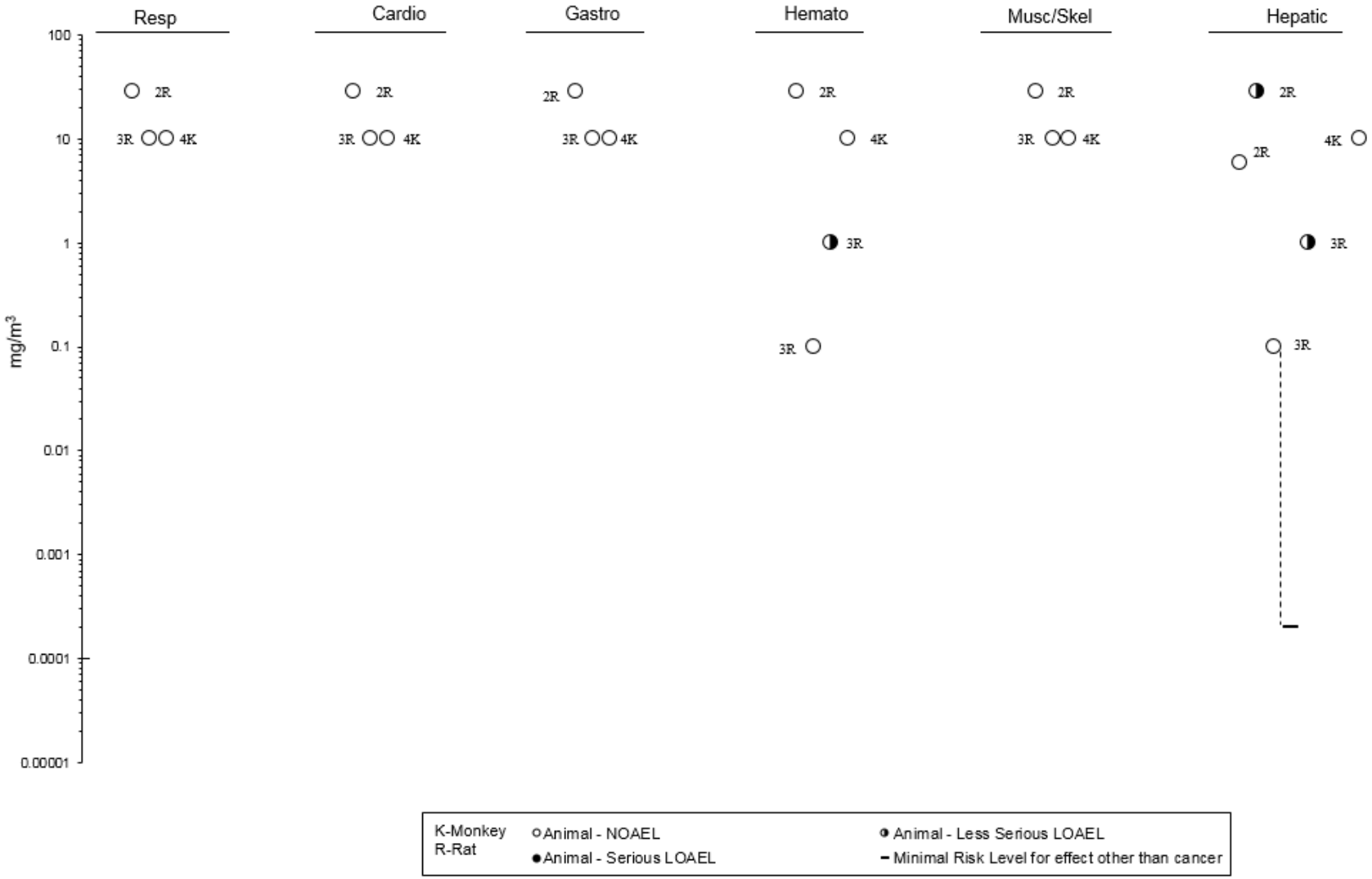


Figure 2-2. Levels of Significant Exposure to Chlordane – Inhalation
Intermediate (15-364 days)

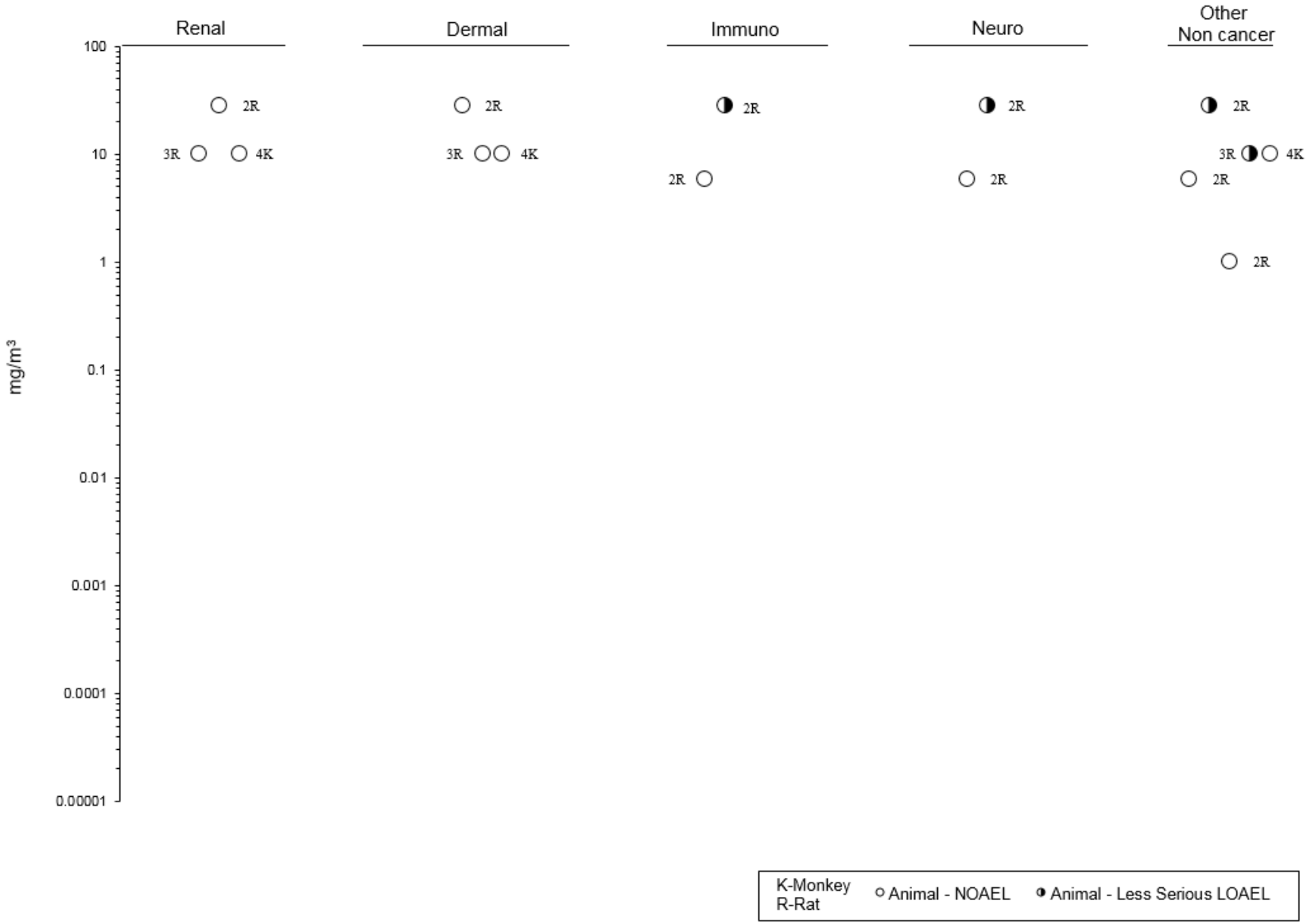


Figure 2-2. Levels of Significant Exposure to Chlordane – Inhalation
Chronic (≥365 days)

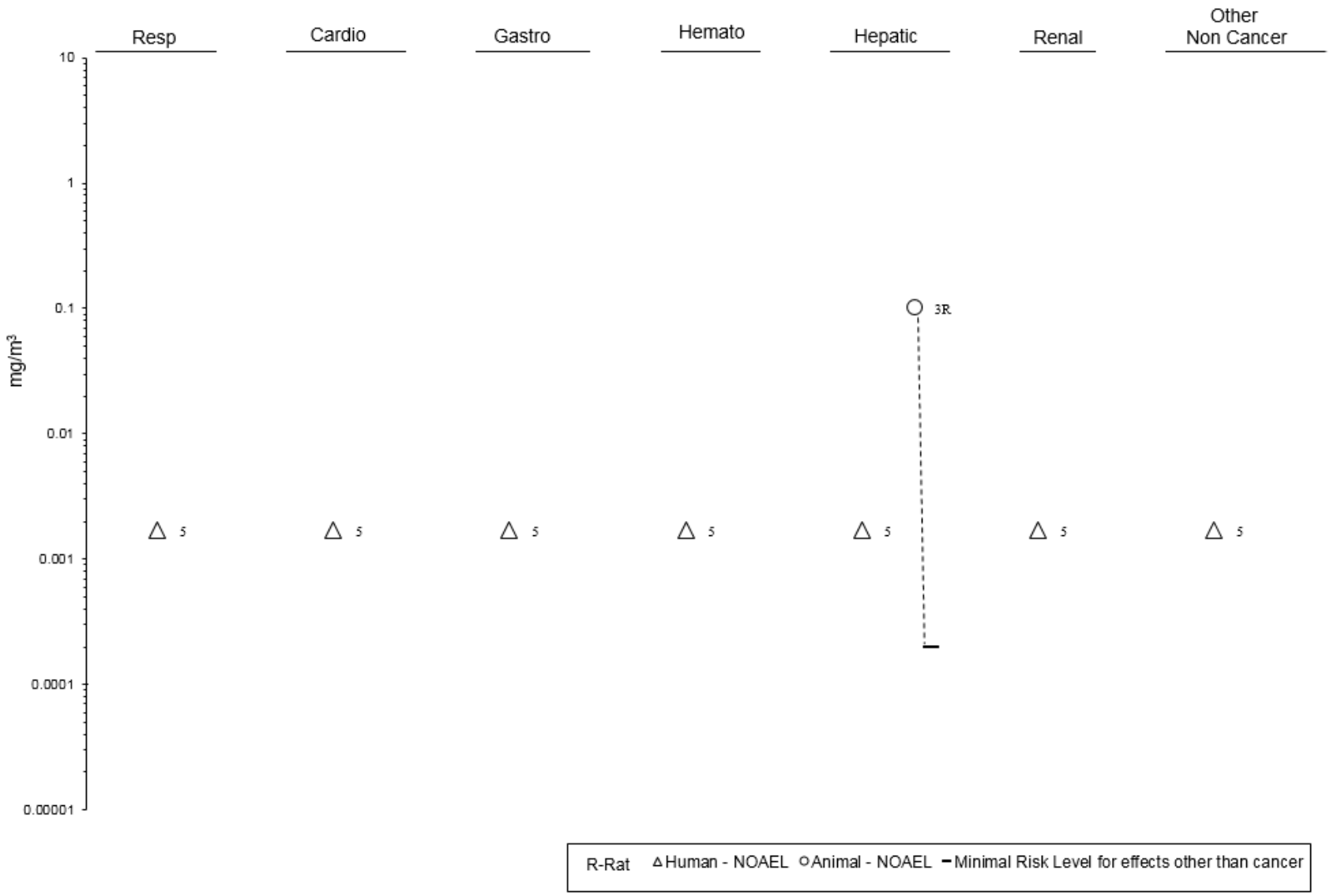


Table 2-2. Levels of Significant Exposure to Chlordane – Oral

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 (Albino) 3–15 M 5–15 F	Once (GO)	0, 200, 300, 400, 500, 600, 700, 800		Death			590	LD_{50}
					Neuro			200	Convulsions
Ambrose et al. 1953a; Chlordane technical									
2	Rat (Albino) 5 (sex NS)	Up to 15 days 1 time/day (GO)	6.25, 12.5, 25, 50, 100, 200		Death			50	50 mg/kg/day: 2/5 died by day 12 100 mg/kg/day: 5/5 died by day 9 200 mg/kg/day: 5/5 died by day 4
					Neuro	25		50	Convulsions and death in two rats on days 9 and 12
Ambrose et al. 1953a; Chlordane technical									
3	Rat (Albino) 5 M 5 F	Up to 7 days (F)	135		Death			135	100% mortality by day 7
Ambrose et al. 1953a; Chlordane technical									
4	Rat (NS)	Once (G)			Death			283	LD_{50}
Ben-Dyke et al. 1970; Chlordane technical									
5	Rat (Wistar)	Once (G)			Death			137	LD_{50}
Boyd and Taylor 1969; Chlordane technical									
6	Rat (NS)	Once (GO)			Death			420	LD_{50}
Deichmann and Keplinger 1970; Chlordane technical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
7	Rat (NS)	Once (GO)			Death			335	LD_{50}
Gaines 1960; Chlordane technical									
8	Rat (NS)	Once (GO)			Death			430	LD_{50}
Gaines 1960; Chlordane technical									
9	Rat (NS)	Once (G)			Death			457	LD_{50}
Lehman 1951; Chlordane technical									
10	Rat (Fischer 344); 8 F	Once (GO)	0, 16, 52, 156, 291	BH, LE, OF	Neuro	52	156	291	≥156: Piloerection, reactivity to handling 291: Clonic-tonic convulsions, tiptoe gait, increased forelimb grip strength
Moser et al. 1995; Chlordane technical									
11	Rat (Fischer 344); 8 F	Up to 14 days (GO)	0, 5, 16, 52, 156	BH, BW, LE, OF	Death			52	100% mortality
					Bd wt	16	52		Body weight loss
					Neuro	16		52	Increased excitability prior to death
Moser et al. 1995; Chlordane technical									
12	Rat (Fischer 344); 19–23 F	GDs 6–19 1 time/day (G)	0, 21, 28	BW, CS, DX, FX, LE, MX, TG	Bd wt			21	33% depressed maternal weight gain
					Develop			21	>30% postnatal pup loss/litter
Narotsky and Kavlock 1995; Chlordane technical									

Table 2-2. Levels of Significant Exposure to Chlordane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
13	Rat (NS)	4 days 1 time/day (GO)			Hepatic		100		Increased serum cholesterol, gamma-GPT; reduced blood sugar, increased relative liver weight and lipid content; increased lipid peroxidation; hepatocellular hypertrophy
Ogata and Izushi 1991; Chlordane technical									
14	Rat (NS)	Once (G)			Musc/skel		260		Hypertonicity of skeletal muscles
Santolucito and Whitcomb 1971; Chlordane technical									
15	Rat (NS)	Once (GO)			Death			350	LD_{50}
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hepatic		200		Increased serum AST and LDH, depressed liver AST, LDH, ChE, G6PDH, hypertrophy, dilatation of centrilobular sinuses, and congestion.
					Renal		200		Congestion, tubular dilation
					Neuro		200		Congestion in the brain
					Other noncancer (adrenal)	200			
Truhaut et al. 1974, 1975; Chlordane technical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
16	Rat (NS)	GDs 7–17 1 time/day (GO)			Death			80	Death in 4/8 dams
					Develop	80			
Usami et al. 1986; Chlordane technical									
17	Mouse (NS)	7 days (3rd trimester) 1 time/day			Develop		1[b]		Altered conditioned avoidance response, open field test, and electroshock seizure threshold
Al-Hachim and Al-Baker 1973; Chlordane technical									
18	Mouse (NS)	7 days 1 time/day (GO)			Death			300	4/10 died
Balash et al. 1987; Chlordane technical									
19	Mouse (NS)	GDs 8–12 1 time/day (GO)			Death			50	3/25 died
					Develop	50			
Chernoff and Kavlock 1982; Chlordane technical									
20	Mouse (NS)	Once (GO)			Death			390	LD_{50}
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hepatic		200		Hepatic hypertrophy, congestion, dilation of centrilobular sinuses, elevated liver ALT and AST and serum ALT and LDH
					Renal		200		Congestion and tubular dilation
					Neuro		200		Congestion in the brain

Table 2-2. Levels of Significant Exposure to Chlordane – 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
					Other noncancer (adrenal)	200			
Truhaut et al. 1975; Chlordane technical									
21	Hamster	Once (GO)			Death			1,720	LD_{50}
					Resp	1,200			
					Cardio	1,200			
					Gastro		1,200		Atrophy of gastric mucosa
					Hepatic		1,200		Decreased liver LDH and increased G6PDH, congestion, dilatation of centrilobular sinuses, and hypertrophy
					Renal		1,200		Congestion and tubular dilatation
					Neuro		1,200		Congestion in the brain
					Other noncancer (adrenal)	1,200			
Truhaut et al. 1974, 1975; Chlordane technical									
22	Rat (NS)	2 weeks ad lib (F)			Death			40 F 80 M	4/5 deaths in females; 5/5 deaths in males
NCI 1977; Chlordane analytical									
23	Rat (NS)	Once (GO)			Neuro		100	200	Paralysis, convulsions
Hrdina et al. 1974; *cis*-Chlordane									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
24	Rat (NS)	Once (GO)			Hepatic		200		Increased blood glucose and urea, decreased liver glycogen, increased gluconeogenesis
					Renal		200		Increased kidney gluconeogenic enzymes, cyclic adenosine monophosphatase, and adenyl cyclase activity
Kacew and Singhal 1973; *cis*-Chlordane									
25	Rat (NS)	Once (GO)			Death			83	LD_{50}
Podowski et al. 1979; *cis*-Chlordane									
26	Mouse (NS)	14 days 1 time/day (GO)			Bd wt	8			
					Hemato	4	8		52% increased lymphocytes
					Immuno	8			
Johnson et al. 1986; *trans*-Chlordane									
INTERMEDIATE EXPOSURE									
27	Rat (Albino) 5 M, 5 F	Up to 163 days (F)	67		Death			32	100% mortality
Ambrose et al. 1953a; Chlordane technical									
28	Rat (NS)	15 days 7 days/week (GO)			Bd wt	25	50		Unspecified body weight loss
					Hepatic		6.25		Intracytoplasmic bodies
Ambrose et al. 1953a; Chlordane technical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
29	Rat (NS)	Weaning through mating, gestation and lactation (F)			Repro			16	Decreased fertility and survivability
Ambrose et al. 1953a; Chlordane technical									
30	Rat (Sprague-Dawley); 7 M, 7 F	28 days 1 time/day (GO)	0, 0.25, 2.5, 25	BC, BW, CS, DI, EA, FI, GN, HE, HP, LE, OF, OW, TM, UR, WI	Bd wt	25			
					Hemato	25			
					Hepatic	M: 0.25 F: 2.5	M: 2.5 F: 25		Increased liver weight, hepatocellular hypertrophy
					Renal	F: 25	M: 0.25		Epithelial hyperplasia, protein and cell debris in tubule luminae
					Endocr	M: 0.25 F: 2.5	M: 2.5 F: 25		Aspherical follicles in thyroid
Bondy et al. 2000; Chlordane technical									
31	Rat (NS)	12 weeks ad lib (F)	0, 2.15, 4.3, 8.6		Neuro	4.3		8.6	Convulsions
Drummond et al. 1983; Chlordane technical									
32	Rat (NS)	2–9 months ad lib (F)			Hepatic		0.125		Centrilobular hypertrophy, cytoplasmic inclusion bodies
					Renal	1.25			
Ortega et al. 1957; Chlordane technical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
33	Rat (NS)	90 days ad lib (F)			Repro		19.5		360% increase in androgen receptor content of the ventral prostate gland
Shain et al. 1977; Chlordane technical									
34	Rat (NS) 7 M, 7 F	28 days 1 time/day (GO)	0, 0.25, 2.5, 25	BW, CS, OF, OW	Bd wt Immuno	25 25			
Tryphonas et al. 2003; Chlordane technical									
35	Mouse (NS)	30 days 1 time/day (GO)			Repro		100		Reduced size of seminiferous tubules, degeneration in spermatogenic epithelium.
Balash et al. 1987; Chlordane technical									
36	Mouse (NS)	18 days GDs 1–18 (F)			Develop	4	8		Decreased delayed hypersensitivity response in offspring
Barnett et al. 1985a; Chlordane technical									
37	Mouse (NS)	19 days GDs 1–19 (F)			Develop		4		Decreased delayed hypersensitivity, mixed lymphocyte reactivity
Barnett et al. 1985b; Chlordane technical									
38	Mouse (NS)	18 days 7 days/week (F)			Immuno Develop	8	4		Decreased liver cell-colony forming capacity
Barnett et al. 1990a; Chlordane analytical									
39	Mouse (NS)	18 days GDs 1–18 (F)			Develop		8		Decreased liver cell-colony forming capacity
Barnett et al. 1990b; Chlordane analytical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
40	Mouse (BALB-C)	GDs 1–18 1 time/day (peanut butter)	0, 8	CS, DX, MX	Develop		8		Depressed numbers of bone marrow colony forming units-granulocyte/ macrophage in female offspring
Blyler et al. 1994; Chlordane analytical									
41	Mouse (NS)	19 days GDs 1–19 (F)			Develop			8.0	Death of 55% of offspring
Cranmer et al. 1984; Chlordane analytical									
42	Mouse (NS)	6 weeks ad lib (F)			Death			20.8	2/5 deaths in males
NCI 1977; Chlordane analytical									
43	Mouse (NS)	19 days GDs 1–19 (F)			Develop	0.16		8	Decreased cell-mediated immunity response
Spyker-Cranmer et al. 1982; Chlordane analytical									
44	Mouse (NS)	18 days GDs 1–18 1 time/day (GO)			Develop		8.0		Decreased 5'-nucleotidase activity in macrophages; activation of macrophages to inflammatory state in mice exposed prenatally
Theus et al. 1992; Chlordane analytical									
45	Rat (NS)	10–20 week 2 times/week (F)			Hepatic		0.1		Increased cytochrome P-450 content at 10 weeks; decreased microsomal protein at 20 weeks
Mahon et al. 1978; *cis*- and *trans*-Chlordane									

Table 2-2. Levels of Significant Exposure to Chlordane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
46	Rat (Albino) 5 M, 5 F	Up to 407 days (F)	0, 0.48, 0.97, 1.9, 3.9, 7.75, 15.5		Bd wt	7.75	15.5		11–18% decrease in body weight
					Hemato	15.5			
					Hepatic	1.9	3.9		Increased liver weight
Ambrose et al. 1953a; Chlordane technical									
47	Rat (Fischer 344) 80 M, 80 F	30 months ad lib (F)	M: 0, 0.045, 0.23, 1.18 F: 0, 0.055, 0.27, 1.41		Bd wt	M 1.18 F 1.41			
					Resp	M 1.18 F 1.41			
					Cardio	M 1.18 F 1.41			
					Gastro	M 1.18 F 1.41			
					Hemato	M 1.18 F 1.41			
					Musc/skel	M 1.18 F 1.41			
					Hepatic	M 1.18 F 0.055[c]	F 0.273		Hepatocellular hypertrophy
					Renal	M 1.18 F 1.41			
					Dermal	M 1.18 F 1.41			
EPA 1985a; Khasawinah and Grutsch 1989a; Chlordane technical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
48	Mouse (ICR) 80 M, 80 F	24 months ad lib (F)	M: 0, 0.12, 0.65, 1.65 F: 0, 0.14, 0.65, 1.65		Bd wt	1.65			
					Resp	1.65			
					Cardio	1.65			
					Gastro	1.65			
					Hemato	1.65			
					Musc/skel	1.65			
					Hepatic	M 0.12 F 0.14	M 0.65 F 0.65		Hepatocellular hypertrophy in males and females
					Renal	1.65			
					Dermal	1.65			
					Cancer			1.65	CEL: hepatocellular adenoma and hemangioma in males
EPA 1985a; Khasawinah and Grutsch 1989b; Chlordane technical									
49	Mouse (CD-1)	18 months ad lib (F)			Death			6.5	86–86% mortality
					Cancer			3.25	CEL: hepatocellular carcinoma
IRDC 1973; Epstein 1976; Chlordane technical									
50	Mouse (B6C3F1) 210 M	Up to 2 years (F)	0, 9.4	BW, CS, GN, HP, LE, OW	Bd wt	9.4			
					Hepatic		9.4		Increased liver weight, hepatocellular hypertrophy
					Cancer			9.4	CEL: liver tumors
Malarkey et al. 1995; Chlordane technical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
51	Mouse (B6D2F1) 160 M	Up to 2 years (F)	0, 9.4	BW, CS, GN, HP, LE, OW	Bd wt	9.4			
					Hepatic		9.4		Increased liver weight, hepatocellular hypertrophy
					Cancer			9.4	CEL: liver tumors
Malarkey et al. 1995; Chlordane technical									
52	Rat (NS)	80 weeks ad lib (F)	M: 0, 16.07, 32.13 F: 0, 11.08, 22.15		Death			F 11.08	18% decreased survival
					Bd wt	M 32.13 F 22.15			
					Resp	M 32.13 F 22.15			
					Cardio	M 32.13 F 22.15			
					Gastro	M 32.13 F 22.15			
					Musc/skel	M 32.13 F 22.15			
					Hepatic	M 32.13 F 22.15			
					Renal	M 32.13 F 22.15			
					Dermal	M 32.13 F 22.15			
					Neuro	M 32.13 F 11.08		22.15	Tremors in females
NCI 1977; Chlordane analytical									

Table 2-2. Levels of Significant Exposure to Chlordane – 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
53	Mouse (NS)	80 weeks ad lib (F)	M: 0, 5.13, 9.64 F: 0, 5.20, 11.02		Death			M 5.13	40% decreased survival of males
					Bd wt	M 9.64 F 11.02			
					Resp	M 9.64 F 11.02			
					Cardio	M 9.64 F 11.02			
					Gastro	M 9.64 F 11.02			
					Musc/skel	M 9.64 F 11.02			
					Hepatic	M 9.64 F 11.02			
					Renal	M 9.64 F 11.02			
					Dermal	M 9.64 F 11.02			
					Neuro	M 5.13 F 5.20		M 9.64 F 11.02	Tremors
					Cancer			M: 5.13 F: 11.02	CEL: hepatocellular carcinoma

NCI 1977; Chlordane analytical

Table 2-2. Levels of Significant Exposure to Chlordane – 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
54	Mouse (C57B1/ 10J) 100 M	24 months (F)	0, 8.6	GN, HP	Cancer			8.6	CEL: liver tumors

Barrass et al. 1993; Chlordane (form not specified)

[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 acute-duration oral minimal risk level (MRL) of 0.001 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive intermediate- and chronic-duration oral MRLs of 0.0006 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd wt or BW = body weight; BC = biochemistry; BH = behavioral; Cardio = cardiovascular; CEL = cancer effect level; ChE = cholinesterase; CS = clinical signs; Develop = developmental; DI = distribution; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; G6PDH = glucose-6-phosphate dehydrogenase; (G) = gavage-not specified; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil vehicle oil; GPT = glutamyl transpeptidase; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose, 50% kill; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Resp = respiratory; TG = teratogenicity; TM = tissue metabolites; UR = urinalysis; WI = water intake

Figure 2-3. Levels of Significant Exposure to Chlordane – Oral

Acute (≤14 days)

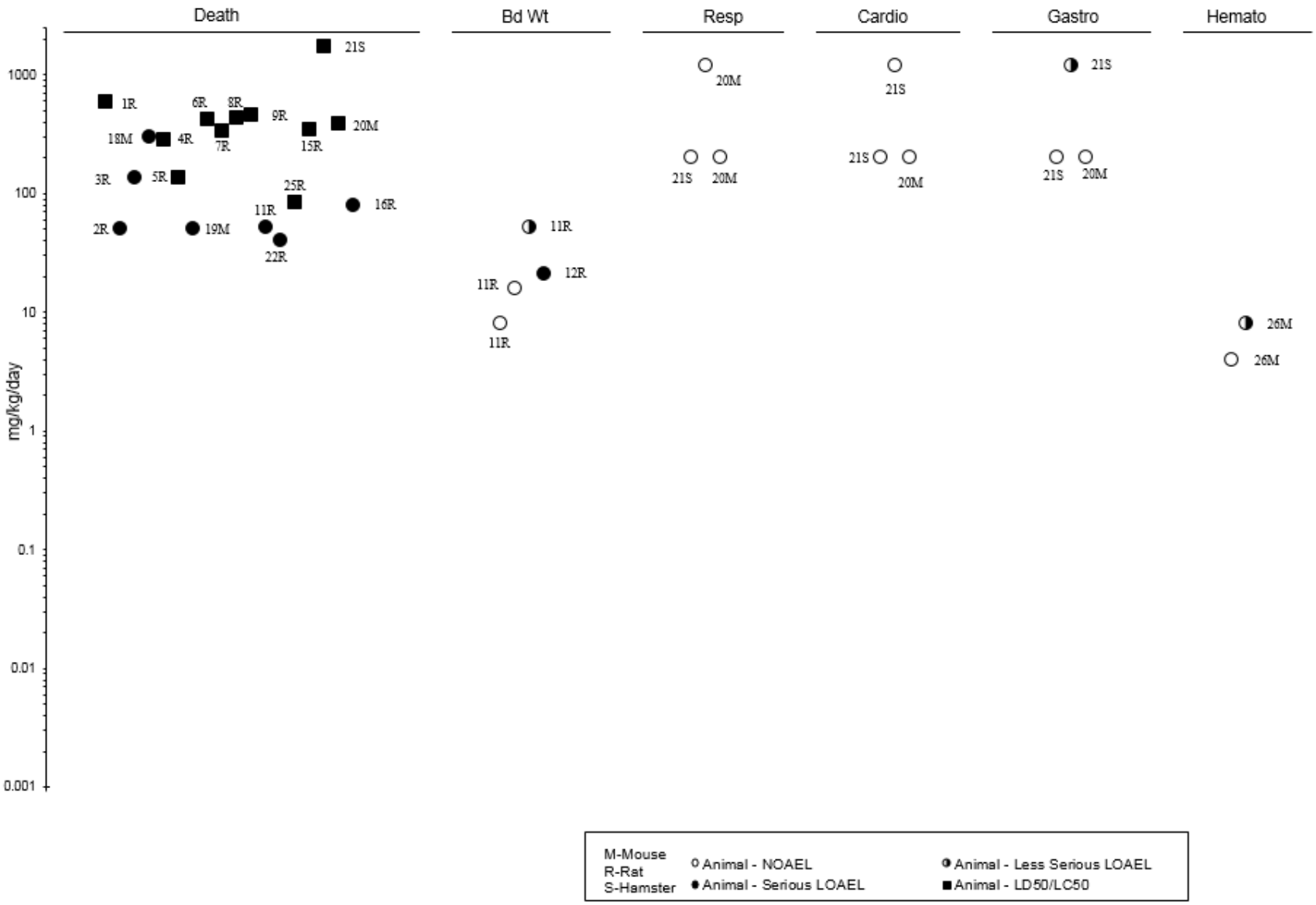


Figure 2-3. Levels of Significant Exposure to Chlordane – Oral
Acute (≤14 days)

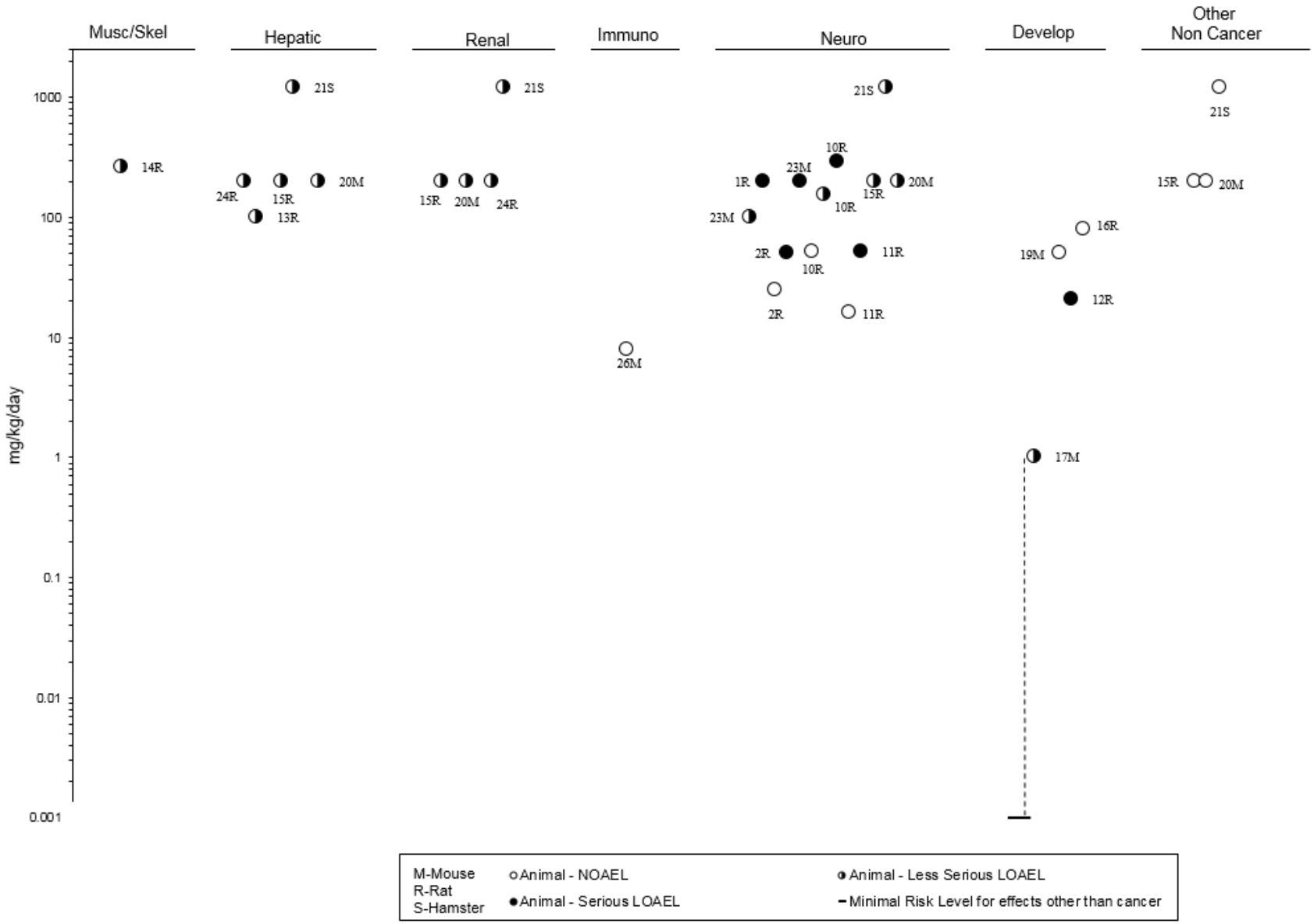


Figure 2-3. Levels of Significant Exposure to Chlordane – Oral
Intermediate (15-364 days)

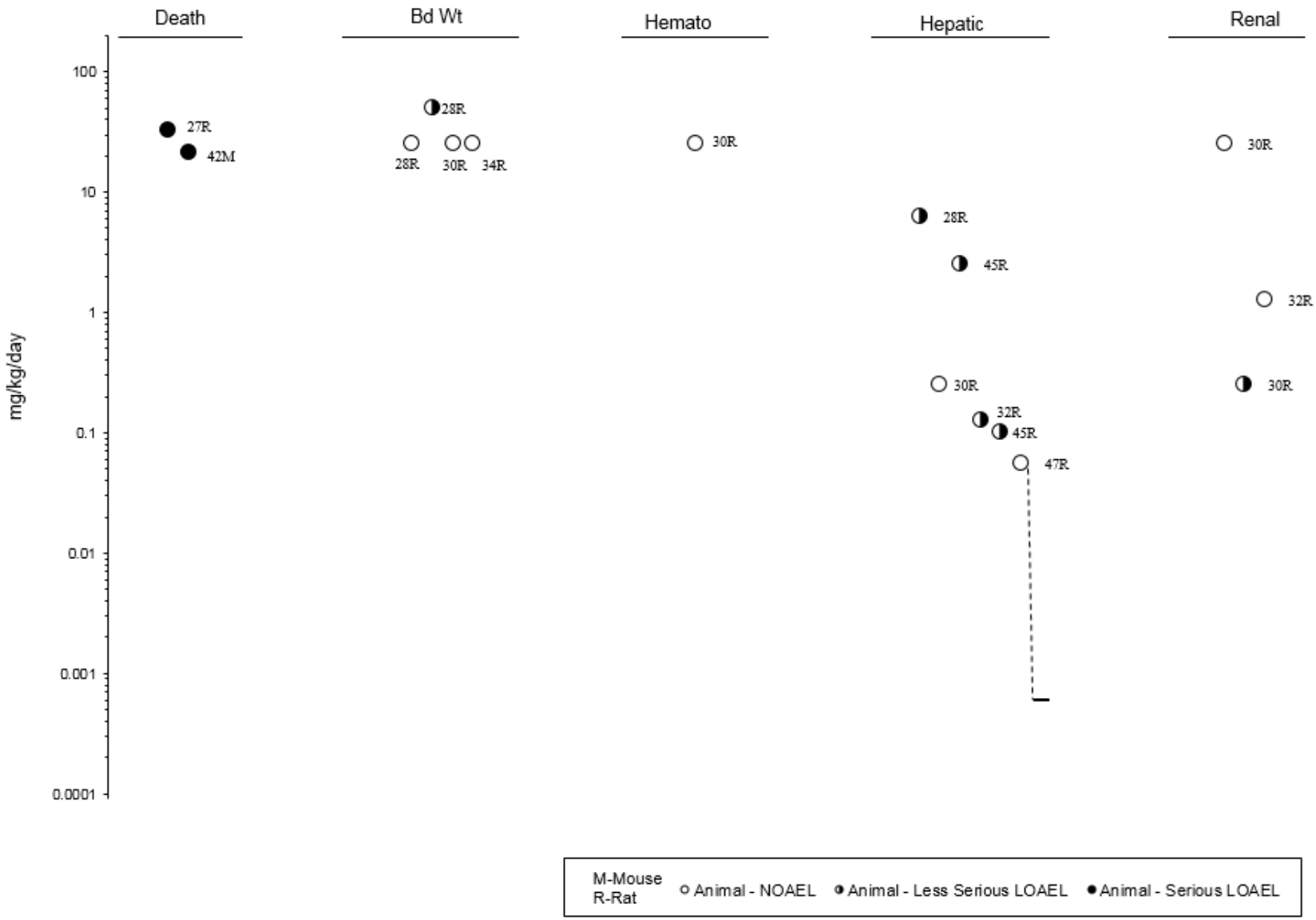


Figure 2-3. Levels of Significant Exposure to Chlordane – Oral
Intermediate (15-364 days)

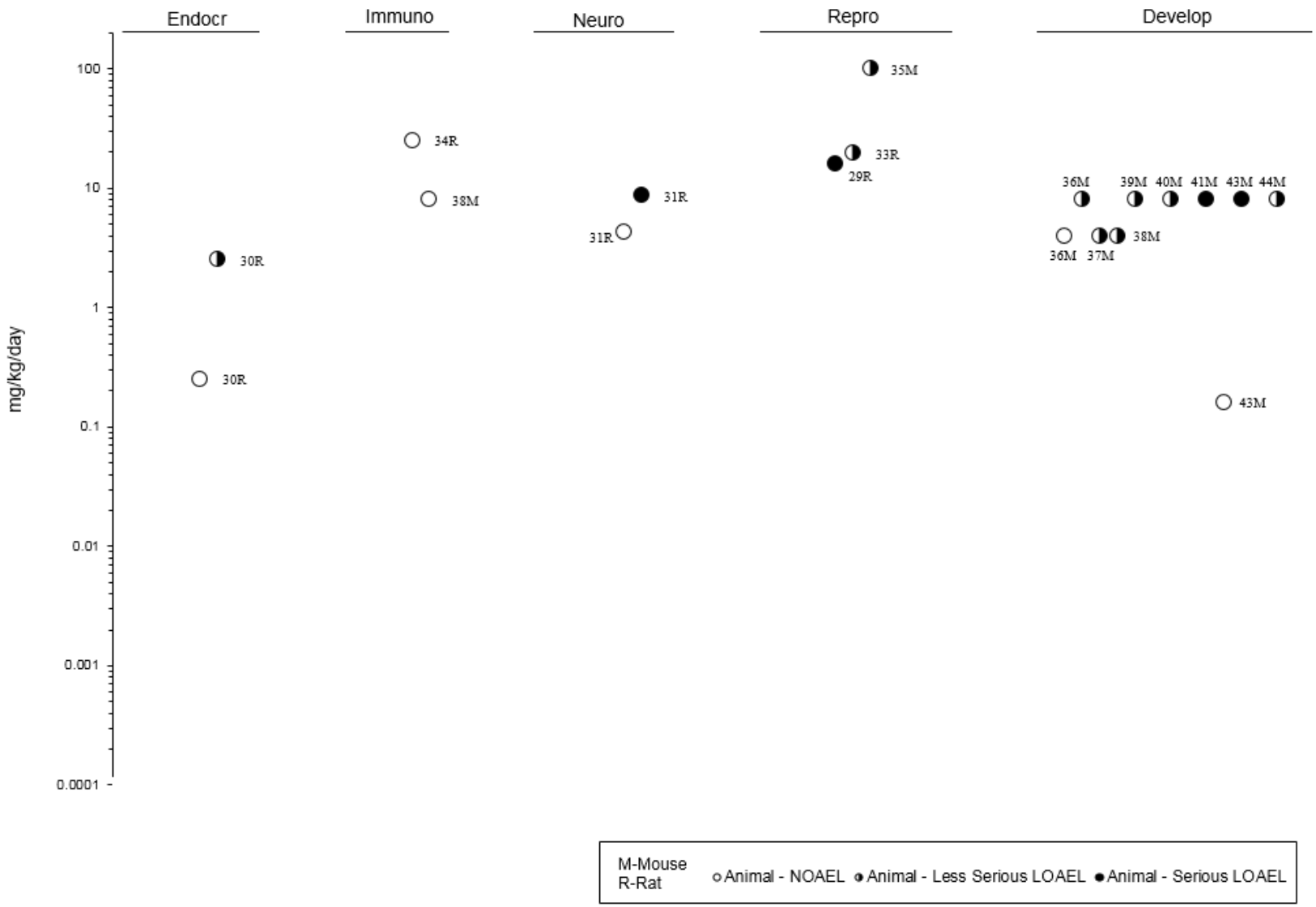


Figure 2-3. Levels of Significant Exposure to Chlordane – Oral
Chronic (≥365 days)

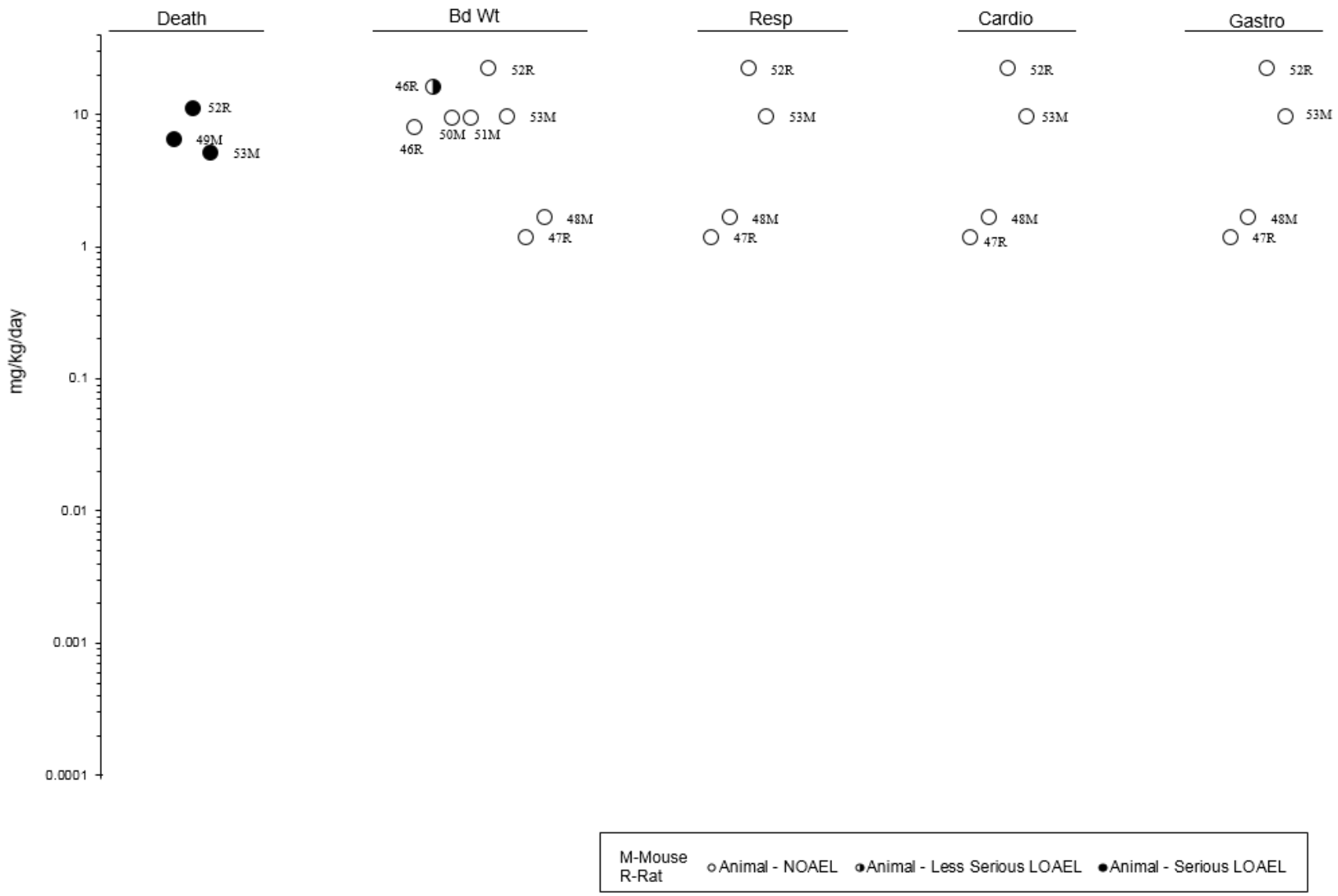


Figure 2-3. Levels of Significant Exposure to Chlordane – Oral
Chronic (≥365 days)

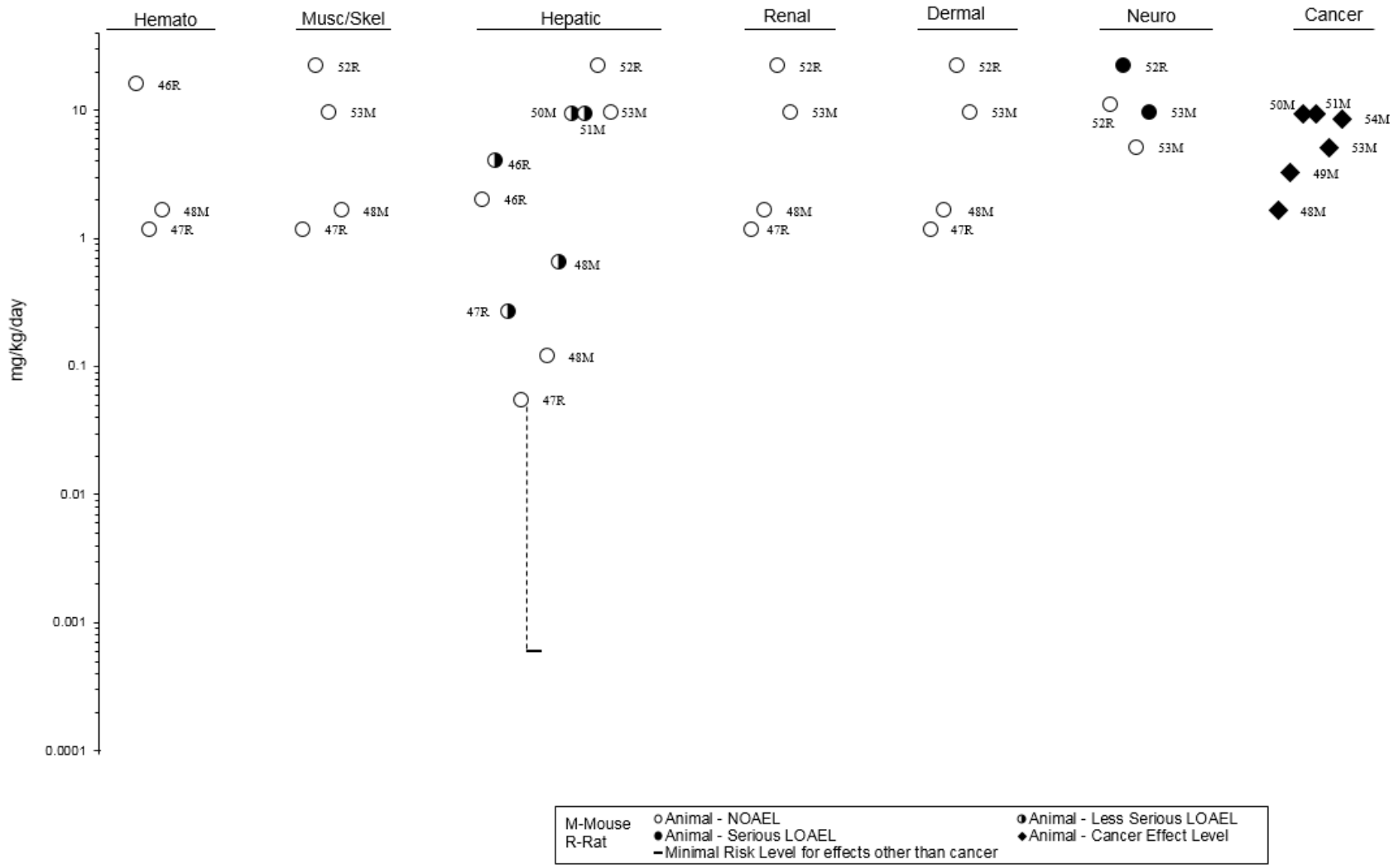


Table 2-3. Levels of Significant Exposure to Chlordane – Dermal

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								
Rat (NS)	1–4 days 1 time/day		Death				217	1/5 died
Ambrose et al. 1953a; Chlordane technical								
Rat (NS)	Once		Death				840 M 530–690 F	LD_{50}
Gaines 1960; Chlordane technical								
Rabbit (NS)	Once		Death				1,150	LD_{50}
Ingle 1965; Chlordane technical								
INTERMEDIATE EXPOSURE								
Guinea pig (NS)	90 days		Dermal			168		Hyperkeratosis
Datta et al. 1977; Chlordane technical								

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

2.2 DEATH

Available epidemiological studies that evaluated mortality among chlordane-exposed workers have serious limitations, including unquantified exposure concentrations and exposure to other pesticides. Retrospective cohort mortality studies of workers in chlordane and other organochlorine manufacturing plants reported no increase in mortality rate and no increase in any specific cause of death attributed to chlordane exposure (MacMahon et al. 1988; Shindell and Ulrich 1986). Wang and MacMahon (1979b) reported no increase in mortality rate in a prospective study of pesticide applicators. In a retrospective mortality study of 1,403 men employed for 23 months at two plants, a significantly increased risk of death from cerebrovascular disease was found, but the authors could not definitively attribute this excess to chlordane exposure (Wang and MacMahon 1979a). In another retrospective mortality study of a cohort of 327 workers exposed for ≥6 months, an increased risk of death due to stomach cancer (standardized mortality ratio [SMR] 303; 95% confidence limit [CL] 61–885) was reported (Ditraglia et al. 1981). However, the study included only three cases of stomach cancer. Furthermore, an 11-year follow-up study of this cohort found no statistically significant excess risk of death from any cause (Brown 1992).

Most cases of acute human oral exposure to chlordane involved accidental ingestion by children (Aldrich and Holmes 1969; Curley and Garrettson 1969; EPA 1980a). The estimated doses of chlordane ingested were 11.0 mg/kg; complete recovery generally followed medical intervention. In humans, an estimated acute oral lethal dose of chlordane (WHO 1984) was between 25 and 50 mg/kg, but documentation was not provided and the method of estimation was not discussed. A man who accidentally ingested an unknown quantity of chlordane developed convulsions shortly after the ingestion and subsequently died (Kutz et al. 1983). No studies were located regarding lethality in humans following longer-term oral exposure to chlordane.

Only one report was found regarding mortality in humans following dermal exposure to chlordane. The usefulness of this report is limited, however, because the individual was exposed to chlordane, DDT, Velsicol AR50, and triton X-100 mixed together in the form of a suspension. After a woman spilled the suspension on the front of her clothes, she became confused, developed convulsions, and died within minutes after exposure (Derbes et al. 1955). At autopsy, the brain, lungs, and kidneys were found to have nonspecific pathological changes. Deaths were not reported in a compilation of cases and personal reports of acute human dermal exposure to chlordane (EPA 1980a).

In a range-finding study, male and female rats (10/sex/group) were exposed by inhalation to chlordane technical for 8 hours/day at 0, 5.8, 28.2, 154, or 413 mg/m^3 for up to 28 days (Khasawinah et al. 1989). The 154 and 413 mg/m^3 exposure levels were terminated after 11 and 3 exposures, respectively, due to unspecified numbers of mortalities; females were reported to die earlier than males. All rats exposed for 28 days at 28.2 mg/m^3 survived. There was no mortality in rats or monkeys exposed to technical chlordane at 10 mg/m^3 for 8 hours/day, 5 days/week for 90 days (EPA 1987f; Khasawinah et al. 1989).

Acute oral LD_{50} values for technical-grade chlordane in the rat range from 137 to 590 mg/kg (Ambrose et al. 1953a; Ben-Dyke et al. 1970; Boyd and Taylor 1969; Deichmann and Keplinger 1970; Gaines 1960). Acute oral LD_{50} values for mice (Truhaut et al. 1974) and hamsters (Truhaut et al. 1974, 1975) were 390 and 1,720 mg/kg, respectively. Truhaut et al. (1975) speculated, on the basis of different activities of liver microsomal enzymes in rats, mice, and hamsters, that species differences in LD_{50} values may reflect differences in the rate of metabolism of the constituents of chlordane. The *cis*-chlordane isomer appears to be somewhat more lethal than chlordane technical; a rat acute oral LD_{50} of 83 mg/kg/day was reported for this isomer (Podowski et al. 1979).

Daily oral dosing of rats or mice for 5–14 days at 50–156 mg/kg/day was lethal (Ambrose et al. 1953a; Chernoff and Kavlock 1982; Moser et al. 1995; Usami et al. 1986). All rats dosed at 32 mg/kg/day died during up to 163 days of treatment (Ambrose et al. 1953a). Decreased survival was observed in mice treated at 6.5 mg/kg/day for up to 18 months (IRDC 1973; Epstein 1976). Oral exposure of female rats to analytical-grade chlordane for up to 80 weeks at 11.08 mg/kg/day resulted in 18% decreased survival; however, survival was not affected in male rats treated at up to 32.13 mg/kg/day (NCI 1977). Oral exposure of male mice to analytical-grade chlordane for up to 80 weeks at 5.13 mg/kg/day resulted in 40% decreased survival; however, survival was not affected in female mice treated at up to 11.02 mg/kg/day (NCI 1977).

Acute dermal LD_{50} values for rats (Gaines 1960) and rabbits (Ingle 1965) treated with technical-grade chlordane were 530–840 and 1,150 mg/kg, respectively.

2.3 BODY WEIGHT

Body weight loss (magnitude not specified) was reported in rats intermittently exposed to chlordane technical by inhalation for up to 12 days at 154 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). Body weight loss was also reported in rats administered chlordane technical by daily gavage for up to 14 days at

52 mg/kg/day; however, this dose level also resulted in 100% mortality (Moser et al. 1995). In a study of rats administered chlordane technical in the food for up to 80 weeks (NCI 1977), body weights of high-dose males (32.13 mg/kg/day) and high-dose females (22.15 mg/kg/day) were slightly less than those of controls throughout most of the study. However, body weights were never less than 90% of control body weights; therefore, the effect is not considered adverse. There were no treatment-related effects on body weight in similarly-treated male and female mice at doses up to 9.64 and 11.02 mg/kg/day, respectively (NCI 1977).

2.4 RESPIRATORY

Physical examination of library workers acutely exposed to high but unquantified concentrations of chlordane from a spill revealed no indication of respiratory effects (NIOSH 1984a). Chest pains, dyspnea, and shortness of breath were reported in a compilation of cases and personal reports of humans accidentally exposed to chlordane by inhalation (EPA 1980a); exposures frequently involved a mixture of chemicals (such as other related and nonrelated pesticides) and vehicles (including petroleum distillates). Therefore, these effects cannot be attributed to chlordane alone. Results of a questionnaire indicated increases, compared with the National Center for Health Statistics 1979 National Health Interview Survey, in sore throat and respiratory infections in humans shortly after their homes were treated for termites (Menconi et al. 1988). Chronic exposure in pesticide treated homes was associated with bronchitis and sinusitis, which increased in incidence with higher concentrations of pesticides in the air. Because aldrin and heptachlor were included with chlordane in the analysis for pesticides in the indoor air, these effects cannot be attributed unequivocally to chlordane exposure. Other limitations of the Menconi et al. (1988) study include self-selection of respondents. Respiratory effects generally were not found in occupational exposure studies (Alvarez and Hyman 1953; Fishbein et al. 1964; Princi and Spurbeck 1951). In a retrospective mortality study of a cohort of 327 workers exposed for ≥6 months at a chlordane manufacturing plant (Ditraglia et al. 1981) and 11 years of follow-up (Brown 1992), there was no increased risk of death from noncancer respiratory disease.

In a series of experiments, rats exposed to 413 mg technical chlordane/m^3 for 3 days had epithelial degeneration and cellular debris in the bronchi and alveoli (EPA 1987f; Khasawinah et al. 1989). Respiratory tract lesions were not observed in rats intermittently exposed to technical chlordane at ≤28.2 mg/m^3 for 28 days or rats or monkeys intermittently exposed at 10 mg/m^3 for 90 days (EPA 1987f; Khasawinah et al. 1989).

No signs of chlordane-induced respiratory tract effects were seen in oral or dermal animal studies that evaluated the respiratory system (EPA 1985a; Khasawinah and Grutsch 1989a, 1989b; NCI 1977; Truhaut et al. 1974, 1975; Velsicol Chemical Co. 1983a, 1983b).

2.5 CARDIOVASCULAR

Tachycardia was among the symptoms attributed to chlordane exposure in a compilation of cases and personal reports of accidental human inhalation exposure to high concentrations of chlordane (EPA 1980b). Cardiovascular effects were not reported in library workers acutely exposed to high but unquantified concentrations of chlordane from a spill (NIOSH 1984a). Cardiovascular effects were not found in occupational exposure studies (Alvarez and Hyman 1953; Fishbein et al. 1964; Princi and Spurbeck 1951). Equivocal evidence of increased risk of cerebrovascular disease was reported in workers involved in the manufacture of chlordane (Wang and MacMahon 1979a).

No signs of chlordane-induced cardiovascular effects were seen in inhalation or oral animal studies that evaluated the cardiovascular system (EPA 1985a; Khasawinah and Grutsch 1989a, 1989b; NCI 1977; Truhaut et al. 1974, 1975).

2.6 GASTROINTESTINAL

Gastrointestinal effects (cramps, diarrhea, nausea) were a consistent observation in a compilation of cases and personal reports of accidental human inhalation exposure to high concentrations of chlordane (EPA 1980a). NIOSH (1984a) also reported gastrointestinal symptoms (nausea, diarrhea) in 4 of 13 humans within 4 days of inhalation and/or dermal exposure as a result of 1% chlordane being spilled in a subterranean library room. The greatest prevalence of symptoms occurred in those directly involved in the cleanup, where potential for exposure to higher concentrations was greatest. Concentrations in air, taken ≈4.5 months after the spill, ranged from 0.0001 to 0.0003 mg/m^3. Because air concentration data are not available for the first 4 days of exposure, concentrations associated with the observed effects cannot be estimated. Occupational exposure, however, has not been associated with gastrointestinal effects. Alvarez and Hyman (1953) reported no gastrointestinal effects in a group of 24 workers involved in chlordane manufacture. Both inhalation and dermal exposure occurred. Princi and Spurbeck (1951) reported no effects in workers involved in the manufacture of insecticides (chlordane, aldrin, and dieldrin) when air concentrations of total chlorinated hydrocarbons were ≤10 mg/m^3; exposure was by inhalation and skin contact for 11–36 months. Fishbein et al. (1964) reported no gastrointestinal effects in

production workers exposed to chlordane concentrations of 0.0012–0.0017 mg/m^3 over a period of 1–15 years.

Atrophy of gastric mucosa was reported in hamsters following single gavage dosing of chlordane technical at 1,200 mg/kg (Truhaut et al. 1974, 1975). No signs of chlordane-induced gastrointestinal effects were seen in other inhalation or oral animal studies that evaluated the gastrointestinal system (EPA 1985a; Khasawinah and Grutsch 1989a, 1989b; NCI 1977; Truhaut et al. 1974, 1975).

2.7 HEMATOLOGICAL

A questionnaire survey revealed that 4% of persons living in homes treated with chlordane to control termites reported anemia as a chronic effect (Menconi et al. 1988). The effect cannot be attributed to chlordane alone, because the quantitative amounts of aldrin and heptachlor were combined with the chlordane measurement in the analysis of indoor air. A number of anecdotal reports of blood dyscrasia associated with organochlorine pesticides (chlordane, lindane, DDT) suggest that there may be an unusually susceptible subpopulation (Ellenhorn and Barceloux 1988). Several cases of blood dyscrasia (aplastic anemia, hemolytic anemia, thrombocytopenic purpura, acute disseminated hemorrhages, pernicious anemia, megaloblastic anemia) were observed in persons exposed to chlordane or heptachlor in their home or garden or as a result of their profession as pest control operators (Epstein and Ozonoff 1987; Infante et al. 1978). The usefulness of these reports is limited because exposure to chlordane was unquantified, the individuals were exposed to other chemicals, and there were other confounding factors. No effects on hemoglobin concentrations or sedimentation rates were found in a group of 24 men employed in chlordane manufacture, where exposure was both via inhalation and dermal contact (Alvarez and Hyman 1953). No effects on typical hematological parameters were found in 34 workers exposed to chlordane at unspecified concentrations (Princi and Spurbeck 1951) or in 15 workers exposed to 0.0012–0.0017 mg/m^3 (Fishbein et al. 1964).

Limited information is available regarding chlordane-induced hematological effects in animals. Among male and female rats intermittently exposed to chlordane technical at 1.0 mg/m^3 for 90 days, females (but not males) exhibited 8% increased leukocyte counts and 26% decreased platelet counts (EPA 1987f; Khasawinah et al. 1989). However, no hematological effects were observed in rats intermittently exposed at ≤28.2 mg/m^3 for 28 days or 154 mg/m^3 for 11 days, or in monkeys similarly exposed to ≤10 mg/m^3 for 90 days (EPA 1987f; Khasawinah et al. 1989). Increased lymphocyte count (52% greater than controls) was reported in mice administered *trans*-chlordane by gavage for 14 days at 8 mg/kg/day (Johnson et al.

1986). However, there were no effects on hematology among rats administered chlordane technical by gavage for 38 days at 25 mg/kg/day (Bondy et al. 2000), other male and female rats receiving chlordane technical from the diet for 30 months at 1.18 and 1.41 mg/kg/day, respectively, or male and female mice receiving chlordane technical from the diet for 24 months at 1.65 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989a, 1989b).

2.8 MUSCULOSKELETAL

Information regarding chlordane-related musculoskeletal effects is limited. In a study of 115 men from the general Swedish male population, persistent organochlorine serum concentrations, including oxychlordane (a chlordane metabolite) and *trans*-nonachlor (a component of chlordane technical) were not associated with bone mineral density (Glynn et al. 2000). No musculoskeletal effects were reported in a compilation of cases and personal reports of acute human exposure (EPA 1980a).

Hypertonicity of skeletal muscles was noted in rats administered chlordane technical once by gavage at 260 mg/kg (Santolucito and Whitcomb 1971). However, these results are not interpreted as indicating that oral exposure to chlordane was associated with musculoskeletal effects because there was no effect on the mechanical response of the muscle measured with a strain-gauge transducer *in situ*. Furthermore, no significant increase in the serum level of creatine phosphokinase was found in rats treated orally with 100 mg/kg/day technical chlordane for 4 days (Ogata and Izushi 1991). Comprehensive histopathological examination performed on rats receiving analytical-grade chlordane from the diet for 80 weeks at up to 32.13 and 22.15 mg/kg/day (males and females, respectively) (NCI 1977) or chlordane technical from the diet for 30 months at up to 1.18 and 1.41 mg/kg/day (males and females, respectively) (EPA 1985a; Khasawinah and Grutsch 1989a) revealed no evidence of effects in the musculoskeletal system. Comprehensive histopathological examinations performed on mice receiving analytical-grade chlordane from the diet for 80 weeks at up to 9.64 and 11.02 mg/kg/day (males and females, respectively) (NCI 1977) or chlordane technical from the diet for 24 months at up to 1.65 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989b) revealed no evidence of effects in the musculoskeletal system.

2.9 HEPATIC

Hepatic effects were not reported in library workers acutely exposed to high but unquantified concentrations of chlordane from a spill (NIOSH 1984a). Jaundice, reflecting liver effects, was sometimes reported in cases of inhalation exposure to chlordane in a compilation of cases and personal reports of accidental exposure (EPA 1980a). When reported, jaundice was frequently associated with

continued exposure such as living in a house in which chlordane had been used to control termites (EPA 1980a). Occupational exposures to chlordane have not generally been associated with liver effects (Alvarez and Hyman 1953; Fishbein et al. 1964; Princi and Spurbeck 1951). However, elevated serum levels of triglycerides, lactic acid dehydrogenase, and gamma-glutamyl transferase were measured in pesticide applicators (Ogata and Izushi 1991). There is little information concerning hepatic effects in humans following oral exposure to chlordane. A compilation of cases and personal reports of human exposure (EPA 1980a) did not suggest that liver effects are a predominant part of the clinical picture for acute exposure. Results of various liver function and damage tests were within normal limits in a 20-month-old male who ingested an unknown amount of technical grade (74%) chlordane (Curley and Garrettson 1969). Evaluations were made at 20 hours to 3 days after exposure.

Biochemical evidence of liver damage (increased serum aspartate transaminase [AST], alanine transaminase [ALT], glutamate dehydrogenase [GDH], bile acids, and cholesterol), as well as hepatocellular enlargement and vacuolation, were observed in rats intermittently exposed to chlordane technical by inhalation at 154 mg/m^3 for 11 exposures or 413 mg/m^3 for 3 exposures (EPA 1987f; Khasawinah et al. 1989). Serum chemistry changes indicative of liver damage occurred in females, and increased liver weight occurred in males intermittently exposed at 28.2 mg/m^3 for 28 days (EPA 1987f; Khasawinah et al. 1989). Both sexes exposed to 28.2 mg/m^3 had centrilobular hepatocyte enlargement. Lesions in the rats exposed to 154 mg/m^3 for 11 exposures included hepatocellular enlargement and vacuolation; frank necrosis occurred in rats exposed to 413 mg/m^3 for 3 exposures. A 90-day inhalation study in male and female rats exposed intermittently to technical chlordane at 0, 0.1, 1.0, or 10 mg/m^3 reported mild liver lesions (hepatocellular enlargement or vacuolization) and slight changes in serum chemistry at ≤1.0 mg/m^3 and increased liver weight in both sexes at 10 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). The lowest concentration, 0.1 mg/m^3, was judged a NOAEL. In monkeys exposed by the same protocol, no effects occurred at 1.0 mg/m^3, but 10 mg/m^3 was associated with increased mean liver weight. The NOAEL of 0.1 mg/m^3 in rats was used to derive intermediate- and chronic-duration inhalation MRLs for chlordane technical as described in the footnote to Table 2-1 and Appendix A.

Liver effects from acute oral exposure to chlordane include liver microsomal enzyme induction, alterations in the activities of mitochondrial enzymes, histochemical and histomorphological alterations, and increased liver weight. In a 14-day feeding study in rats, Den Tonkelaar and Van Esch (1974) reported significant liver drug metabolizing enzyme induction (aniline hydroxylase, aminopyrine demethylase, and hexobarbital oxidase) at dietary concentrations equivalent to 0.50–2.5 mg/kg/day, but not at 0.25 mg/kg/day. Liver microsomal enzyme induction is considered an adaptative effect rather than

an adverse effect. It should be noted, however, that in the case of exposure to chlordane, which induces enzymes associated with its own metabolism, some of the metabolites of chlordane are potentially more toxic than the parent compound. A single oral dose of 200 mg/kg *cis*-chlordane in rats significantly decreased liver glycogen and significantly increased the activities of hepatic enzymes associated with gluconeogenesis (i.e., pyruvate carboxylase, fructose-1,6-diphosphatase, and glucose-6-phosphatase) when measured 1 hour after treatment (Kacew and Singhal 1973; Singhal and Kacew 1976). These investigators also found that the activity of adenyl cyclase increased in the livers of these rats and that levels of hepatic cyclic adenosine monophosphate (cAMP) correspondingly increased. Rats treated by gavage with 100 mg/kg/day technical chlordane for 4 days had increased liver weight and liver lipid content, hypertrophy, and increased serum triglyceride, cholesterol, and gamma-glutamyl transferase (Ogata and Izushi 1991). There were no effects on activities of serum AST, ALT, creatinine phosphokinase, or lactate dehydrogenase (LDH). Liver toxicity characterized by hypertrophy, dilatation of centrilobular sinuses, and congestion by increased serum ALT and LDH and decreased serum cholinesterase, and by decreased liver AST, LDH, cholinesterase, and glucose-6-phosphate dehydrogenase occurred in rats given a single oral dose of 200 mg/kg (Truhaut et al. 1974, 1975). In mice given 200 mg/kg, hepatic hypertrophy, congestion, and dilatation of centrilobular sinuses were also seen (Truhaut et al. 1975). In addition, serum ALT and LDH were increased, as were hepatic ALT and AST. In hamsters given a single gavage dose of 1,200 mg/kg, serum cholinesterase was depressed, while hepatic LDH was decreased and hepatic glucose-6-phosphate dehydrogenase was increased (Truhaut et al. 1974, 1975). Hamsters also had congestion, dilatation of centrilobular sinuses, and hypertrophy. In mice treated by gavage for 2 weeks, liver weight increased at 8 mg/kg/day, but not at 4 mg/kg/day (Johnson et al. 1986); liver histopathology was not performed in this study.

Intracytoplasmic bodies were found in the liver cells of rats administered chlordane technical by gavage for 15 days at ≥6.25 mg/kg/day (Ambrose et al. 1953a). Centrilobular hypertrophy and cytoplasmic inclusions were found in rats exposed to technical chlordane in the diet for 2–9 months at doses ≥0.125 mg/kg/day (Ortega et al. 1957). No histopathological liver lesions or increased levels of serum ALT or alkaline phosphatase were found in rats exposed to chlordane in the diet at 0.1 mg/kg/day for 10–20 weeks (Mahon et al. 1978). However, cytochrome P-450 content was significantly increased at 10 weeks, and microsomal protein content was significantly decreased at 20 weeks, when compared with controls.

In a study of male and female rats administered technical chlordane by daily gavage for 28 days, significantly increased liver weights (59–87% higher than controls) and histopathologic liver lesions

(hypertrophy and changes in the appearance of cytoplasm in males and females; anisokaryosis in females) were observed at 25 mg/kg/day (Bondy et al. 2000). Males also exhibited 13% increased liver weight at a dose level of 2.5 mg/kg/day; there were no apparent effects on the liver at 0.25 mg/kg/day.

In a 30-month oral study of chlordane technical in rats, no liver effects occurred in males at up to 1.18 mg/kg/day, but regional liver hypertrophy occurred in females at 0.27 mg/kg/day (EPA 1985a, Khasawinah and Grutsch 1989a). The NOAEL for liver effects in the female rats was 0.055 mg/kg/day; this NOAEL served as the basis for deriving intermediate- and chronic-duration oral MRLs for chlordane as described in the footnote in Table 2-2 and Appendix A. Significantly increased liver weight, liver cell inclusion bodies, and hepatocellular hypertrophy were found in rats given technical chlordane in the diet at doses ≥4 mg/kg/day for 407 days (Ambrose et al. 1953a). These lesions were not observed at 2 mg/kg/day. A 24-month oral study of chlordane technical in mice identified NOAELs of 0.12 and 0.14 mg/kg/day (males and females, respectively) and a LOAEL of 0.65 mg/kg/day for histopathologic liver lesions in both sexes (hepatocellular swelling and degeneration in males and females and necrosis in males) (EPA 1985a; Khasawinah and Grutsch 1989b). In an unpublished 18-month dietary study in mice (IRDC 1973), which was reviewed by Epstein (1976), significantly increased liver weights and hepatocytomegaly were observed at all dose levels tested (0.65–6.5 mg/kg/day).

Malarkey et al. (1995) reported chlordane-induced hepatocellular hypertrophy, frequent micronucleate hepatocytes, and hepatoproliferative lesions composed predominantly of acidophilic hepatocytes in nearly 100% of male B6C3F1 and B6D2F1 mice administered technical chlordane in the diet for a lifetime at an estimated dose of 9.4 mg /kg/day. Centrilobular hypertrophy was detected within 50 days after the initiation of treatment, persisted in virtually all treated mice, and declined in prevalence and severity as tumor development progressed. Barrass et al. (1993) reported chlordane-induced hepatocellular hypertrophy in male C57B1/10J mice that received chlordane in the diet for up to 2 years at an estimated dose of 8.6 mg/kg/day.

NCI (1977) reported no compound-related liver lesions in male or female rats receiving analytical-grade chlordane (72% *cis* and 23% *trans* isomers) from the diet for up to 80 weeks at doses as high as 32.13 and 22.15 mg/kg/day, respectively. NCI (1977) reported no compound-related nonneoplastic liver lesions in similarly-treated male or female mice at doses as high as 9.64 and 11.02 mg/kg/day, respectively.

Results from several studies provide evidence for mechanisms of chlordane-induced liver toxicity. The primary effect, induction of hepatic cytochrome P-450 and other microsomal protein, is accompanied by a

large increase in the volume of the smooth endoplasmic reticulum, which results in hepatocellular enlargement and hypertrophy (Khasawinah et al. 1989). These effects appear to be reversible. In mice treated repeatedly over several weeks, the body burden of the chlordane isomers decreased, and the body burden of oxychlordane increased with time (Hirasawa and Takizawa 1989). This suggests that chlordane induces its own metabolism, probably to intermediates that bind to and disrupt the function of vital cellular macromolecules (Brimfield and Street 1981). The components and metabolites of chlordane may exert their effects by altering the permeability of the mitochondrial membrane, inhibiting mitochondrial oxidative phosphorylation (Ogata et al. 1989). Also, chlordane may induce production of superoxide (Suzaki et al. 1988), which may result in lipoperoxidation, a known mechanism of toxicity to the liver. In support, Bagchi and coworkers (Bagchi et al. 1995; Stohs et al. 1997) reported 3-fold increased lipid peroxidation in the liver of female rats administered chlordane by gavage.

2.10 RENAL

Evidence of altered renal function was not reported in library workers acutely exposed to high but unquantified concentrations of chlordane from a spill (NIOSH 1984a), or in a compilation of cases and personal reports of accidental exposure (EPA 1980a). No kidney effects were found in occupational studies of chlordane manufacture (Alvarez and Hyman 1953; Fishbein et al. 1964; Princi and Spurbeck 1951). Few data were located regarding renal effects in humans after oral exposure to chlordane. A compilation of cases and personal reports (EPA 1980a) did not mention kidney effects as a part of the clinical picture of acute human exposure. In one case report, no apparent renal effects were observed in an 18-year-old girl 24–48 hours after an acute exposure to 32 mg/kg of chlordane (Dadey and Kammer 1953). Because the patient vomited after ingestion, the dose of 32 mg/kg does not reflect the dose available for absorption.

The kidney was evaluated in a series of intermediate-duration studies that employed inhalation exposure to chlordane technical (EPA 1987f; Khasawinah et al. 1989). Increased kidney weight (magnitude not specified), in the absence of histopathologic kidney lesions, was reported for male (but not female) rats intermittently exposed for 28 days at 28.2 mg/m^3; therefore, the 28.2 mg/m^3 level is considered a NOAEL. Elevated kidney weights (9–11% higher than controls) were reported in both sexes of rats intermittently exposed for 90 days at 10 mg/m^3, in the absence of histopathologic kidney lesions; therefore, the 10 mg/m^3 level is considered a NOAEL. No kidney effects were observed in monkeys exposed for 90 days at 10 mg/m^3.

In acute gavage studies of chlordane technical, Truhaut et al. (1974, 1975) reported congestion of the kidneys in rats and mice treated at 200 mg/kg and hamsters treated at 1,200 mg/kg, but kidney weight was unaffected. A single oral dose of 200 mg/kg *cis*-chlordane significantly increased kidney gluconeogenic enzymes, kidney basal and fluoride-stimulated adenyl cyclase, and cyclic AMP (Kacew and Singhal 1973). No histopathological renal lesions were found in rats exposed to chlordane technical for 2–9 months at 1.25 mg/kg/day (Ortega et al. 1957). No histopathological lesions of the kidney were observed in male or female rats receiving analytical-grade chlordane from the diet for up to 80 weeks at doses as high as 32.13 and 22.15 mg/kg/day, respectively, or in male or female mice at doses up to 9.64 and 11.02 mg/kg/day, respectively (NCI 1977). No histopathological lesions of the kidney, no blood chemistry alterations suggesting kidney effects, and no effects on urinalysis were reported in male or female rats receiving chlordane technical from the diet for up to 30 months doses as high as 1.18 and 1.41 mg/kg/day, respectively, or male or female mice treated for up to 24 months at doses as high as 1.65 mg/kg/day (EPA 1985a, Khasawinah and Grutsch 1989b). Histological examination of the kidneys of rats receiving chlordane technical from the diet for up to 407 days at doses as high as 16 mg/kg/day revealed no lesions (Ambrose et al. 1953a).

Bondy et al. (2000) reported significantly increased mean absolute (but not relative) kidney weight in male (but not female) rats administered chlordane technical by gavage for 28 days at 25 mg/kg/day; clinical chemistry analysis revealed significantly increased blood urea nitrogen (BUN) and significantly decreased serum creatine kinase. There was clear evidence of histopathologic kidney lesions at 25 mg/kg/day. There was some evidence for treatment-related kidney lesions in male rats at 0.25 and 2.5 mg/kg/day as well (incidences of 2/7 and 3/7, respectively, compared to 0/7 controls).

2.11 DERMAL

Dermatitis was reported to occur in persons living in homes treated with chlordane at a greater frequency than in a reference population (Menconi et al. 1988). The effects, however, cannot be attributed to chlordane alone, because aldrin and heptachlor were included in the analysis for chlordane in the indoor air. A compilation of cases and personal reports (EPA 1980a) did not mention dermal effects as a part of the clinical picture of acute human exposure.

No dermal effects were found in rats intermittently exposed to technical chlordane by inhalation for 28 days at up to 28.2 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). There was no histopathological evidence of chlordane-induced dermal effects in male or female rats receiving chlordane technical from

the diet for 30 months at up to 1.18 and 1.41 mg/kg/day, respectively (EPA 1985a; Khasawinah and Grutsch 1989a), or male or female mice receiving chlordane technical from the diet for up to 24 months at doses up to 1.65 mg chlordane/kg/day (EPA 1985a; Khasawinah and Grutsch 1989b). There was no histopathological evidence of treatment-related dermal effects following dietary administration of analytical-grade chlordane for up to 80 weeks to male and female rats at up to 32.13 and 22.15 mg/kg/day, respectively, or male or female mice treated at up to 9.64 and 11.02 mg/kg/day, respectively (NCI 1977).

2.12 OCULAR

A compilation of cases and personal reports (EPA 1980a) did not mention ocular effects as a part of the clinical picture of acute human exposure.

No ocular effects were found in rats intermittently exposed to technical chlordane by inhalation for 28 days at up to 28.2 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). No ophthalmoscopic or histopathological changes were observed in the eyes or skin of rats or monkeys similarly exposed at 10 mg/m^3 for 90 days (EPA 1987f; Khasawinah et al. 1989). There was no histopathological evidence of chlordane-induced ocular effects in male or female rats receiving chlordane technical from the diet for 30 months at doses up to 1.18 and 1.41 mg/kg/day, respectively (EPA 1985a; Khasawinah and Grutsch 1989a), or male or female mice receiving chlordane technical from the diet for up to 24 months at doses up to 1.65 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989b). There was no histopathological evidence of treatment-related dermal effects following dietary administration of analytical-grade chlordane for up to 80 weeks to male and female rats at doses up to 32.13 and 22.15 mg/kg/day, respectively, or male or female mice similarly treated at doses up to 9.64 and 11.02 mg/kg/day, respectively (NCI 1977).

2.13 ENDOCRINE

Nagayama et al. (2007) reported approximately 2-fold higher concentrations of selected organochlorine substances (polychlorinated biphenyls [PCBs], dioxin-like compounds, DDT, hexachlorocyclohexanes, chlordane, and hexachlorobenzene) in the breast milk of Japanese mothers who gave birth to neonates with cretinism (congenital hypothyroidism usually owing to maternal hypothyroidism; n=22) compared with a group of 102 mothers who gave birth to normal neonates. After adjustments for parity and mother's age, separate significant associations were noted for hexachlorobenzene, DDT, chlordane, and hexachlorocyclohexanes.

Increased height of thyroid follicular epithelial cells was observed in male rats exposed to chlordane technical by inhalation at 154 mg/m^3, 8 hours/day, 5 days/week for up to 11 exposures (EPA 1987f; Khasawinah et al. 1989) and in other male rats similarly exposed at 28.2 mg/m^3 for 28 days; thyroid weight was increased in a group of male rats exposed at 5.8 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). In similarly-designed 90-day inhalation experiments in rats and monkeys, a slightly increased height in the follicular cells of the thyroid was found in rats exposed at 10 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). In studies that employed single gavage dosing of chlordane technical, no histopathological lesions of the adrenal were found in rats or mice dosed at 200 mg/kg or hamsters dosed at 1,200 mg/kg (Truhaut et al. 1974, 1975).

2.14 IMMUNOLOGICAL

Chlordane caused statistically significant immune alterations in humans who had been exposed to chlordane aerosols in the home or in the workplace for periods ranging from 3 days to 15 months (average exposure period, 5.84 months) (McConnachie and Zahalsky 1992). The length of time from exposure to testing ranged from 4 months to 10 years, and the mean interval was 2.4 years. Impaired proliferative responses to all three plant mitogens tested suggested that chlordane exposure was associated with immune deficiency. Eleven of 12 subjects tested for autoimmunity demonstrated an increased titer of a form of autoantibody.

Tryphonas et al. (2003) administered technical chlordane, *trans*-nonachlor, or *cis*-nonachlor to male and female Sprague-Dawley rats by gavage for 28 days at doses up to 25 mg/kg/day. Significantly increased serum IgM was observed in high-dose female rats. Both the *trans*- and *cis*-nonachlor-treated groups exhibited more pronounced immunological effects than did those treated with technical chlordane.

Reduced thymus weight was observed in female rats, but not male rats, intermittently exposed by inhalation to chlordane technical for 28 days at 28.2 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). There was no effect on thymus weight among male or female rats exposed for 90 days at 10 mg/m^3 and no histological lesions in thymus or lymph nodes of similarly-exposed monkeys. However, immune function was not assessed.

In single-dose gavage treatment with chlordane technical, no histopathological lesions of the spleen were found in rats or mice treated at 200 mg/kg or in hamsters treated at 1,200 mg/kg, but tests of immune

function were not performed (Truhaut et al. 1974, 1975). In a 14-day gavage study, no definitive evidence of immune dysfunction was observed in mice treated at 8 mg/kg/day, but leukocytosis associated with lymphocytosis were noted (Johnson et al. 1986). Oral treatment of adult mice for 18 days with 8 mg/kg/day had no effect on granulocyte-macrophage and spleen colony forming stem cell populations in the bone marrow (Barnett et al. 1990a). No effects on spleen weight or spleen histology were found in rats receiving technical chlordane from the diet for 2–9 months at 0.125 or 1.25 mg/kg/day (Ortega et al. 1957) or in other rats treated for up to 407 days at up to 16 mg/kg/day (Ambrose et al. 1953a). However, only six rats/sex/group were used and immune function was not assessed.

Miyagi et al. (1998) examined the effect of chlordane on chemotaxis of monkey neutrophils and monocytes *in vitro*. Chlordane was found to inhibit chemotaxis of neutrophils and monocytes toward interleukin-8 and RANTES (chemokines), respectively, suggesting that chlordane might alter leukocyte-related immune functions.

2.15 NEUROLOGICAL

Central nervous system effects including ataxia, headache, dizziness, irritability, excitability, confusion, incoordination, muscle tremors, seizures, convulsions, and coma have been described in a compilation of cases and personal reports of humans accidentally exposed by inhalation to unquantified concentrations of chlordane and following acute oral exposure to insecticidal formulations of chlordane (EPA 1980a).

EPA (1986d) reported three cases of optic neuritis that may have been due to chlordane exposure in homes treated for termites. Humans experienced neurological symptoms (headache, fatigue, sleeping disturbance, blurred vision, weakness, fainting, confusion) shortly after their homes were treated for termites (Menconi et al. 1988). Chronic exposure in the treated homes was associated with migraines and neuritis/neuralgia, which increased in incidence with higher concentrations of pesticide in the air. Because aldrin and heptachlor were included in the analysis for chlordane in indoor air, these effects cannot be attributed unequivocally to chlordane. NIOSH (1984a) reported neurological symptoms (headache, dizziness, blurred vision, irritability, paresthesia, muscle dysfunction) in 4 of 13 humans within 4 days of inhalation and/or dermal exposure as a result of 1% chlordane being spilled in a subterranean library room. The greatest prevalence of symptoms occurred in those directly involved in the cleanup, where the potential for exposure to the highest concentrations was greatest. Concentrations in air, taken ≈4.5 months after the spill, ranged from 0.1 to 0.3 $\mu g/m^3$. Because air concentration data were not available for the first 4 days of exposure, concentrations associated with the observed effects

cannot be estimated. No neurological effects, however, were found in epidemiological studies of workers in chlordane manufacture (Alvarez and Hyman 1953; Fishbein et al. 1964; Princi and Spurbeck 1951). In a retrospective mortality study of 1,403 men employed for ≥3 months at two plants, a significantly increased risk of death from cerebrovascular disease was found, but the authors could not definitively attribute this excess to chlordane exposure (Wang and MacMahon 1979a).

By accident, part of the public water system of Chattanooga, Tennessee, became contaminated with chlordane, and the tap water of 42 houses had concentrations ranging from 0.1 to 92,500 ppb (Harrington et al. 1978). When the affected residents were surveyed, 18% reported neurological symptoms consistent with acute chlordane toxicity. Serum levels of *trans*-nonachlor and oxychlordane, however, were approximately twice as high in asymptomatic as in symptomatic individuals, raising serious questions about the validity of the association between exposure to chlordane and the reported effects. Most of the information on acute human oral exposure comes from cases of accidental or suicidal ingestion; therefore, doses of ingested chlordane are not readily quantifiable. Determination of a dose-effect response is further complicated because vomiting or lavage reduced the amount of ingested chlordane actually available for systemic absorption. In one such case, ingestion of 32 mg/kg of chlordane by a girl resulted initially in diplopia, blurred vision, and twitching of the extremities, followed by vomiting and eventually muscle tremors and generalized convulsions (Dadey and Kammer 1953). The investigators also estimated that after vomiting, only about 10 mg/kg was available for absorption. In another case, a man who ingested 3,041 mg/kg chlordane developed seizures and became comatose (Olanoff et al. 1983), but he also vomited, invalidating this dose. Clonic convulsions also developed in a 4-year-old girl who ingested chlordane (Aldrich and Holmes 1969). A dose of 0.15 mg/kg was estimated after gastric lavage. In a 15-month-old child who ingested 11.1 mg/kg chlordane, tremors and convulsions began about 3 hours after ingestion, which was prior to gastric lavage (Lensky and Evans 1952). These subsided by the second day, followed by moderate ataxia and irritability. Convulsions were also observed in patients who ingested unknown quantities of chlordane (Curley and Garrettson 1969; Kutz et al. 1983).

Kilburn and Thornton (1995) assessed measures of neurobehavioral function in a group of 216 adults who had been exposed to chlordane at an apartment complex in April of 1987 following application to external wood surfaces and soil. Later in 1987 and in 1988, the group was exposed to additional chlordane and chlorpyrifos applications. Tests for chlordane residue in 1990 and 1991 revealed concentrations ≥0.5 μg/929 cm^2 on 85% of 81 samples from external wood surfaces. Indoor concentrations as high as 13.6 μg/929 cm^2 were obtained on wipe samples, and 8-hour air samples taken from some of the apartments revealed chlorinated insecticide levels >0.5 $\mu g/m^3$. Eight subjects occupying the apartments

had elevated blood levels of heptachlor (range 110–186 ppb), oxychlordane (70–150 ppm), and *trans*-nonachlor (76–200 ppm). During June–September 1994, each of the 216 subjects underwent a battery of neurophysiological and neuropsychological testing and provided information regarding the frequency of 35 respiratory, neurologic, and vegetative complaints. A referent group of 174 adults of similar age, educational level, weight, height, and sex ratio was likewise assessed. Compared to the referents, exposed subjects exhibited significantly impaired performance of balance, reaction times, Culture Fair (measure of nonverbal nonarithmetical intelligence), digit symbol, verbal recall, and trail-making (visual attention and task switching); significantly elevated mood-state scores (tension, depression, anger, vigor, fatigue, confusion); and elevated frequencies of respiratory, neurobehavioral, and rheumatic symptoms.

Abnormal respiratory movements, excess salivation, and convulsions occurred in rats intermittently exposed by inhalation to chlordane technical for 11 exposures at 154 mg/m^3 or 3 exposures at 413 mg/m^3 (EPA 1987; Khasawinah et al. 1989). Female rats intermittently exposed by inhalation for 28 days at 28.2 mg/m^3 showed hypersensitivity to touch from day 16 onward (EPA 1987f; Khasawinah et al. 1989). There were no overt signs of neurotoxicity or histopathologic brain lesions in rats or monkeys intermittently exposed by inhalation for 90 days at 10 mg/m^3.

Central nervous system effects consisting of tremors, convulsions, and paralysis of the hindlimbs occurred in rats following single gavage doses of *cis*-chlordane ≥200 mg/kg; hypothermia was noted at (Hrdina et al. 1974). Histological examination of the brains of rats and mice given a single oral dose of chlordane technical at 200 mg/kg and hamsters given a single dose of 1,200 mg/kg revealed congestion in the brain (Truhaut et al. 1975). In rats administered chlordane technical by gavage once at ≥200 mg/kg/day or for 9–12 days at 50 mg/kg/day, convulsions preceded death (Ambrose et al. 1953a). No ataxia or change in the level of cerebral amino acids were observed in mice treated by gavage with 25 mg/kg/day for 45 consecutive days (Matin et al. 1977). In a 12-week dietary study, a dose of 5 mg/kg/day caused convulsions in rats (Drummond et al. 1983). In an 80-week study, analytical-grade chlordane induced tremors in female rats at 22.15 mg/kg/day, but not at 11.08 mg/kg/day and only during week 44 (NCI 1977). Similar signs were not observed in male rats, which were tested at up to 32.13 mg/kg/day. No brain lesions were found in rats of either sex. Similarly-treated male and female mice exhibited tremors at 9.64 and 11.02 mg/kg/day, respectively, in the absence of histopathologic brain lesions (NCI 1977). Neither clinical signs nor histopathological lesions of the nervous system were observed in a 30-month study in which rats received chlordane technical from the diet at up to 1.18 and 1.41 mg/kg/day, respectively (EPA 1985a; Khasawinah and Grutsch 1989a) or a similarly-designed

24-month dietary study of mice at doses up to 1.65 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989b).

2.16 REPRODUCTIVE

Chronic exposure in homes treated with chlordane for termites was associated with an increased incidence of unspecified ovarian and uterine disease, compared with a reference population (Menconi et al. 1988). Because aldrin and heptachlor were included in the analysis for chlordane in indoor air, these effects cannot be unequivocally attributed to chlordane.

There was no histopathological evidence of treatment-related effects on the reproductive organs of rats intermittently exposed to chlordane technical by inhalation for 28 days at 28.2 mg/m^3, or other rats or monkeys similarly exposed for 90 days at 10 mg/m^3 (EPA 1987; Khasawinah et al. 1989). However, reproductive function was not assessed. Histological examination of the testes of rats and mice given a single oral dose of 200 mg/kg or hamsters given a single oral dose of 1,200 mg/kg revealed no lesions (Truhaut et al. 1975), but reproductive function was not assessed. In the only evaluation of fertility with oral exposure, Ambrose et al. (1953a) reported reduced fertility, reflected as a reduction in the number of mated females that delivered litters, when male and female rats were fed a diet that provided chlordane technical at 16 mg/kg/day. Treatment began at weaning of the parental generation and continued through lactation. None of the litters survived to weaning. Treatment of male mice by gavage at 100 or 300 mg/kg/day for 30 days resulted in reduced size of seminiferous tubules and degeneration of spermatogenic epithelium (Balash et al. 1987). Consumption of chlordane from the diet at 19.5 mg/kg/day by male rats for 90 days increased androgen receptor sites in the ventral prostate (Shain et al. 1977). There were no effects on ventral prostate or testicular weight, or on plasma testosterone level, and the toxicological significance of this observation to humans is unclear.

No treatment-related histopathological lesions were observed in the reproductive tracts of male or female rats consuming chlordane technical for up to 30 months at doses up to 1.18 and 1.41 mg/kg/day, respectively (EPA 1985a; Khasawinah and Grutsch 1989a), or in male and female mice similarly treated for up to 24 months at doses up to 1.65 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989b). In male and female rats given diets providing up to 16 mg/kg/day chlordane technical for 407 days, no histopathological lesions were found in reproductive organs (Ambrose et al. 1953a). However, only five rats/sex/group were used. No treatment-related histopathological lesions were observed in the reproductive tracts of male or female rats consuming analytical-grade chlordane for up to 80 weeks at

doses up to 32.13 and 22.15 mg/kg/day, respectively, or in similarly treated male and female mice at doses up to 9.64 and 11.02 mg/kg/day, respectively (NCI 1977).

2.17 DEVELOPMENTAL

Trabert et al. (2012) assessed the association between *in utero* exposure to chlordane and cryptorchidism (absence of one or both testes in scrotum) and hypospadias (abnormal positioning of urethra opening). Levels of *trans*-chlordane and oxychlordane were measured among pregnant women enrolled in the Collaborative Perinatal Project (CPP) from 1959 to 1965 who delivered sons with cryptorchidism or hypospadias and sons without either condition. Results did not support an association between chlordane levels and cryptorchidism and hypospadias.

Gladen et al. (2003) assessed whether weight at birth is associated with prenatal exposure to persistent organochlorine compounds, including *trans*-nonachlor and oxychlordane. From 1993 to 1994, organochlorine compounds were measured in breast milk 4–5 days after birth and were used as the index for prenatal exposure for 197 singleton infants selected from the at-large population in two Ukrainian cities. Infants within the upper tertile of oxychlordane (82 ng/g milk fat) and *trans*-nonachlor (73 ng/g milk fat) had slightly smaller, though statistically insignificant, mean birth weights compared with the lower tertile. Seven of eight preterm infants were in the upper oxychlordane tertile, but the small number of preterm births in this study prevented the authors from drawing any conclusions. The authors reported that prenatal exposure to the concentrations of chemicals studied did not affect weight at birth.

Fenster et al. (2006) found no association between selected birth outcomes (length of gestation, birth weight, and crown-heel length) and maternal serum levels of oxychlordane (a chlordane metabolite), *trans*-nonachlor (a major component of technical chlordane), or heptachlor epoxide (a component of technical chlordane and metabolite of heptachlor) in a birth cohort of 385 low-income Latinas living in the agricultural community of Salinas Valley, California.

There was no effect on the incidence of malformations and no evidence of fetal toxicity, including retarded skeletal development, in the fetuses of rats administered chlordane technical by gavage during gestation at up to 80 mg/kg/day, although 4/8 high-dose maternal rats died (Usami et al. 1986). No effects on viability and postnatal growth were observed in the offspring of mice treated with an undescribed sample of chlordane at 50 mg/kg/day during gestation days (GDs) 8–12 (Chernoff and Kavlock 1982). The offspring of mice treated at 1 and 2.5 mg/kg/day during the third trimester exhibited

depressed acquisition of avoidance response, increased seizure threshold, and increased exploratory activity in a study that assessed neurobehavioral effects after in utero exposure (Al-Hachim and Al-Baker 1973). The authors concluded that chlordane affected the fetal brain. Exposure could also have occurred via nursing, because the pups were allowed to nurse the treated dams. The study identified a LOAEL of 1 mg/kg/day, which was used to derive an acute-duration oral MRL as described in the footnote in Table 2-2 and Appendix A.

Cranmer et al. (1984) administered analytical-grade chlordane in peanut homogenate to maternal mice throughout gestation at up to at 8 mg/kg/day to measure endocrinological performance of adult offspring. Although mice in treated groups gave birth to approximately equal numbers of viable offspring of "average" body weight that were grossly normal in appearance, 55% of the offspring of the high-dose dams died within the first week of the nursing period. The authors stated only that the cause of death was not apparent from gross necropsy; however, it is possible that exposure to high levels of chlordane and/or metabolites in the dam's milk may have been responsible for these deaths. Postweaning survival was not affected by treatment. Plasma corticosterone in the offspring measured at 400 days of age was elevated in females at 0.16 mg/kg/day, but not at 8.0 mg/kg/day, and in males at both dose levels. These effects were not apparent at 800 days of age in either sex, although not enough high-dose males survived for evaluation. The investigators hypothesized that elevated plasma levels of corticosterone may reflect the diminished ability of the liver to metabolically reduce corticosterone. The effects on plasma corticosterone levels in females did not occur in a dose-related fashion and the toxicological significance of this effect is unclear. Therefore, this effect is not considered in estimating levels of significant exposure.

In other studies, pregnant mice were treated with chlordane technical, and the effects on the immune system of the offspring were assessed (Barnett et al. 1985a, 1985b; Menna et al. 1985; Spyker-Cranmer et al. 1982). These studies suggested to the investigators that *in utero* and/or neonatal exposure to chlordane suppressed cell-mediated immunity, as manifested by depressed delayed-type hypersensitivity reactions in the offspring of treated mice. There was no effect on humoral-mediated immunity. It is likely that the nursing pups continued to be exposed to chlordane because chlordane is excreted in milk. Subsequent studies by these investigators indicate that prenatal treatment of mice depressed granulocyte-macrophage and spleen-forming stem cells in the bone marrow (Barnett et al. 1990a) and the liver (Barnett et al. 1990b), but had no effect on cytotoxic T-lymphocyte activity (Blaylock et al. 1990). Further mechanistic studies demonstrated that prenatal exposure of mice to chlordane (dams treated with 8 mg/kg/day during GDs 1–18) altered the macrophage in such a manner that it exhibited phenotypic characteristics of a cell

that achieved inflammatory status (Theus et al. 1992). The significance of this effect is not well understood.

Blyler et al. (1994) administered analytical-grade chlordane (in peanut butter) to groups of pregnant BALB/c mice (number per group not specified) on GDs 1–18 at 8 mg/kg/day. Myeloid hemopoietic activity of bone marrow cells from 6-week-old offspring was evaluated for *in vitro* colony-forming units-in-culture in response to exogenously added recombinant forms of the cytokines granulocyte/macrophage-colony stimulating factor (CSF), macrophage-CSF, and interleukin 3 (IL-3). Female, but not male, offspring exhibited a significant depression of the numbers of bone marrow colony forming units-granulocyte/macrophage (CFU-GM), CFU-IL-3, and CFU-M. Chlordane treatment did not significantly affect the number of recoverable, viable bone marrow cells in male or female offspring.

Narotsky and Kavlock (1995) administered technical chlordane to groups of timed-pregnant Fischer 344 rats (19–23/group) by gavage on GDs 6–19 at doses of 0, 21, or 28 mg/kg/day and assessed maternal and developmental effects. Both chlordane groups exhibited initial maternal weight loss (GDs 6–8) and significantly depressed gestational weight gain (GDs 6–20; approximately 30 and 55%, respectively, less than controls). No clinical signs of maternal toxicity were reported. No significant, treatment-related effects appeared in numbers of implants, resorptions, or live litters at birth. Both chlordane groups exhibited significantly decreased mean numbers of live pups at 6 days postpartum (5.2 and 1.5 pups/litter for the 21 and 28 mg/kg/day groups, respectively, compared with 7.9 pups/litter in controls). No gross signs of treatment-related malformations were observed.

Cassidy et al. (1994) assessed the pre- and postnatal effects of technical chlordane in Sprague-Dawley rats. The study included oral administration of chlordane to groups of pregnant rats (5/group) from GD 4 throughout gestation, parturition, and lactation at doses of 0, 0.1, 0.5, or 5 mg/kg/day and oral dosing of the offspring on postnatal days (PNDs) 22–80. In tests conducted between PND 77 and 85, the chlordane-exposed offspring exhibited sex- and dose-related effects on testosterone levels, selected behavioral tests of spatial abilities, and body weight. Female, but not male, offspring exhibited significant increases in body weight, decreases in testosterone levels, improved spatial abilities, and increases in auditory startle-evoked responses. Chlordane-exposed male rats exhibited significant increases in male-typical mating behaviors and decreases in Cl^- uptake in brain microsacs. Male rats did not show a significant decrease in testosterone levels at any dose, though a 10% decrease in testosterone was observed in male rats dosed at 5 mg/kg/day. The authors interpreted these results as indicative of

chlordane-induced masculinization of sexually dimorphic functions and behaviors by mimicking sex steroids, limiting their levels, or both.

2.18 OTHER NONCANCER

Everett and Matheson (2010) used the National Health and Nutrition Examination Survey (NHANES), 1999–2004 to evaluate the associations of total diabetes and prediabetes (glycohemoglobin 5.7–6.4%) with eight pesticide and pesticide metabolites, including oxychlordane, *trans*-nonachlor, and heptachlor epoxide. In separate adjusted logistic regressions, oxychlordane, *trans*-nonachlor, and heptachlor epoxide were positively associated with total diabetes. In a combined logistic regression, oxychlordane and heptachlor epoxide were positively associated with total diabetes. Heptachlor epoxide was positively associated with prediabetes in both the separate and combined models.

Lee et al. (2010) reported a nonlinear association between type 2 diabetes and serum levels of both *trans*-nonachlor and oxychlordane in a nested case-control study that included 90 cases and 90 controls enrolled in a Coronary Artery Risk Development in Young Adults (CARDIA) cohort. Montgomery et al. (2008) reported an increased risk of diabetes among chlordane-using licensed pesticide applicators (372 diabetics and 7,365 nondiabetics) enrolled in an Agricultural Health Study between 1993 and 2003. In a study that included 1,303 Mexican Americans 20–74 years of age from the Hispanic Health and Nutrition Examination Survey, 1982–1984, Cox et al. (2007) reported significant positive associations between self-reported diabetes and serum levels of both *trans*-nonachlor and oxychlordane.

2.19 CANCER

Studies that evaluated possible associations between exposure to chlordane and risk of cancers are largely limited due to unquantified exposure frequency, duration, and concentration, exposure to other compounds, and other confounding factors.

Retrospective mortality studies of workers involved in the manufacture of chlordane (Shindell and Ulrich 1986; Wang and MacMahon 1979a) reported no increased incidence of total deaths due to cancer or to a specific type of cancer. In a prospective study of pesticide applicators, Wang and MacMahon (1979b) reported an increased SMR for death due to bladder cancer that was "on the borderline of statistical significance," but did not attribute this observation to exposure to chlordane because a similar effect was not observed in the manufacturing study (Wang and MacMahon 1979a). A follow-up study on a larger cohort of pesticide applicators found no association of exposure to chlordane with total deaths due to

cancer or to a specific type of cancer (MacMahon et al. 1988). In another retrospective mortality study of four cohorts (305–1,155 workers/plant exposed for ≥6 months) from four manufacturing plants, there was a significantly increased risk of death from noncancer respiratory disease, and a slight excess risk of cancer of the esophagus, rectum, liver, and hematopoietic system at plant 3, and a slightly greater risk of stomach cancer at plant 1 (Ditraglia et al. 1981). However, chlordane was the only pesticide manufactured at plant 1, while aldrin, dieldrin, endrin, and dichlorodiphenyltrichloroethane were manufactured at plant 3. The statistical power did not allow for a conclusion that no association existed between cause-specific mortality and employment at the plants. However, in a follow-up to the study by Ditraglia et al. (1981), the carcinogenic risk among workers exposed to organochlorines was assessed (Brown 1992). This study added 11 years to the previous follow-up study, thus providing 40 years of observation for the cohort. As 23 years was the minimum time elapsed since each cohort member was first employed at the study plants, this allowed more time for diseases with long latency periods to develop. The investigator concluded that the mortality for all causes and all malignant neoplasms was lower than expected.

A small but insignificant positive association between reported chlordane use and risk of non-Hodgkin's lymphoma was reported among farmers exposed to chlordane in a case-control study (Woods and Polissar 1989). Several cases of leukemia and neuroblastoma were reported in persons exposed to chlordane or heptachlor in their home or garden, or as a result of their profession as pest control operators (Epstein and Ozonoff 1987; Infante et al. 1978). A small case-control study found that levels of chlordane residues (heptachlor epoxide, oxychlordane, *trans*-nonachlor) in the breast fat from 20 women with malignant breast disease were not significantly different from 20 women with benign breast disease (largely nonproliferative fibrocystic changes) (Falck et al. 1992).

A number of case-control studies examined possible associations between risk of selected cancer endpoints and levels of chlordane or chlordane-related substances such as *cis*- and *trans*-nonachlor (major components of technical chlordane) or oxychlordane (a metabolite of chlordane) in plasma or serum samples or adipose tissue. Most case-control studies found no significant associations between levels of chlordane or chlordane-related compounds and risk of breast cancer (Demers et al. 2000; Gammon et al. 2002; Ward et al. 2000; Wolff et al. 2000; Zheng et al. 2000), endometrial cancer (Weiderpass et al. 2000), prostate cancer (Aronson et al. 2010; Ritchie et al. 2003; Sawada et al. 2010), or non-Hodgkin's lymphoma (Cantor et al. 2003).

McGlynn et al. (2008) reported significant positive associations between risk of testicular germ cell tumors and serum levels of *cis*-nonachlor, *trans*-nonachlor, and total chlordanes. McGlynn et al. (2008) also reported significant associations for seminoma (i.e., testicular tumors arising from sperm-forming tissues) and *cis*-nonachlor, *trans*-nonachlor, and oxychlordane. Cook et al. (2011) reported significant positive associations between exposure to *cis*-nonachlor, and *trans*-nonachlor with testicular germ-cell tumors. Hardell et al. (2003) reported a significant association between risk of testicular cancer and lipid-adjusted plasma *cis*-nonachlor levels. Hardell et al. (2003) reported significant positive associations between risk of testicular cancer and plasma levels of *trans*-nonachlor and *cis*-nonachlor in the serum of mothers of the testicular cancer cases. Assessment according to testicular tumor type resulted in significant associations between risk of seminoma and maternal plasma *cis*-chlordane levels and between risk of nonseminoma and maternal plasma *trans*- and *cis*-nonachlor levels. In a subsequent analysis of testicular cancer cases and age-matched controls (Hardell et al. 2006b), no significant association was found between the sum of chlordanes in maternal blood and risk of testicular cancer.

Spinelli et al. (2007) reported significant positive associations between risk of non-Hodgkin's lymphoma and lipid-adjusted plasma levels of oxychlordane and *trans*-nonachlor in a population-based, case-control study involving 422 non-Hodgkin's lymphoma cases and 460 control subjects.

Quintana et al. (2004) reported a significant positive association between risk of non-Hodgkin's lymphoma and levels of oxychlordane in adipose tissue samples collected from cadavers and surgical patients within the EPA National Human Adipose Tissue Survey. Hardell et al. (2006a) reported a significant association between risk of prostate cancer and *trans*-chlordane in adipose tissue. Hardell and colleagues also reported a significant positive association for those prostate cancer cases with prostate-specific antigen (PSA) levels >10 ng/mL. Hardell et al. (2007) reported significant positive associations between risk of pancreatic cancer and adipose tissue levels of *trans*-chlordane, oxychlordane, *trans*-nonachlor, *cis*-nonachlor, and their sum. Hardell et al. (1996) reported a significant positive association between risk of non-Hodgkin's lymphoma and *trans*-nonachlor level in adipose tissue. This study also found significantly increased mean concentrations of *trans*-nonachlor, *cis*-nonachlor, and oxychlordane in adipose tissues from non-Hodgkin's lymphoma patients versus controls.

Possible associations between chlordane and selected cancer endpoints were evaluated in population-based case-control studies. In one study, the risk of non-Hodgkin's lymphoma among farmers was significantly elevated for personal handling, mixing, or application of chlordane as an animal insecticide or as a crop insecticide (Cantor et al. 1992). The odds ratio for non-Hodgkin's lymphoma was also

greater among farmers who first used chlordane before 1965 (15–18 years before diagnosis) or those farmers who did not use protective equipment.

Colt et al. (2006) examined non-Hodgkin's lymphoma risk and use of insecticides in the home and garden. The study included 1,321 non-Hodgkin's lymphoma cases and 1,057 controls from four areas of the country (Iowa, Los Angeles county, Detroit, and Seattle). Study subjects were given a questionnaire regarding the use of insecticides for eight specific types of pests including termites. Termite treatment was associated with a "modest," but not significant elevated risk for non-Hodgkin's lymphoma in all areas except Seattle; and only if treatments were before 1988, when the use of chlordane for termite treatment was banned. Insecticide levels were measured in dust taken from used vacuum cleaner bags (682 cases and 513 controls). A significant positive trend for non-Hodgkin's lymphoma and α-chlordane residue concentrations in dust was observed, and a marginally significant trend was observed for increased levels of γ-chlordane.

Mills and Yang (2005) performed a registry-based, case-control study of breast cancer in farm labor-union members in California. Using available records of pesticide applications between 1970 and 1999, exposures to selected pesticides—including chlordane—were estimated as no exposure, low exposure, or high exposure. Among breast cancer cases diagnosed between 1988 and 1994, a significant positive association was observed between reported "high" use of chlordane and risk of breast cancer. No significant association was observed for breast cancer cases diagnosed between 1995 and 2001. These results may reflect patterns of chlordane use, given that the pesticide was phased out in the 1980s.

Purdue et al. (2006) investigated relationships between cancer incidence and organochlorine insecticide use among pesticide applicators enrolled in the Agricultural Health Study of licensed applicators in Iowa and North Carolina between 1993 and 1997. Information on "ever use" (having ever used) of selected organochlorine pesticides—including chlordane—was collected from self-administered questionnaires at the time of enrollment. A total of 51,011 of the enrolled pesticide applicators reported "ever use" of the selected organochlorine pesticides; 7,244 of these pesticide applicators reported "ever use" of chlordane. Through December 2002, among the chlordane-exposed subjects, 33 cases of rectal cancer had been diagnosed. Among the pesticide applicators with no reported chlordane use (n=43,767), 42 rectal cancer cases had been diagnosed. The study authors reported a significant positive association between "ever use" of chlordane and risk of rectal cancer. However, they found no significant associations between "ever use" of chlordane and other cancers (prostate, lung, colon, bladder, non-Hodgkin's lymphoma, leukemia, and melanoma) or all cancers combined.

Xu et al. (2010) examined possible associations between serum concentrations of organochlorine pesticides and selected metabolites (including the chlordane metabolites oxychlordane and *trans*-nonachlor) among 4,237 participants of the 1999–2004 NHANES (4,109 individuals without cancer, 63 breast cancer cases, and 65 prostate cancer cases). No significant association was found between serum oxychlordane and risk of breast cancer. However, a significant positive association was reported for serum *trans*-nonachlor and risk of prostate cancer.

Chronic exposure of humans in homes treated with chlordane for termites was associated with greater incidence of unspecified skin neoplasms, compared with a reference population (Menconi et al. 1988).

Studies using three different strains of mice (one strain had an historically low incidence of spontaneous liver tumors) have demonstrated that dietary administration of chlordane is associated with the development of hepatocellular carcinomas. An unpublished study by IRDC (1973), which was available only in reviews by EPA (1986c, 1987e), Epstein (1976), IRIS (1992), and Reuber (1978), found significant increases in the incidence of hepatocellular carcinomas in male and female CD-1 mice fed analytical-grade technical chlordane in the diet at doses of 3.25 and 6.5 mg/kg/day for 18 months. In an NCI (1977) chronic dietary study with a mixture of analytical-grade chlordane (72% *cis* and 23% *trans* isomers), there was a dose-related increase in the incidence of hepatocellular carcinomas in male and female B6C3Fl mice that was statistically significant in both treated groups of males (doses of 5.13 and 9.64 mg/kg/day) and in the high-dose females (11.02 mg/kg/day). An increased incidence of hepatocellular adenomas and hemangiomas developed in male mice, but not female mice, maintained on a diet providing ≈1.65 mg chlordane/kg/day for 2 years (EPA 1985a; Khasawinah and Grutsch 1989b).

Barrass et al. (1993) reported approximately 50% incidence of hepatocellular tumors among male C57B1/10J mice that had received chlordane in the diet at a concentration of 50 ppm for 2 years (estimated intake of 8.6 mg chlordane/kg/day); hepatic tumor incidence among 400 control mice at the same research facility was approximately 2%. Malarkey et al. (1995) reported 100% incidences of hepatocellular adenomas in groups of male B6C3F1 mice (10 or 20 per group) administered technical chlordane at 55 ppm in the diet for periods of 513–568 days (estimated intake of 9.4 mg chlordane/kg/day). Hepatocellular carcinomas during the same time period were noted in 80–100% of the chlordane-treated mice. Incidences of hepatocellular adenomas and carcinomas in a group of untreated controls at 759 days were 7/43 (16%) and 3/43 (7%), respectively. Results from similar exposure of male B6D2F1 mice indicated that male B6C3F1 mice are more sensitive than are male B6D2F1 mice.

Although chlordane clearly induces liver cancer in mice (EPA 1985a; IRDC 1973; Khasawinah and Grutsch 1989b; NCI 1977), epidemiological data provide no convincing evidence that it induces cancer in humans (Ditraglia et al. 1981; MacMahon et al. 1988; Shindell and Ulrich 1986; Wang and MacMahon 1979a, 1979b). Most genotoxicity tests with chlordane yielded negative results (see Section 2.20), suggesting an epigenetic mechanism of carcinogenicity. Chlordane inhibited gap junction intercellular communication in the rat hepatocyte/liver epithelial system metabolic cooperation assay (Tong and Williams 1988) and in the Lucifer yellow CH dye-coupling test in rat and mouse hepatocytes (Ruth et al. 1990). These results suggest that chlordane acts as a tumor promoter, depressing intercellular communication that checks uncontrolled proliferation of transformed or neoplastic cells (Tong and Williams 1988). Rought et al. (1999) demonstrated the ability of chlordane to reduce retinoblastoma tumor-suppressor gene expression in CEM x 174 cells (a hybrid of human T and B lymphocytes). These results suggest that chlordane is capable of down-regulating retinoblastoma expression at the post-transcriptional level. The authors indicated that such a mechanism could be involved in chlordane's immune-modulatory and tumor-promoting effects. Ruth et al. (1990) suggested that inhibition of intercellular communication may involve alteration of cAMP-dependent protein kinase phosphorylation of hepatocellular gap junction proteins, which would increase permeability at the gap junctions. Moser and Smart (1989), who noted that chlordane stimulated protein kinase C activity in several tissues of mice *in vitro*, provide support for this theory. Nonetheless, Suzaki et al. (1988) did not observe a chlordane-induced increase in protein kinase C activity *in vitro* in the rat brain.

The U.S. Department of Health and Human Services has not classified chlordane as to its carcinogenicity (NTP 2016). EPA categorized it as a probable human carcinogen (Group B2) (IRIS 2002). The International Agency for Research on Cancer categorized it as possibly carcinogenic to humans (Group 2B) (IARC 2001, 2017). The cancer classifications are based on sufficient evidence of carcinogenicity in animal studies and inadequate evidence in humans.

2.20 GENOTOXICITY

Chlordane has been evaluated for genotoxicity in a limited number of *in vivo* tests (Table 2-4). Chlordane induced DNA damage in liver cells of orally-exposed rats (Bagchi et al. 1995; Hassoun et al. 1993) and chromosomal aberrations in bone marrow cells of orally-exposed mice (Sarkar et al. 1993). A weakly positive result was obtained for micronuclei in bone marrow of dermally-treated mice (Schop et al. 1990). Chlordane did not induce dominant lethality in male mice treated orally or intraperitoneally (Arnold et al.

1977; Epstein et al. 1972) or DNA adduct formation in liver cells of orally-exposed mice (Whysner et al. 1998).

Table 2-4. Genotoxicity of Chlordane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Rat liver cells (oral)	DNA damage	+	Hassoun et al. 1993
Rat liver cells (oral)	DNA damage	+	Bagchi et al. 1995
Mouse (oral, intraperitoneal)	Dominant lethal	–	Arnold et al. 1977
Mouse (oral, intraperitoneal)	Dominant lethal	–	Epstein et al. 1972
Mouse bone marrow (dermal)	Micronuclei	(+)	Schop et al. 1990
Mouse bone marrow (oral)	Chromosomal aberrations	+	Sarkar et al. 1993
Mouse liver (oral)	DNA adducts	–	Whysner et al. 1998

+ = positive result; (+) = weakly positive result; – = negative result

Chlordane has been evaluated for genotoxicity in a variety of *in vitro* tests (Table 2-5). Chlordane was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* (Gentile et al. 1982; Mortelmans et al. 1986; Probst and Hill 1981; Simmon et al. 1977), rat liver cells (Telang et al. 1981), or Chinese hamster lung V79 diphtheria toxin resistant cells (Tsushimoto et al. 1983). However, in the absence of exogenous metabolic activation, chlordane was mutagenic in assays of human fibroblasts (Tong et al. 1981), mouse lymphoma L5178Y cells (McGregor et al. 1988), and Chinese hamster lung V79 cells (Ahmed et al. 1977b). Negative results were obtained from assays of unscheduled DNA synthesis in a variety of prokaryotic and mammalian test systems (Brandt et al. 1972; Maslansky and Williams 1981; Probst and Hill 1981; Rashid and Mumma 1986; Williams 1980); the only exception was a positive result in human SV-40 fibroblasts when an exogenous metabolic activation system was added (Ahmed et al. 1977a). Chlordane was positive for prophage induction in *E. coli* with and without exogenous metabolic activation (Houk and DeMarini 1987). In *E. coli*, chlordane was also positive for SOS repair induction (Venkat et al. 1995) and DNA strand breaks (Griffin and Hill, 1978) without exogenous metabolic activation. Chlordane induced mitotic gene conversion in *Saccharomyces cerevisiae* (Gentile et al. 1982) with exogenous metabolic activation and sister chromatid exchange in human lymphoid cells (Sobti et al. 1983) with and without exogenous metabolic activation. When exposed to chlordane in the absence of exogenous metabolic activation, Syrian hamster embryo cells were positive for cell transformation but negative for the formation of DNA adducts (Bessi et al. 1995).

Table 2-5. Genotoxicity of Chlordane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Prokaryotic organisms				
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	ND	–	Simmon et al. 1977
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	Gentile et al. 1982
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Mortelmanns et al. 1986
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, G46, C3076, D3052	Gene mutation	–	–	Probst and Hill 1981
Escherichia coli WP2, WP2 *uvrA*	Gene mutation	–	–	Probst and Hill 1981
E. coli $WP2_s$	Prophage induction	+	+	Houk and DeMarini 1987
E. coli PQ37	SOS repair induction	ND	+	Venkat et al. 1995
E. coli K12ColE1	DNA strand breaks	ND	+	Griffin and Hill 1978
S. typhimurium TA1538/TA1978	Unscheduled DNA synthesis	–	–	Rashid and Mumma 1986
E. coli K-12	Unscheduled DNA synthesis	–	–	Rashid and Mumma 1986
Eukaryotic fungal and bacterial cells				
S. cerevisiae D4	Mitotic gene conversion	+	–	Gentile et al. 1982
Mammalian cells				
Human fibroblasts	Gene mutation	–	+	Tong et al. 1981
Rat liver epithelial ARL cells	Gene mutation	ND	-	Telang et al. 1981;
Mouse lymphoma L5178Y cells	Gene mutation	ND	+	McGregor et al. 1988
Chinese hamster lung V79 cells, ouabain resistant	Gene mutation	ND	+	Ahmed et al. 1977b
Chinese hamster lung V79 cells, diphtheria toxin resistant	Gene mutation	ND	–	Tsushimoto et al. 1983
Chinese hamster lung V79 cells, *hprt* locus	Gene mutation	ND	–	Tsushimoto et al. 1983
Human VA-4 fibroblasts	Unscheduled DNA synthesis	–	+	Ahmed et al. 1977a
Human HeLa cells	Unscheduled DNA synthesis	ND	–	Brandt et al. 1972

Table 2-5. Genotoxicity of Chlordane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Rat, mouse, hamster hepatocytes	Unscheduled DNA synthesis	ND	–	Maslansky and Williams 1981
Rat hepatocytes	Unscheduled DNA synthesis	ND	–	Probst and Hill 1981; Williams 1980
Human LAZ-007 lymphocytes	Sister chromatid exchange	+	+	Sobti et al. 1983
Syrian hamster embryo cells	Cell transformation	ND	+	Bessi et al. 1995
Syrian hamster embryo cells	DNA adducts	ND	-	Bessi et al. 1995

– = negative result; + = positive result; +/– = inconclusive results; DNA = deoxyribonucleic acid; ND = no data

2.21 MECHANISMS OF ACTION

2.21.1 Pharmacokinetic Mechanisms

Although the data suggest that chlordane is readily absorbed from the respiratory (Nye and Dorough 1976) and gastrointestinal tracts (Ohno et al. 1986), and that dermal absorption is sufficient to cause toxicity in humans and animals (Derbes et al. 1955; Gaines 1960), data regarding the mechanisms of absorption were not located. Generally, highly lipophilic organic compounds cross membranes largely by passive diffusion. Since chlordane is highly lipophilic, it is expected that absorption of chlordane by all routes of exposure would involve primarily passive diffusion. This is consistent with the observation by Ohno et al. (1986) that little difference in the extent of gastrointestinal absorption occurred over a 10-fold difference in dose.

The metabolism of the components of chlordane and the lipophilicity of the components and metabolites influence their distribution. Initial distribution to the liver and kidneys is more rapid than to fat (Ohno et al. 1986), probably reflecting differences in vascularity of these sites. Subsequently, redistribution results in higher levels in the fat than other tissues. Low levels of *cis*- and *trans*-chlordane in fat and relatively higher levels of oxychlordane and trans-nonachlor reflect the relative lability of the chlordane isomers and stability of the latter two compounds (Hirasawa and Takizawa 1989; Sasaki et al. 1991a, 1992).

Metabolism of the *cis* and *trans* isomers of chlordane by humans and laboratory animals appears to be qualitatively similar (Kutz et al. 1976, 1979), although monkeys may be less efficient than rats

(Khasawinah 1989), and rats may metabolize *trans*-nonachlor more efficiently than humans (Tashiro and Matsumura 1978). Metabolism appears to be largely oxidative, involving hepatic microsomal cytochrome P-450 (Kawano et al. 1989). Epoxide hydrolase is probably the predominant enzyme involved in further degradation of oxychlordane, but the process appears to be slow in animals and humans. In addition, reductive dehalogenation, probably resulting in the formation of reactive free radical intermediates, may be important in the toxicity of chlordane (Brimfield and Street 1981; Kawano et al. 1989).

The strong lipophilicity and relatively weak hydrophilicity of chlordane and its metabolites suggest that excretion would be largely by passive diffusion. This is supported by the observation that fecal (biliary) excretion exceeds urinary excretion in humans and rats (Aldrich and Holmes 1969; Ohno et al. 1986), indicating that renal tubular excretion is probably not a major factor in excretion. Passive tubular resorption probably accounts for the lesser role that renal excretion plays in the fate of chlordane, compared with most organic chemicals, for which biotransformation results in the formation of more polar (hydrophilic) products.

Cis- and *trans*-chlordane and their metabolites bind irreversibly with cellular macromolecules such as protein, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA) (Brimfield and Street 1981). Binding to these macromolecules may lead to cell death or altered cellular function. In addition, *cis*- and *trans*-chlordane, heptachlor, and heptachlor epoxide increase the generation of superoxide in cultures of guinea pig polymorphonuclear leukocytes (Suzaki et al. 1988). This was probably an indirect effect of activation of phospholipase C, or of increasing the intracellular concentration of free ionized calcium, rather than a direct effect on protein kinase C.

2.21.2 Mechanisms of Toxicity

Potential mechanisms of chlordane-induced liver effects, immunotoxicity, and cancer are discussed in Sections 2.9, 2.14, and 2.19, respectively. Other potential mechanisms of toxicity are discussed here.

Gauthier and Girard (2001) found that chlordane-induced neutrophil superoxide production in human neutrophils in a concentration-related manner occurred similarly to that induced by the known neutrophil-agonist, phorbol 12-myristate 13-acetate. Chlordane was further shown to enhance neutrophil phagocytosis of sheep red blood cells without altering chemotaxis and apoptosis. Evidence that chlordane-induced superoxide production might involve protein kinase C-dependent mechanisms

included findings that staurosporine and calphostin C (transduction signal inhibitors) inhibited the effect of chlordane on superoxide production.

Bagchi and coworkers (Bagchi et al. 1995; Stohs et al. 1997) examined the effects of chlordane on the production of hepatic and brain lipid peroxidation and DNA single-strand breaks (indices of oxidative stress and oxidative tissue damage) in female rats administered two ¼LD_{50} gavage doses of chlordane 21 hours apart and sacrificed 3 hours later. Chlordane treatment resulted in approximately 3- and 2-fold increases in lipid peroxidation in liver and brain, respectively, and approximately 4- and 1.8-fold increases in single-strand breaks in liver and brain, respectively. The investigators also assessed chlordane-induced changes in the release of lactate dehydrogenase (a measure of cellular damage and cytotoxicity) and DNA single-strand breaks from cultured neuroactive PC-12 cultures. Increases in both releases of lactate dehydrogenase and DNA single-strand breaks were observed. The *in vivo* and *in vitro* results support the notion of chlordane-induced generation of reactive oxygen species.

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

3.1 TOXICOKINETICS

- Chlordane (a highly lipophilic substance) appears to be readily absorbed, regardless of the route of exposure.
- Initially, tissue levels are highest in the liver and kidneys; subsequently, chlordane and its metabolites are relocated to fat, where they persist for long periods of time.
- Metabolism results in a number of oxidation products, including oxychlordane, which persist in body fat as the predominant chlordane residues. Free radicals formed by reductive dehalogenation may play an important role in the toxicity of chlordane.
- Chlordane induces its own metabolism to toxic intermediates.
- Except for the rabbit, chlordane and its metabolites are excreted more readily in the bile than in the urine, due to the general lack of polarity and high lipophilicity of the terminal metabolites. Substantial amounts are also excreted via lactation.

3.1.1 Absorption

Data obtained from humans exposed to chlordane in termite-treated homes in Japan (Taguchi and Yakushiji 1988) or as the result of pesticide spraying (Kawano and Tatsukawa 1982; Saito et al. 1986; Takamiya 1987) indicate that blood or tissue levels of chlordane and/or its metabolites increase with exposure duration. These data indicate that chlordane can be readily absorbed across the respiratory tract.

Observations of chlordane residues in adipose tissue and systemic effects following inhalation exposure to chlordane technical confirm that absorption from the respiratory tract occurs (Asakawa et al. 1996; EPA 1987f; Khasawinah et al. 1989). An intratracheal study suggests that absorption of chlordane by the respiratory system of rats is rapid. A peak blood concentration of radioactivity equivalent to ≈4% of an intratracheal dose of radiolabeled chlordane was reached in <5 minutes (Nye and Dorough 1976). In reviewing the data from this study, Nomeir and Hajjar (1987) noted that ≈24% of the dose of radioactivity was present in the lungs 1 hour after treatment and concluded that ≈76% of the dose had been absorbed from the respiratory tract.

Information on the absorption of chlordane following oral exposure in humans comes largely from case reports involving accidental ingestion. A chlordane level of 2.71 mg/L was measured in the blood of a 20-month-old boy at 2.75 hours after he had ingested an unknown amount of technical-grade chlordane (Curley and Garrettson 1969). A chlordane concentration of 3.4 mg/L was measured in a serum sample taken from a 4-year-old girl at an unspecified time following the ingestion of an unknown amount of a

45% chlordane formulation (Aldrich and Holmes 1969). Chlordane was found in the blood plasma and in a variety of tissues from a 59-year-old male approximately 2 hours after he had ingested an unknown amount of chlordane (Kutz et al. 1983). A whole-blood chlordane concentration of 5 mg/L was measured in a 62-year-old male at 3.5 hours after he had ingested 300 mL of a 75% chlordane solution (Olanoff et al. 1983).

Chlordane appears to be rapidly absorbed from the gastrointestinal tract of rats; peak blood levels of radioactivity occurred 2–4 hours following administration of oral doses ranging from 0.1 to 1 mg/kg (Ewing et al. 1985; Ohno et al. 1986). Peak blood levels of radioactivity following a 1 mg/kg dose of ^{14}C-chlordane were between 81 ng chlordane equivalents/mL for the *cis* isomer (Ewing et al. 1985) and 175 ng chlordane equivalents/mL for the *trans* isomer (Ohno et al. 1986). Absorption in the mouse was slower than in the rat; a peak blood level of 113 ng equivalents/mL of blood was observed in the mouse 8 hours after oral administration of a 1 mg/kg dose of ^{14}C-*cis*-chlordane (Ewing et al. 1985). Absorption was not quantified following oral dosing in the mouse, but intraperitoneal studies indicated that a significant degree of biliary excretion also occurs in this species (Ewing et al. 1985). Administration of a mixture (1:1) of *cis* and *trans* isomers of chlordane (20 mg/kg for each of the isomers) to male mice resulted in peak absorption within 24 hours (Satoh and Kikawa 1992). In rabbits, the estimated absorption of chlordane following various repeated oral dosing regimens with radiolabeled *cis* and/or *trans* isomers has been estimated at 30–50%, based on radioactivity eliminated in the urine (Balba and Saha 1978; Barnett and Dorough 1974; Poonawalla and Korte 1971).

No quantitative data were located regarding absorption in humans after dermal exposure to chlordane. Derbes et al. (1955) reported a case of accidental death preceded by neurological signs typical of chlordane toxicity in a woman who was dermally exposed to a mixture of chlordane and other chemicals. This finding indicates that chlordane can be absorbed through human skin. Other studies indicate that absorption of chlordane through the skin is related to the application medium. Ambrose et al. (1953a) indicated that a topical dose of chlordane in rats (50 mg/kg) is more readily absorbed when the compound is administered in an oil vehicle instead of ethyl alcohol. In an *in vitro* study using diffusing cells in which ^{14}C-chlordane was applied to human skin from cadavers for 24 hours, the amount of the applied dose of radioactivity recovered from the receptor fluid (human plasma) was 0.04% when the application medium was soil and 0.07% when the application medium was acetone (Wester et al. 1992). Much larger proportions (0.34% from soil and 10.9% from acetone) were retained within the layers of the skin. In an *in vivo* study, ^{14}C-chlordane in soil or acetone was applied to the skin of monkeys for 24 hours (Wester et

al. 1992). Absorption accounted for 4.2% of the dose in soil and 6% of the dose in acetone, based on recovery of ^{14}C in the urine.

3.1.2 Distribution

Several studies report chlordane residues in the blood or fat of pest control operators, residents in homes treated for termites, or residents with no known mode of exposure other than background. Background exposures include inhalation of the material in ambient air and ingestion through food (Dearth and Hites 1991a; Sasaki et al. 1991a; Wariishi and Nishiyama 1989); dermal exposure also may be possible, although data regarding dermal exposure were not located. In pesticide spray applicators properly attired in protective clothing, the inhalation route is probably most important (Takamiya 1987). Nevertheless, most humans with any body burden of chlordane residues were probably exposed by multiple routes. Generally, levels of total chlordane residues in blood and milk fat increase as duration of exposure increases (Ogata and Izushi 1991; Saito et al. 1986; Taguchi and Yakushiji 1988; Takamiya 1987). Human milk fat contained total mean chlordane residues of ≤188 ppm, and blood levels were ≤0.015 ppm in exposed individuals (Ogato and Izushi 1991; Taguchi and Yakushiji 1988). Levels in fat and liver exceeded levels in the blood (Mussalo-Rauhamaa 1991).

Information on the distribution of chlordane and/or its metabolites in humans after oral exposure is from case reports involving ingestion of the compound. Approximately 2 hours after a 59-year-old male ingested a fatal dose of chlordane, autopsy revealed the following concentrations of chlordane: adipose tissue 22 µg, spleen 19.15 µg/g, brain 23.27 µg/g, kidney 14.10 µg, and liver 59.93 µg/g (Kutz et al. 1983). The level of chlordane in the adipose tissue of a 20-month-old boy who drank an unknown amount of technical-grade chlordane was 3.12 µg/g approximately 30 minutes after ingestion (Curley and Garrettson 1969). The concentration in adipose tissue peaked at 30–35 µg/g fat approximately 8 days following the incident. Fifty-eight days after a 62-year-old male ingested 215 g of chlordane, the reported levels of chlordane components and metabolites (oxychlordane, *trans*-nonachlor, and heptachlor epoxide) in the adipose tissue were 5 µg/g fat (Olanoff et al. 1983).

Other human data include reports of chlordane residues in blood, adipose tissue, and cord blood (Brock et al. 1998; Glynn et al. 2000; Kang et al. 2008; Rhainds et al. 1999; Tanabe et al. 1993), and adipose tissue and brain and liver autopsy samples (Dewailly et al. 1999).

The pattern of tissue distribution of chlordane and/or its metabolites in animals after oral exposure does not appear to depend on the size of the dose or whether exposure is to single or multiple doses. The tissue distribution patterns of radioactivity in rats, 1 day after exposure to a single oral dose of a 3:l mixture of radiolabeled *cis*- and *trans*-chlordane, were similar over a dose range of 0.05–1.0 mg/kg (Barnett and Dorough 1974). Levels of tissue radioactivity increased with increasing dose; at all dose levels, the highest concentrations of radioactivity were found in the fat followed, in order, by the liver and kidney. Lower concentrations were found in the brain and muscle. In this same study, oral administration of chlordane over a longer period of time did not change the distribution pattern of radioactivity from that observed following a single oral exposure. Rats fed the same mixture of chlordane for 56 days at dietary concentrations of 1, 5, or 25 ppm were observed to have high levels of radioactivity in the fat and much lower levels of radioactivity (in decreasing order) in the liver, kidney, brain, and muscle. The concentrations of radioactivity measured in these tissues were dose-dependent.

The accumulation of chlordane and its metabolites in fat appears to depend on exposure duration. Takeda et al. (1984) treated rats by gavage with technical chlordane at 10 μg/kg/day for 7 or 14 days. Chlordane and metabolites measured in the fat reached 30.4 μg/g wet tissue at the end of 7 days of treatment and 77.4 μg/g at the end of 14 days of treatment. Distribution to the liver and kidneys of rats after a single oral dose of chlordane is more rapid than distribution to adipose tissue. Levels of radioactivity peaked in the liver and kidneys of rats 2–4 hours after the administration of a single oral dose of radiolabeled γ-chlordane (0.05 or 10 mg/kg) (Ohno et al. 1986). In this same study, the level of radioactivity in the adipose tissue peaked at 16 hours (dose of 10 mg/kg) and 4 days (dose of 0.05 mg/kg) after administration of the compound. The concentrations of γ-chlordane equivalents in adipose tissue 10 days after the administration of either dose (0.05 or 10.0 mg/kg) were approximately 10 times higher than levels in the liver and kidney.

Dearth and Hites (1991b) measured the half-lives of depuration of 14 different chlordane components (e.g., *cis*- and *trans*-chlordane and *cis*- and *trans*-nonachlor) and metabolites (e.g., heptachlor epoxide, oxychlordane) from the fat of rats fed chlordane in the diet for 28 days. Half-lives ranged from 5.92 days (*cis*-chlordane) to 54.1 days (nonachlor III) and were apparently related to the metabolism rate of the various compounds. Structural characteristics associated with slowed depuration included an increasing number of chlorines on ring 1, the chlorine on Cl existing in an endo- (compared with an exo-) configuration, and the presence of two chlorines on C2. In mice treated once or every other day for 29 days, the whole-body content of *cis*- and *trans*-chlordane remained at very low levels; the content of *cis*- and t*rans*-nonachlor and oxychlordane continued to increase with continued treatment (Hirasawa and

Takizawa 1989). The investigators concluded that the chlordane isomers were readily metabolized, but that the nonachlor isomers were not. Oxychlordane, a metabolic intermediate of both chlordane isomers, is very slowly metabolized and tends to persist.

Elimination of radioactivity from the liver and kidney of rats treated with radiolabeled chlordane differs from elimination of radioactivity from peritesticular adipose tissue. Elimination of radioactivity from the kidneys and livers of rats treated with either high (10 mg/kg) or low (0.05 mg/kg) doses of γ-chlordane was biphasic; the initial rapid phase had half-lives in both organs ranging from 5.9 to 9.6 hours (Ohno et al. 1986). Half-lives for the slower, terminal phase of elimination in these organs ranged from 4.4 to 5.0 days. In contrast, elimination of radioactivity from peritesticular adipose tissue was monophasic and relatively slow (elimination half-lives of 9.1 days in the low-dose group and 8.4 days in the high-dose group). Skin retained radioactivity longer than any other tissue (elimination half-lives of 15.2 and 10.4 days for the low- and high-dose groups, respectively). Ewing et al. (1985) confirmed that peak concentrations of radioactivity were found in the livers of rats and mice 2–4 hours after administration of a single oral dose of radiolabeled *cis*-chlordane (1.0 mg/kg). The investigators observed that radioactivity was eliminated much more slowly from the livers of mice than from the livers of rats. They speculated that this may explain the susceptibility of mice to the development of hepatocellular carcinomas, whereas rats appear to be relatively insensitive to the formation of this tumor following chlordane administration (NCI 1977).

Several oral studies (Ambrose et al. 1953b; Barnett and Dorough 1974; Bondy et al. 2000; Street and Blau 1972) reported that female rats had higher levels of radioactivity in the fat than did the males. Bondy et al. (2000) observed dose-related increasing concentrations of oxychlordane, *cis*-nonachlor, *trans*-nonachlor, heptachlor, and *trans*-chlordane in adipose tissue of male and female rats administered technical chlordane by gavage at doses ranging from 0.25 to 25 mg/kg/day for 28 days. Oxychlordane and *trans*-nonachlor represented the majority of chlordane residues in adipose tissues and levels of these residues were >2-fold higher in dosed female rats compared with similarly dosed male rats. Levels of radioactivity in perirenal adipose tissue from female rats were as much as twice the levels observed in males (Ambrose et al. 1953b), and females tended to store a much larger proportion of this radioactivity in abdominal fat in the form of oxychlordane (Street and Blau 1972). Another recurrent observation in these distribution studies is an isomer effect on the amount of radioactivity that is distributed to the various tissues. Studies by Barnett and Dorough (1974) and Street and Blau (1972) indicated that significantly higher concentrations of radioactivity are stored in the tissues of rats following oral administration of the *trans* isomer, compared to the concentrations observed following administration of

the *cis* isomer. This observation also holds true for rabbits. Balba and Saha (1978) administered four doses of either *cis*-chlordane (67 mg/kg body weight/dose) or *trans*-chlordane (30 mg/kg body weight/dose) to rabbits for 4 days. Although the administered dose of the *cis* isomer was more than twice the dose of the *trans* isomer, tissue levels of radioactivity were higher in animals given the *trans* isomer. When a 1:l mixture of *cis*- and *trans*-chlordane (total dose: 40 mg/kg) was administered to mice, higher concentrations of the *cis*- isomer were found in muscle liver, kidney, brain, and spleen (Satoh and Kikawa 1992). Concentrations of *cis*- and *trans*-chlordane were similar in blood. Oxychlordane concentrations peaked in the liver (1,918 ppb) at day 2, and peaked at day 1 in the following tissues: muscle (569 ppb), kidney (326 ppb), brain (226 ppb), spleen (126 ppb), and blood (103 ppb). The level of oxychlordane in adipose tissue was 2,890 ppb on week 8, but by week 52, it had decreased to 648 ppb. In addition, oxychlordane levels were higher in adipose tissue than any other tissue at 52 weeks.

3.1.3 Metabolism

Information on the metabolism of chlordane in humans is limited. Tashiro and Matsumura (1978) identified the metabolites of *cis*- and *trans*-chlordane following incubation of these compounds with human liver microsomal preparations. The following metabolites (in order of decreasing concentration) were identified: chlordene chlorohydrin, monohydroxylated dihydrochlordene, oxychlordane, and relatively smaller but similar amounts of 1,2-dichlorochlordene, 1-hydroxy-2-chlorochlordene, 1-hydroxy-2-chloro-2,3-epoxychlordene, 1,2-hydroxychlordene, trihydroxydihydrochlordene, and β-glucuronide-1-hydroxydihydrochlordene. Patterns of metabolites were similar whether the starting material was the *cis* or *trans* isomer. Kutz et al. (1976, 1979) reported the presence of oxychlordane in most adipose tissue samples taken at surgery or necropsy from humans. Data were not located regarding the levels of chlordane metabolites in the urine of exposed humans.

Tashiro and Matsumura (1978) reported that experiments with liver microsomal preparations from rats yielded results nearly identical to those for human preparations. These investigators noted, however, that rat microsomal preparations efficiently metabolized *trans*-nonachlor (a predominant component of technical chlordane) to *trans*-chlordane, but that human microsomal preparations did not. These data suggest that the metabolism of pure isomers of chlordane by humans and rats is similar, but that metabolism of components other than the pure isomers present in the technical product may differ.

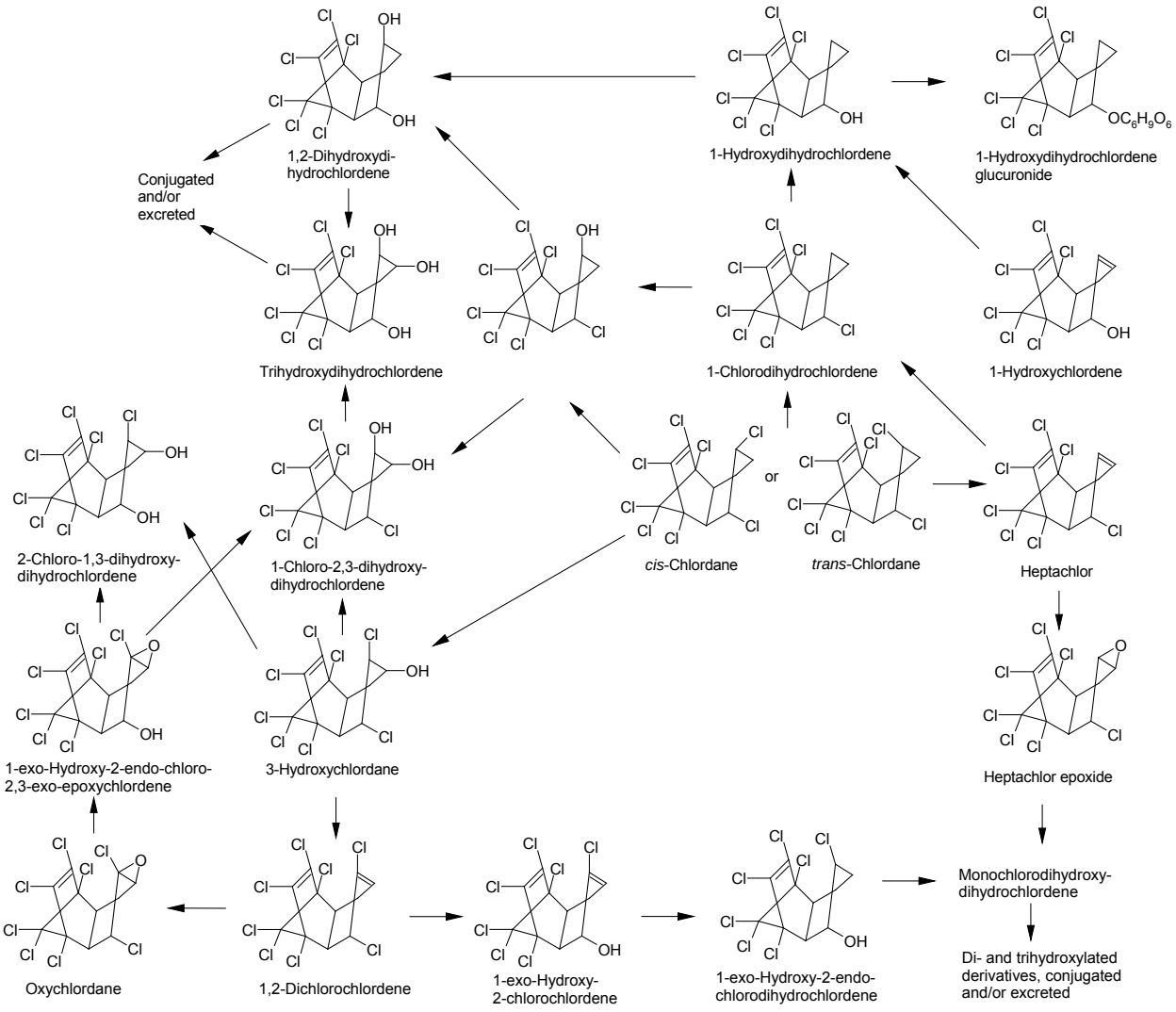
Data regarding the nature of tissue residues in rats and monkeys following continual inhalation exposure for 90 days indicate that monkeys are less efficient metabolizers of chlordane than are rats (Khasawinah

1989). Oxychlordane is the predominant metabolite of *trans*-chlordane in rats and monkeys (Khasawinah 1989; Sasaki et al. 1992).

Chlordane has been known to undergo biotransformation in animals since the mid-1960s, when it was demonstrated by Poonawalla and Korte (1964) that 10–80% of the radioactivity found in the tissues and excreta of rats given an intravenous dose of radiolabeled *cis*-chlordane was in the form of water soluble metabolites. Subsequently, several metabolic schemes have been proposed based on information obtained from *in vivo* and *in vitro* studies in rats (Barnett and Dorough 1974; Brimfield et al. 1978; Tashiro and Matsumura 1978) and rabbits (Balba and Saha 1978; Poonawalla and Korte 1971). These proposed schemes lack consistency, and controversial issues include: differences in the identity of metabolites observed in *in vivo* versus *in vitro* experiments, possible isomer differences (i.e., *cis* versus *trans*) in the routes of metabolism followed, and whether metabolites thought to be terminal by some investigators (e.g., oxychlordane) are capable of undergoing further biotransformation by mammals. The metabolic scheme for chlordane in animals presented in Figure 3-1 was proposed as a synthesis of the available information by Nomeir and Hajjar (1987). This scheme involves four routes of metabolism for the chlordane molecule. No distinction is made between *cis*- and *trans*-chlordane in the qualitative nature of the metabolites formed. The first proposed metabolic route starts with hydroxylation at position three of the molecule to form 3-hydroxychlordane. This reaction is thought to be mediated by the microsomal mixed-function oxidase (MFO) system. Dehydration of 3-hydroxychlordane leads to 1,2-dichlorochlordene and eventually to other metabolites such as oxychlordane and 1-hydroxy-2-chlorochlordene. Alternatively, 3-hydroxychlordane may undergo replacement of chlorines by hydroxyl groups to form monochlorodihydroxylated and -trihydroxylated derivatives. The second pathway starts with dehydrochlorination to form heptachlor. The mechanism of this reaction is not completely understood but is thought to be mediated by the cytochrome P-450 system and/or by glutathione-S-transferase type enzymes. Further metabolism of heptachlor leads to 1-hydroxychlordene, heptachlor epoxide, or eventually to 1-chloro-2,3-dihydroxydihydrochlordene. The third pathway starts with dehalogenation of chlordane to form 1-chlorodihydrochlordene, probably mediated by microsomal MFO systems. Further reactions probably involve hydrolysis and conjugation with glucuronic acid. The fourth metabolic pathway, and probably the least understood, involves hydrolytic removal of a chlorine atom and its replacement by a hydroxyl group to form 1-chloro-2-hydroxychlordene chlorohydrin. This product may undergo further metabolism to form monochlorodihydroxy- and trihydroxy- derivatives of dihydrochlordene. Studies with rat hepatic microsomes suggest that cytochrome P-450 may be the most important enzyme to catalyze degradation of *trans*-chlordane (Kawano et al. 1989). Epoxide hydrolase is probably the predominant enzyme to catalyze degradation of oxychlordane. Reductive dehalogenation,

with the production of free radicals, may also be important in the toxicity of chlordane (Brimfield and Street 1981; Kawano et al. 1989).

Figure 3-1. Proposed Metabolic Pathways for Chlordane



Source: Nomeir and Hajjar 1987

The metabolic rate of various chlordane components appears to depend on three structural features (Dearth and Hites 1991b). First, compounds with two chlorines on ring 1 are metabolized 3 times as rapidly as those with three chlorines. Second, compounds with the chlorine on C2 in an exoconfiguration are metabolized 20–25% more quickly than compounds with an endo-configuration. Third, compounds with one chlorine on C2 are metabolized 3 times as rapidly as those with two chlorines. Dechlorination

of compounds with three chlorines on ring one appears to be the first and rate-limiting step of metabolism of these compounds.

In mice treated orally every other day for 28 days with technical chlordane, *cis*- and *trans*-chlordane reached peak levels in the whole body on the first day and declined to lower levels in spite of repeated dosing; *cis*- and *trans*-nonachlor and oxychlordane increased during the entire study period (Hirasawa and Takizawa 1989). The ratio of *cis*-to *trans*-chlordane and *cis*-to *trans*-nonachlor in the test sample (6:7 and 1:4, respectively) and in the mouse body at termination of the experiment (5:3 and 1:7, respectively) suggests that *trans*-chlordane is metabolized more readily than *cis*-chlordane and that *cis*-nonachlor is metabolized more readily than *trans*-nonachlor. The decreasing content of the chlordane isomers and the increasing content of oxychlordane with repeated dosing suggests that chlordane induces its own metabolism.

3.1.4 Excretion

Information regarding excretion following inhalation exposure to chlordane is limited to the observation that recovery of radioactivity for 6 days following endotracheal administration of radiolabeled chlordane to rats was 52% in the feces and 12% in the urine (Nye and Dorough 1976).

Information regarding the excretion of chlordane and/or its metabolites from the human body after oral exposure is from case reports of accidental ingestion. These reports conclude that elimination from the plasma was biphasic in nature (Aldrich and Holmes 1969; Curley and Garrettson 1969; Olanoff et al. 1983). Marked differences existed, however, in the reported half-life of the terminal (slow) phase. Values reported for the terminal phase were 88 days (Aldrich and Holmes 1969), 21 days (Curley and Garrettson 1969), and 34 days (Olanoff et al. 1983). Small amounts of chlordane have been excreted in the urine of humans after oral ingestion of the compound. Aldrich and Holmes (1969) reported that the urinary concentration of chlordane decreased from 1.93 to 0.05 mg/L over the first 3 days following the ingestion of an unknown amount of chlordane by a 4-year-old girl. Curley and Garrettson (1969) reported a chlordane concentration in the urine of 0.309 mg/L at 24 hours after the ingestion of an unknown amount of chlordane by a 20-month-old boy. Fecal chlordane concentrations of 719 and 105 ppm have been reported on days 2 and 3, respectively, following chlordane ingestion by a 4-year-old girl (Aldrich and Holmes 1969).

The excretion of chlordane and/or its metabolites has been studied in animals following oral administration. In rats, 70–90% of the radioactivity administered (depending on the isomer) was eliminated within 7 days following a single oral dose of the radiolabeled pesticide (Barnett and Dorough 1974; Ewing et al. 1985; Tashiro and Matsumura 1977). In these studies, the *cis* isomer was eliminated more quickly than the *trans* isomer. From 70 to 90% of the radioactivity orally administered to rats was excreted in the feces; excretion of radioactivity in the urine ranged from 2 to 8% of the administered dose (Barnett and Dorough 1974). In another study, *cis*- and *trans*-chlordane were cleared from the blood within 7 days after male mice received a total dose of 40 mg/kg chlordane mixture (1:1) of both isomers (Satoh and Kikawa 1992). Although the *cis* isomer tended to accumulate more than the *trans* isomer, no difference in the half-lives in tissues (0.6–2 days) was observed between the two isomers. Both isomers were rapidly metabolized to oxychlordane. Oxychlordane was eliminated very slowly compared to the isomers and its half-life in blood was determined to be 25 days.

Studies by Ohno et al. (1986) and Ewing et al. (1985) indicate that biliary excretion of chlordane and/or its metabolites is significant in both rats and mice and is the source of fecal excretion by these species. Ewing et al. (1985) administered a 1 mg/kg dose of radiolabeled *cis*-chlordane to rats and mice by intraperitoneal injection and recovered 47% (rats) and 67% (mice) of the dose in the feces within 7 days. By using bile duct-cannulated rats, Ohno et al. (1986) showed that biliary excretion occurred more rapidly after oral administration than after intravenous administration, probably as a result of the first pass of blood from the digestive tract through the liver via hepatic portal circulation. The relative proportions of fecal and urinary excretion of radioactivity after oral administration of radiolabeled chlordane in rats do not appear to change significantly with dose over ranges of 0.05–10.0 mg/kg (Barnett and Dorough 1974; Ohno et al. 1986). In addition, longer-term administration of chlordane in the diet (1, 5, or 25 ppm for 56 days) did not change the excretion pattern significantly in rats from that observed following single oral dosing (Barnett and Dorough 1974).

In contrast to the excretion pattern of radioactivity observed in rats following oral exposure to radiolabeled chlordane, rabbits tend to excrete larger percentages of the administered dose in the urine. The percentage of the administered radioactivity excreted in the urine of rabbits following multiple oral doses ranged from 28 to 47% (Balba and Saha 1978; Poonawalla and Korte 1971). In these same studies, fecal excretion in the rabbit ranged from 22 to 48% of the administered dose. The greater urinary excretion of radioactivity in rabbits compared with rats may be due to the greater ability of rabbits to form water-soluble conjugates of chlordane metabolites. Biliary excretion was not studied in these experiments.

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.

No PBPK models were identified for chlordane.

3.1.6 Animal-to-Human Extrapolations

Data in rats, mice, and rabbits following oral exposure to chlordane indicate that there are some species differences in absorption, distribution, and excretion (Balba and Saha 1978; Barnett and Dorough 1974; Bondy et al. 2000; Ewing et al. 1985; Ohno et al. 1986; Poonawalla and Korte 1971; Satoh and Kikawa 1992). The available data on metabolites in human tissues and *in vitro* studies both indicate qualitatively that metabolism of chlordane in rats and humans is similar (Tashiro and Matsumura 1978).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

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

Humans with chronic liver disease or impaired liver function may be unusually susceptible to chlordane toxicity. Infante et al. (1978) speculated on the existence of an unusually susceptible population prone to the development of blood dyscrasia (i.e., aplastic anemia and leukemias) following exposure to chlordane. Such a population was thought to have some sort of idiosyncratic response to chlordane exposure, but identification of this population was not thought to be possible. Although data are not available, humans exposed to other chemicals that induce hepatic microsomal enzymes may be unusually susceptible to chlordane, because the induced enzymes may enhance the transformation of chlordane to more highly toxic metabolites. Studies with rats show that males generally respond more than females to xenobiotic-induced enzyme induction (Kinoshita et al. 1966), but information regarding sex differences in enzyme induction in humans was not located.

Evidence in mice indicates that the fetus may be particularly susceptible to compromised immuno-competence due to altered stem cell populations of key immunoactive cells (Barnett et al. 1990a, 1990b). Infants may be unusually susceptible to a chronic seizure disorder following exposure to chlordane, particularly if they have a hereditary predisposition, such as a positive familial history of febrile convulsions (Bernad 1989).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,2-dibromo-3-chloropropane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see

http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,2-dibromo-3-chloropropane 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 1,2-dibromo-3-chloropropane 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

It is possible to measure chlordane and/or a number of its metabolites in a variety of human tissues and fluids (i.e., blood, adipose tissue, brain, liver, kidney, milk, sebum [or skin lipids], urine, and feces). Generally, total chlordane residue levels are higher in fat and liver than in the blood (Mussalo-Rauhamaa 1991). There is no information in the literature, however, correlating the levels found in these tissues and fluids with the environmental chlordane concentrations to which the individual was exposed. Furthermore, the data do not reveal how long after exposure residues may be detected in the various body tissues and fluids.

Kawano and Tatsukawa (1982) measured “total” chlordane (*cis*-and *trans*-chlordane, heptachlor epoxide, oxychlordane, and *trans*-nonachlor) residues in the blood of pest control operators and nonexposed workers in Japan. Not all of these residues (e.g., heptachlor epoxide) are specific for exposure to chlordane. Levels in the blood of four of five unexposed workers were below 0.10 ng/g, the limit of detection. A level of 0.13 ng/g was reported for the fifth unexposed worker, who had lived for 2 years in a termite-treated home. Levels in the blood of 21 pest control operators ranged from 0.57 to 83 ng/g, with

an average of 12 ng/g, approximately two orders of magnitude greater than levels in unexposed workers. There was no mention or indication of signs of chlordane toxicity in either the unexposed workers or pest control operators. Kutz (1983) reported mean levels in human serum for each of four components or metabolites of chlordane at <l ppb. It was not possible, however, to estimate the mean level of "total" chlordane from these data. Kutz et al. (1976, 1979) reported mean levels of heptachlor epoxide of approximately 0.1 ppm in adipose tissue samples collected from the U.S. population. Levels of oxychlordane in these samples also averaged 0.1 ppm. There appeared to be no significant change in the concentration of either chlordane metabolite over a 5-year period from 1970 to 1975. The individuals sampled by Kutz (1983) and Kutz et al. (1976, 1979) are assumed to be asymptomatic, so the reported levels were not associated with effects of chlordane toxicity. Oxychlordane has been measured at concentrations ranging from 0.002 to 0.005 mg/L in human breast milk (whole milk basis) in samples taken at random from subjects with infants assumed to be asymptomatic (Barnett et al. 1979; Strassman and Kutz 1977). In Finnish human milk samples, total chlordane residues in positive samples averaged 0.41 mg/kg of milk fat (Mussalo-Rauhamaa et al. 1988).

Several components of chlordane (*trans*-and *cis*-chlordane, *trans*-and *cis*-nonachlor, heptachlor, gamma-chlordene) were detected in the skin lipids of humans (Sasaki et al. 1991b). The samples were taken by swabbing the face with cotton soaked with 70% ethanol 3–4 hours after the face was washed with soap. Because all of the samples from inhabitants of an area known to be contaminated with chlordane contained chlordane residues, and because the profile of chlordane components in skin lipids closely resembled those in technical chlordane, the authors suggested that skin lipid analysis is a satisfactory indicator of dermal exposure to airborne chlordane, such as occurs in homes treated for termites. Oxychlordane in the skin lipids was positively correlated (correlation coefficient 0.68, $p<0.01$) with concentrations in internal adipose tissue. The authors concluded that the concentration of oxychlordane in skin lipids was a satisfactory indicator of body accumulation of chlordane.

A later study in monkeys confirmed that chlordane residues in skin lipids correlate closely with residues in blood (Sasaki et al. 1992). In this study, monkeys were given five consecutive, weekly, subcutaneous doses of 1 or 10 mg *trans*-chlordane/kg, and blood, adipose tissue and skin lipids were sampled up to 28 weeks after the last treatment for analysis for *trans*-chlordane and oxychlordane. *trans*-Chlordane concentrations in adipose tissue declined rapidly after the last dose; oxychlordane concentrations increased for about 5 weeks and leveled off. The correlation coefficients for *trans*-chlordane in the adipose tissue and blood, and in the adipose tissue and skin lipids were 0.93 and 0.72, respectively. The correlation coefficients for oxychlordane in the adipose tissue and blood, and in the adipose tissue and

skin lipids, were 0.94 and 0.83, respectively. These data suggest that *trans*-chlordane concentrations in skin lipids are a satisfactory biomarker of recent exposure, and that oxychlordane concentrations in skin lipids are a satisfactory marker of previous exposure and of the body burden (in adipose tissue) of oxychlordane.

Data are available that correlate exposure to chlordane with levels of the pesticide and/or its metabolites in biological samples taken from humans. Total chlordane residues in the blood were 3–16 times higher in pesticide applicators, and 1.5–10 times higher in residents of a heavily contaminated area, where many of the houses were treated for termites with chlordane, than in residents of a relatively noncontaminated area (Wariishi and Nishiyama 1989). Recent information indicates a relatively strong correlation between the length of exposure to atmospheric chlordane in a termite-treated home and the concentration of chlordane in human milk fat (Taguchi and Yakushiji 1988); however, actual atmospheric chlordane concentrations were not reported. A relatively strong correlation between blood chlordane concentration and the number of days that a pest control operator has sprayed has been reported by Saito et al. (1986). Takamiya (1987) demonstrated a strong correlation between total chlordane residues (i.e., *trans*-nonachlor plus oxychlordane) in the blood of pest control operators and their duration of exposure. The atmospheric concentrations of chlordane to which these pest control operators had been exposed were not reported (Saito et al. 1986; Takamiya 1987). Kawano and Tatsukawa (1982) showed that the levels of heptachlor epoxide, oxychlordane, and *trans*-nonachlor in the blood of pest control operators in Japan increased with increased duration of exposure (years of employment).

Elevated serum levels of creatine phosphokinase (CPK) were measured in Japanese pest control operators exposed to chlordane (Ogata and Izushi 1991). Levels of ALT and AST were not elevated, and the investigators concluded that elevated CPK was somewhat specific for exposure to chlordane, compared with other organochlorine compounds.

3.3.2 Biomarkers of Effect

The most sensitive indicators of acute chlordane toxicity in humans are central nervous system effects including headache, confusion, behavioral aberrations, and tremors (EPA 1980a; Harrington et al. 1978). Effects on the liver appear to be the only manifestations in humans of chronic exposure to chlordane (EPA 1980a; Ogata and Izushi 1991). Changes in indicators of compromised liver function may serve as biomarkers of chlordane toxicity; however, these indicators are not specific to chlordane toxicity.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Chlordane, like other organochlorine insecticides, functions as a potent inducer of hepatic microsomal enzymes. Induction of these enzymes following chlordane administration is associated with an increased rate of metabolism of many endogenous and xenobiotic compounds, including therapeutic drugs and hormones (Welch and Harrison 1966; Welch et al. 1971). Exposure to other pesticides or chemicals that induce hepatic microsomal enzymes may increase the toxicity of chlordane, probably by enhancing the transformation of chlordane to more highly toxic metabolites. For example, previous exposure to aldrin, dieldrin, or DDT increased the acute toxicity of chlordane to rats by 2.3–4.6 times (Deichmann and Keplinger 1970). When given simultaneously to rats or mice, the acute lethal effects of chlordane in combination with most pesticides appeared to be roughly additive, except that aldrin or endrin and chlordane, and methoxychlor and chlordane were more than additive in mice (Keplinger and Deichmann 1967).

The acute toxicity of chlordane in rats increased when rats were fed protein-deficient diets (Boyd and Taylor 1969). Chlordane treatment has also been demonstrated to enhance the hepatotoxic effects produced by carbon tetrachloride in rats, as indicated by its effect on ALT levels, presumably by inducing the metabolism of carbon tetrachloride to its toxic metabolite (Mahon et al. 1978; Stenger et al. 1975). On the other hand, chlordane provided some protection against carbon tetrachloride-induced liver necrosis in rats, possibly by inducing a type of cytochrome P-450 with diminished ability to metabolize carbon tetrachloride to its toxic metabolite (Mahon et al. 1978). Pretreatment of rats with chlordane accelerated the metabolism of lindane, presumably by inducing the metabolism of lindane to its toxic metabolite (Chadwick et al. 1977).

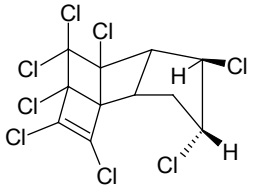
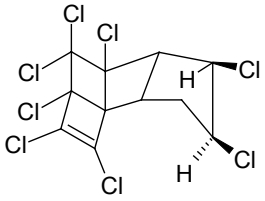
Chlordane-induced testicular effects in mice were markedly increased when lead oxide was coadministered (Al-Omar et al. 2000).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of chlordane are listed in Table 4-1. Technical chlordane is a mixture of >140 related compounds, 120 of which have been identified by high resolution gas spectroscopy with electron capture, negative ionization mass spectroscopy (Dearth and Hites 1991c). Most of these compounds are minor or trace components. Sixty to 85% of technical chlordane consists of the stereoisomers *cis*- and *trans*-chlordane (Buchert et al. 1989; Worthing and Walker 1987). The ratio of the *cis* and *trans* isomers depends on the manufacturing process (Buchert et al. 1989). *cis*-Chlordane (1α,2α,3aα,4β,7β,7aα) is also known as α-chlordane. *trans*-Chlordane (1α,2 β,3aα,4β,7β,7aα) is commonly known as γ-chlordane, although it is occasionally referred to as ß-chlordane (CAS 1992; EPA 1984; Worthing and Walker 1987). This is particularly confusing because γ-chlordane is also the common name of the 2,2,4,5,6,7,8,8-octachloro isomer. This toxicological profile for chlordane uses the names *cis*- and *trans*-chlordane to avoid confusion.

Table 4-1. Chemical Identity of Chlordane

Characteristic	Information	Reference
Chemical name	1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene	CAS 1987
Synonym(s) and registered trade name(s)	1,2,4,5,6,7,8,9-Octachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden; Chlordan; Velsicol 1068®; Octachlor®	Anonymous 1988; CAS 1987
Chemical formula	$C_{10}H_6Cl_8$	CAS 1988
Chemical structure	*trans*  *cis* 	CAS 1988
CAS Registry Number	12789-03-6 (technical) 57-74-9 (nonstereospecific) 5103-71-9 (*cis*-chlordane or α-chlordane) 5103-74-2 (*trans*-chlordane or γ-chlordane)	CAS 1988; Worthing and Walker 1987

CAS = Chemical Abstracts Service

Other major constituents of technical chlordane are chlordene; heptachlor; *cis*-, and *trans*-nonachlor; α-, ß-, and γ-chlordene; 3a,4,5,5a,6-exo-hexachloro-1a,2,3,3a,5a,5b-hexahydro-1,4-methano-

1H-cyclobuta[cd]pentalene; and 2,4,4,5,6,6,7,8-octachloro-2,3,3a,4,5,7a-hexahydro-1,4-methano-1H-indene (Miyazaki et al. 1985; Parlar et al. 1979).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of chlordane are presented in Table 4-2. The physical and chemical properties of technical chlordane are difficult to specify since there are many components in the technical mixture. For example, technical chlordane is a viscous liquid made of a mixture of many compounds that are solids when pure (a eutectic mixture). The state of the technical product alone will determine the specific properties of the product. For example, the vapor pressure of individual components of chlordane will be lower than that of the technical product because individual components are solids and have crystal lattice energies that reduce their vapor pressures relative to a liquid (Bidleman and Foreman 1987). The vapor pressure of the mixture will also change over time since the more volatile components will be removed faster, changing the composition of the mixture. Compositional changes with time may also result from different rates of degradation and transport among the constituents of the mixture. Additionally, physical properties are not always available for the technical product, which makes comparing properties difficult and increases the uncertainty of any calculated properties. Finally, the overall effect of these differences cannot be evaluated since a complete set of physical properties for the components and technical product is not available.

Table 4-2. Physical and Chemical Properties of Chlordane

Property	Information	Reference
Molecular weight	409.76 (pure chlordane)	Windholz 1983
Color	Amber Colorless	Windholz 1983 Hawley 1981
Physical state	Viscous liquid (technical product)	Windholz 1983
Melting point		
cis-chlordane	106–107°C	Worthing and Walker 1987
trans-chlordane	104–1-5°C	Worthing and Walker 1987
Boiling point	175°C at 2 mmHg	Hawley 1981
Density at 25°C	1.59–1.63 g/cm^3	Windholz 1983
Odor	Odorless Mild pungent	Hawley 1981 NRCC 1974
Odor threshold:	0.0084–0.0419 mg/m^3	Ruth 1986
Solubility:[a]		
Water at 25°C	0.056 mg/L for *cis:trans* (75:25) 1.850 mg/L[b]	Sanborn et al. 1976 Weil et al. 1974
Organic solvents	Miscible with hydrocarbon solvents	Whetstone 1964; Worthing and Walker 1987
Partition coefficients:		
Log K_{ow}	5.54 (estimated for pure chlordane)	EPA 1986b
Log K_{oc}	3.49–4.64[c] 6.3 (*trans*-) suspended solids	Lyman 1982 Lau et al. 1989
Vapor pressure:[d]		Foreman and Bidleman 1987
cis-chlordane		
(supercooled liquid)	2.2x10^{-5} mmHg	
(crystal)[e]	3.0x10^{-6} mmHg	
trans-chlordane		
(supercooled liquid)	2.9x10^{-5} mmHg	
(crystal)[e]	3.9x10^{-6} mmHg	
Henry's law constant at 25°C	4.85x10^{-5} atm-m^3/mol[b] 8.31x10^{-5} atm-m^3/mol (*trans*-) 4.8x10^{-5} atm-m^3/mol	Suntio et al. 1988 Fendinger et al. 1989 Cotham and Bidleman 1991
Autoignition temperature	No data	
Flashpoint	56°C (open cup)	OHM/TADS 1988
Flammability limits	No data	
Conversion factors	1 ppm (v/v) = 16.75 mg/m^3 in air 1 mg/m^3 = 0.0597 ppm (v/v) in air	HSDB 1988
Explosive limits	No data	

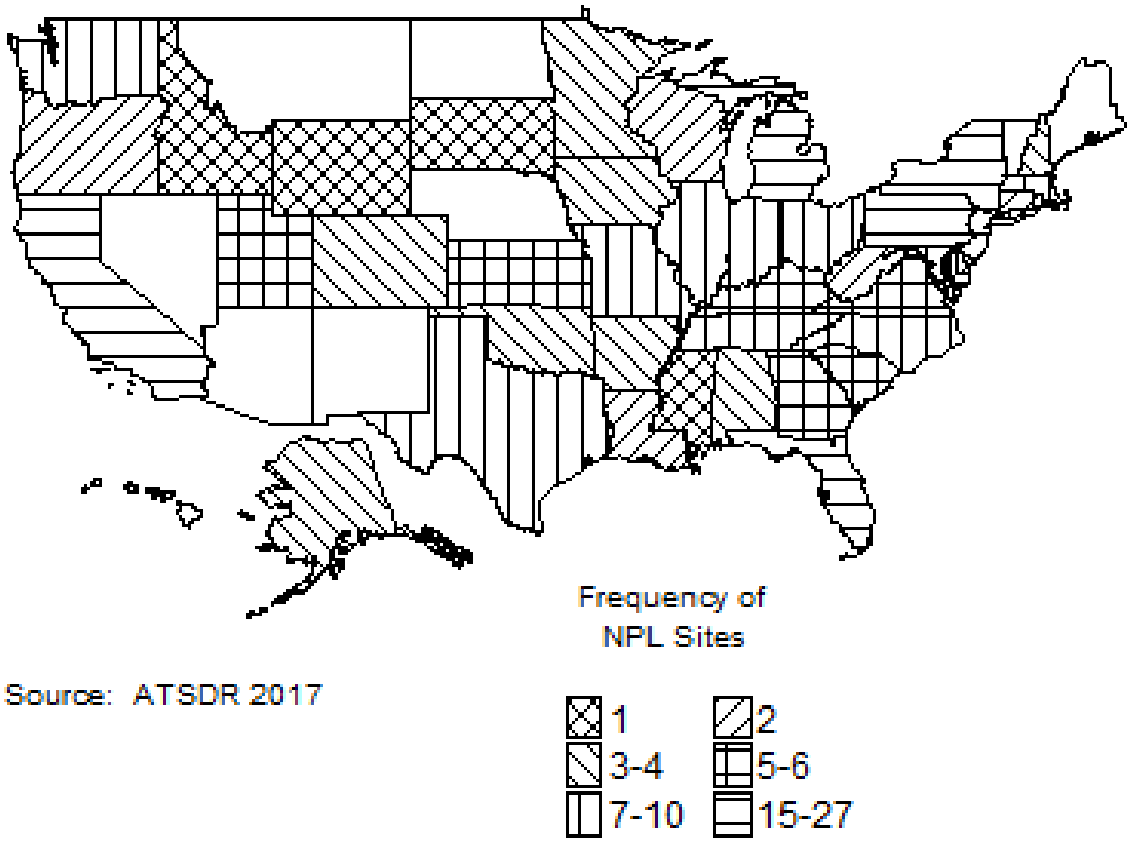
[a]The solubility of the components of technical chlordane may differ from the solubility of the technical product.
[b]Study did not specify whether test substance was technical grade or a mixture.
[c]Estimated for pure chlordane using Equations 4-5 and 4-8 in Lyman (1982).
[d]Vapor pressure for technical chlordane may differ from that of individual components of technical chlordane.
[e]Calculated from the supercooled value.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chlordane has been identified in at least 285 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which chlordane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 283 are located within the United States and 1 is located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Chlordane Contamination



Source: ATSDR 2017

- The most likely sources of potential exposure of the general population to chlordane are from exposure in homes that were treated with chlordane to control termites or eating chlordane-contaminated food or drinking water than may have been contaminated from chlordane when it was used as a pesticide prior to 1988.

- People who live near hazardous waste sites containing chlordane may be exposed from contaminated air, surface water or groundwater, or soil.
- Daily intakes from food have been estimated.
- Chlordane would be expected to volatilize from surface water and surface soil; in air, chlordane is expected to degrade by photolysis and oxidation. Residues in soil that do not leach or volatilize appear to be persistent.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Chlordane is produced by chlorinating cyclopentadiene to form hexachlorocyclopentadiene and condensing the latter with cyclopentadiene to form chlordene. The chlordene is further chlorinated at high temperature and pressure to chlordane (Dearth and Hites 1991c; Whetstone 1964). EPA (1987g) estimated that ≈3.5–4.0 million pounds of chlordane were distributed in 1986. In 1990, Velsicol Chemical Company in Memphis, Tennessee, was the only U.S. manufacturer of chlordane; between 100,000 and 1 million pounds of chlordane were produced (SRI 1990; TRI90 1992). It was the only domestic manufacturer of chlordane at the time that the EPA canceled its registration for commercial production, delivery, sale, and use in the United States (EPA 1988c; SRI 1988). This cancellation became effective April 14, 1988 (EPA 1988c). Technical heptachlor contains 20–22% *trans*-chlordane (Kutz et al. 1991). The registration of heptachlor was also canceled by EPA. Table 5-1 summarizes information on U.S. companies that manufactured or used chlordane in 2016 (TRI16 2017).

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	100,000	999,999	9, 12
CA	1	100	999	12
ID	1	1,000	9,999	12
IL	1	0	99	12
IN	1	0	99	1, 2, 9, 13, 14
NE	1	10,000	99,999	12
OH	2	100	99,999	12
OR	1	10,000	99,999	12
TX	2	1,000	99,999	1, 5, 11, 12

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
UT	1	100,000	999,999	9, 12
VA	1	100	999	9

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

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

Source: TRI16 2017 (Data are from 2016)

5.2.2 Import/Export

Chlordane is not produced in the United States and is not imported from any sources.

5.2.3 Use

As of April 14, 1988, all commercial use of chlordane in the United States was canceled (EPA 1988c). Between July 1, 1983 and April 14, 1988, the sole use for chlordane was to control subterranean termites (EPA 1987g). For this purpose, chlordane was applied primarily as a liquid that was poured or injected around the foundation of a building (Wallace 1991). Chlordane, in conjunction with heptachlor, was at one time widely used as a pesticide for the control of insects on various types of agricultural crops and vegetation. The use pattern for chlordane in the mid-1970s was as follows: 35% used by pest control operators, mostly on termites; 28% on agricultural crops, including corn and citrus; 30% for home lawn and garden use; and 7% on turf and ornamentals (HSDB 1988). On March 6, 1978, a final cancellation notice was issued, which called for the suspension of the use of chlordane except for subsurface injection to control termites and for dipping roots and tops of nonfood plants. Minor use of chlordane for treating nonfood plants was canceled by 1983 (EPA 1987g). The use of chlordane decreased drastically in the 1970s when EPA moved to cancel all uses other than subterranean termite control (Kutz et al. 1991).

5.2.4 Disposal

Chlordane may be disposed of by dissolving it in a flammable solvent and incinerating it under controlled conditions. The incinerator should be equipped with an afterburner and an acid scrubber to remove halo acids from the effluent gas, and adequate ash disposal procedures should be followed (EPA 1991; HSDB 1988; OHM-TADS 1988). Before disposing waste residue containing chlordane (including waste sludge) on land, environmental regulatory agencies should be consulted for guidance on acceptable disposal practices (HSDB 1988). EPA promulgated standards for the disposal of waste chlordane in sewage sludge (EPA 1993).

In situ vitrification is a thermal treatment technology in which substantial quantities of energy are introduced into contaminated soil, thereby destroying organic compounds and immobilizing inorganic compounds (Dragun 1991). This technology has been applied to chlordane-contaminated soils.

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 39 pounds (~0.02 metric tons) of chlordane to the atmosphere from 13 domestic manufacturing and processing facilities in 2016, accounted for about 0.13% of the estimated total

environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	1	0	0	0	0	1	0	1
CA	1	0	0	0	235	0	235	0	235
ID	1	0	0	0	1,018	0	1,018	0	1,018
IL	1	No data	No data	No data	No data	No data	No data	No data	No data
IN	1	No data	No data	No data	No data	No data	No data	No data	No data
NE	1	23	0	0	6,183	0	23	6,183	6,206
OH	2	4	0	0	0	0	4	0	4
OR	1	0	0	0	22,256	0	22,256	0	22,256
TX	2	11	0	0	0	0	11	0	11
UT	1	No data	No data	No data	No data	No data	No data	No data	No data
VA	1	No data	No data	No data	No data	No data	No data	No data	No data
Total	13	39	0	0	29,691	0	23,548	6,183	29,731

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

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

5.3.2 Water

There were no releases of chlordane to surface water or publicly owned treatment works (POTWs from 13 domestic manufacturing and processing facilities in 2016 required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

5.3.3 Soil

Estimated releases of 29,691 pounds (~13.47 metric tons) of chlordane to soils from 13 domestic manufacturing and processing facilities in 2016, accounted for about 99.9% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). No chlordane was released via underground injection (TRI16 2017). These releases are summarized in Table 5-2.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Chlordane may be transported long distances in the atmosphere. The United States appears to be the main source of chlordane in the air over the North Atlantic (Bidleman et al. 1987). Concentrations of *cis*-chlordane ≤0.0054 ng/m^3 in the Norwegian Arctic are believed to originate in the Soviet Union, thousands of miles away (Pacyna and Oehme 1988). Similarly, the source of chlordane-related compounds in brown snow in the central Canadian Arctic, based on back-trajectories of air masses, was probably western China (Welch et al. 1991). It is estimated that ≈3,300 kg of chlordane were deposited annually in the Arctic regions (from 60° N latitude to the pole) (Cotham and Bidleman 1991).

There is a large body of information concerning the transport and partitioning of chlordane in the environment. In outdoor air, chlordane exists predominantly in the vapor phase (Atlas and Giam 1988; Bidleman et al. 1986; Bidleman and Foreman 1987; Foreman and Bidleman 1987), whereas particle-adsorbed chlordane will contribute relatively minor amounts to the environmental burden (Starr et al. 1974; Tucker and Preston 1984). Air monitoring data are derived by the following method: chlordane is first pulled through a fiber filter and then trapped on a solid adsorbent; the amounts of chlordane retained on the filter and on the adsorbent are used to estimate the proportion of particulate-bound and vapor-phase chemical. Air monitoring data derived by this method indicate that 0.7 and 11% of chlordane is bound to particulate matter at 20 and 0°C, respectively (Bidleman et al. 1986). At 28°C (the average temperature at which one of the arctic air monitoring studies was performed), about 45% of chlordane is bound to

particulate matter (Patton et al. 1991). However, the small amount of adsorbed chlordane at ordinary temperatures appears to play an important role in atmospheric deposition. In samples collected in a rural area of Texas, 98% of the chlordane-scavenged rain was particle-bound chlordane, rather than vapor-phase chlordane that partitioned into rain drops (Atlas and Giam 1988). The chlordane concentration in rain was 1,900 times the concentration in air. The contribution of dry deposition to total (wet and dry) deposition in a 24-hour period was 8.9%. Chlordane applied to the foundation of homes for termite treatment can enter the home through cracks in the foundation or in heating ducts in the slabs. Chlordane disperses through the house by diffusion and convection (Livingston and Jones 1981).

Chlordane in water will both adsorb to bed and suspended sediments and volatilize. The partitioning of chlordane to sediment correlates with the organic carbon content of the sediment. The mean log K_{oc} for *trans*-chlordane to samples of suspended particulate matter from the St. Clair and Detroit Rivers was 6.3 (Lau et al. 1989). Where concentrations of suspended sediment are high, such as in rivers near sources of industrial discharge, substantial amounts of pollutants like chlordane would be transported with suspended sediment. The rate of volatilization of chlordane from water depends to a large extent on the amount, size, and composition (i.e., percent organic matter) of the suspended material in the water body, since adsorption to suspended solids and sediments attenuates the rate of volatilization (Oloffs et al. 1972, 1973). The rate of volatilization is also affected by temperature, wind, and water turbulence. Chlordane adsorbed almost completely to sediments in laboratory experiments over a period of ≈6 days (Oloffs et al. 1972, 1973). It also volatilizes reasonably rapidly from water (Huang 1970), and it appears that volatilization kinetics may be faster than adsorption kinetics. The majority of chlordane, however, probably enters water as runoff from urban and agricultural soils, and is adsorbed to particulates before entering a body of water. The chlordane repartitions in the water and volatilizes rapidly near the water surface. Using the EPA EXAMS model (EPA 1985b), the estimated volatilization half-lives of chlordane from a typical pond and lake are <10 days. Nonetheless, monitoring data indicate that sediment concentrations of chlordane are much higher than the overlying water, suggesting that volatilization from water may not be as fast as predicted. A field experiment was performed to study the persistence and mobility of technical chlordane applied to an intertidal sandflat (Smith et al. 1992). The chlordane was applied at mid-tide level to a depth of 10 cm and sediment cores to a depth of 10 cm were sampled before treatment and 1, 3, 5, 13, 19, 44, 71, 112, and 199 tides after treatment. The overall change of mass was about 62% over a period of 106 days with more than half occurring during the first tide cycle. The main decrease in concentration was in the top 2 cm where mass transport and bioaccumulation are most effective. Concentrations for the 2–5- and 5–10-cm depth intervals showed little change between tides 3 and 71. Thus, after some initial displacement, possibly into more organically-enriched sediment, there

was little vertical movement of chlordane. The composition of the technical chlordane was essentially constant during the experiment, which suggested that processes such as hydrolysis, dechlorination, and volatilization were much less important pathways for chlordane removal from this environment than sediment transport.

Chlordane will bioconcentrate in both marine species (bioconcentration factor 3,000–12,000 [Zaroogian et al. 1985]) and fresh water species (bioconcentration factor 18,500 in rainbow trout [Oliver and Niimi 1985]), as well as bacteria (bioconcentration factor of 200–55,900 [Grimes and Morrison 1975]). See Gobas et al. (1988) and Isnard and Lambert (1988) for further information on bioaccumulation in fish. Biomagnification of chlordane-related compounds, including heptachlor epoxide, was studied at three trophic levels in the Arctic marine food chain, namely, Arctic cod, ringed seals, and polar bears (Muir et al. 1988). Biomagnification was 7.3/4.7 from fish to seal (male/female) and 6.6/9.5 between seal (male/female) and bear (resulting in an overall fish to bear biomagnification factor of 44.2). Both chlordane isomers decrease in higher trophic levels with only the metabolite oxychlordane present in polar bears (Hargrave et al. 1992). It should be noted that biomagnification of chlordane is a tricky concept because the compositional pattern of chlordane compounds and metabolites varies among different trophic levels and species (Kawano et al. 1988). Chlordane is taken up by rooted aquatic vascular plants both from the water and from the sediment. The bioconcentration factor of chlordane in the submerged vascular plant, *Hydrillu verticillatu*, was 1.060 (Hinman and Klaine 1992). Chlordane also bioconcentrates in the roots from contaminated sediment and translocates into the shoots. However, acropetal translocation is not extensive.

In soil, chlordane adsorbs to the organic matter and volatilizes slowly over time. Chlordane does not leach significantly. In general, chlordane remains in the top 20 cm of most soils and for some soils, it stays at this level for >20 years (Beeman and Matsumura 1981; Bennett et al. 1974). Its behavior is somewhat dependent on the composition of the soil (Bennett et al. 1974; Carter and Stringer 1971; Haque and Freed 1974; Jury et al. 1987a; Sears and Chapman 1979; Stewart and Chisholm 1971; Stewart and Fox 1971; Tafuri et al. 1977). A study by the California Department of Food and Agriculture classified chlordane as a “nonleacher” based on records of groundwater contamination following normal agricultural use (Gustafson 1989). The distribution coefficient between chlordane and geologic material collected near a hazardous waste site in Memphis, Tennessee, ranged from 18 to 220 mL/g or K_{oc} of 20,000–76,000 (Johnson-Logan et al. 1992). Chlordane will bind tenaciously to dissolved organic carbon (DOC) in water, which will result in increased apparent solubility and mobility in the presence of DOC. For example, the solubility of chlordane in groundwater downstream of a hazardous waste site in

Memphis, Tennessee, was 150 µg/L, compared to 30 µg/L in purified water due to the presence of DOC (Johnson-Logan et al. 1992). Therefore, it is expected that chlordane mobility will be enhanced at this site. Volatilization from soil is a major loss mechanism for chlordane; the rate depends on such parameters as the soil organic content, water content, temperature, and relative humidity as well as its vapor pressure and adsorption to soil (Atallah et al. 1979; Glotfelty and Schomburg 1989; Glotfelty et al. 1984; Jury et al. 1987b; Nash 1983a, 1983b; Wilson and Oloffs 1973). In general, sandy soils and soils with small amounts of organic matter retain chlordane less than soils with high clay and/or organic content (Wiese and Basson 1966). Soil moisture, however, is the most important factor. Within an hour of being sprayed on the surface of moist bare soil in a pesticidal mixture, the vapor pressure of chlordane near the soil surface was 5.8×10^{-7} mmHg (Glotfelty and Schomburg 1989). The time for 50% of the chlordane to volatilize is 2–3 days. In time, the spray penetrates the soil and longer-term volatilization is controlled by back diffusion out of the soil layer. Losses are also highest near noon and lowest at night. It has been shown that the loss rate of chlordane applied to the surface of moist soil is proportional to the amount of remaining residue and inversely proportional to the square root of the daylight hours since application. In dry soil, the organic vapors are much more strongly adsorbed with a resulting decrease in volatilization (Glotfelty and Schomburg 1989; Nash 1983a). Incorporation of chlordane into the soil reduces volatilization because of dilution and because volatilization depends on slow diffusion and convective flow processes. It is estimated that 4.0 cm of sandy soil or 3.9 cm of clay soil is sufficient to restrict chlordane volatilization losses to <0.7% of the mass incorporated in the soil (Jury et al. 1990). Volatilization in some cases will continue for many years, as evidenced by the detection of indoor air concentrations of chlordane 15 years after application (Livingston and Jones 1981). Crop cover does not markedly alter the rate of volatilization. In a 3-year field experiment in which chlordane was incorporated into the top 10 cm of sandy loam soil, the half-lives of chlordane in cropped and fallow plots were 93.2 and 154 days, respectively (Singh et al. 1991). Initially, the dissipation rate of *cis*-chlordane was slightly higher in the fallow plots. *trans*-Chlordane disappeared from the soil column after 210 days, but then reappeared, suggesting that *cis*-chlordane was isomerizing to *trans*-chlordane. At the end of the experiment, the highest residues were in the top 10 cm of soil for both the cropped and fallow plots. However, the proportion of *trans*-chlordane was markedly lower in the cropped plots. Small amounts of chlordane can translocate from contaminated soil into plants, and there is some evidence that *cis*-chlordane can isomerize to *trans*-chlordane in plants (Singh et al. 1990, 1991). The amount taken up varies with species and stage of plant development.

5.4.2 Transformation and Degradation

Air. Chlordane degrades in air by both photolysis and oxidation. *trans*-Chlordane photochemically degrades more readily than *cis*-chlordane. This is indicated from the fact that the *trans:cis* ratio of chlordane transported long distances to the Norwegian Arctic changes from around 1 in the winter to 0.5 in the summer (Oehme 1991). Many papers have been published that detail the photoproducts of chlordane (principally *cis*-chlordane) and mechanisms of photoproduct formation (Feroz et al. 1981; Ivie et al. 1972; Onuska and Comba 1975; Parlar and Korte 1973, 1977, 1979, 1980; Podowski et al. 1979; Vollner et al. 1971). The most common photoproduct for *cis*-chlordane is the cage configuration that results from proton migration to the dichloroethylene moiety and carbon-carbon bond formation from one of the cyclopentane carbons. These photoreactions may also occur on leaf surfaces (Parlar 1978; Podowski et al. 1979), although the significance of this reaction to the overall removal of chlordane is not clear. Hydroxyl radical reactions of chlordane may be a significant removal mechanism in addition to photolysis. Atkinson (1987) developed a method to estimate the rate of reaction for hydroxyl radicals with organic vapors in the atmosphere. This method is based on the molecular structure of the organic compound. Using this method, an overall reaction rate of 12.4×10^{-12} cm^3/molecule-second was calculated. Assuming an average ambient hydroxyl radical concentration of 5×10^5 molecules/cm^3, averaged over a 24-hour time period (Atkinson 1985), this reaction rate yields an atmospheric half-life of 1.3 days for chlordane vapor.

Water. The degradation of chlordane in water has not been extensively studied. Eichelberger and Lichtenberg (1971) reported results of a river die-away test in which 85% of the original concentration of chlordane added to river water remained at the end of 2 weeks and persisted at that level for 8 weeks. Oloffs et al. (1972) found that 2.3–50.7% of the chlordane added to three river water samples remained in the aqueous phase after 12 weeks. It was concluded that at least some of the loss was from volatilization. Speidel et al. (1972) reported that chlordane adsorbed to microbially-generated floe, and Tabak et al. (198la, 1981b) reported no degradation in 7 days using domestic waste water as a seed. These studies indicate that chlordane will not degrade rapidly in water and that transport is probably a faster removal mechanism than degradation. No information is available on whether chlordane undergoes photochemical reactions in the aquatic environment.

Sediment and Soil. Numerous papers have detailed the degradation of chlordane in soils. In general, chlordane appears to persist for potentially long periods of time (>20 years) in some soils, but much shorter times in other soils. Beeman and Matsumura (1981), Bennett et al. (1974), Lichtenstein and

Schulz (1959), Nash and Woolson (1967), Stewart and Chisholm (1971), and Stewart and Fox (1971) all reported finding chlordane residues in excess of 10% of the initially applied amount, ≥10 years after application. Other authors (Harris and Sans 1976; Mullins et al. 1971; Tafuri et al. 1977; Wiese and Basson 1966) have reported faster removal from soils, but detectable concentrations appear to remain for at least 10 years for most application rates. At chlordane-treated subterranean sites on the University of Missouri-Columbia campus, >70% of the originally applied chlordane could be accounted for 7 years after application (Puri et al. 1990). The fact that the chromatographic profiles of the technical chlordane components were almost identical to the original formulation indicates that little chemical or biochemical transformation had occurred. Sethunathan (1973) reported that chlordane does not degrade under anaerobic conditions in flooded soils. A 1989 study of organochlorine pesticide residues in 12 vegetable farms (four of each of three soil types), in the Fraser Valley of British Columbia, found a marked difference in residue levels with soil type. Farms with loamy sand soil had no detectable chlordane, while one of those with silt loam soil contained mean concentrations of total chlordane of 170 ppb (dry weight), and three muck farms contained mean chlordane levels of 830 ppb (Szeto and Price 1991). Chlordane was used extensively on farms in this region as a soil insecticide on potatoes prior to the mid-1970s. These findings support the theory that organochlorine pesticides persist much longer in heavy soils with high organic content. The dissipation of chlordane from the loamy sand soil may be due to high initial volatilization. Hirano et al. (2007) evaluated the anaerobic biodegradation of *cis*- and *trans*-chlordane in sediment samples taken from a river in Japan; during 20 weeks of incubation in the dark at 30°C, an initial lag period of approximately 4 weeks was noted and 20-week residual ratios were 88 and 67%, respectively.

Only a few microorganisms have been isolated that are capable of degrading chlordane. Iyengar and Prabhakara Rao (1973) reported that a pure culture of *Aspergillus niger* degraded chlordane after adaptation, but Beeman and Matsumura (1981) found it to be inactive and speculated that the former authors had not considered other factors such as adsorption to glass and volatilization. Beeman and Matsumura (198l), however, reported that a *Nocardiopsis* sp. isolated from chlordane treated soil was capable of degrading chlordane to dichlorochlordene, oxychlordane, heptachlor, heptachlor endoepoxide, chlordane chlorohydrin, and 3-hydroxy-*trans*-chlordane. More recently, the lignin-degrading white rot fungus, *Phanerochaete chrysosporium*, was found to extensively degrade chlordane (Kennedy et al. 1990). In inoculated soil cultures, 28% of the chlordane degraded and 14.9% mineralized to carbon dioxide in 60 days. In liquid cultures, 36.8% of the chlordane degraded and 9.4% mineralized in 30 days. More mineralization occurs under low nutrient nitrogen concentrations (Aust 1990). The bulk of the

literature indicates that chlordane does not degrade rapidly in soils and persists for over 20 years in some cases.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chlordane depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of chlordane 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 chlordane 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	0.15 µg/m^3	Hsu et al. 1988
Drinking water	0.002 µg/L	Reding 1987
Surface water and groundwater	0.14 µg/L	EPA 1986a
Soil	9.4 µg/kg	EPA 1986a
Sediment	0.14 µg/L	EPA 1986a
Whole blood	0.01 µg/L	Wariishi et al. 1986

[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 Chlordane

Media	Low	High	For more information
Outdoor air (ng/m^3)	<0.1	58	Table 5-6
Indoor air (ng/m^3)	0.01	1	Table 5-6
Surface water (ppb)	<0.1	8	Table 5-7
Ground water (ppb)	<0.1	830	Table 5-7
Drinking water (ppb)	<0.1	1,200,000	Table 5-7
Soil	<1.0	14.46	Table 5-8
Food (ppb)	<1.0	370	Table 5-9

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

Table 5-5. Chlordane 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
Chlordane					
Water (ppb)	0.6	0.81	22,000	29	20
Soil (ppb)	8,200	12,700	38,300	110	66
Air (ppbv)	0.008	0.027	1,897	10	8
cis-Chlordane					
Water (ppb)	0.15	1.55	109,000	12	11
Soil (ppb)	44	98.8	17,400	33	27
Air (ppbv)			No data		
trans-Chlordane					
Water (ppb)	0.077	0.0812	8,050	14	13
Soil (ppb)	59	78.6	16,500	33	28
Air (ppbv)			No data		

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

5.5.1 Air

Table 5-6 summarizes results from studies that measured chlordane levels in air prior to 1992. Chlordane was detected in outside urban and rural air, in indoor air, and in the breathing zone during personal monitoring. In urban air, mean concentrations ranged from below detection limits (generally <0.1 ng/m^3) to 58 ng/m^3, whereas rural and background concentrations were much lower (generally <0.1–l ng/m^3).

Chlordane concentrations in indoor air were much higher than in either urban or rural air. Indoor air levels in the living areas of treated homes often exceeded 1 μg/m^3 in the vapor phase. These data, however, may be skewed since most of the indoor monitoring was performed on homes that had been sprayed with chlordane to control termites. Thus, the frequency of detection data may not be representative of the general population. Dust vacuumed from homes of controls, farmers, and formulators had mean chlordane levels of 7.6, 5.8, and 23.1 ppm, respectively (Starr et al. 1974). Since chlordane was poured or injected into soil around foundations of houses, the appearance of chlordane vapor in living quarters of treated houses may indicate the intrusion of soil gas through cracks, drains, or

Table 5-6. Detection of Chlordane in Air[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ng/m^3) Range	Concentration (ng/m^3) Mean	Percent occurrence	Reference
Urban air								
Columbia, South Carolina	5/79–10/80	4[b]	High volume	GC/ECD	0.54–1.74	1.3	100	Billings and Bidleman 1983
Denver, Colorado	1/80	3[b]	High volume	GC/ECD	0.012–0.080	0.063	100	Billings and Bidleman 1983
New Bedford, Massachusetts landfill	6/80	1[b]	High volume	GC/ECD	0.20–0.36	0.24	100	Billings and Bidleman 1983
Baltimore, Maryland	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Fresno, California	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Riverside, California	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Salt Lake City, Utah	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Southeastern United States	8/85	9[b]	High/low volume	GC/ECD-MS	<1–210	58	67	Lewis et al. 1986
Bloomington, Indiana	11/85–10/86	2	Low volume	GC/MS	0.5–1.5	1.0	100	Anderson and Hites 1988
Miami, Florida	1973–1974	14	NS	NS	ND–2.3	0.2	7	Lewis and Lee 1976
Jacksonville, Florida	8/86–9/86	60	24-hour/low volume	GC/ECD	ND–628	38.4	23	EPA 1990b
Jacksonville, Florida	3/87–4/87	72	24-hour/low volume	GC/ECD	ND–66	9.5	12	EPA 1990b
Jacksonville, Florida	1/88–2/88	70	24-hour/low volume	GC/ECD	ND–175	27.4	73	EPA 1990b
Springfield/Chicopee, Massachusetts	5/87–6/87	49	24-hour/low volume	GC/ECD	ND–75	3.1	8	EPA 1990b
Springfield/Chicopee, Massachusetts	3/88	50	24-hour/low volume	GC/ECD	ND–89	2.0	16	EPA 1990b
Denver, Colorado	10/85, 1/86	8	High volume	GC/ECD	0.026–0.104[c]	0.060	100	Foreman and Bidleman 1990

Table 5-6. Detection of Chlordane in Air[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ng/m^3) Range	Concentration (ng/m^3) Mean	Percent occurrence	Reference
Rural air								
Buffalo, New York	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Dothan, Alabama	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Iowa City, Iowa	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Orlando, Florida	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
Stoneville, Mississippi	8/67–8/68	4	Filter/impinger	GC/ECD	<0.1	ND	0	Stanley et al. 1971
College Station, Texas	1979–1980	16	High/low volume	GC/ECD	0.32–2.64	1.05	100	Atlas and Giam 1988
Southern Ontario	7/88–9/89	143	High volume	GC/ECD	0.00067–0.211[d]	0.039[d]	100	Hoff et al. 1992
Background areas								
Everglades National Park, Florida	1973–1974	14	NS	NS	ND–0.8	0.06	7	Lewis and Lee 1976
Indian Ocean	3/86	6	High volume	GC/ECD	0.010–0.016	0.013	100	Wittlinger and Ballschmiter 1990
Adirondacks, New York[e]	1985	4	High volume	GC/ECD	0.390–0.650	0.480	100	Knap and Binkley 1991
Newport News, Virginia[e]	1988	4	High volume	GC/ECD	0.015–0.129	0.054	100	Knap and Binkley 1991
Bermuda[e]	1985–1988	24	High volume	GC/ECD	0.003–0.062	0.019	100	Knap and Binkley
Canadian Arctic	2/88–4/88	10	High volume	GC/ECD	0.0014–0.0081[f]	0.0039[f]	100	Patton et al. 1991
Bering Sea	7/88–8/88	4	High volume	GC/MS	0.0053–0.0141[g]	0.0093[g]	100	Hinckley and Bidleman 1991
Northwest Atlantic	1/88, 7/89–8/89	8	High volume	GC/ECD	0.0077–0.0242[g]	0.015[g]	100	Bidleman et al. 1992

Table 5-6. Detection of Chlordane in Air[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ng/m^3) Range	Mean	Percent occurrence	Reference
Indoor air								
Southeastern United States	8/85	9[h]	High/low volume	GC/ECD-MS	<1–1,700	510	89	Lewis et al. 1986
New Jersey (living areas)	4/85–10/86	12[h]	Low volume	GC/ECD	<90–1,400	165	20–47[j]	Louis and Kisselbach 1987
New Jersey (nonliving areas)	4/85–10/86	12[h]	Low volume	GC/ECD	<90–5,870[i]	798	62–92[j]	Louis and Kisselbach 1987
New Jersey (living areas)	1976–1985	157[h]	Low volume	GC/ECD	<200–55,400	NS	12–34[k]	Fenske and Sternbach 1987
New Jersey (nonliving areas)	1976–1985	157[h]	Low volume	GC/ECD	<200–610,000	NS	44–48[k]	Fenske and Sternbach 1987
Military base apartments	1980	498[h]	Low volume	GC/ECD	NS–37,800	1,900	73	Livingston and Jones 1981
Military housing	1981–1982	3,957	NS	NS	ND–>5,000	NS	20.1	EPA 1983
North Carolina	NS	9[h]	Low volume	GC	2,750–5,810	NS	100	Wright and Leidy 1982
North Carolina	6/83–10/83	60[h,l]	NS	GC/ECD	<50–9,900	2,200	NS	Leidy et al. 1985; Fenske and Sternbach 1987
Bloomington, Indiana	11/85–10/86	12	Low volume	GC/MS	0.8–49	NS	100	Anderson and Hites 1988
Gainesville, Florida	1985–1986	11	Low volume	GC/ECD	ND–335	134	27	Moye and Malagodi 1987
Athens, Georgia	1985–1986	9	Low volume	GC/ECD	ND	ND	0	Moye and Malagodi 1987
Van Buren, Missouri	8/83	21	NS	NS	330–27,000	NS	NS	NIOSH 1984b
Jacksonville, Florida	8/86–9/86	65	24-hour/low volume	GC/ECD	ND–3,020	324.0	62	EPA 1990b
Jacksonville, Florida	3/87–4/87	72	24-hour/low volume	GC/ECD	ND–4,380	245.5	72	EPA 1990b

Table 5-6. Detection of Chlordane in Air[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ng/m^3) Range	Concentration (ng/m^3) Mean	Percent occurrence	Reference
Jacksonville, Florida	1/88–2/88	71	24-hour/low volume	GC/ECD	ND–2,050	220.3	71	EPA 1990b
Springfield/Chicopee, Massachusetts	5/87–6/87	49	24-hour/low volume	GC/ECD	ND–1,700	199.3	49	EPA 1990b
Springfield/Chicopee, Massachusetts	3/88	52	24-hour/low volume	GC/ECD	ND–735	34.8	51	EPA 1990b
Lincoln/Omaha, Nebraska (pretreatment)	NS	19[h]	4-hour at 2 L/minute	GC/ECD	NS	250	100	Kamble et al. 1992
Lincoln/Omaha, Nebraska (during treatment)	NS	19[h]	4-hour at 2 L/minute	GC/ECD	NS	1,210	100	Kamble et al. 1992
Lincoln/Omaha, Nebraska (24-hour posttreatment)	NS	19[h]	4-hour at 2 L/minute	GC/ECD	NS	690	100	Kamble et al. 1992
Lincoln/Omaha, Nebraska (180-day posttreatment)	NS	19[h]	4-hour at 2 L/minute	GC/ECD	NS	290	100	Kamble et al. 1992
Breathing zone								
Southeastern United States	8/85	9[b]	High/low volume	GC/ECD-MS	<1–4,200	680	67	Lewis et al. 1986
Jacksonville, Florida	8/86–9/86	63	24-hour/low volume	GC/ECD	ND–1,340	212.0	53	EPA 1990b
Jacksonville, Florida	3/87–4/87	71	24-hour/low volume	GC/ECD	ND–2,990	190.7	50	EPA 1990b
Jacksonville, Florida	1/88–2/88	71	24-hour/low volume	GC/ECD	ND–2,200	194.8	93	EPA 1990b
Springfield/Chicopee, Massachusetts	5/87–6/87	48	24-hour/low volume	GC/ECD	ND–2,200	252.9	50	EPA 1990b

Table 5-6. Detection of Chlordane in Air[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ng/m^3)		Percent occurrence	Reference
					Range	Mean		
Springfield/Chicopee, Massachusetts	3/88	52	24-hour/low volume	GC/ECD	ND–467	35.9	87	EPA 1990b
Lincoln/Omaha, Nebraska (applicators)	NS	29	30 minutes at 2 L/minute	GC/ECD	610–116,330	16,600	100	Kamble et al. 1992

[a]No distinction is made between the isomers of chlordane. In cases where the original papers made a distinction, the data were combined.
[b]Sample periods.
[c]A 9th sample with vapor phase only contained 0.068 ng/m^3 of chlordane.
[d]Annual mean and range of *cis*-chlordane, *trans*-chlordane, and *trans*-nonachlor.
[e]Samples taken from aircraft at various altitudes.
[f]Sum of *cis*-chlordane, *trans*-chlordane, and *trans*-nonachlor in total (vapor and particulate) sample.
[g]Sum of *cis*-chlordane, *trans*-chlordane, and *trans*-nonachlor.
[h]Sample locations.
[i]High detection was in sample taken prior to treatment.
[j]Percent detectable varied with the time after treatment.
[k]Percent >5,000 ng m^{-3}.
[l]Site selection not influenced by application procedures.

GC = gas chromatography; ECD = electron capture detector; MS = mass spectroscopy; ND = not detected; NS = not specified

ducting in basements or ground floor spaces (Anderson and Hites 1989; Wallace 1991). Several studies indicate that concentrations of chlordane were much higher in the basement than in upper levels of homes (Anderson and Hites 1989; Fenske and Sternbach 1987). Anderson and Hites (1989) found that the basement concentrations of chlordane were often a factor of 3–10 higher than in upper areas and 2–3 orders of magnitude higher than outdoors. Fenske and Sternbach (1987) additionally reported that homes with crawl spaces and forced air heating systems had significantly higher levels of chlordane (11.2 μg/m^3 median) than homes with basements and forced air heat (0.33 μg/m^3), radiant heat (0.93 μg/m^3), or in-slab ducts and forced air heat (3.42 μg/m^3). However, misapplication of chlordane by the pest control company (as determined by the New Jersey Department of Environmental Protection) had occurred in all of the homes with the 11.2 μg/m^3 median level and in 67% of the homes with the 3.42 μg/m^3 median level. When misapplication occurred, living area samples had median levels of 3.28 μg/m^3 with 40% of samples exceeding 5 μg/m^3, compared with <0.1 μg/m^3 and no samples exceeding 5 μg/m^3 in homes with no misapplication (Fenske and Sternbach 1987).

More recent reports are available regarding levels of chlordane compounds in outdoor and/or indoor air within various regions of North America (Aulagnier and Poissant 2005; Bidleman et al. 1998; Cortes et al. 1998; Hung et al. 2002; Jantunen et al. 2000; Leone et al. 2001; Moreau-Guigon et al. 2007; Offenberg et al. 2004; Shen et al. 2005; Sun et al. 2006). Chlordane levels in sampled outdoor air were consistently <1 ng/m^3. One study reported higher average air concentrations indoors than outdoors at test locations in Los Angeles County, California; Elizabeth, New Jersey; and Houston, Texas (average indoor levels of 1.98, 1.3, and 4.18 ng/m^3, respectively, versus average outdoor levels of 0.58, 0.17, and 0.28 ng/m^3, respectively) (Offenberg et al. 2004).

5.5.2 Water

Table 5-7 summarizes results from studies that measured chlordane levels in water and sediments prior to 1990. Chlordane was detected in surface water, groundwater, suspended solids, sediments, bottom detritus, drinking water, sewage sludge, urban runoff, and rain. Concentrations of chlordane in ocean and lake water were <0.0001 ng/L. Studies in the Great Lakes indicate that the level of the *cis*-chlordane in water were roughly 2–3 times that of *trans*-chlordane (Biberhofer and Stevens 1987; Stevens and Neilson 1989). The presence of chlordane in drinking water appears to almost always result from an accidental event, such as back-siphoning during dilution of a pesticide spray (CDC 1976), but concentrations can persist for months.

Table 5-7. Detection of Chlordane in Water and Sediments[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb)		Percent occurrence	Reference
					Range	Mean		
Surface water								
Wolf River, Tennessee	NS	30	Grab	NS	NS	0.15	NS	Jaffe et al. 1982
Wolf River, Tennessee	NS	0	Grab	NS	NS	0.42	NS	Jaffe et al. 1982
Mississippi River, Louisiana	1974	NS	Continuous	GC/ECD	0.00045–0.00115	NS	100	Brodtmann 1976
Niagara River, New York	4/79–12/81	NS	Continuous	GC/ECD	NS	0.004	66	Kuntz and Warry 1983
Lower Fox River, Wisconsin	1976–1977	250	Grab	GC+GC/MS	NS	NS	NS	Peterman et al. 1980
Surface waters in New Jersey	NS	603	NS	NS	<0.1–0.8	0.1[b]	56	Page 1981
Hawaii Kai Marina, Hawaii	4/74–7/74	12	Grab	GC/ECD	NS	NS	55	Tanita et al. 1976
Hawaii Kai Marina, Hawaii	4/72–11/72	5	Grab	NS	<0.001–0.01	NS	40	Tanita et al. 1976
Belmont Lake, New York	1982	NS	Grab	GC/ECD	0.003–0.099	NS	NS	Wood et al. 1986
177 River stations of the United States	1975–1980	2,943	Grab	NS	NS	NS	0.6[c]	Gilliom 1984
Gulf of Mexico and Southeast Coast[d]	1987	9	Grab	GC/ECD	0.000004–0.000034	NS	NS	Sauer et al. 1989
Lake Ontario	10/83	14	Pump (1 m)	GC/ECD	0.000034–0.000108	0.000060	100	Biberhofer and Stevens 1987
Four Great Lakes, including Georgian Bay	1986	95	Pump (1 m)	GC/ECD	ND–0.000202	NS	71	Stevens and Neilson 1989
Bering Sea	7/88	1	Grab	NS	0.00014[e]	0.00014[e]	100	Hinckley and Bidleman 1991
Suspended solids								
Niagara River	NS	15	Grab	NS	0.006–0.011	0.0085	13	Maguire et al. 1983
Niagara River	4/79–12/81	NS	Continuous	GC/ECD	NS	4.5	73	Kuntz and Warry 1983

Table 5-7. Detection of Chlordane in Water and Sediments[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb)		Percent occurrence	Reference
					Range	Mean		
Sediments								
Streams near San Francisco Bay	2/72–3/72	29–39	Grab	GC/ECD-MS	ND–800	120	90	Law and Goerlitz 1974
Fore River and Back Cove, Maine	11/80	8	Grab	GC/ECD	<0.03–9.8	1.8	75	Ray et al. 1983
Apalachicola River, Florida	8/79–5/80	12	Grab	GC	<1–3	NS	17	Elder and Mattraw 1984
Hawaii Kai Marina, Hawaii	4/74–7/74	12	Grab	GC/ECD	1.73–10.4	5.27	97	Tanita et al. 1976
Hawaii Kai Marina, Hawaii	1972–1973	11	Grab	NS	NS	5.32	100	Tanita et al. 1976
Belmont Lake, New York	1982	NS	Grab	GC/ECD	20–580	NS	NS	Wood et al. 1986
171 River stations	1975–1980	1,014	Grab	NS	NS	NS	30[c]	Gilliom 1984
Great Lakes harbors	5/89	5	Grab	GC/ECD	1.44–14.34[f]	3.66[f]	100	Verbrugge et al. 1991
NPL site (on-site) in Marshall, Illinois	NS	NS	NS	NS	ND–1,000,000	NS	NS	ATSDR 1989b
NPL site (off-site) in Marshall, Illinois	NS	NS	NS	NS	ND–250,000	NS	NS	ATSDR 1989b
Gulf of Mexico (51 site)[g]	1986	153	Surface	GC/ECD	<0.02–8.66[h]	0.26	77	Sericano et al. 1990
Gulf of Mexico (50 site)[g]	1987	148	Surface	GC/ECD	<0.02–43.5[h]	1.18	72	Sericano et al. 1990
Bottom detritus								
Apalachicola River, Florida	8/79–5/80	7	Grab	GC	1700–10,000	NS	100	Elder and Mattraw 1984
Groundwater								
Groundwaters in New Jersey	NS	1,076	NS	NS	<0.1–0.4	<0.1[b]	40	Page 1981
NPL site in Plumstead Township, New Jersey[i]	NS	NS	NS	NS	0.02	NS	NS	VIEW 1988

Table 5-7. Detection of Chlordane in Water and Sediments[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb)		Percent occurrence	Reference
					Range	Mean		
NPL site in Cape Giradeau, Missouri[j]	NS	NS	NS	NS	830	NS	NS	VIEW 1988
NPL site in Holbrook, Massachusetts[j]	NS	NS	NS	NS	48	NS	NS	VIEW 1988
NPL sites at 11 other locations[k]	NS	NS	NS	NS	NS	NS	NS	VIEW 1988
NPL site (on-site) in Marshall, Illinois	NS	NS	NS	NS	ND–0.6	NS	NS	ATSDR 1989b
NPL site (off-site) in Marshall, Illinois	NS	NS	NS	NS	ND	NS	NS	ATSDR 1989b
Cape Cod golf courses	1986–1987	16[l]	Pump/bail	GC/ECD	ND–7.20	NS	44	Cohen et al. 1990
Drinking water								
Pittsburgh, Pennsylvania	12/80	NS	Grab	NS	<0.1–6600[m]	NS	NS	CDC 1981
Seven U.S. cities	1965–1967	63	Grab	NS	NS	NS	22	Schafer et al. 1969
Chattanooga, Tennessee	3/24/76	NS	Grab	GC/ECD	NS–1,200,000	NS	NS	Harrington et al. 1978
Kansas farmstead well survey[n]	12/85–2/86	103	Grab	GC/ECD	ND–0.53	NS	0.97	Steichen et al. 1988
Sewage sludge								
Unspecified states	NS	44	NS	NS	NS	NS	73	Fricke et al. 1985
Urban runoff								
Fresno, California	NS	NS	Grab	NS	0.1–0.3	0.1[b]	NS	Nightingale 1987
Lake Quinsigamond, Massachusetts and Kansas City, Missouri	NS–7/82	NS	Grab	NS	0.01–10[o]	NS	5	Cole et al. 1984
11 Canadian Great Lakes basin sites	NS	124	Grab	GC/ECD	NS	0.00121	20	Marsalek and Schroeter 1988

Table 5-7. Detection of Chlordane in Water and Sediments[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb)		Percent occurrence	Reference
					Range	Mean		
Street sediment								
11 Canadian Great Lakes basin sites	NS	110	Grab	GC/ECD	NS	0.046	35	Marsalek and Schroeter 1988
Rain								
Lake Superior	1983	NS	NS	GC/ECD	<0.00005	ND	0	Strachan 1985
College Station, Texas	1979–1980	24	Collector	GC/ECD	0.0006–0.0091	0.00214	100	Atlas and Giam 1988
Great Lakes (4 remote sites)	2/86–7/86	93	Collector	GC/ECD	ND–0.0023	NS	33	Chan and Perkins 1989
Bermuda	1983–1984	36	Collector	GC/ECD	ND–0.000486	0.000077	97	Knap et al. 1988

[a]No distinction is made between the isomers of chlordane. In cases where the original papers made a distinction, the data were combined.
[b]Median.
[c]Percentage of stations with detections.
[d]Open-ocean seawater (filtrate) samples. Chlordane was not detected in microlayer samples.
[e]Sum of *cis*-chlordane, *trans*-chlordane, and *trans*-nonachlor.
[f]Wet weight.
[g]NOAA's Status and Trends Mussel Watch Program.
[h]*cis* isomer.
[i]On-site.
[j]Off-site.
[k]Arlington, Tennessee; Brick Township, New Jersey; Brunswick, Maine; Sorreto, Louisiana; Gallaway, Tennessee; Niagara Falls, New York; Lewisburg, Tennessee; Sacramento, California; Toone, Illinois; Marshall, Illinois; Jacksonville, Arkansas.
[l]Sites, includes background, green, tee, and fairway sites at four golf courses.
[m]Concentrations above the solubility limit may be the result of a cosolvent such as kerosene.
[n]Random sample.
[o]Range of positive detections.

ECD = electron capture detector; GC = gas chromatography; MS = mass spectroscopy; ND = not detected; NPL = National Priorities List; NS = not specified

Groundwater monitoring data from 479 disposal site investigations detected chlordane in 23 samples at 10 sites, ranking it 80th among the 208 RCRA Appendix IX organic chemicals investigated (Plumb 1991). According to the EPA database Pesticides in Groundwater, chlordane was confirmed in groundwater only in Massachusetts as a result of normal agricultural use and only in Idaho from a point source (Ritter 1990; Williams et al. 1988b). Based on average chlordane concentrations in EPA's STORET database for 1978–1987, the western south-central section of the United States had the highest concentrations of chlordane in groundwater and New England had the lowest (Phillips and Birchard 1991). The presence of chlordane in groundwater at Cape Cod golf courses is thought to be due to macropore flow of particle-bound pesticide or contamination during well construction (Cohen et al. 1990). Chlordane was used at these golf courses from the 1950s to 1970s.

5.5.3 Sediment and Soil

Table 5-8 summarizes results from studies that measured chlordane levels in soils prior to 1990. Chlordane was detected in both rural and urban soils in concentrations from <1 ppb to 141 ppm. In general monitoring programs of rural and urban soils, chlordane was consistently found; however, detections generally mirrored use patterns and were, for the most part, from studies performed in the late 1960s to middle 1970s. Very few more recent general soil monitoring data were available; these data show that chlordane was still present in soils, but insufficient detections are available to estimate any trends. A sampling of soil around New Orleans' houses treated with chlordane showed that chlordane levels were variable. Mean residue levels sampled at 30 houses varied from 22 to 2,540 ppm (Delaplane and LaFage 1990).

Sediment concentrations of chlordane in Great Lakes harbors and a tributary of the Missouri River in Missouri ranged from 1.4 to 14 ppb and 1.5 to 310 ppb, respectively (Puri et al. 1990; Verbrugge et al. 1991). A Missouri study performed in the 1980s demonstrated that chlordane in sediment of Missouri streams correlated with urban development (Puri et al. 1990). Chlordane levels in sediment from predominately agricultural areas were approximately 2 orders of magnitude lower than in urban areas. Based on average chlordane concentrations in EPA's STORET database for 1978–1987, the western north-central section of the United States had the highest concentrations of chlordane in sediment, and New England had the lowest (Phillips and Birchard 1991).

Table 5-8. Detection of Chlordane in Soils[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm) Range	Concentration (ppm) Mean	Percent occurrence	Reference
Urban								
Baltimore, Maryland	1971	156	NS	GC/ECD	0.01–12.35	0.21	37	Carey et al. 1979a
Gadsden, Alabama	1971	55	NS	GC/ECD	0.04–0.46	0.07	5	Carey et al. 1979a
Hartford, Connecticut	1971	48	NS	GC/ECD	0.02–141	4.0	48	Carey et al. 1979a
Macon, Georgia	1971	43	NS	GC/ECD	0.07–0.91	0.8	26	Carey et al. 1979a
Newport News, Virginia	1971	78	NS	GC/ECD	0.09–7.29	0.16	13	Carey et al. 1979a
Bakersfield, California	1969	50	Grab	GC/ECD	0.07–20.5	0.78	30	Wiersma et al. 1972
Camden, New Jersey	1969	50	Grab	GC/ECD	0.39–5.90	0.36	16	Wiersma et al. 1972
Houston, Texas	1969	50	Grab	GC/ECD	0.04–12.9	0.66	34	Wiersma et al. 1972
Manhattan, Kansas	1969	50	Grab	GC/ECD	0.03–4.86	0.30	40	Wiersma et al. 1972
Miami, Florida	1969	50	Grab	GC/ECD	0.04–16.9	1.59	64	Wiersma et al. 1972
Milwaukee, Wisconsin	1969	50	Grab	GC/ECD	0.05–10.2	0.45	34	Wiersma et al. 1972
Salt Lake City, Utah	1969	50	Grab	GC/ECD	0.02–7.50	0.41	38	Wiersma et al. 1972
Waterbury, Connecticut	1969	50	Grab	GC/ECD	0.02–8.74	0.96	28	Wiersma et al. 1972
Fresno-Clovis, California	NS	NS	Grab	NS	<0.03–2.70	NS	NS	Nightingale 1987
Belmont Lake, New York bank soil	1982	NS	Grab	GC/ECD	<0.002–0.003	NS	NS	Wood et al. 1986
New Orleans, Louisiana (30 treated homes)	10/86	240	Grab	GC/ECD	0.6–14,464	854.9	100	Delaplane and LaFage 1990

Table 5-8. Detection of Chlordane in Soils[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Rural								
Illinois	1970	69	NS	GC/ECD	0.05–1.32	0.09	23	Carey et al. 1973
Indiana	1970	36	NS	GC/ECD	0.29–4.30	0.20	8.3	Carey et al. 1973
Iowa	1970	76	NS	GC/ECD	0.17–3.35	0.13	15	Carey et al. 1973
Kansas	1970	28	NS	GC/ECD	0.32–0.54	0.03	7.1	Carey et al. 1973
Kentucky	1970	1	NS	GC/ECD	ND	ND	0	Carey et al. 1973
Michigan	1970	14	NS	GC/ECD	ND	ND	0	Carey et al. 1973
Minnesota	1970	37	NS	GC/ECD	0.87	0.02	3	Carey et al. 1973
Missouri	1970	31	NS	GC/ECD	0.14–0.53	0.02	6	Carey et al. 1973
Nebraska	1970	47	NS	GC/ECD	ND	ND	0	Carey et al. 1973
Ohio	1970	29	NS	GC/ECD	ND	ND	0	Carey et al. 1973
South Dakota	1970	26	NS	GC/ECD	ND	ND	0	Carey et al. 1973
Wisconsin	1970	5	NS	GC/ECD	0.05	0.01	20	Carey et al. 1973
Everglades National Park	5/76	25	Grab	GC/ECD	<0.001–0.0048	0.00226	52	Requejo et al. 1979
Agricultural land, Florida	5/76	7	Grab	GC/ECD	<0.001–0.195	0.088	43	Requejo et al. 1979
Cropland, California	1969	NS	Grab	GC/ECD	NR	0.01	NR	Wiersma et al. 1972
Cropland, New Jersey, Delaware, Maryland	1969	NS	Grab	GC/ECD	NR	<0.01	NR	Wiersma et al. 1972
Cropland, Florida	1969	NS	Grab	GC/ECD	NR	0.36	NR	Wiersma et al. 1972
Cropland, Wisconsin	1969	NS	Grab	GC/ECD	NR	0.01	NR	Wiersma et al. 1972

Table 5-8. Detection of Chlordane in Soils[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm) Range	Concentration (ppm) Mean	Percent occurrence	Reference
Urban								
Cropland, Arizona, New Mexico, Nevada, Utah	1969	NS	Grab	GC/ECD	NR	0.02	NR	Wiersma et al. 1972
Cropland, Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut	1969	NS	Grab	GC/ECD	NR	0.01	NR	Wiersma et al. 1972
Cropland, 37 states	1971	1,486	Grab	GC/ECD	0.01–6.98	0.06	8	Carey et al. 1978
Cropland, 37 states	1972	1,483	Grab	GC/ECD	0.01–7.89	0.05	7.9	Carey et al. 1979b
Other								
Cape Cod golf courses	1986–1987	12[b]	Soil core	GC/ECD	ND–4.310	2.278[c]	58	Cohen et al. 1990
NPL sites								
Holbrook, Massachusetts	NS	NS	NS	NS	NS	NS	NS	VIEW 1988
Sorreto, Louisiana	NS	NS	NS	NS	NS	NS	NS	VIEW 1988
Cape Girardeau, Missouri	NS	NS	NS	NS	30[d]	NS	NS	VIEW 1988
Lewisburg, Tennessee	NS	NS	NS	NS	0.1[e]	NS	NS	VIEW 1988
Memphis, Tennessee	NS	NS	NS	NS	57[e]	NS	NS	VIEW 1988
West Chester, Ohio	NS	NS	NS	NS	NS	NS	NS	VIEW 1988
Toome, Tennessee	NS	NS	NS	NS	NS	NS	NS	VIEW 1988
Marshall, Illinois	NS	NS	NS	NS	48.3[e]	NS	NS	VIEW 1988
Jacksonville, Arkansas	NS	NS	NS	NS	NS	NS	NS	VIEW 1988
Marshall, Illinois	NS	NS	NS	NS	ND–69[d]	NS	NS	ATSDR 1989b

Table 5-8. Detection of Chlordane in Soils[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Marshall, Illinois	NS	NS	NS	NS	ND–0.760[e]	NS	NS	ATSDR 1989b
Holbrook, Massachusetts	NS	36[f]	Grab	GC/ECD	ND–334	NS	86	Callahan et al. 1991

[a]No distinction is made between the isomers of chlordane. In cases where the original papers made a distinction, the data were combined.
[b]Three sites and four depths.
[c]Average of three surface cores; not detected at and below 2.0, 24, and 5.8 feet at three sites.
[d]On-site.
[e]Off-site.
[f]Locations.

ECD = electron capture detector; GC = gas chromatography; ND = not detected; NPL = National Priorities List; NS = not specified

More recently, Martinez et al. (2012) conducted an urban soil study analyzing chlordane in 66 soil samples taken on August 25th, 2008, in Cedar Rapids, Iowa, where major flooding occurred 70 days prior to the samples being taken. The samples were primarily taken from residential land use areas in the flooding zone downstream and west of the main urban river (Cedar River) that flooded. Chlordane levels in Cedar River had not been previously identified, though chlordane was detected at high levels in an urban lake that also flooded. Chlordane samples were analyzed using a gas chromatography/mass selective detector mode (GC/MSD) in selected ion monitoring mode. Chlordane concentrations in soil ranged from 0 to 7,500 ng/g dry weight, though the distribution was highly skewed (median 4 ng/g dry weight; mean 130 ng/g dry weight). Generally, *trans*-nonachlor (median 1.8 ng/g dry weight; mean 24.0 ng/g dry weight) was found at higher concentrations than *cis*-chlordane (median 1.0 ng/g dry weight; mean 64.0 ng/g dry weight) and *trans*-chlordane (median 0.86 ng/g dry weight; mean 40 ng/g dry weight). No spatial correlation between the samples was found. Additionally, no significant difference was found between samples collected inside or outside the flooding area. The mean ratios for the soil samples in this study are: *cis*-chlordane:*trans*-chlordane 1.40±0.48; *trans*-chlordane:*trans*-nonachlor 40±1.50; and *cis*-chlordane:*trans*-nonachlor 0.96±1.50. Given these ratios, it is likely that significant weathering of technical chlordane occurred if direct soil application was the source of the observed concentrations.

5.5.4 Other Media

Chlordane has been detected in many other media. Tables 5-9, 5-10, 5-11, and 5-12 summarize results from studies that evaluated chlordane in food, aquatic organisms, terrestrial organisms, and human samples, respectively, prior to 1992.

Based on average chlordane concentrations in EPA's STORET database for 1978–1987, the western south-central section of the United States had the highest concentrations of chlordane in fish tissue, and New England had the lowest (Phillips and Birchard 1991). Total chlordane concentrations in bluefish fillet were reduced an average 29% by trimming those portions of fillet with the highest concentrations of lipid, such as the skin, dorsal fat, and bellyflap (Sanders and Haynes 1988). Cooking did not significantly change the chlordane concentration in bluefish (Trotter et al. 1989).

Table 5-9. Detection of Chlordane in Food[a]

Media type/ location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Total adult food groups								
United States[b]	1990–1991	936	Composite	NS	NS	NS	1	FDA 1991
United States[b]	1989–1990	936	Composite	NS	NS	NS	<1	FDA 1990
United States[b]	1987–1988	1,170	Composite	NS	NS	NS	4	FDA 1989a
United States[b]	1982–1984	1,872	Composite	NS	NS	NS	<1	Gunderson 1988
10 State survey	1988–1989	13,085	Composite	NS	NS	NS	0.09	Minyard and Roberts 1991
10 State survey	1987–1988	13,980	Composite	NS	NS	NS	0.05	Minyard and Roberts 1991
United States[b]	1978–1985	1,044	Composite	NS	NS	NS	7	Yess et al. 1991
United States	1980–1982	324	Composite	GC/MS	ND–0.0021	0.0004	1.2	Gartrell et al. 1986a
United States	1979–1980	240	Composite	GC/MS	ND–0.0107	0.003	0.42	Gartrell et al. 1985a
United States	1977–1978	240	Composite	NS	ND–0.001	NS	1.25	Podrebarac 1984a
United States	1976–1977	300	Composite	GC/MS	ND–trace	NS	0.67	Johnson et al. 1984b
United States	1975–1976	240	Composite	GC/MS	ND–trace	NS	0.83	Johnson et al. 1981a
United States	1973–1974	360	Composite	GC+TLC	ND–trace	NS	0.28	Manske and Johnson 1977
United States	1972–1973	360	Composite	NS	ND–trace	NS	0.28	Johnson and Manske 1976
United States	1971–1972	420	Composite	NS	ND–0.59	NS	0.24	Manske and Johnson 1975
United States	1969–1970	360	Composite	GC/ECD+TLC	ND	ND	0	Corneliussen 1972

Table 5-9. Detection of Chlordane in Food[a]

Media type/ location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
United States	1968–1969	360	Composite	GC/ECD+TLC	0.026–0.043[c]	0.035[c]	0.56	Corneliussen 1970
United States	1966–1967	360	Composite	GC/ECD+TLC	0.005–0.02[c]	0.013[c]	0.56	Martin and Duggan 1968
United States	1965–1966	432	Composite	GC+TLC	ND–0.37	NS	0.23	Duggan et al. 1967
United States	1964–1965	216	Composite	GC/ECD+TLC	ND–0.033	NS	0.46	Duggan et al. 1966
Total toddler food groups								
United States	1980–1982	143	Composite	GC/MS	ND–0.005	NS	0.7	Gartrell et al. 1986b
United States	1979–1980	110	Composite	GC/MS	ND–0.0008	NS	0.91	Gartrell et al. 1985b
United States	1977–1978	606	Composite	GC/MS	0.010–0.028[c]	0.019[c]	0.33	Podrebarac 1984b
United States	1976–1977	687	Composite	GC/MS	ND–trace	NS	0.15	Johnson et al. 1984a
United States	1975–1976	NS	Composite	GC/MS	ND–0.137	NS	NS	Johnson et al. 1981b
Total infant food groups								
United States	1977–1978	417	Composite	GC/MS	ND–0.020	NS	0.24	Podrebarac 1984b
United States	1976–1977	445	Composite	GC/MS	ND–trace	NS	0.22	Johnson et al. 1984a
United States	1975–1976	NS	Composite	GC/MS	ND–trace	NS	NS	Johnson et al. 1981b

Table 5-9. Detection of Chlordane in Food[a]

Media type/ location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Dairy products								
Illinois	1972–1981	3,618	Individual	GC, bovine milk	ND–>0.3	NS	53.4	Steffey et al. 1984
United States	NS	NS	Cow milk, cheese	GC/MS	NS	Detected[d]	NS	Lawrence et al. 1970
Animal products								
Ontario, Canada	1986–1988	539	Abdominal fat	GC/ECD	<0.001	NS	NS	Frank et al. 1990
Domestic animals								
Ontario, Canada	1986–1988	63	Hen's eggs	GC/ECD	<0.001	NS	NS	Frank et al. 1990
Seafood								
United States aquaculture areas	1990	172	Fish/shellfish	NS	<0.01–0.13	NS	5	FDA 1991
Produce								
United States	1989–1991	6,970	Fruits/vegetables	GC/ECD	ND[e]	ND	0	Schattenberg and Hsu 1992

[a]No distinction is made between the isomers of chlordane. In cases where the original papers made a distinction, the data were combined.
[b]FDA's Total Diet Study.
[c]Range of positive detection.
[d]Chlordane and a metabolite of chlordane (1-exo-2-endo-4,5,6,7,8,8-octachloro-2,3-exo-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene) were detected.
[e]Detection limit is 0.625 ppm.

ECD = electron capture detector; FDA = U.S. Food and Drug Administration; GC = gas chromatography; MS = mass spectroscopy; ND = not detected; NS = not specified; TLC = thin-layer chromatography

Table 5-10. Detection of Chlordane in Aquatic Organisms

Isomer	Sampling location	Dates	Number of samples	Sample type	Analytical method (detection limit)	Concentration (ppm)		Percent occurrence	Reference
						Range	Mean		
Fish									
cis, trans	Major United States watersheds[a]	1980–1981	315	Whole fish, composite	GC (0.01 ppm wet weight)	ND–0.36	0.03	73.8	Schmitt et al. 1985
			315			ND–0.22	0.02	72.0	
cis, trans	Major United States watersheds[a]	1978–1979	NS	Whole fish, composite	GC (0.01 ppm wet weight)	ND–2.53	0.07	94.4	Schmitt et al. 1985
			NS			ND–0.54	0.02	70.4	
cis, trans	Major United States watersheds[a]	1976–1977	NS	Whole fish, composite	GC (0.01 ppm wet weight)	ND–0.93	0.06	92.5	Schmitt et al. 1985
			NS			ND–0.32	0.03	84.0	
cis, trans	13 Lake Michigan tributaries	Fall 1983	26	Whole fish, composite	GC/ECD (0.005 ppm wet weight)	ND–0.211	NS	NS	Camanzo et al. 1987
			26			ND–0.025	NS	NS	
cis, trans	Grand Traverse Bay (Lake Michigan)	Fall 1983	2	Whole fish[b,c] composite	GC/ECD (0.005 ppm wet weight)	0.015–0.037	NS	NS	Camanzo et al. 1987
			2			0.003–0.005	NS	NS	
cis, trans	Wabash River (Indiana)	NS	1	Whole fish, composite	MID GC/MS (0.0005 ppm wet weight)	–	0.00854	100	Kuehl et al. 1980
			1			–	0.01298	100	
cis and *trans*	Ashtabula River (Oklahoma)	NS	1	Whole fish, composite	MID GC/MS (0.0005 ppm wet weight)	–	ND	0	Kuehl et al. 1980
cis, trans	Great Lakes and major watersheds of the Great Lakes	1979	48	Whole fish, composite	MID GC/MS (0.020 ppm wet weight)	ND–0.61	0.090	79.2	Kuehl et al. 1983
			48			ND–0.52	0.098	87.5	
cis and *trans*	Major United States watersheds	1976	58	Whole fish, composite	GC/MS	NS	NS	36.2	Veith et al. 1979
cis and *trans*	13 sites located along a 125-mile stretch of the Kansas River	1986	25	Whole fish, composite	GC/ECD (0.03 ppm wet weight)	ND–2.1	0.25	68.0	Arruda et al. 1987

Table 5-10. Detection of Chlordane in Aquatic Organisms

Isomer	Sampling location	Dates	Number of samples	Sample type	Analytical method (detection limit)	Concentration (ppm)		Percent occurrence	Reference
						Range	Mean		
cis and *trans*	Siskiwit Lake on Isle Royal in Lake Superior	1983	4 4	Whole fish, composite[c]	GC/MS (0.001 ppm)[d]	0.23–0.77[d]	0.42[d]	NS	Swackhamer and Hites 1988
cis and *trans*	Siskiwit Lake on Isle Royal in Lake Superior	1983	3 3	Whole fish, composite[e]	GC/MS (0.001 ppm)[d]	0.14–0.33[d]	0.26[d]	NS	Swackhamer and Hites 1988
cis and *trans*	Lake Texoma (Texas and Oklahoma)	October 1979	14[f]	Fillets	GC/ECD (0.001 ppm)	0.002 (maximum)[f]	0.017 (median)[f]	NS	Hunter et al. 1980
			47[g]			0.008 (maximum)[g]	NS	NS	
			38[h]			0.024 (maximum)[h]	NS	NS	
cis and *trans*	Tuttle Creek Lake (Kansas)	1985	20	Fillets	EPA method 608 (0.0008 ppm)	ND–0.113	NS	90	KDHE 1988
trans	Atchafalaya River basin (Louisiana)	June 1981	NS	Whole fish, composite	GC/ECD (NS)	ND–0.1	NS	NS	Winger and Andreasen 1985
cis and *trans*	Chesapeake Bay and tributaries (Maryland)	1980	24	Fillets[i]	GC/ECD (0.001 ppm wet weight)	0.004–0.31	0.12	NS	Eisenberg and Topping 1985
cis and *trans*	Chesapeake Bay and tributaries (Maryland)	1979	98	Fillets[i]	GC/ECD (0.001 ppm wet weight)	ND–0.70	0.08	NS	Eisenberg and Topping 1985
cis and *trans*	Chesapeake Bay and tributaries (Maryland)	1978	15	Fillets[i]	GC/ECD (0.001 ppm wet weight)	ND–0.50	0.013	NS	Eisenberg and Topping 1985
cis and *trans*	San Joaquin River and tributaries (California)	July 1981	8	Whole fish, composite[j]	GC/ECD (0.004 ppm wet weight)	ND–0.021	0.011	50	Saiki and Schmitt 1986
cis and *trans*	San Joaquin River and tributaries (California)	July 1981	8	Whole fish, composite[b]	GC/ECD (0.004 ppm wet weight)	0.012–0.273	0.077	100	Saiki and Schmitt 1986

Table 5-10. Detection of Chlordane in Aquatic Organisms

Isomer	Sampling location	Dates	Number of samples	Sample type	Analytical method (detection limit)	Concentration (ppm)		Percent occurrence	Reference
						Range	Mean		
cis and *trans*	Lake Ontario (4 sites)	1977–1978	1,718	Whole fish	GC/ECD	0.04–0.14[c,k]	NS	NS	Borgmann and Whittle 1991
cis and *trans*	Major United States watersheds (112 sites)[l]	1984	321	Fish tissue, composite	GC/ECD	<1.01[m]	0.06	85[n]	Schmitt et al. 1990
Chlordanes[o]	Major United States watersheds (112 sites)[l]	1984	321	Fish tissue, composite	GC/ECD	<2.75[p]	0.11[q]	89[n]	Schmitt et al. 1990
trans	Lower Mississippi basin	7/87–8/87	17[u]	Whole catfish	GC/MS	0.011–0.170	0.062	100	Leiker et al. 1991
Oysters									
cis	Gulf of Mexico (49 site)[r]	1986	147	Composite	GC/ECD	0.91–96.3[s]	10.9	100	Sericano et al. 1990
cis	Gulf of Mexico (48 site)[r]	1987	143	Composite	GC/ECD	0.65–292[t]	14.1	100	Sericano et al. 1990

Table 5-10. Detection of Chlordane in Aquatic Organisms

Isomer	Sampling location	Dates	Number of samples	Sample type	Analytical method (detection limit)	Concentration (ppm)		Percent occurrence	Reference
						Range	Mean		
Clams									
cis and *trans*	Portland (Maine)	November 1980	2	Whole body, composite	GC/FID (0.00003 ppm)	ND–0.0018	NS	50	Ray et al. 1983

[a]107 stations located at key locations in major rivers throughout the United States and Great Lakes.
[b]Carp.
[c]Lake trout.
[d]Expressed on a lipid basis.
[e]Whitefish.
[f]Herbivores (gizzard shad).
[g]Detrivores (carp, channel catfish, smallmouth buffalo, river carpsucker).
[h]Carnivores (striped bass, white crappie, largemouth bass, blue catfish, flathead catfish).
[i]Finfish.
[j]Bluegill sunfish.
[k]Range of annual logarithmic means.
[l]National Contaminant Biomonitoring Program.
[m]Highest station mean Honolulu, Hawaii (0.6 ppm), next highest station (0.3 ppm), Saugatuck, Michigan.
[n]Positive sites (for isomer with highest number of positive sites).
[o]*cis*- and *trans*-chlordane, oxychlordane, and *cis*- and *trans*-nonachlor.
[p]Highest station mean in Honolulu, Hawaii (1.8 ppm), next highest station (0.8 ppm), Saugatuck, Michigan. Component composition is 1.00 ppm *trans*-nonachlor, 0.66 ppm *cis*-chlordane, 0.45 ppm *cis*-nonachlor, 0.35 ppm *trans*-chlordane, and 0.29 oxychlordane.
[q]Component composition is 0.03 *trans*-nonachlor, 0.03 ppm *cis*-chlordane, 0.02 ppm *cis*-nonachlor, 0.02 ppm *trans*-chlordane, and 0.01 ppm oxychlordane.
[r]NOAA's Status and Trends Mussel Watch Program.
[s]The range, mean, and frequency for *trans*-nonachlor are 0.60–71.9 ppb, 10.0 ppb, and 100%, respectively.
[t]The range, mean, and frequency for *trans*-nonachlor are <0.25–289 ppb, 11.6 ppb, and 99%, respectively.
[u]Sites; number of fish per site varied from 1 to 4.

EPA = U.S. Environmental Protection Agency; GC = gas chromatography; ECD = electron capture detector; FID = flame ionization detector; MS = mass spectroscopy; MID = multiple ion detector; ND = not detected; NS = not stated

Table 5-11. Detection of Chlordane in Terrestrial Organisms[a]

Species/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Birds								
Herons, egrets, kingfishers, sandpipers								
Corpus Christi, Texas	1983	10	Eggs	GC/ECD	ND–0.88	0.14[b]	NS	White and Krynitsky 1986
Loving, New Mexico	1983	10	Eggs	GC/ECD	ND	ND	NS	White and Krynitsky 1986
Artesia, New Mexico	1983	10	Eggs	GC/ECD	ND–0.36	0.07[b]	NS	White and Krynitsky 1986
Louisiana	1978–1979	<10	Whole body	GC/ECD	<0.05	ND	NS	Dowd et al. 1985
Colorado Wyoming	1979	147	Eggs	GC/ECD+MS	0.08–0.23[c]	0.14	5.4	McEwen et al. 1984
United States	1966–NS	105	Carcass	GC/ECD+MS	ND–1.8[d]	NS	23.8	Ohlendorf et al. 1981
United States	1966–NS	48	Brains	GC/ECD+MS	ND–1.4	NS	42.2	Ohlendorf et al. 1981
Sheboygan River, Wisconsin	1976–1980	11	Carcass, brains	GC/ECD+MS	ND–0.22	NS	NS	Heinz et al. 1984
Re-footed booby, sooty tern and shearwater								
Hawaii	1980	143	Eggs, stomach	GC/ECD+MS	ND	ND	0	Ohlendorf and Harrison 1986
Brown or white pelicans								
Louisiana	1971–1976	117	Eggs	GC/ECD	ND–1.31	0.36	NS	Blus et al. 1979
Klamath Basin, California	1969–1981	45	Eggs	GC/MS	<0.1–0.12	NS	6.7	Boellstorff et al. 1985
Comorant, black skimmer, western grebe								
Galviston Bay, Texas	1980–1981	6	Eggs	GC/ECD+MS	ND–0.6	NS	<50	King and Krynitsky 1986
Galviston Bay, Texas	1980–1982	13	Eggs	GC/ECD+MS	ND–0.7	NS	<50	King and Krynitsky 1986

Table 5-11. Detection of Chlordane in Terrestrial Organisms[a]

Species/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
South Texas and Mexico	1983	30	Carcass	NS	<0.1–<0.3	NS	20	White et al. 1985
Klamath Basin, California	1981	12	Eggs	GC/MS	<0.1–0.25[e]	NS	>16.7	Boellstorff et al. 1985
Clapper rails, gallinules and limpkins, dunlins								
Avalon, New Jersey	1973	NS	Carcass	GC/ECD+MS	ND–0.12[f]	NS	NS	Klaas and Belisle 1977
Virginia, South Carolina, New Jersey	1972–1973	49	Eggs	GC/ECD+MS	ND–<0.10[c]	NS	20[c]	Klaas et al. 1980
Florida, South Carolina, Louisiana	1973–1974	NS	Eggs	GC/ECD+MS	ND	ND	0	Klaas et al. 1980
Sarnish Bay, Washington	1980	8	Whole body	GC/MS	0.008–0.06	0.02	100	Schick et al. 1987
Bowerman Basin, Washington	1980	5	Whole body	GC/MS	0.003–0.005	0.004	100	Schick et al. 1987
Gulls, common eider								
Virginia, Maine	1977	116	Eggs	GC	0.00–0.50[f]	0.09[c]	>26.7	Szaro et al. 1979
Appledore Island, Massachusetts	1977	30	Eggs	GC	ND	ND	0	Szaro et al. 1979
Appledore Island, Massachusetts	1977	28	Eggs	GC	0.0–0.50	0.04	21.4	Szaro et al. 1979
Appledore Island, Massachusetts	1977	28	Eggs	GC	0.0–0.43[f]	0.22	96.4	Szaro et al. 1979
Galviston, Texas	1980–1981	10	Eggs	GC/ECD+MS	0.1–1.2[c]	0.29	>50	King and Krynitsky 1986
Bangs Island, Massachusetts	1977	30	Eggs	GC	ND	ND	0	Szaro et al. 1979

Table 5-11. Detection of Chlordane in Terrestrial Organisms[a]

Species/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Ducks								
Atlantic flyway	1976–1977	NS	Wings	GC/ECD	0.01–0.06	NS	57	White 1979
Mississippi flyway	1976–1977	NS	Wings	GC/ECD	0.01–0.02	NS	22	White 1979
Central flyway	1976–1977	NS	Wings	GC/ECD	0.01–0.02	NS	14	White 1979
Pacific flyway	1976–1977	NS	Wings	GC/ECD	0.01–0.02	NS	14	White 1979
United States	1981–1982	NS	Wings	GC/MS	<0.01–0.05	NS	10[g]	Prouty and Bunck 1986
Chesapeake Bay, Maryland	1973, 1975	142	Carcass	GC/MS	ND–NS	0.19	6.3	White et al. 1979
Osprey, eagles, owls, hawks								
Barnegat Bay, New Jersey	1971, 1974	9	Eggs	GC/ECD+MS	ND–0.55[e]	0.20[c]	78	Wiemeyer et al. 1978
Avalon-Stone Harbor, New Jersey	1979, 1972	8	Eggs	GC/ECD+MS	ND–0.08[e]	0.03	50	Wiemeyer et al. 1978
United States	1964–1973	26	Carcass, brains	GC/ECD+MS	<0.1–1.7[e,h]	NS	>69.2	Wiemeyer et al. 1980
United States	1971–1974	38	Carcass	GC/MS	NS	27[e]	NS	Barbehenn and Reichel 1981
United States	1971–1974	38	Brain	GC/MS	NS	0.27[e]	NS	Barbehenn and Reichel 1981
United States	1971–1974	24	Carcass	GC/MS	NS	15[f]	NS	Barbehenn and Reichel 1981
United States	1971–1974	24	Brain	GC/MS	NS	0.15[f]	NS	Barbehenn and Reichel 1981
United States	1969–1979	6	Eggs	GC/ECD+MS	ND–3.6	0.39[c]	63.5	Wiemeyer et al. 1984
Maryland, Alabama	1978–1981	2	Carcass, brains	NS	1.1–2.4	1.65	100	Blus et al. 1983
Corvallis, Oregon	1980	1	Brains	NS	0.1	1.1	100	Blus et al. 1983

Table 5-11. Detection of Chlordane in Terrestrial Organisms[a]

Species/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Starling								
United States	1979, 1982	NS	Carcass	GC/MS	<0.01–0.04	0.02[c]	3.3[i]	Bunck et al. 1987
Pheasants								
Kansas	1982–1983	NS	Carcass	NS	ND	ND	0	Layher et al. 1985
Other vertebrates								
Turtles								
Merritt Island National Wildlife Refuge, Laurel Maryland	1979	56	Eggs	GC/ECD+MS	ND–<0.008[f]	ND	28.6[f]	Clark and Krynitsky 1985
New Jersey, Maryland	1981–1982	32	Visceral fat	GC/ECD+MS	ND–>9.33[f]	3.9[c]	>88[f]	Albers et al. 1986
Crocodiles								
Patuxent Wildlife Research Center, Laurel, Maryland	1977–1978	23	Eggs	GC/ECD	<0.01–0.07	0.02[f,c]	87.5[j]	Hall et al. 1979
Raccoons								
Lake Verret, Louisiana	1978–1979	<10	Leg muscles	GC/ECD	<0.05	ND	NS	Dowd et al. 1985
Plaquemine-Brule, Louisiana	1978–1979	<10	Leg muscles	GC/ECD	<0.05	ND	NS	Dowd et al. 1985
East Franklin, Louisiana	1978–1979	<10	Leg muscles	GC/ECD	<0.05–NS	0.017[k]	NS	Dowd et al. 1985
Big brown bats								
Gaithersburg, Maryland	1973	18	Carcass, brains	GC/ECD	ND–<0.40[f]	NS	50	Clark and Lamont 1976
Earthworms								
Holbrook, Massachusetts	NS	29[l]	Whole body	GC/ECD	0.8–12.9	NS	45	Callahan et al. 1991

Table 5-11. Detection of Chlordane in Terrestrial Organisms[a]

Species/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppm)		Percent occurrence	Reference
					Range	Mean		
Insects								
Moths								
Washington, DC–Baltimore, Maryland	1977–1979	NS	Whole body	GLC/MS	<0.05–0.75	0.22	NS	Beyer and Kaiser 1984
Meadow grasshopper								
Palermo, New Jersey	1973	NS	NS	GC/ECD+MS	ND–0.02[e]	NS	NS	Klaas and Belisle 1977
Honey bees								
Connecticut	1983–1985	NS	Whole body, 20 brood combs	GC/ECD	0.06–0.69[c]	NS	7.5[m]	Anderson and Wojtas 1986

[a]No distinction is made between the isomers of chlordane. In cases where the original papers made a distinction, the data were combined.
[b]Geometric mean.
[c]Range of positive detections.
[d]Oxychlordane and *trans*-nonachlor were reported in paper at ranges of ND–0.87 and ND–3.0, respectively.
[e]*cis*-Chlordane and/or *trans*-nonachlor.
[f]Oxychlordane included in mixture.
[g]Value describes number of detections divided by the number of pools.
[h]Oxychlordane was also detected, range ND–0.15, frequency >12%.
[i]Percent of pools with detectable residues of organochlorine compounds.
[j]*cis*-Chlordane, *trans*-nonachlor or oxychordane was detected in 7 out of 8 clutches.
[k]Mean was exceeded by the standard error.
[l]Earthworms were exposed on-site for 7 days.
[m]Chlordane was detected in 4 out of 57 apiaries.

ECD = electron capture detector; GC = gas chromatography; GLC = gas-liquid chromatography; MS = mass spectroscopy; ND = not detected; NS = not specified

Table 5-12. Detection of Chlordane in Human Samples[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb)		Percent occurrence	Reference
					Range	Mean		
Human adipose tissue								
United States	1976–1980	785	General	GC/ECD+MS	ND–>10[b]	NS	95	Murphy et al. 1983
United States	NS	8	General	NCI/MS	ND–>1	NS	87.5	Dougherty et al. 1980
Florida	1978	10	General	GC/ECD	ND	ND	0	Barquet et al. 1981
Florida	1978	10	General	GC/ECD	70–490[b]	193	100	Barquet et al. 1981
United States	1972–1975	NS	General	GC/ECD+MS	ND–>100[b]	100[c]	>90	Kutz et al. 1979
Bloomington, Indiana	1987–1988	23	Breast	GC/ECD+MS	0.6–10.2 42–260[b]	2.0[d] 88[d]	100 100	Dearth and Hites 1991a
North Texas	1987–1988	35	Abdominal	GC/ECD	12–261[b,e]	95[d,f]	100	Adeshina and Todd 1990
Canada	1985	108	General	GC/ECD+MS	<11 <103[b]	4 33	100 100	Mes et al. 1990
British Columbia, Canada	NS	25	Most abdominal[g]	GC/ECD	<134.20[h]	42.5[i]	100	Mes 1992
Japan[j]	1986–1988	23	NS	GC/ECD	130–2,160	670	100	Sasaki et al. 1991a
Human blood sera								
United States	1976–1980	4,200	General	GC/ECD+MS	ND–>1[b]	NS	4	Murphy et al. 1983
Welds County, Colorado	1968	358	Nonoccupational	GC/ECD	ND	ND		Starr et al. 1974
Welds County, Colorado	1968	93	Farm	GC/ECD	ND	ND	0	Starr et al. 1974
Welds County, Colorado	1968	175	Occupational	GC/ECD	60–233[k]	151	3.4	Starr et al. 1974
British Columbia, Canada	NS	25	Whole blood[g]	GC/ECD	<0.30[l]	0.10[m]	100	Mes 1992
Japan[j]	1986–1988	23	General	GC/ECD	ND–280	0.58	100	Sasaki et al. 1991a

Table 5-12. Detection of Chlordane in Human Samples[a]

Media type/location	Sampling dates	Number of samples	Sample type	Analytical method	Concentration (ppb)		Percent occurrence	Reference
					Range	Mean		
Japan	1989–1990	240	General	GC-MS	0.06–3.85[n]	0.34[o]	100	Hirai and Tomokuni 1991b
Human milk								
United States	NS	1,436	General	GC/ECD	ND–>500[b]	95.8	74	Savage et al. 1981
United States	NS	1,436	General	GC/ECD	ND	ND	0	Savage et al. 1981
Hawaii and U.S. mainland	1979–1980	156	General	GC/ECD	ND	ND	0	Takei et al. 1983
U.S. mainland	1979–1980	102	General	GC/ECD	ND–440	54	99	Takei et al. 1983
Hawaii	1979–1980	54	General	GC/ECD	11–550	68	100	Takei et al. 1983
France	1991	20	General	GC/ECD	ND–294[p]	70[p]	90	Bordet et al. 1993
Human seminal fluid								
United States	NS	NS	General	GC/ECD	ND–detected	NS	NS	Dougherty et al. 1980

[a]No distinction is made between the isomers of chlordane. In cases where the original papers made a distinction, the data were combined.
[b]Oxychlordane.
[c]Approximate number.
[d]Geometric mean.
[e]Occupational unexposed people.
[f]Geometric mean (age group): 38 ppb (21–40 years), 88 ppb (41–60 years), and 154 ppb (61+ years).
[g]Paired blood and biopsy fat samples from selected patients. Relationship established for oxychlordane at 99% confidence level.
[h]Sum of oxychlordane (44.9), α-chlordane (2.1), γ-chlordane (2.2), *trans*-nonachlor (74.0), and *cis*-nonachlor (11.0).
[i]Median. Sum of oxychlordane (16.5), α-chlordane (0.3), γ-chlordane (0.5), *trans*-nonachlor (22.6), and *cis*-nonachlor (2.6).
[j]Total chlordane; same individuals sampled for adipose tissue and serum.
[k]All positive samples were obtained from one individual.
[l]Median. Sum of oxychlordane (0.07), α-chlordane (0.02), and γ-chlordane (0.01).
[m]Sum oxychlordane (0.16), α-chlordane (0.05), γ-chlordane (0.05), and *trans*-nonachlor (0.04).
[n]Nonachlor. Ranges for chlordane and oxychlordane are ND–0.60 ppb and ND–0.62, respectively.
[o]Median.
[p]ng of α-chlordane plus γ-chlordane/g of milk fat.

ECD = electron capture detector; GC = gas chromatography; MS = mass spectroscopy; NCI = negative chemical ionization; ND = not detected; NS = not specified

5.6 GENERAL POPULATION EXPOSURE

A major route of exposure to chlordane in the United States is from living in chlordane-treated houses. Many of these houses are in the deep south and far southwest where termites are a significant problem, but moderate to heavy use of chlordane extended from Pennsylvania and the lower New England states south and west to the lower portion of Colorado and up to northern California. Chlordane vaporizes gradually in treated homes for over 10 years. It accumulates in residents' bodies by inhalation of the vapor, by eating food that has adsorbed the vapor, or dermal contact with the chemical. Prior to 1992, indoor air concentrations often exceed 1 μg/m^3 (see Table 5-6) and persisted for many years (Livingston and Jones 1981). A study of chlordane concentrations in 19 houses treated for subterranean termite control indicated that the chlordane concentration in the indoor air occurred during treatment and declined significantly after 24 hours (Kamble et al. 1992). While there was a slight reduction in chlordane concentration from the 24-hour levels 7 days posttreatment, these changes were not significant. Concentrations of chlordane remained essentially the same from 30 to 180 days after treatment, and these concentrations were similar to pretreatment levels. The EPA (1987g) estimated that, up until 1988, 1.3–1.8 million people per year were exposed to cyclodiene termiticides, as occupants of newly treated structures. They further estimated that ≈30 million structures had been treated for termites with these chemicals, resulting in the exposure of over 80 million people. Of these structures, ≈65% were treated with chlordane, or 19.5 million structures, resulting in the exposure of 52 million people. The exact concentrations to which they were exposed are difficult to estimate from the available data. A Japanese study showed that the concentration of chlordane and oxychlordane in the milk fat of lactating women living in chlordane-treated houses was 13.8 and 33.6 ppb, respectively, versus 3.6 and 19.3 ppb for unexposed controls (Taguchi and Yakushiji 1988). Chlordane and oxychlordane levels in milk increased with years since treatment.

A major study of general population exposure to pesticides, including chlordane, was included in the Nonoccupational Pesticide Exposure Study (NOPES) (EPA 1990b). This study applied probabilistic population sampling techniques, indoor, outdoor, and personal breathing zone air monitoring, and human activity pattern data for multiple routes of exposure to assess total human exposure. These techniques were applied to the communities of Jacksonville, Florida, and Springfield/Chicopee, Massachusetts, over three and two seasons, respectively. For Jacksonville, the personal breathing zone air concentration was relatively stable, and the yearly means for 1986–1988 ranged from 191 to 212 ng/m^3 over all three seasons, with 50–93% of samples containing detectable levels of chlordane. The corresponding results for Springfield/Chicopee were 36 ng/m^3 in winter and 253 ng/m^3 in the spring; 50–87% of the samples

had detectable levels of chlordane. Several observations were made from the study. Indoor levels of chlordane were highest in summer and lowest in winter. They were higher in older housing units and households with reported termiticide use. For chlordane, mean air exposure in homes with detectable levels of chlordane was always much higher (~25 times) than exposure from food. Routine sampling of the public water supplies prior to NOPES and tap water in Jacksonville, Florida, and Springfield/ Chicopee, Massachusetts, revealed no detectable levels of chlordane in drinking water.

In addition to living in chlordane-treated structures, ingestion of contaminated food is another major route of exposure. Duggan et al. (1983) and Gartrell et al. (1985a, 1985b, 1985c, 1985d, 1986a, 1986b) estimated yearly dietary intake of chlordane since 1965 for 16–19-year-old males. In more recent years, toddlers and infants were included in these estimates (Gunderson 1988). FDA (1989a, 1990, 1991) estimated dietary chlordane intake for various age/sex groups for 1982–1984, 1989, 1990, and 1991. Their results are listed in Table 5-13. The data show a relatively steady intake over the years from 1977 to 1982, indicating that chlordane residues had not decreased significantly in agricultural soils (if that is where the chlordane originated). In addition, infants and toddlers would generally have higher intakes of chlordane than adults because of the high fat content of the foods they eat. The results for the 1991 FDA Total Diet Study were 0.0013 µg/kg/day for infants and 0.0005–0.0015 µg/kg/day for teenagers and adults (FDA 1991). The total daily dietary intake of chlordane per unit body weight, according to results of the 1982–1984 FDA's Total Diet Study was 0.0051 µg/kg/day for infants, 0.0065 µg/kg/day for toddlers, and 0.002–0.0027 µg/kg/day for teenagers and adults (Gunderson 1988). The Total Diet Study analyzes foods prepared for consumption. After 1982, 234 foods were selected to represent 5,000 different food items identified in dietary surveys.

Table 5-13. Chlordane Intake from Food[a]

	Chlordane intake (µg/kg body weight/day)			
Year	14–19-Year-old males[b]	60–65-Year-old females	Toddlers	Infants
1965–1970	Not detected	Not reported	Not performed	Not performed
1971	Not detected	Not reported	Not performed	Not performed
1972	0.01	Not reported	Not performed	Not performed
1973	Trace	Not reported	Not performed	Not performed
1974	Trace	Not reported	Not performed	Not performed
1975	Trace	Not reported	Not performed	Not performed
1976	Trace	Not reported	Not performed	Not performed
1977	0.004	Not reported	0.005	0.001
1978	0.004	Not reported	0.032	0.010
1979	0.004	Not reported	0.003	<0.001

Table 5-13. Chlordane Intake from Food[a]

	Chlordane intake (µg/kg body weight/day)			
Year	14–19-Year-old males[b]	60–65-Year-old females	Toddlers	Infants
1980	0.003	Not reported	0.005	0.003
1981–1982	0.004	Not reported	0.003	0.002
1984[c]	0.0025	0.0026	0.0065	0.0051
1989[d]	0.0007	0.0010	Not reported	0.0007
1990[d]	0.0001	0.0001	Not reported	0.001
1991[d]	0.0005	0.0015	Not reported	0.0013

[a]Data from Duggan et al. (1983) and Gartell et al. (1985a, 1985b, 1985c, 1985d, 1986a, 1986b) unless otherwise noted.
[b]16–19-Year-old males for studies in years 1965–1982, 14–16-year-old males for studies 1984–1991.
[c]Gunderson 1988.
[d]FDA 1989, 1990, 1991.

Dermal exposures may result from children or adults coming into contact with contaminated soils or house dust near treated houses, lawns, or gardens. Dermal exposures cannot be quantified with the available information.

Previous exposure to chlordane is often gauged by the concentration of chlordane compounds (usually oxychlordane or *trans*-nonachlor) in human adipose tissue. According to EPA's National Human Monitoring Program and other broad based U.S. surveys, the geometric mean concentration of oxychlordane in human adipose tissue ranged from 90 to 120 ppb between 1971 and 1983 with no clear temporal trend (Adeshina and Todd 1990; Kutz et al. 1991). North Texas and Canadian studies showed increasing oxychlordane levels with age in selected age groups, but no difference in levels according to sex (Adeshina and Todd 1990; Mes et al. 1990).

The Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2009) includes information regarding serum levels of chlordane metabolites oxychlordane and *trans*-nonachlor according to various age groups, sex, and race/ethnicity for the years 1999–2004. Tables 5-14 and 5-15 depict lipid adjusted and whole weight oxychlordane levels, respectively. Tables 5-16 and 5-17 depict lipid adjusted and whole weight *trans*-nonachlor levels, respectively. Lipid adjusted and whole weight oxychlordane levels for the years 2005–2009 (CDC 2017) are depicted in Tables 5-18 and 5-19, respectively. Lipid adjusted and whole weight *trans*-nonachlor levels for the years 2005–2009 (CDC 2017) are depicted in Tables 5-20 and 5-21, respectively. These data demonstrate that the U.S. population continues to exhibit measurable amounts of chlordane metabolites in serum; concentrations are higher in older age groups than younger age groups without significant male-female or race/ethnicity differences.

Table 5-14. Geometric Mean and Selected Percentiles of Serum Oxychlordane (Lipid Adjusted) Serum Concentrations (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total	1999–2000	*[b]	<LOD[c]	20.8 (17.8–23.0)	34.4 (30.5–38.6)	44.8 (40.2–49.6)	1,661
	2001–2002	11.4 (<LOD–12.5)	11.1 (<LOD–12.5)	21.7 (19.3–24.4)	36.4 (31.5–41.4)	49.7 (42.0–61.2)	2,249
	2003–2004	9.37 (8.69–10.1)	10.3 (9.20–11.0)	18.0 (16.8–20.1)	29.0 (26.8–32.1)	37.7 (34.8–43.8)	1,978
Age group							
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	663
	2001–2002	*	<LOD	<LOD	<LOD	11.5 (<LOD–12.6)	752
	2003–2004	*	<LOD	<LOD	9.20 (<LOD–11.5)	11.5 (8.10–18.9)	595
≥20 years	1999–2000	*	<LOD	23.3 (21.0–25.9)	37.7 (32.3–43.5)	47.7 (43.1–50.8)	998
	2001–2002	12.9 (11.7–14.3)	13.3 (11.4–14.9)	23.9 (21.2–26.7)	38.5 (33.4–45.9)	53.1 (44.1–65.9)	1,497
	2003–2004	10.6 (9.82–11.5)	11.4 (10.6–12.4)	19.9 (17.9–21.5)	31.3 (28.8–33.2)	39.2 (36.5–44.8)	1,383
Gender							
Males	1999–2000	*	<LOD	18.1 (16.1–19.6)	31.3 (25.9–38.2)	42.4 (35.3–49.6)	793
	2001–2002	11.1 (<LOD–12.6)	11.1 (<LOD–12.6)	20.6 (16.6–24.9)	33.1 (27.5–43.8)	48.1 (40.2–56.9)	1,049
	2003–2004	9.10 (8.20–10.1)	9.90 (8.30–11.2)	17.1 (15.6–18.4)	27.6 (25.3–32.2)	36.0 (32.7–39.2)	963
Females	1999–2000	*	<LOD	22.3 (20.1–25.9)	36.9 (31.5–40.3)	46.2 (39.1–51.8)	868
	2001–2002	11.7 (10.7–12.7)	11.0 (<LOD–12.9)	23.1 (20.7–25.0)	37.5 (34.5–42.1)	52.8 (42.7–70.0)	1,200
	2003–2004	9.63 (8.89–10.4)	10.6 (9.10–11.3)	20.1 (17.4–21.7)	30.3 (27.5–32.7)	41.9 (36.3–45.5)	1,015
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	16.3 (<LOD–19.9)	28.9 (18.8–42.0)	39.9 (26.8–61.0)	628
	2001–2002	*	<LOD	13.9 (11.0–18.4)	27.2 (21.0–33.1)	37.9 (29.9–42.0)	557
	2003–2004	*	<LOD	12.8 (10.1–15.8)	22.9 (15.8–31.4)	31.4 (22.4–51.6)	462
Non-Hispanic blacks	1999–2000	*	<LOD	18.7 (<LOD–32.2)	39.9 (26.5–47.3)	48.6 (43.5–65.5)	350
	2001–2002	11.7 (<LOD–13.6)	<LOD	22.8 (17.2–28.3)	41.4 (30.6–53.7)	56.5 (41.8–73.5)	501
	2003–2004	8.74 (<LOD–10.2)	8.70 (<LOD–10.6)	18.9 (15.9–21.5)	35.1 (25.4–40.2)	44.2 (37.7–56.8)	493

Table 5-14. Geometric Mean and Selected Percentiles of Serum Oxychlordane (Lipid Adjusted) Serum Concentrations (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	1999–2000	*	<LOD	21.8 (18.6–24.6)	34.2 (28.9–40.9)	44.0 (37.2–49.8)	559
	2001–2002	12.1 (11.0–13.3)	11.8 (10.5–13.9)	23.0 (20.1–25.7)	37.5 (31.6–45.1)	52.2 (41.0–67.4)	1,031
	2003–2004	10.2 (9.36–11.1)	11.2 (10.0–12.1)	19.7 (17.2–21.7)	30.3 (26.8–33.6)	37.7 (34.3–45.5)	898

[a]The limit of detection for survey years 1999–2000, 2001–2002, and 2003–2004 were 14.5, 10.5, and 7.8 ng/g, respectively.
[b]Not calculated: proportion of results below limit of detection was too high to provide a valid result.
[c]Less than the limit of detection.

CI = confidence interval; LOD = limit of detection

Source: CDC 2009, 2017

Table 5-15. Geometric Mean and Selected Percentiles of Serum Oxychlordane (Whole Weight) Serum Concentrations (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	*[b]	<LOD[c]	0.140 (0.120–0.150)	0.260 (0.200–0.290)	0.310 (0.290–0.340)	1,661
	2001–2002	0.070 (<LOD–0.077)	0.070 (<LOD–0.080)	0.140 (0.130–0.160)	0.250 (0.220–0.300)	0.350 (0.290–0.440)	2,249
	2003–2004	0.057 (0.053–0.062)	0.063 (0.058–0.068)	0.119 (0.106–0.133)	0.204 (0.189–0.213)	0.269 (0.246–0.291)	1,978
Age group							
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	663
	2001–2002	*	<LOD	<LOD	<LOD	0.060 (<LOD–0.070)	752
	2003–2004	*	<LOD	<LOD	0.047 (<LOD–0.063)	0.066 (0.048–0.092)	595
≥20 years	1999–2000	*	<LOD	0.150 (0.140–0.180)	0.280 (0.230–0.300)	0.330 (0.300–0.400)	998
	2001–2002	0.082 (0.074–0.091)	0.080 (0.070–0.090)	0.160 (0.140–0.180)	0.270 (0.230–0.320)	0.370 (0.310–0.450)	1,497
	2003–2004	0.067 (0.061–0.073)	0.073 (0.066–0.079)	0.130 (0.115–0.146)	0.210 (0.203–0.227)	0.286 (0.258–0.320)	1,383

Table 5-15. Geometric Mean and Selected Percentiles of Serum Oxychlordane (Whole Weight) Serum Concentrations (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	*	<LOD	0.120 (0.100–0.140)	0.220 (0.180–0.280)	0.300 (0.260–0.340)	793
	2001–2002	0.069 (<LOD–0.079)	0.070 (<LOD–0.080)	0.130 (0.120–0.160)	0.230 (0.190–0.300)	0.320 (0.250–0.430)	1,049
	2003–2004	0.056 (0.050–0.063)	0.063 (0.055–0.076)	0.115 (0.100–0.126)	0.189 (0.168–0.207)	0.258 (0.216–0.302)	963
Females	1999–2000	*	<LOD	0.140 (0.130–0.170)	0.270 (0.200–0.310)	0.320 (0.290–0.400)	868
	2001–2002	0.071 (0.065–0.077)	0.070 (<LOD–0.080)	0.150 (0.130–0.160)	0.260 (0.230–0.310)	0.370 (0.280–0.510)	1,200
	2003–2004	0.058 (0.053–0.064)	0.063 (0.057–0.068)	0.126 (0.104–0.146)	0.208 (0.199–0.231)	0.286 (0.245–0.331)	1,015
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	0.100 (<LOD–0.130)	0.210 (0.130–0.320)	0.290 (0.190–0.410)	628
	2001–2002	*	<LOD	0.100 (0.070–0.130)	0.200 (0.150–0.240)	0.280 (0.210–0.360)	557
	2003–2004	*	<LOD	0.083 (0.066–0.104)	0.149 (0.108–0.230)	0.230 (0.148–0.373)	462
Non-Hispanic blacks	1999–2000	*	<LOD	0.110 (<LOD–0.170)	0.240 (0.170–0.290)	0.320 (0.240–0.430)	350
	2001–2002	0.066 (<LOD–0.077)	<LOD	0.130 (0.090–0.170)	0.260 (0.180–0.350)	0.350 (0.240–0.560)	501
	2003–2004	0.049 (<LOD–0.057)	0.050 (<LOD–0.062)	0.112 (0.087–0.136)	0.225 (0.165–0.287)	0.315 (0.253–0.348)	493
Non-Hispanic whites	1999–2000	*	<LOD	0.140 (0.120–0.170)	0.270 (0.200–0.300)	0.320 (0.280–0.380)	559
	2001–2002	0.075 (0.068–0.083)	0.080 (0.070–0.090)	0.150 (0.130–0.170)	0.250 (0.220–0.310)	0.370 (0.280–0.450)	1,031
	2003–2004	0.063 (0.058–0.070)	0.070 (0.063–0.077)	0.128 (0.110–0.148)	0.207 (0.190–0.223)	0.271 (0.242–0.315)	898

[a]The limit of detection for survey years 1999–2000, 2001–2002, and 2003–2004 were 14.5, 10.5, and 7.8 ng/g, respectively.
[b]Not calculated: proportion of results below limit of detection was too high to provide a valid result.
[c]Less than the limit of detection.

CI = confidence interval; LOD = limit of detection

Source: CDC 2017

Table 5-16. Geometric Mean and Selected Percentiles of Serum *trans*-Nonachlor (Lipid Adjusted) Serum Concentrations (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	18.3 (16.7–20.0)	17.9 (16.1–20.1)	31.9 (28.9–36.0)	55.1 (48.4–62.6)	79.4 (67.6–88.1)	1,933
	2001–2002	17.0 (15.2–18.9)	17.9 (15.5–20.5)	33.7 (30.2–37.2)	56.3 (49.6–66.0)	78.2 (64.0–113)	2,286
	2003–2004	14.7 (13.1–16.5)	14.8 (13.5–17.0)	30.2 (26.7–32.5)	49.0 (42.6–54.7)	68.3 (58.6–82.3)	1,955
Age group							
12–19 years	1999–2000	*[b]	<LOD[c]	<LOD	18.8 (<LOD–20.6)	25.2 (19.1–28.4)	664
	2001–2002	*	<LOD	<LOD	13.4 (11.8–16.4)	19.2 (15.2–23.5)	758
	2003–2004	*	<LOD	8.70 (<LOD–12.5)	16.1 (10.7–23.7)	22.6 (16.1–34.6)	589
≥20 years	1999–2000	20.8 (19.0–22.8)	20.7 (18.0–23.5)	35.4 (30.9–40.3)	59.9 (51.8–67.6)	82.7 (74.9–89.6)	1,269
	2001–2002	19.8 (17.6–22.3)	20.9 (19.0–23.1)	36.6 (32.8–41.1)	60.6 (52.5–69.9)	84.9 (66.0–123)	1,528
	2003–2004	16.9 (15.1–18.9)	17.3 (14.6–20.0)	31.8 (28.9–35.3)	51.4 (45.9–58.6)	74.7 (59.8–90.0)	1,366
Gender							
Males	1999–2000	17.7 (16.5–19.1)	17.2 (14.9–20.1)	30.2 (27.7–34.2)	51.1 (47.3–58.6)	78.2 (60.2–88.1)	922
	2001–2002	17.0 (14.8–19.5)	18.3 (14.8–21.1)	34.4 (28.3–39.3)	54.8 (45.0–68.9)	78.2 (59.7–113)	1,062
	2003–2004	14.8 (12.7–17.3)	14.6 (12.2–18.0)	30.8 (26.7–35.3)	51.0 (42.0–59.4)	68.6 (56.0–93.8)	955
Females	1999–2000	18.8 (16.7–21.1)	18.4 (16.1–22.2)	32.9 (29.0–38.3)	59.0 (48.4–67.6)	80.8 (71.5–95.5)	1,011
	2001–2002	17.0 (15.4–18.7)	17.6 (15.0–20.3)	32.8 (30.4–36.7)	56.9 (51.9–65.5)	78.1 (65.5–111)	1,224
	2003–2004	14.5 (13.1–16.1)	15.0 (13.8–16.3)	28.2 (25.3–32.8)	48.1 (41.4–52.7)	68.3 (56.8–79.9)	1,000
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	25.1 (22.7–29.5)	40.7 (35.1–51.8)	56.3 (45.8–77.2)	650
	2001–2002	11.9 (<LOD–14.6)	10.6 (<LOD–14.5)	26.0 (19.3–30.4)	47.9 (36.3–57.2)	59.8 (49.3–74.1)	558
	2003–2004	10.2 (7.86–13.2)	9.10 (<LOD–11.1)	20.7 (11.1–34.7)	39.5 (25.9–65.5)	62.2 (36.0–93.4)	457
Non-Hispanic blacks	1999–2000	20.3 (17.0–24.1)	17.5 (15.4–23.5)	35.7 (28.9–45.5)	77.0 (60.8–90.7)	107 (84.0–143)	404
	2001–2002	18.8 (15.4–22.9)	19.2 (14.7–22.0)	36.8 (28.3–50.5)	73.6 (50.8–110)	112 (68.7–160)	514
	2003–2004	14.4 (12.2–17.0)	13.8 (11.2–16.3)	30.8 (26.5–36.1)	59.9 (47.7–77.7)	86.6 (56.8–129)	486

Table 5-16. Geometric Mean and Selected Percentiles of Serum *trans*-Nonachlor (Lipid Adjusted) Serum Concentrations (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	1999–2000	19.1 (17.2–21.1)	19.0 (16.9–22.2)	32.8 (28.0–37.6)	52.5 (44.9–64.4)	74.0 (62.3–86.7)	722
	2001–2002	17.5 (15.6–19.7)	19.0 (16.3–21.1)	34.0 (29.7–38.1)	55.5 (45.9–69.4)	78.7 (59.1–126)	1,052
	2003–2004	15.8 (13.7–18.2)	16.0 (13.8–19.3)	30.8 (26.4–35.0)	48.8 (42.1–55.7)	67.6 (57.5–87.3)	889

[a]The limit of detection for survey years 1999–2000, 2001–2002, and 2003–2004 were 14.5, 10.5, and 7.8 ng/g, respectively.
[b]Not calculated: proportion of results below limit of detection was too high to provide a valid result.
[c]Less than the limit of detection.

CI = confidence interval; LOD = limit of detection

Source: CDC 2009, 2017

Table 5-17. Geometric Mean and Selected Percentiles of Serum *trans*-Nonachlor (Whole Weight) Serum Concentrations (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	0.109 (0.099–0.119)	0.110 (0.090–0.120)	0.210 (0.190–0.240)	0.370 (0.330–0.420)	0.550 (0.470–0.630)	1,933
	2001–2002	0.104 (0.093–0.116)	0.110 (0.100–0.120)	0.220 (0.190–0.250)	0.390 (0.330–0.480)	0.590 (0.430–0.800)	2,286
	2003–2004	0.089 (0.080–0.100)	0.094 (0.084–0.108)	0.191 (0.171–0.211)	0.324 (0.290–0.371)	0.470 (0.410–0.558)	1,955
Age group							
12–19 years	1999–2000	*[b]	<LOD[c]	<LOD	0.090 (<LOD–0.110)	0.120 (0.100–0.130)	664
	2001–2002	*	<LOD	<LOD	0.070 (0.060–0.080)	0.090 (0.080–0.130)	758
	2003–2004	*	<LOD	0.041 (<LOD–0.060)	0.081 (0.054–0.117)	0.109 (0.081–0.161)	589
≥20 years	1999–2000	0.128 (0.116–0.141)	0.130 (0.110–0.150)	0.230 (0.210–0.260)	0.400 (0.360–0.460)	0.580 (0.490–0.690)	1,269
	2001–2002	0.125 (0.111–0.141)	0.130 (0.120–0.150)	0.240 (0.210–0.280)	0.420 (0.350–0.540)	0.640 (0.470–0.840)	1,528
	2003–2004	0.106 (0.095–0.119)	0.112 (0.096–0.127)	0.210 (0.186–0.237)	0.355 (0.301–0.405)	0.520 (0.430–0.594)	1,366

Table 5-17. Geometric Mean and Selected Percentiles of Serum *trans*-Nonachlor (Whole Weight) Serum Concentrations (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	0.106 (0.098–0.114)	0.100 (0.090–0.120)	0.210 (0.180–0.220)	0.350 (0.310–0.400)	0.520 (0.400–0.630)	922
	2001–2002	0.105 (0.091–0.122)	0.110 (0.090–0.130)	0.220 (0.190–0.260)	0.380 (0.310–0.500)	0.580 (0.390–0.830)	1,062
	2003–2004	0.092 (0.079–0.108)	0.098 (0.085–0.126)	0.202 (0.177–0.232)	0.343 (0.285–0.395)	0.458 (0.395–0.594)	955
Females	1999–2000	0.111 (0.099–0.125)	0.110 (0.090–0.130)	0.220 (0.190–0.250)	0.390 (0.310–0.460)	0.580 (0.460–0.690)	1,011
	2001–2002	0.103 (0.093–0.113)	0.110 (0.090–0.120)	0.220 (0.180–0.240)	0.400 (0.340–0.450)	0.590 (0.430–0.830)	1,224
	2003–2004	0.087 (0.078–0.097)	0.092 (0.079–0.098)	0.183 (0.161–0.210)	0.317 (0.286–0.367)	0.470 (0.409–0.565)	1,000
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	0.170 (0.120–0.210)	0.310 (0.240–0.340)	0.390 (0.320–0.520)	650
	2001–2002	0.071 (<LOD–0.091)	0.060 (<LOD–0.090)	0.160 (0.120–0.210)	0.330 (0.270–0.390)	0.470 (0.360–0.590)	558
	2003–2004	0.062 (0.047–0.082)	0.055 (<LOD–0.069)	0.135 (0.069–0.237)	0.288 (0.158–0.559)	0.414 (0.279–0.651)	457
Non-Hispanic blacks	1999–2000	0.112 (0.093–0.134)	0.100 (0.080–0.130)	0.220 (0.180–0.300)	0.490 (0.340–0.600)	0.760 (0.510–0.960)	404
	2001–2002	0.106 (0.085–0.131)	0.110 (0.080–0.130)	0.220 (0.160–0.310)	0.490 (0.320–0.680)	0.680 (0.410–1.20)	514
	2003–2004	0.080 (0.068–0.096)	0.078 (0.061–0.093)	0.186 (0.145–0.242)	0.417 (0.272–0.565)	0.573 (0.497–0.684)	486
Non-Hispanic whites	1999–2000	0.116 (0.104–0.129)	0.120 (0.100–0.140)	0.220 (0.190–0.240)	0.370 (0.300–0.440)	0.510 (0.440–0.630)	722
	2001–2002	0.108 (0.096–0.122)	0.120 (0.100–0.130)	0.220 (0.190–0.250)	0.390 (0.310–0.490)	0.600 (0.400–0.930)	1,052
	2003–2004	0.098 (0.085–0.113)	0.103 (0.090–0.124)	0.205 (0.173–0.234)	0.327 (0.288–0.390)	0.461 (0.397–0.576)	889

[a]The limit of detection for survey years 1999–2000, 2001–2002, and 2003–2004 were 14.5, 10.5, and 7.8 ng/g, respectively.
[b]Not calculated: proportion of results below limit of detection was too high to provide a valid result.
[c]Less than the limit of detection.

CI = confidence interval; LOD = limit of detection

Source: CDC 2009, 2017

Table 5-18. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum Oxychlordane (Lipid Adjusted) (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Non-Hispanic white male	12–19	2005–2006	4.80	1.1	9
		2007–2008	3.52	0.52	6
	20–39	2005–2006	6.50	1.06	12
		2007–2008	6.93	0.75	15
	40–59	2005–2006	14.9	1.4	12
		2007–2008	12.1	0.5	16
	60+	2005–2006	25.4	2.5	15
		2007–2008	26.1	1.4	23
Non-Hispanic white female	12–19	2005–2006	2.98	0.3	10
		2007–2008	3.66	0.74	7
	20–39	2005–2006	5.64	0.56	16
		2007–2008	5.79	0.51	13
	40–59	2005–2006	13.7	1	13
		2007–2008	11.8	0.8	17
	60+	2005–2006	28.9	2.6	17
		2007–2008	31.8	2.3	21
Non-Hispanic black male	12–19	2005–2006	4.08	0.49	13
		2007–2008	2.80	0.75	6
	20–39	2005–2006	4.53	0.9	6
		2007–2008	5.72	0.28	6
	40–59	2005–2006	12.0	1	5
		2007–2008	12.1	1.1	6
	60+	2005–2006	32.7	5.3	5
		2007–2008	26.6	2.5	8
Non-Hispanic black female	12–19	2005–2006	2.92	0.31	14
		2007–2008	*[e]	*	5
	20–39	2005–2006	5.56	0.68	7
		2007–2008	4.45	0.79	8
	40–59	2005–2006	14.5	0.8	7
		2007–2008	14.3	1	8
	60+	2005–2006	52.9	11.7	5
		2007–2008	38.1	1.7	7

Table 5-18. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum Oxychlordane (Lipid Adjusted) (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Mexican American male	12–19	2005–2006	2.54	0.33	11
		2007–2008	2.76	0.45	6
	20–39	2005–2006	5.84	1.22	9
		2007–2008	4.93	0.38	9
	40–59	2005–2006	11.0	1.4	4
		2007–2008	12.0	0.7	6
	60+	2005–2006	18.6	2.4	4
		2007–2008	21.9	2.2	5
Mexican American female	12–19	2005–2006	2.39	0.25	16
		2007–2008	*	*	5
	20–39	2005–2006	4.39	0.5	9
		2007–2008	4.17	0.55	8
	40–59	2005–2006	13.7	1.8	6
		2007–2008	13.4	2.2	6
	60+	2005–2006	27.4	3.8	3
		2007–2008	28.2	4.3	5

[a]The limit of detection for survey years 2005–2006 and 2007–2008 were 1.46 and 1.4 ng/g, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means.
[c]Unadjusted standard errors do not incorporate survey design effects.
[d]Each pool was composed of serum from 8 persons.
[e]Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Source: CDC 2017

Table 5-19. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum Oxychlordane (Whole Weight) (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Non-Hispanic white male	12–19	2005–2006	0.026	0.006	9
		2007–2008	0.018	0.003	6
	20–39	2005–2006	0.049	0.01	12
		2007–2008	0.047	0.006	15
	40–59	2005–2006	0.113	0.013	12
		2007–2008	0.089	0.005	16
	60+	2005–2006	0.171	0.015	15
		2007–2008	0.167	0.009	23
Non-Hispanic white female	12–19	2005–2006	0.016	0.002	10
		2007–2008	0.017	0.004	7
	20–39	2005–2006	0.037	0.004	16
		2007–2008	0.035	0.003	13
	40–59	2005–2006	0.101	0.01	13
		2007–2008	0.079	0.006	17
	60+	2005–2006	0.210	0.017	17
		2007–2008	0.214	0.017	21
Non-Hispanic black male	12–19	2005–2006	0.020	0.002	13
		2007–2008	0.013	0.003	6
	20–39	2005–2006	0.027	0.005	6
		2007–2008	0.032	0.002	6
	40–59	2005–2006	0.076	0.006	5
		2007–2008	0.077	0.007	6
	60+	2005–2006	0.193	0.028	5
		2007–2008	0.162	0.017	8
Non-Hispanic black female	12–19	2005–2006	0.014	0.001	14
		2007–2008	*[e]	*	5
	20–39	2005–2006	0.032	0.004	7
		2007–2008	0.022	0.004	8
	40–59	2005–2006	0.093	0.006	7
		2007–2008	0.086	0.008	8
	60+	2005–2006	0.347	0.067	5
		2007–2008	0.229	0.012	7

Table 5-19. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum Oxychlordane (Whole Weight) (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Mexican American male	12–19	2005–2006	0.014	0.002	11
		2007–2008	0.014	0.002	6
	20–39	2005–2006	0.041	0.007	9
		2007–2008	0.034	0.004	9
	40–59	2005–2006	0.089	0.014	4
		2007–2008	0.087	0.009	6
	60+	2005–2006	0.137	0.025	4
		2007–2008	0.156	0.011	5
Mexican American female	12–19	2005–2006	0.013	0.001	16
		2007–2008	*	*	5
	20–39	2005–2006	0.029	0.003	9
		2007–2008	0.024	0.004	8
	40–59	2005–2006	0.100	0.011	6
		2007–2008	0.090	0.014	6
	60+	2005–2006	0.208	0.035	3
		2007–2008	0.193	0.03	5

[a]The limit of detection for survey years 2005–2006 and 2007–2008 were 1.46 and 1.4 ng/g, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means.
[c]Unadjusted standard errors do not incorporate survey design effects.
[d]Each pool was composed of serum from 8 persons.
[e]Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Source: CDC 2017

Table 5-20. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum *trans*-Nonachlor (Lipid Adjusted) (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Non-Hispanic white male	12–19	2005–2006	9.03[e]	2.84	9
		2007–2008	6.06	1.08	6
	20–39	2005–2006	11.3	2	12
		2007–2008	11.1	1.5	15
	40–59	2005–2006	26.9	3.9	12
		2007–2008	21.5	1.2	16
	60+	2005–2006	49.4	7.9	15
		2007–2008	50.6	4.2	23
Non-Hispanic white female	12–19	2005–2006	4.94	0.52	10
		2007–2008	6.70	0.89	7
	20–39	2005–2006	9.70	1.44	16
		2007–2008	8.95	0.97	13
	40–59	2005–2006	21.8	2.3	13
		2007–2008	16.4	1.5	17
	60+	2005–2006	50.2	6.1	17
		2007–2008	51.7	6.1	21
Non-Hispanic black male	12–19	2005–2006	6.50	0.67	13
		2007–2008	4.71	0.65	6
	20–39	2005–2006	8.24	0.86	6
		2007–2008	8.87	0.97	6
	40–59	2005–2006	22.0	2.6	5
		2007–2008	21.7	2.1	6
	60+	2005–2006	66.4	13.2	5
		2007–2008	54.4	4.9	8
Non-Hispanic black female	12–19	2005–2006	4.44	0.54	14
		2007–2008	3.39[e]	1.18	5
	20–39	2005–2006	9.32	1.22	7
		2007–2008	6.42	0.6	8
	40–59	2005–2006	24.1	1.5	7
		2007–2008	20.4	1.7	8
	60+	2005–2006	89.0	15.4	5
		2007–2008	68.0	3.9	7

Table 5-20. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum *trans*-Nonachlor (Lipid Adjusted) (in ng/g of Lipid or Parts per Billion on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Mexican American male	12–19	2005–2006	3.71	0.49	11
		2007–2008	3.91	0.81	6
	20–39	2005–2006	7.58	0.75	9
		2007–2008	8.43	0.97	9
	40–59	2005–2006	18.8	2.4	4
		2007–2008	24.5	2.9	6
	60+	2005–2006	30.7	6.3	4
		2007–2008	40.3	4.5	5
Mexican American female	12–19	2005–2006	3.53	0.23	16
		2007–2008	*[f]	*	5
	20–39	2005–2006	6.40	0.75	9
		2007–2008	7.55	0.9	8
	40–59	2005–2006	18.5	1.7	6
		2007–2008	22.6	4.4	6
	60+	2005–2006	46.4	9.8	3
		2007–2008	46.9	8	5

[a]The limit of detection for survey years 2005–2006 and 2007–2008 were 0.77 and 1.4 ng/g, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means.
[c]Unadjusted standard errors do not incorporate survey design effects.
[d]Each pool was composed of serum from 8 persons.
[e]Standard error of the mean estimate is >30%.
[f]Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Source: CDC 2017

Table 5-21. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum *trans*-Nonachlor (Whole Weight) (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Non-Hispanic white male	12–19	2005–2006	0.048[e]	0.015	9
		2007–2008	0.030	0.005	6
	20–39	2005–2006	0.086	0.019	12
		2007–2008	0.076	0.011	15
	40–59	2005–2006	0.206	0.034	12
		2007–2008	0.159	0.012	16
	60+	2005–2006	0.331	0.049	15
		2007–2008	0.325	0.028	23
Non-Hispanic white female	12–19	2005–2006	0.026	0.003	10
		2007–2008	0.031	0.004	7
	20–39	2005–2006	0.063	0.01	16
		2007–2008	0.054	0.007	13
	40–59	2005–2006	0.161	0.019	13
		2007–2008	0.108	0.009	17
	60+	2005–2006	0.362	0.04	17
		2007–2008	0.352	0.045	21
Non-Hispanic black male	12–19	2005–2006	0.032	0.003	13
		2007–2008	0.022	0.003	6
	20–39	2005–2006	0.049	0.006	6
		2007–2008	0.050	0.006	6
	40–59	2005–2006	0.140	0.014	5
		2007–2008	0.138	0.013	6
	60+	2005–2006	0.390	0.071	5
		2007–2008	0.331	0.032	8
Non-Hispanic black female	12–19	2005–2006	0.022	0.003	14
		2007–2008	0.016[e]	0.005	5
	20–39	2005–2006	0.054	0.007	7
		2007–2008	0.032	0.003	8
	40–59	2005–2006	0.154	0.009	7
		2007–2008	0.124	0.012	8
	60+	2005–2006	0.588	0.088	5
		2007–2008	0.409	0.027	7

Table 5-21. Weighted Arithmetic Mean and Unadjusted Standard Error of Pooled Serum Concentrations of Serum *trans*-Nonachlor (Whole Weight) (in ng/g of Serum or Parts per Billion) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2005–2008

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Mexican American male	12–19	2005–2006	0.020	0.002	11
		2007–2008	0.020	0.004	6
	20–39	2005–2006	0.054	0.005	9
		2007–2008	0.058	0.008	9
	40–59	2005–2006	0.153	0.022	4
		2007–2008	0.176	0.024	6
	60+	2005–2006	0.228	0.06	4
		2007–2008	0.289	0.028	5
Mexican American female	12–19	2005–2006	0.019	0.001	16
		2007–2008	*[f]	*	5
	20–39	2005–2006	0.042	0.005	9
		2007–2008	0.044	0.006	8
	40–59	2005–2006	0.135	0.011	6
		2007–2008	0.151	0.029	6
	60+	2005–2006	0.360	0.095	3
		2007–2008	0.323	0.058	5

[a]The limit of detection for survey years 2005–2006 and 2007–2008 were 0.77 and 1.4 ng/g, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means.
[c]Unadjusted standard errors do not incorporate survey design effects.
[d]Each pool was composed of serum from 8 persons.
[e]Standard error of the mean estimate is >30%.
[f]Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Source: CDC 2017

Workers may be exposed to chlordane during its manufacture, formulation, shipping, storage, application, and disposal. The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 3,732 workers were potentially exposed to chlordane in the workplace in the United States (NIOSH 1989a). The NOES was based on field surveys of 4,490 businesses employing nearly 1.8 million workers and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States in which eight or more persons are employed in all standard industrial codes except mining or agriculture.

Workplace monitoring data are available from two studies conducted simultaneously by Velsicol (Cahill et al. 1979) and the State of California (Maddy et al. 1979). In these studies, patches were attached to the inside and outside of the applicators' coveralls, and breathing zone air was monitored while chlordane was applied to six houses (three with a crawl space and three on a concrete slab). Cahill et al. (1979)

reported that 0.015–7.96 mg/cm^2 (median 0.175 mg/cm^2, 24 samples) was found on the 100 cm^2 denim patches attached just above the knees and elbows of the applicators' coveralls, whereas Maddy et al. (1979) found 0.005–2.9 mg/cm^2 (median 0.12 mg/cm^2, 23 samples) for 100 cm^2 duck cotton cloth (similar to denim) patches attached below the knees and elbows. Concentrations inside the coveralls were determined by Cahill et al. (1979) by attaching a denim patch to the work pants (worn under the coveralls) at the knee and to the inside of the coveralls at the elbow (but not overlapping the outside elbow patch). Maddy et al. (1979) determined inside concentrations by attaching eight layers of cotton cheese cloth backed by aluminum foil to the inner surface of the duck cloth patches attached below the knees and elbows of the applicators. Cahill et al. (1979) found 0.0053–0.127 mg/cm^2 (median 0.024 mg/cm^2, 24 samples) on the inside patches, whereas Maddy et al. (1979) found 0.009–l.9 mg/cm^2 (median 0.082 mg/cm^2, 23 samples) on the cheese cloth backing.

Air impingers were worn by the applicators both on the lapel and on the chin inside the respirator. Air concentrations were reported for both inside and outside the respirator by Maddy et al. (1979), but only one value was reported by Cahill et al. (1979). Cahill et al. (1979) reported finding chlordane in all four samples analyzed (0.16–14.2 mg/m^3), whereas Maddy et al. (1979) found 0.007, 0.008, and 0.110 mg/m^3 in three of five samples taken outside the respirator and 0.011 and 0.27 mg/m^3 in two of six samples taken inside the respirator. No detection limit was reported by Maddy et al. (1979); therefore, no information is available concerning the samples with concentrations too low to detect.

Kamble et al. (1992) studied the exposure of 29 commercial applicators exposed to Termide® EC (technical chlordane 39.22% plus heptachlor 19.6%), diluted to 0.75% (active ingredient) during subterranean termite treatment of homes. Dermal exposure was monitored using 14 gauze pads for each applicator attached to exterior and interior parts of clothing for an average duration of 138 minutes. Exposure to hands was monitored by hand rinses immediately after application. Respiratory exposure was assessed with personnel-type air samplers (see Table 5-6). Total dermal exposure of applicators to chlordane was 2.5 µg/kg/hour. The most exposed body regions in descending order were: hands, forearms, head, lower legs, thighs, back trunk, front trunk, upper arms, and back of the neck. Approximately 25% of the chlordane on the exterior surface of clothing was likely to penetrate through the fabric. Respiratory exposure was 0.04 µg/kg/hour.

Elia et al. (1983) reported that chlordane was detected in the water and air of a sewage treatment plant near Memphis, Tennessee, and suggested that occupational exposures to semi-volatile compounds such as chlordane could occur at these plants. No chlordane data, however, were presented. Former occupational

exposures, in addition to termite control, included chlordane manufacturing, formulation, distribution, and agricultural and lawn care pesticide application. Since chlordane is no longer manufactured or used commercially in the United States (EPA 1988c), these occupational exposures no longer exist. No data are available that would allow the estimation of workplace levels during manufacture and use.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

A segment of the general population with potentially high exposure to chlordane includes those people living in structures that were treated with chlordane for termite control or people digging in soil around these houses. The majority of these structures are located in the deep south and far southwest where termites are a significant problem, but moderate to heavy use of chlordane extended from Pennsylvania and the lower New England states south and west to the lower portion of Colorado and up to northern California. The available data indicate that these exposures would be much greater than exposures from other sources of chlordane. Persons involved in the manufacture of chlordane and persons involved in the application of chlordane before its use was banned on April 14, 1988, may have been exposed to relatively high levels. Similarly, lawn care workers and farmers that handled chlordane before above-ground uses were banned may have been exposed to high levels of the chemical. Populations living near waste disposal sites containing chlordane may have been exposed to elevated levels of chlordane.

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 chlordane 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 chlordane.

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.

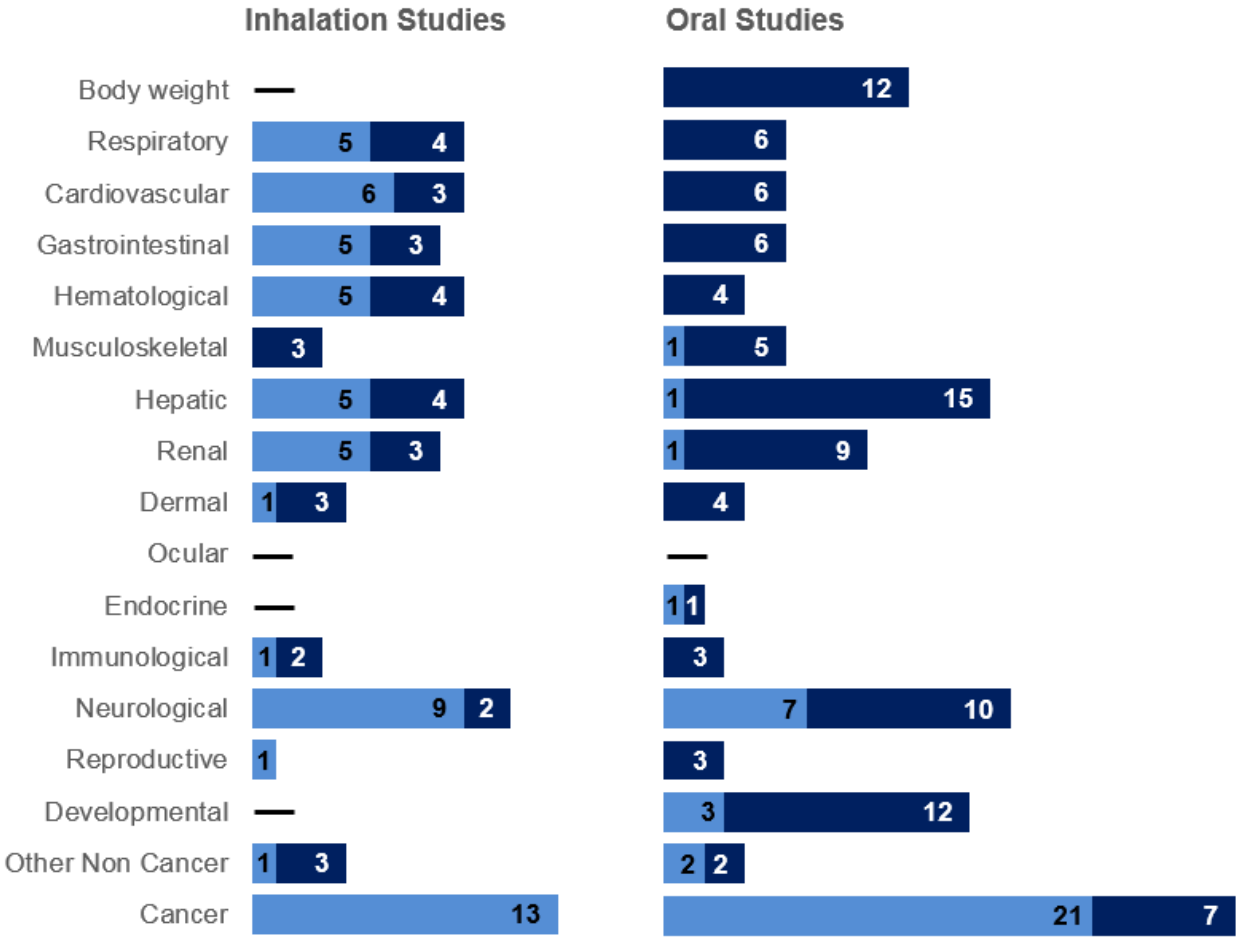
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chlordane 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 chlordane. 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.

Although most occupational exposure scenarios and residential exposures following application of chlordane to homes for termite control likely involved inhalation and dermal exposure, these exposure scenarios were classified as inhalation exposures and are presented as such in Figure 6-1. Studies that evaluated potential health effects in humans based on blood levels of chlordane, chlordane constituents, and/or chlordane metabolites were assumed to have involved oral exposure in cases where information regarding the likelihood of inhalation exposure was not available.

Figure 6-1. Summary of Existing Health Effects Studies on Chlordane By Route and Endpoint*

Hepatic, neurological, and cancer endpoints were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Human studies that may have involved dermal exposure were summarized as inhalation studies. Dermal studies in animals focused on acute lethality.

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 1989a), 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.

Acute-Duration MRLs. Sufficient information was not available on the health effects of chlordane to derive an MRL for acute-duration inhalation exposure. Lethality was noted at the same exposure levels at which other effects were observed. Additional animal studies should be designed to evaluate nonlethal effects associated with acute-duration inhalation exposure, particularly if human populations can be identified with potential for significant exposure to chlordane.

Intermediate-Duration MRLs. The database of information regarding effects of intermediate-duration exposure of laboratory animals to chlordane was considered sufficient for inhalation and oral exposure to derive intermediate-duration inhalation and oral MRLs. It does not appear necessary to perform additional intermediate-duration inhalation or oral studies in animals.

Chronic-Duration MRLs. The database of information regarding effects of intermediate- and/or chronic-duration exposure of laboratory animals to chlordane was considered sufficient for inhalation and oral exposure to derive chronic-duration inhalation and oral MRLs. The chronic-duration inhalation MRL is based on results from an intermediate-duration inhalation study; an uncertainty factor of 10 was applied to account for extrapolation from an intermediate- to chronic-duration exposure scenario. A well-designed chronic-duration inhalation study in animals could serve as the basis for deriving a chronic-duration inhalation MRL, particularly if present human populations can be identified with potential for significant chronic-duration inhalation exposure to chlordane. Well-designed, chronic-duration oral studies in animals provide adequate information to support the chronic-duration oral MRL.

Health Effects.

Respiratory. Respiratory effects have been associated with exposure to chlordane among humans (EPA 1980a; Menconi et al. 1988) and in inhalation studies of animals (EPA 1987f; Khasawinah et al. 1989). No signs of respiratory effects were observed in animal studies that

employed oral or dermal exposure routes (EPA 1985a; Khasawinah and Grutsch 1989a, 1989b; NCI 1977; Truhaut et al. 1974, 1975). People living in areas where chlordane may be detected in air should be monitored for possible exposure-related effects on the respiratory system.

Cardiovascular. Tachycardia was among the symptoms attributed to chlordane exposure in a compilation of cases and personal reports of accidental human inhalation exposure to high concentrations of chlordane (EPA 1980b). No signs of chlordane-induced cardiovascular effects were seen in inhalation or oral animal studies that evaluated the cardiovascular system (EPA 1985a; Khasawinah and Grutsch 1989a, 1989b; NCI 1977; Truhaut et al. 1974, 1975). People living in areas where chlordane may be detected should be monitored for possible exposure-related effects on the cardiovascular system.

Gastrointestinal. Gastrointestinal effects (cramps, diarrhea, nausea) were a consistent observation in a compilation of cases and personal reports of accidental human inhalation exposure to high concentrations of chlordane (EPA 1980a). NIOSH (1984a) also reported gastrointestinal symptoms (nausea, diarrhea) in 4 of 13 humans within 4 days of inhalation and/or dermal exposure as a result of 1% chlordane being spilled in a subterranean library room. Atrophy of gastric mucosa was reported in hamsters following single gavage dosing of chlordane technical at 1,200 mg/kg (Truhaut et al. 1974, 1975). No signs of chlordane-induced gastrointestinal effects were seen in other inhalation or oral animal studies that evaluated the gastrointestinal system (EPA 1985a; Khasawinah and Grutsch 1989a, 1989b; NCI 1977; Truhaut et al. 1974, 1975). Human populations are not likely to be exposed to chlordane levels high enough to elicit adverse gastrointestinal effects.

Hematological. Limited information is available regarding potential chlordane-induced effects on hematological endpoints. Cases of blood dyscrasia have been observed in persons exposed to chlordane or heptachlor (Epstein and Ozonoff 1987; Infante et al. 1978). However, limitations include unquantified exposure to chlordane and confounding by exposure to other substances as well. Increased leukocytes and decreased platelets were reported in rats intermittently exposed to chlordane technical by inhalation for 90 days at 1 mg/m^3 (EPA 1987f; Khasawinah et al. 1989). Increased lymphocytes were reported in mice administered *trans*-chlordane by gavage for 14 days at 8 mg/kg/day (Johnson et al. 1986). However, no data were located to provide support to these findings, including inhalation and oral studies of longer exposure duration. Additional animal studies could be designed to support or refute existing evidence for chlordane-induced

hematological effects. People living in areas where chlordane may be detected should be monitored for possible exposure-related effects on the hematological system.

Hepatic. Hepatic effects have been infrequently associated with chlordane exposure in humans (EPA 1980a). However, adverse liver effects were commonly observed in laboratory animals exposed by inhalation or oral routes (Ambrose et al. 1953a; Bondy et al. 2000; Den Tonkelaar and Van Esch 1974; EPA 1985a, 1987f; Khasawinah and Grutsch 1989a, 1989b; Khasawinah et al. 1989; Malarkey et al. 1995; Ogata and Izushi 1991; Truhaut et al. 1974, 1975). People living in areas where chlordane may be detected should be monitored for possible exposure-related hepatic effects.

Endocrine. There is limited evidence of chlordane-induced effects on the thyroid in humans (Nagayama et al. 2007) and animals (EPA 1987f; Khasawinah et al. 1989). People living in areas where chlordane may be detected should be monitored for possible exposure-related thyroid effects.

Reproductive. Data from one human case report involving a woman who was exposed to a lethal dermal dose of chlordane (Derbes et al. 1955) and a cross-sectional epidemiological investigation involving women exposed to chlordane vapors (Menconi et al. 1988) did not provide conclusive evidence that the reproductive system is a potential target organ in humans exposed to chlordane. Inhalation and oral acute-, intermediate-, or chronic-duration exposure studies in animals, in which the reproductive organs were examined histopathologically, did not identify lesions in the reproductive organs (EPA 1985a, 1987f; Khasawinah and Grutsch 1989a, 1989b; Khasawinah et al. 1989; NCI 1977; Truhaut et al. 1975). However, animal studies have identified the male reproductive system as a target of chlordane toxicity (Balash et al. 1987; Truhaut et al. 1975). Ambrose et al. (1953a) reported reduced fertility among male and female rats fed chlordane in the diet. The pharmacokinetic data in animals indicated that absorption occurs following any route of exposure, and that chlordane residues tend to accumulate in body fat; therefore, impaired reproductive performance in humans may occur following any route of exposure. Because of the tendency for chlordane residues to accumulate in body fat, multi-generation reproduction studies in animals by the inhalation and oral routes are recommended. Epidemiological investigations of reproductive effects in humans living in homes previously treated with chlordane, or those exposed during its manufacture or use as a pesticide, would also be useful if adequate populations can be identified.

Developmental. Limited information is available regarding potential for chlordane-induced developmental effects in human (Fenster et al. 2006; Gladen et al. 2003; Trabert et al. 2012). Available animal data suggest that subtle behavioral and immunological effects occur in developing mice (Al-Hachim and Al-Baker 1973; Barnett et al. 1985a, 1985b, 1990a, 1990b; Chernoff and Kavlock 1982; Cranmer et al. 1984; Menna et al. 1985; Spyker-Cranmer et al. 1982; Theus et al. 1992; Usami et al. 1986). Additional developmental studies in other animal species may clarify the developmental effects that could be anticipated in humans. Particularly useful would be studies designed to locate thresholds for subtle immunological and neurological effects following both pre- and postnatal exposure. Epidemiological investigation of developmental effects in humans living in homes treated with chlordane, or those exposed during its manufacture or use as a pesticide, would also be useful if adequate populations can be identified.

Immunotoxicity. Data from one human study suggest that chlordane may cause autoimmunity as well as impaired proliferative responses to plant mitogens following inhalation exposure to chlordane (McConnachie and Zahalsky 1992). *In vitro* studies with rhesus monkey peripheral blood mononuclear cells suggest that chlordane may impair cell-mediated immunity (Chuang et al. 1992). Mice exposed to chlordane exhibited leukocytosis and decreased thymus weight (Johnson et al. 1986; Khasawinah et al. 1989). Decreased myeloid cell colony forming capacity and depressed delayed type hypersensitivity occurred in the offspring of mice exposed orally to chlordane during gestation (Barnett et al. 1985a, 1985b, 1990a, 1990b; Menna et al. 1985; Spyker-Cranmer et al. 1982). Further testing of immune function in mice and other animals may provide useful information regarding chlordane-induced immunotoxicity in humans. In addition, epidemiology studies, perhaps comparing persons with high and low levels of chlordane residues in the blood, fat, or breast milk, may provide useful information. Parameters evaluated may include the frequency of allergic and autoimmune disorders, susceptibility to opportunistic infections (e.g., colds or flu), and alterations in absolute and differential leukocyte counts.

Neurotoxicity. Neurotoxicity is a consistent and predictable finding in humans (Aldrich and Holmes 1969; Balistreri et al. 1973; Barnes 1967; Curley and Garrettson 1969; Dadey and Kammer 1953; EPA 1980a, 1986d; Harrington et al. 1978; Kilburn and Thornton 1995; Lensky and Evans 1952; Menconi et al. 1988; NIOSH 1984a; Olanoff et al. 1983) and animals (Drummond et al. 1983; Frings and O'Tousa 1950; Hrdina et al. 1974; Ingle 1952; Khasawinah et

al. 1989; NCI 1977; Stohlman et al. 1950) exposed to chlordane. In the human studies, clinical signs and symptoms included migraines, convulsions, and seizures following inhalation, oral, or dermal routes of exposure. In the animal studies, convulsions and seizures were consistent findings after inhalation, oral, and dermal routes of exposure to chlordane (Ambrose et al. 1953a; EPA 1987f; Hrdina et al. 1974; Ingle 1953; Khasawinah et al. 1989; NCI 1977). Further testing should be designed to investigate subtle effects on neurobehavior and central nervous system function. Epidemiological investigation of subtle neurological and behavioral effects in humans living in homes treated with chlordane, or those exposed during its manufacture or use as a pesticide, would also be useful if adequate populations can be identified.

Cancer. Many available epidemiology studies have found no convincing evidence for the carcinogenicity of chlordane in humans (Brown 1992; Cantor et al. 2003; Demers et al. 2000; Falck et al. 1992; Gammon et al. 2002; MacMahon et al. 1988; Shindell and Ulrich 1986; Wang and MacMahon 1979a; Ward et al. 2000; Weiderpass et al. 2000; Wolff et al. 2000). Other studies reported slight (statistically significant) associations between serum or adipose tissue levels of selected chlordane components and/or metabolites and risk of cancer of the male reproductive system (Cook et al. 2011; Hardell et al. 2003, 2006a; McGlynn et al. 2008), non-Hodgkin's lymphoma (Hardell et al. 1996; Quintana et al. 2004; Spinelli et al. 2007), and pancreatic cancer (Hardell et al. 2007). Other population-based studies reported significant associations between self-reported chlordane use and risk of breast cancer (Mills and Yang 2005), non-Hodgkin's lymphoma (Cantor et al. 1992; Colt et al. 2006), and rectal cancer (Purdue et al. 2006), except for a weak association with leukemia and neuroblastoma (Epstein and Ozonoff 1987; Infante et al. 1978). However, epidemiological studies are typically limited by lack of quantitative exposure data and the likelihood of significant exposure to other potentially toxic substances as well.

Oral studies in animals have confirmed that chlordane induces liver tumors in mice, but not rats, exposed to high levels (Becker and Sell 1979; EPA 1985a; Epstein 1976; IRDC 1973; Khasawinah and Grutsch 1989a, 1989b; NCI 1977; Williams and Numoto 1984). Chronic-duration inhalation and dermal studies were not located, but it seems likely that the carcinogenicity of chlordane in mice is not route-dependent, because the pharmacokinetic data in animals indicate that absorption occurs following any route of exposure, and because the liver is a target organ for noncancer effects regardless of route of exposure. Most genotoxicity tests with chlordane yielded negative results (Arnold et al. 1977; Ashby and Tennant 1988; Blevins and

Sholes 1978; Brandt et al. 1972; Maslansky and Williams 1981) (see Section 2.20), suggesting an epigenetic mechanism of carcinogenicity. In support of this theory, chlordane inhibited gap junction intercellular communication (Ruth et al. 1990; Tong and Williams 1988). These results suggest that chlordane acts as a tumor promoter, depressing intercellular communication that checks uncontrolled proliferation of transformed or neoplastic cells. Further mechanistic studies may provide useful information regarding the potential carcinogenicity to humans chronically exposed to low levels. These studies are important because humans may be chronically exposed by living in previously treated homes or near hazardous waste sites.

Genotoxicity. Studies of genotoxic effects in humans are limited to an *in vitro* study of chlordane-induced sister chromatid exchange in lymphoid cells and a positive response was obtained (Sobti et al. 1983). *In vivo* mouse studies provided mixed results; chlordane did not induce dominant lethal mutations (Arnold et al. 1977; Epstein et al. 1972) or DNA adducts (Whysner et al. 1998) in mice, but did induce micronucleus formation (Schop et al. 1990) and chromosomal aberrations (Sarkar et al. 1993) in mouse bone marrow cells and nuclei aberrations in hair follicles (Schop et al. 1990). The most prevalent metabolite of the chlordane isomers, oxychlordane, although an epoxide, appears to be relatively inert (Khasawinah 1989; Sasaki et al. 1992), and probably does not bind strongly to tissue macromolecules. Free radicals formed as a result of reductive dehalogenation, however, may bind to DNA and other macromolecules (Brimfield and Street 1981; Kawano et al. 1989), inducing genetic defects or interfering with DNA repair. Additional *in vivo* mutation and chromosomal aberration tests in animals may clarify the ability of chlordane to induce genotoxicity in humans.

Epidemiology and Human Dosimetry Studies. Several epidemiological studies have investigated the cancer and noncancer effects of chlordane in humans exposed in their homes or occupationally in the manufacture of chlordane or in its application as a pesticide (Alvarez and Hyman 1953; Brown 1992; Cantor et al. 1992; Ditraglia et al. 1981; Kawano and Tatsukawa 1982; MacMahon et al. 1988; Menconi et al. 1988; Ogata and Izushi 1991; Wang and MacMahon 1979a, 1979b; Woods and Polissar 1989). Limitations of these studies include unquantified exposure levels of chlordane, exposure to a mixture of chemicals, and failure to investigate subtle neurological, behavioral, and hepatic effects in the exposed persons. Additional multi-endpoint epidemiological studies should be designed to study these subtle effects, as well as hematological effects such as blood dyscrasia and leukemia, in the exposed populations mentioned above. Further, case-control and longitudinal epidemiological studies would help to establish a cause/effect relationship among a better defined population.

Biomarkers of Exposure and Effect. Biomarkers of exposure include various components of commercial chlordane (principally *cis*- and *trans*-chlordane, *cis*- and *trans*-nonachlor) and its metabolites (principally oxychlordane). These substances are specific for exposure to chlordane. Detection of heptachlor and its metabolite, heptachlor epoxide, could reflect exposure to chlordane, because heptachlor is a component of commercial chlordane, or exposure to heptachlor, which is an insecticide in its own right.

Detectable levels in urine would probably reflect recent or ongoing exposure, because urinary excretion is not prominent for chlordane (Aldrich and Holmes 1969; Barnett and Dorough 1974; Ewing et al. 1985; Ohno et al. 1986; Tashiro and Matsumura 1977). Higher levels of chlordane residues occur in the feces of acutely poisoned humans (Aldrich and Holmes 1969). Generally, levels of chlordane residues in blood are below those in liver and fat (Mussalo-Rauhamaa 1991); blood levels may be reasonable indicators of recent or ongoing exposure (Ogam and Izushi 1991).

Some studies evaluated the use of levels of chlordane residues in skin surface lipids as a biomarker of exposure to avoid the invasive techniques necessary to obtain blood or body fat (Sasaki et al. 1991b; Wariishi and Nishiyama 1989). In monkeys, levels of *trans*-chlordane and oxychlordane in surface skin lipids correlated fairly well with levels in subcutaneous fat. Further refinement of this technique could increase the utility of chlordane residues in skin surface lipids as biomarkers of exposure.

Known biomarkers of effect are limited to slight alterations in serum chemistry. Evidence of liver effects (elevated serum triglycerides, CPK, and LDH) were observed in pesticide workers (Ogata and Izushi 1991). The elevated CPK was considered somewhat specific for chlordane exposure. Carefully performed epidemiological studies might provide data that clarify the relation between exposure to chlordane and optic neuritis or other disease states. Such studies may also identify alterations in blood chemistry indices or other clinicopathological endpoints that are useful for identifying the presence or pathogenesis of disease states associated with chlordane exposure.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative absorption data regarding human exposure by any route. However, that chlordane is absorbed by humans is indicated from measurement of blood and tissue levels of chlordane in persons exposed via inhalation from homes treated for termite control (Kawano and Tatsukawa 1982; Saito et al. 1986; Taguchi and Yakushiji 1988; Takamiya 1987), in case reports of accidental ingestion (Aldrich and Holmes 1969; Curley and Garrettson

1969; Kutz et al. 1983; Olanoff et al. 1983), and from systemic toxicity after dermal exposure (Barnes 1967). One human study also attempted to correlate skin chlordane levels with blood chlordane levels in 248 male and 227 female outpatients (Hirai and Tomokuni 1993). Although chlordane was potentially absorbed by the dermal route, the data from this study did not demonstrate any strong correlations between skin chlordane levels and blood chlordane levels. The rat data for inhalation absorption are limited to an intratracheal study, which is inadequate for estimating absorption via the respiratory tract (Nye and Dorough 1976). Oral data in rats and mice indicate that gastrointestinal absorption occurs readily (Ewing et al. 1985; Ohno et al. 1986). Quantitative dermal absorption data are lacking, but absorption is indicated by lethality in rats and rabbits exposed dermally (Gaines 1960; Ingle 1965). Quantitative inhalation and dermal absorption data would be useful, because these routes are toxicologically significant to humans.

Distribution data available for humans are limited; levels of chlordane metabolites in several tissues after acute poisoning, and in blood, liver, fat, and breast milk after chronic-duration exposure were reported for the oral route (Aldrich and Holmes 1969; Curley and Garrettson 1969; Dearth and Hites 1991a; Hirai and Tomokuni 1991a, 1991b; Kutz 1983; Kutz et al. 1976, 1983; Mussalo-Rauhamaa 1991; Ogata and Izushi 1991; Olanoff et al. 1983; Sasaki et al. 1991a; Wariishi and Nishiyama 1989). Other human data include reports of chlordane residues in blood, adipose tissue, and cord blood (Brock et al. 1998; Glynn et al. 2000; Kang et al. 2008; Rhainds et al. 1999; Tanabe et al. 1993), and adipose tissue and brain and liver autopsy samples (Dewailly et al. 1999). Rat studies regarding inhalation, oral, and parenteral exposure demonstrate that initial distribution is to the liver and kidney, followed by redistribution to body fat (Ambrose et al. 1953b; Balba and Saha 1978; Barnett and Dorough 1974; Dearth and Hites 1991b; Ewing et al. 1985; Khasawinah 1989; Nye and Dorough 1976; Ohno et al. 1986; Poonawalla and Korte 1971; Sasaki et al. 1992; Street and Blau 1972; Takeda et al. 1984). One oral study in mice demonstrated that chlordane is initially distributed to the muscles and that the *cis* isomer accumulates in tissues to a greater extent than the *trans* isomer (Satoh and Kikawa 1992). Additional dermal exposure studies would be useful for elucidating patterns of distribution by this route. Of particular interest would be studies of distribution to the central nervous system, since neurological effects are a consistent part of the clinical picture in humans exposed by any route. The ability of chlordane to cross the placenta and its presence in milk should also be investigated, because data show that prenatally exposed mice are more sensitive than adults to the immunological effects of chlordane (Barnett et al. 1985a, 1985b; Menna et al. 1985; Spyker-Cranmer et al. 1982). Determination of apparent volume of distribution and the extent of binding to tissue proteins may provide data that would be useful in the management of clinical cases of poisoning.

Human metabolism data are limited to *in vitro* studies (Kutz et al. 1976, 1979; Tashiro and Matsumura 1978). *In vivo* and *in vitro* animal studies, however, are sufficient to propose probable metabolic pathways (Balba and Saha 1978; Barnett and Dorough 1974; Brimfield et al. 1978; Nomeir and Hajjar 1987; Poonawalla and Korte 1964; Sasaki et al. 1992; Tashiro and Matsumura 1978). Further studies could be designed to estimate metabolic rate constants and to determine the levels at which saturation of specific pathways occurs with different routes of exposure.

Data from environmentally exposed humans suggest that substantial excretion occurs via lactation (Barnett et al. 1979; Strassman and Kutz 1977; Taguchi and Yakushiji 1988; WHO 1984). Data regarding acute poisoning in humans after acute oral exposure to chlordane indicate that most chlordane-derived material is excreted in the feces (Aldrich and Holmes 1969; Curley and Garrettson 1969; Olanoff et al. 1983). Studies involving intratracheal dosing of rats and acute, oral dosing of rats, mice, and rabbits confirm that fecal, probably biliary, excretion is more important than renal excretion (Barnett and Dorough 1974; Ewing et al. 1985; Tashiro and Matsumura 1977; Nye and Dorough 1976; Ohno et al. 1986). Additional animal studies might elucidate the relative importance of various routes of excretion following inhalation and dermal exposure, and might provide useful information regarding the rate and extent of excretion via lactation.

Comparative Toxicokinetics. Data in rats, mice, and rabbits following oral exposure to chlordane indicate that there are some species differences in absorption, distribution, and excretion (Balba and Saha 1978; Barnett and Dorough 1974; Ewing et al. 1985; Ohno et al. 1986; Poonawalla and Korte 1971; Satoh and Kikawa 1992). The available data on metabolites in human tissues and *in vitro* studies both indicate qualitatively that metabolism of chlordane in rats and humans is similar (Tashiro and Matsumura 1978). Analysis of the urine of humans with known exposure to chlordane (e.g., those living in previously treated houses) could provide a means of further studying the differences and similarities between animal species and humans and of monitoring humans for exposure. Additional studies could be designed to further evaluate the adequacy of using rats and/or mice as models for toxicokinetics of chlordane in humans.

Children's Susceptibility. Evidence in mice indicates that the fetus may be particularly susceptible to compromised immunocompetence due to altered stem cell populations of key immunoactive cells (Barnett et al. 1990a, 1990b). Infants may be unusually susceptible to a chronic seizure disorder following exposure to chlordane, particularly if they have a hereditary predisposition, such as a positive familial history of febrile convulsions (Bernad 1989). Since chlordane is no longer used as a pesticide,

the general population is not likely to be exposed to the chemical. However, if a population is identified with documented exposure to chlordane, it should be monitored for potential effects on the young.

Physical and Chemical Properties. The physical and chemical properties of chlordane listed in Table 4-2 are not complete. These properties are difficult to specify since the technical product is a mixture of over 140 compounds. The composition of technical chlordane varies according to conditions during its manufacture. In addition, properties of a mixture differ from the properties of the components. Even minor components can affect physical and chemical properties. Some of the properties reported in Table 4-2 are those of particular components such as *cis*- and *trans*-chlordane. The value for log K_{ow} listed in Table 4-2 is a particularly crude estimate for technical chlordane since this value was estimated for the chlordane structure. In addition, the values for water solubility of chlordane vary widely. This is probably due to differences in composition of the chlordane studied. Suntio et al. (1988) and Weil et al. (1974) did not indicate whether the chlordane used in their studies was technical grade or a mixture of chlordane isomers. Despite the limitations discussed above, the physical-chemical properties available for chlordane are adequate to estimate its partitioning in the environment. More significantly, there are numerous monitoring studies that have been performed over several decades that give us this information concerning chlordane's fate in the environment.

Production, Import/Export, Use, Release, and Disposal. Although the use of chlordane in the United States has been banned since April 1988, chlordane may be manufactured for export. Since chlordane is extremely persistent in the environment, knowledge of the former use pattern for this compound is useful in making estimations concerning potential for human exposure and sources of release. Environmental burdens of chlordane can be roughly estimated by relying on production and use data and by using a few basic assumptions. Production methods for chlordane are documented in the literature; however, recent production volumes are not available. A breakdown of the former uses of chlordane and its use pattern is available, which indicates that chlordane was widely used in the home, on food and nonfood crops, and on lawns and gardens. Disposal information is useful in determining environmental burden and potential concentrations where environmental exposures may be high. This type of information may be obtained by polling the manufacturer or other commercial organizations to determine methods of chlordane disposal. For example, asking exterminators how they disposed of contaminated materials or unused product may provide disposal information for much of the chlordane not directly applied to soils or dwellings. Current disposal practices are not known. Chlordane has been designated as a hazardous waste, and regulations guide the disposal of such waste. Chlordane is also regulated in effluent by provisions of the Clean Water Act.

Environmental Fate. Data are available to characterize the partitioning and transport of chlordane (Atallah et al. 1979; Atlas and Giam 1988; Beeman and Matsumura 1981; Bennett et al. 1974; Bidleman and Foreman 1987; Bidleman et al. 1986, 1987; Cotham and Bidleman 1991; Foreman and Bidleman 1987; Glotfelty and Schomburg 1989; Glotfelty et al. 1984; Gustafson 1989; Jury et al. 1987a; Lau et al. 1989; Oliver and Niimi 1985; Oloffs et al. 1972, 1973; Pacynba and Oehme 1988; Singh et al. 1991; Zaroogian et al. 1985). Monitoring studies demonstrate that chlordane is very persistent in soil, lasting over 20 years in some soils (Beeman and Matsumura 1981; Bennett et al. 1974; Harris and Sans 1976; Lichtenstein and Schulz 1959; Mullins et al. 1971; Nash and Woolson 1967; Stewart and Chisholm 1971; Stewart and Fox 1971; Szeto and Price 1991; Tafuri et al. 1977; Wiese and Basson 1966). However, chlordane's degradation products in soil have not been reported. More information would be useful on the transformation of chlordane in the environment. There are data needs regarding biodegradation and photolysis of chlordane in water systems and oxidation of this compound in air. Natural water grab sample biodegradation studies carried out under both aerobic and anaerobic conditions would be useful in establishing the biodegradation half-life of chlordane. A number of studies have been carried out that show chlordane is photolyzed in air; however, there is a lack of data pertaining to photolysis of chlordane that is adsorbed to particulate matter in air or in water and its significance for the removal of chlordane from these media. A photolysis study carried out under conditions simulating those found in the environment would be useful in establishing the significance of this reaction in air and natural waters. One of the dominant removal mechanisms for vapor phase chlordane in air is expected to be reaction with photochemically generated hydroxyl radicals; however, no experimental data are available concerning the kinetics of this reaction, the reaction pathway, or the products of these types of reactions. Photolysis, photooxidation, and biodegradation of particulate-bound chlordane is unknown. These types of data would be useful in understanding the fate of this compound in the environment.

Bioavailability from Environmental Media. Data are available that correlate length of exposure to atmospheric chlordane and levels of chlordane and/or metabolites in human blood and milk (Kawano and Tatsukawa 1982; Saito et al. 1986; Taguchi and Yakushiji 1988; Takamiya 1987). Similar data are not available for human exposure to chlordane in water or soil. A deficiency in the inhalation studies is that exposure concentrations have not been quantified. Therefore, it is not possible to correlate levels of chlordane and/or metabolites in human biosamples with specific concentrations in air, soil, or water. Studies in animals may provide valuable information regarding bioavailability and bioaccumulation of chlordane residues from air, water, and soil.

Food Chain Bioaccumulation. Chlordane has been found to bioconcentrate in marine and freshwater fish and shellfish, and biomagnify in animals that prey upon these fish. Available data indicate that organisms that have bioaccumulated chlordane are geographically distributed across the United States. This type of information is useful in determining how levels in the environment affect the food chain and potentially impact on human exposure levels.

Exposure Levels in Environmental Media. In general, the monitoring database for chlordane is not very broadly based or recent. Data for soils are especially out of date. Chlordane levels in soil and sediment are particularly important, as these are the repositories for chlordane, and broadly-based monitoring data in these media are the best way of assessing environmental trends. Reliable monitoring data for the levels of chlordane in contaminated media at hazardous waste sites are needed. Such information could be used in combination with the known body burden of chlordane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Estimates have been made for the human intake of chlordane from food, air, and water. Chlordane has been measured in adipose tissue, blood, serum, sebum, and seminal fluid. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Studies examining potential exposure sources for children would be useful because limited human and animal data provide suggestive evidence that the fetus and young child may be at increased susceptibility to chlordane toxicity (see Section 3.2).

Analytical Methods. Levels of various components of technical chlordane (principally *cis*- and *trans*-chlordane, *cis*- and *trans*-nonachlor) and its metabolites (principally oxychlordane) in body tissue and fluids are elevated in individuals exposed to chlordane. While analytical methods are available (Aldrich and Holmes 1969; Barquet et al. 1981; EPA 1977; Griffith and Blanke 1974; LeBel and Williams 1986; Mussalo-Rauhamaa 1991; Saito et al. 1985; Tojo et al. 1986; Wariishi et al. 1986) for the quantification of chlordane compounds and their metabolites in biological matrices, there are no data correlating these levels with environmental chlordane concentrations to which a person was exposed.

The levels of chlordane in different environmental media can be used to indicate exposure of humans to mixture compounds through the inhalation of air, ingestion of drinking water and foods, and exposure to soils containing chlordane. If a correlation with human tissue or body fluid levels is available, the intake levels from different environmental sources can be used to estimate the body burden of the chemical in

humans. Although the products of biotic and abiotic processes of chlordane in the environment are known, few systematic studies are available in which the concentrations of its reaction products were measured in the environment. In instances where products of an environmental reaction are more toxic than the parent compound, it is important that the level of the degradation products in the environment be known. Analytical methods for the determination of chlordane compounds and their degradation products in air, water, soil, sediment, and food are available, and these methods have good sensitivity and specificity. The methods for determining degradation products of chlordane compounds are similar to those for the parent compounds.

6.3 Ongoing Studies

A search of the National Institutes of Health (NIH) RePORTER (2017) revealed the following ongoing studies.

Dr. George E. Howell, in the Schools of Veterinary Medicine at Mississippi State University, is evaluating the effects of exposure to organochlorine pesticides (including chlordane) on hepatic lipid metabolism in Type 2 diabetes. The study is sponsored by the National Institute of Environmental Health Sciences.

Dr. Victoria W. Persky, in the Schools of Public Health at the University of Illinois at Chicago, is studying possible relationships between persistent organic pollutants (presumably including chlordane), endogenous hormones, and diabetes in Latinos. The study is sponsored by the National Institute of Environmental Health Sciences.

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Table 7-1. Regulations and Guidelines Applicable to Chlordane

Agency	Description	Information	Reference
	Air		
EPA	RfC	$7x10^{-4}$ mg/m^3 [a]	IRIS 2002
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water health advisories		EPA 2012
	1-Day (10-kg child)	0.06 mg/L	
	10-Day (10-kg child)	0.06 mg/L	
	DWEL	0.02 mg/L	
	Life-time	0.004 mg/L	
	mg/L at 10^{-4} cancer risk	0.01	
	National primary drinking water regulations		EPA 2009
	MCL	0.002 mg/L[b]	
	PHG	Zero	
	RfD	$5x10^{-4}$ mg/kg-day[c]	IRIS 2002
WHO	Drinking water quality guidelines		WHO 2017
	Guideline value	0.0002 mg/L (0.2 µg/L)[d,e]	
	PTDI	0.5 µg/kg body weight[f]	
FDA	EAFUS	No data	FDA 2013
	Allowable level in bottled water	0.002 mg/L	FDA 2016
	Cancer		
ACGIH	Carcinogenicity classification	A3[g,h]	ACGIH 2001, 2016
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	B2[i,j]	IRIS 2002
IARC	Carcinogenicity classification	Group 2B[k,l]	IARC 2001

Table 7-1. Regulations and Guidelines Applicable to Chlordane

Agency	Description	Information	Reference
	Occupational		
ACGIH	TLV	0.5 mg/m^3 [m]	ACGIH 2016
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	0.5 mg/m^3 [m]	OSHA 2016a, 2016b, 2016c
NIOSH	REL (up to 10-hour TWA)	0.5 mg/m^3 [m,n]	NIOSH 2016
	IDLH	100 mg/m^3 [n,o]	NIOSH 2014
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
AIHA	ERPGs	No data	AIHA 2015
DOE	PACs-air		DOE 2016a
	PAC-1[p]	4.5 mg/m^3	
	PAC-2[p]	50 mg/m^3	
	PAC-3[p]	500 mg/m^3	

[a]Based on hepatic effects in a rat subchronic inhalation study.
[b]Potential health effects from long-term exposure above the MCL: liver or nervous system problems; increased risk of cancer.
[c]Based on hepatic necrosis effects in a mouse 104-week oral study.
[d]Guideline value derivation based on allocation to water (1% of PTDI), weight (60 kg adult), and consumption (2L/day).
[e]Chlordane is listed under the Stockholm Convention on Persistent Organic Pollutants, so monitoring may occur in addition to that required by drinking water guidelines.
[f]Based on a NOAEL of 50 µg/kg-body weight/day for increased liver weights, serum bilirubin levels, and incidence of hepatocellular swelling, derived from a long-term dietary study in rats, and using an uncertainty factor of 100 (10 each for interspecies and intraspecies variation).
[g]A3: confirmed animal carcinogen with unknown relevance to humans.
[h]Based on liver cancer reported in mice fed chlordane in their diets.
[i]B2: probable human carcinogen.
[j]Based on sufficient evidence of carcinogenicity in animals.
[k]Group2B: possibly carcinogenic to humans.
[l]Based on inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of chlordane.
[m]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route.
[n]Potential occupational carcinogen.
[o]Based on acute oral toxicity data in humans and animals.
[p]Definitions of PAC terminology are available from the U.S. Department of Energy (DOE 2016a).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; 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; 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; PTDI = provisional tolerable daily intake; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

*ACGIH. 1991. Threshold limit values and biological exposure indices for 1988-1989. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 14.

*ACGIH. 2001. Chlordane. Documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. July 26, 2017.

*ACGIH. 2016. Chlordane. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. July 26, 2017.

*Adeshina F. 1989. Organochlorine compounds in human adipose tissue and carcinogenic risk: A case study of chlordane/heptachlor. Diss Abstr Int 49:5207B.

*Adeshina F, Todd EL. 1990. Organochlorine compounds in human adipose tissue from north Texas. J Toxicol Environ Health 29:147-156.

*Ahmed FE, Hart RW, Lewis NJ. 1977a. Pesticide induced DNA damage and its repair in cultured human cells. Mutat Res 42:161-174.

*Ahmed FE Lewis NJ, Hart RW. 1977b. Pesticide induced ouabain resistant mutants in Chinese hamster V-+9 cells. Chem Biol Interact 19:369-374.

*AIHA. 2015. Current ERPG Values (2015). Fairfax, VA: American Industrial Hygiene Association. https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2015%20ERPG%20Levels.pdf. March 22, 2016.

*Al-Hachim GM, Al-Baker A. 1973. Effects of chlordane on conditioned avoidance response, brain seizure threshold and open-field performance of prenatally-treated mice. Br J Pharmacol 49:311-315.

*Albers PH, Sileo L, Mulhem BM. 1986. Effects of environmental contaminants on snapping turtles of a tidal wetland. Arch Environ Contam Toxicol 15:39-49.

*Albrecht R, Manchon P. 1974. Environmental influence on the metabolism of exogenic materials in liver microsomes. Ann Nutr Aliment 28:351-363.

Albright L, Oloffs PC, Szeto SY. 1972. Fate and behavior of five chlorinated hydrocarbons in three natural waters. Can J Microbiol 18:1393-1398.

*Aldrich FD, Holmes JH. 1969. Acute chlordane intoxication in a child: Case report with toxicological data. Environ Health 19:129-132.

*Alford-Stevens AL, Eichelberger JW, Budde WL. 1988. Multi-laboratory study of automated determinations of polychlorinated biphenyls and chlorinated pesticides in water, soil, and sediment by gas chromatography/mass spectrometry. Environ Sci Technol 22:304-312.

*Al-Omar MA, Abbas AK, Al-Obaidy SA. 2000. Combined effect of exposure to lead and chlordane on the testicular tissues of swiss mice. Toxicol Lett 115(1):1-8.

*Alvarez, WC, Hyman S. 1953. Absence of toxic manifestations in workers exposed to chlordane. Arch Ind Hyg Occup Med 8:480-483.

*Ambrose AM, Christenson HC, Robbins DJ, et al. 1953a. Toxicological and pharmacological studies on chlordane. Arch Ind Hyg Occup Med 7:197-210.

*Ambrose AM, Christenson HC, Robbins DJ. 1953b. Pharmacological observations on chlordane [Abstract]. Fed Am Soc Exp Biol 12:298.

*Anderson DJ, Hites RA. 1988. Chlorinated pesticides in indoor air. Environ Sci Technol 22:717-720.

*Anderson DJ, Hites RA. 1989. Indoor air: Spatial variations of chlorinated pesticides. Atmos Environ 23:2063-2066.

*Anderson JF, Wojtas MA. 1986. Honey bees (Hymenoptera: Apidae) contaminated with pesticides and polychlorinated biphenyls. J Econ Entomol 79:1200-1205.

*Cited in text

*Anonymous. 1988. Chlordane. Rev Environ Contam Toxicol 104:47-62.
*Arnold DW, Kennedy Jr GL, Keplinger ML, et al. 1977. Dominant lethal studies with technical chlordane, HCS-3260, and heptachlor:heptachlor epoxide. J Toxicol Environ Health 2:547-555.
*Aronson KJ, Wilson JW, Hamel M, et al. 2010. Plasma organochlorine levels and prostate cancer risk. J Expo Sci Environ Epidemiol 20(5):434-445. 10.1038/jes.2009.33.
*Arruda JA, Cringan MS, Gilliland D, et al. 1987. Correspondence between urban areas and the concentrations of chlordane in fish from the Kansas River. Bull Environ Contam Toxicol 39:563-570.
*Asakawa F, Jitsunari F, Shiraishi H, et al. 1996. Accumulation of chlordanes in adipose tissues of mice caused by long-term exposure of low level technical chlordane. Bull Environ Contam Toxicol (6):909-916.
*Ashby J, Tennant RW. 1988. Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. Mutat Res 204:17-115.
*Atallah YH, Whitacre DM, Hoo BL. 1979. Comparative volatility of liquid and granular formulations of chlordane and heptachlor from soil. Bull Environ Contam Toxicol 22:570-574.
*Atkinson R. 1985. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Chem Rev 85:69-201.
*Atkinson R. 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. Int J Chem Kinet 19:799-828.
*Atlas E, Giam CS. 1988. Ambient concentrations and precipitation scavenging of atmospheric organic pollutants. Water Air Soil Pollut 38:19-36.
*Atlas E, Foster R, Giam CS. 1982. Air-sea exchange of high molecular weight organic pollutants: Laboratory studies. Environ Sci Technol 16:283-286.
*ATSDR. 1989a. Decision guide for identifying substance-specific data needs related to toxicological profiles. Atlanta, GA: Agency for Toxic Substances and Disease Registry. U.S. Department of Health and Human Services.
*ATSDR. 1989b. Health assessment for Velsicol Chemical Corporation NPL site, Marshall, Clark County, Illinois, Region 5. CERCLIS No. ILD000814673. Atlanta, GA: Agency for Toxic Substances and Disease Registry.
*ATSDR. 1992. 1989 and 1990 Biennial report. Atlanta, GA: Agency for Toxic Substances and Disease Registry.
*ATSDR. 2017. Chlordane. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/SPL/resources/index.html. October 6, 2017.
*Aulagnier F, Poissant L. 2005. Some pesticides occurrence in air and precipitation in Quebec, Canada. Environ Sci Technol 39(9):2960-2967.
*Aust SD. 1990. Degradation of environmental pollutants by *Phanerochaete chrysoporium*. Microb Ecol 20:197-209.
*Aust SD. 1992. Persistence of pesticide residues: Transport, fate and effects. Utah State University, Chemistry & Biochemistry, Logan, UT.
*Ault JA, Spurgeon TE. 1984. Multi-residue gas chromatographic method for determining organochlorine pesticides in poultry fat: Collaborative study. J Assoc Off Anal Chem 67:284-289.
*Ault JA, Spurgeon TE, Gillard DS, et al. 1985. Multi-residue gas chromatographic method for determining organochlorine pesticides in meats validation study for swine and beef fats. J Assoc Off Anal Chem 68:941-944.
*Azamoff DL. 1977. Insecticides: Effect on drug metabolism [Abstract]. Clin Pharmacol Ther 22:817-822.
*Bagchi D, Bagchi M, Hassoun EA, et al. 1995. *In vitro* and *in vivo* generation of reactive oxygen species, DNA damage and lactate dehydrogenase leakage by selected pesticides. Toxicology 104(1-3):129-140.

*Balash KJ, Al-Omar MA, Abdul Latif BM. 1987. Effect of chlordane on testicular tissues of Swiss mice. Bull Environ Contam Toxicol 39:434-442.

*Balba HM, Saha JG. 1978. Studies on the distribution, excretion, and metabolism of alpha and gamma isomers of (14^C) chlordane in rabbits. J Environ Sci Health 13:211-233.

*Balistreri WF, Partin JC, Schubert WK. 1973. Hepatic necrosis following accidental chlordane exposure [Abstract]. Pediatr Res 7:319.

*Barbehenn KR, Reichel WL. 1981. Organochlorine concentrations in bald eagles: Brain/body lipid relations and hazard evaluation. J Toxicol Environ Health 8:325-330.

*Barnes R. 1967. Poisoning by the insecticide chlordane. Med J Austr 54:972-973.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:47l-486.

*Barnett JR, Dorough HW. 1974. Metabolism of chlordane in rats. J Agric Food Chem 22:612-619.

*Barnett JB, Blaylock BL, Gandy J, et al. 1990a. Long-term alteration of adult bone marrow colony formation by prenatal chlordane exposure. Fundam Appl Toxicol 14:688-695.

*Barnett JB, Blaylock BL, Gandy J, et al. 1990b. Alteration of fetal liver colony formation by prenatal chlordane exposure. Fundam Appl Toxicol 15:820-822.

*Barnett RW, D'Ercole AJ, Cain JD, et al. 1979. Organochlorine pesticide residues in human milk samples from women living in north-west and north-east Mississippi, 1973-1975. Pestic Monit J 13:47-51.

*Barnett JB, Holcomb D, Menna JH, et al. 1985a. The effect of prenatal chlordane exposure on specific anti-influenza cell-mediated immunity. Toxicol Lett 25:229-238.

*Barnett JB, Soderberg LSF, Menna JH. 1985b. The effect of prenatal chlordane exposure on the delayed hypersensitivity response of Balb/c mice. Toxicol Lett 25:173-183.

*Barquet A, Morgade C, Pfaffenberger CD. 1981. Determination of organochlorine pesticides and metabolites in drinking water, human blood serum, and adipose tissue. J Toxicol Environ Health 7:469-479.

*Barrass N, Stewart M, Warburton S, et al. 1993. Cell proliferation in the liver and thyroid of C57Bl/10J mice after dietary administration of chlordane. Environ Health Perspect 101 Suppl 5:219-223.

Barril CR, Obillo MLA. 1979. Determination of organochlorine pesticide residues in milk by a rapid gas chromatographic methodology. Philippine Agriculturalist 62:296-308.

*Becker FF, Sell S. 1979. α-Fetoprotein levels and hepatic alterations during chemical carcinogenesis in C57BL/6N mice. Cancer Res 39:3491-3494.

*Beeman RW, Matsumura F. 1981. Metabolism of cis-and trans-chlordane by a soil microorganism. J Agric Food Chem 29:84-89.

*Ben-Dyke R, Sanderson DM, Noakes DN. 1970. Acute toxicity data for pesticides. Wildlife Review Pesticides Control 9:119.

*Bennett GW, Ballee EL, Hall RC, et al. 1974. Persistence and distribution of chlordane and dieldrin applied as termiticides. Bull Environ Contam Toxicol 11:64-69.

*Bernad PG. 1989. Review: EEG and pesticides. Clin Electroencephalogr 20:9-10.

*Bessi H, Rast C, Rether B, et al. 1995. Synergistic effects of chlordane and TPA in multistage morphological transformation of SHE cells. Carcinogenesis 16(2):237-244.

*Beyer WN, Kaiser TE. 1984. Organochlorine pesticide residues in moths from the Baltimore, MD, Washington, DC area. Environ Monit Assess 4:129-137.

Bhatnagar VK, Patel JS, Variya MR, et al. 1992. Levels of organochlorine insecticides in human blood from Abmedabad (rural), India. Bull Environ Contam Toxicol 48:302-307.

*Biberhofer J, Stevens RJJ. 1987. Organochlorine contaminants in ambient waters of Lake Ontario. Scientific Series - Canada, Inland Waters/Lands Directorate 159:1-11.

*Bidleman TF, Foreman WT. 1987. Vapor-particle partitioning of semivolatile organic compounds. Adv Chem Ser 216:27-56.

*Bidleman TF, Alegria H, Ngabe B, et al. 1998. Trends of chlordane and toxaphene in ambient air of Columbia, South Carolina. Atmos Environ 32(11):1849-1856.

8. REFERENCES

*Bidleman TF, Billings WN, Foreman WT. 1986. Vapor-particle partitioning of semivolatile organic compounds: Estimates from field collections. Environ Sci Technol 20:1038-1043.
*Bidleman TF, Wideqvist U, Jansson B, et al. 1987. Organochlorine pesticides and polychlorinated biphenyls in the atmosphere of southern Sweden. Atmos Environ 21:641-654.
*Bidleman TF, Cotham WE, Addison RF, et al. 1992. Organic contaminants in the northwest Atlantic atmosphere at Sable Island, Nova Scotia, 1988-1989. Chemosphere 24:1389-1412.
*Billings WN, Bidleman TF. 1980. Field comparison of polyurethane foam and tenax-GC resin for high-volume air sampling of chlorinated hydrocarbons. Environ Sci Technol 14:679-683.
*Billings WN, Bidleman TF. 1983. High volume collection of chlorinated hydrocarbons in urban air using 3 solid adsorbents. Atmos Environ 17:383-392.
*Biros FJ, Enos HF. 1973. Oxychlordane residues in human adipose tissue. Bull Environ Contam Toxicol 10:257-260.
*Blaylock BL, Soderberg LSF, Gandy J, et al. 1990a. Cytotoxic T-lymphocyte and NK responses in mice treated prenatally with chlordane. Toxicol Lett 51:41-49.
*Blevins BD, Sholes TE. 1978. Response of HeLa cells to selected pesticides and hallucinogens. Growth 42:478-485.
*Blus L, Cromartie E, McNease L, et al, 1979. Brown pelican: Population status, reproductive success, and organochlorine residues in Louisiana, 1971-1976. Bull Environ Contam Toxicol 22:128-135.
*Blus LJ, Pattee OH, Henny CJ, et al. 1983. First records of chlordane-related mortality in wild birds. J Wildl Manage 47:196-198.
*Blyler G, Landreth KS, Barnett JB. 1994. Gender-specific effects of prenatal chlordane exposure on myeloid cell development. Fundam Appl Toxicol 23(2):188-193.
*Boellstorff DE, Ohlendorf HM, Anderson DW, et al. 1985. Organochlorine chemical residues in white pelicans and western grebes from the Klamath Basin, California. Arch Environ Contam Toxicol 14:485-493.
*Bondy GS, Newsome WH, Armstrong CL, et al. 2000. *trans*-Nonachlor and *cis*-nonachlor toxicity in Sprague-Dawley rats: Comparison with technical chlordane. Toxicol Sci 58(2):386-398.
*Bordet F, Mallet J, Borrel S, et al. 1993. Organochlorine pesticide and PCB congener content of French human milk. Bull Environ Contam Toxicol 50:425-32.
*Borgmann U, Whittle DM. 1991. Contaminant concentration trends in Lake Ontario lake trout (*Salvelinus-namuycush*)- 1977 to 1988. J Great Lakes Res 17:368-381.
*Boyd EM, Taylor FI. 1969. The acute oral toxicity of chlordane in albino rats. Ind Med Surg 38:42-49.
*Brandt WN, Flamm WG, Bemheim NJ. 1972. The value of hydroxyurea in assessing repair synthesis of DNA in HeLa cells. Chem Biol Interact 5:327-339.
*Brimfield AA, Street JC. 1981. Microsomal activation of chlordane isomers to derivatives that irreversibly interact with cellular macromolecules. J Toxicol Environ Health 7:193-206.
*Brimfield AA, Street JC, Futrell J, et al. 1978. Identification of products arising from the metabolism of cis-and trans-chlordane in rat liver microsomes *in vitro*: Outline of a possible metabolic pathway. Pestic Biochem Physiol 9:84-95.
*Brock JW, Melnyk LJ, Caudill SP, et al. 1998. Serum levels of several organochlorine pesticides in farmers correspond with dietary exposure and local use history. Toxicol Ind Health 14(1-2):275-289. 10.1177/074823379801400117.
*Brodtmann Jr NV. 1976. Continuous analysis of chlorinated hydrocarbon pesticides in the lower Mississippi River. Bull Environ Contam Toxicol 15:33-39.
*Brown DP. 1992. Mortality of workers employed at organochlorine pesticide manufacturing plants: An update. Scand J Work Environ Health 18:155-161.
*Buchert H, Class T, Ballschmiter, K. 1989. High-resolution gas chromatography of technical chlordane with electron-capture and mass-selective detection. Fresenius J Anal Chem 333:211-217.
*Bunck CM, Prouty RM, Krynitsky AJ. 1987. Residues of organochlorine pesticides and polychlorobiphenyls in starlings (*Sturnus vulgaris*) from the continental USA, 1982. Environ Monit Assess 8:59-76.

8. REFERENCES

*Buser HR, Muller MD, Rappe C. 1992. Enantioselective determination of chlordane components using chiral high-resolution gas chromatography-mass spectrometry with application to environmental samples. Environ Sci Technol 26:1533-1540.

*Cahill WP, Stumphy MK, and Raltech Scientific Services, Inc. 1979. Applicator and inhabitant exposure to chlordane during and after termiticide applications in California. Velsicol Chemical Corporation.

*Callahan CA, Menzie CA, Burmaster DE, et al. 1991. On-site methods for assessing chemical impact on the soil environment using earthworms: A case study at the Baird and McGuire Superfund site, Holbrook, MA. Environ Toxicol Chem 10:817-826.

*Camanzo J, Rice CP, Jude DJ, et al. 1987. Organic priority pollutants in nearshore fish from 14 Lake Michigan tributaries and embayments, 1983. J Great Lakes Res 13:296-309.

*Campbell MA, Gyorkos J, Leece B, et al. 1983. The effects of twenty-two organochlorine pesticides as inducers of the hepatic drug-metabolizing enzymes. Gen Pharmacol 14:445-454.

*Cantor KP Blair A, Everett G, et al. 1992. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res 52:2447-2455.

*Cantor KP, Strickland PT, Brock JW, et al. 2003. Risk of non-Hodgkin's lymphoma and prediagnostic serum organochlorines: β-hexachlorocyclohexane, chlordane/heptachlor-related compounds, dieldrin, and hexachlorobenzene. Environ Health Perspect 111(2):179-183.

*Carey AE, Douglas P, Tai H, et al. 1979a. Pesticide residue concentrations in soils of five United States cities, 1971. Pestic Monit J 13:17-22.

*Carey AE, Gowen JA, Tai H, 1978. Pesticide residue levels in soils and crops, 1971 - National Soils Monitoring Program (III). Pestic Monit J 12:117-136.

*Carey AE, Gowen JA, Tai H, et al. 1979b. Pesticide residue levels in soils and crops from 37 States, 1972 - National Soils Monitoring Program (IV). Pestic Monit J 12:209-229.

*Carey AE Wiersma GB, Tai H, et al. 1973. Pesticides in soil. Organochlorine pesticide residues in soils and crops of the corn belt region, United States, 1970. Pestic Monit J 6:369-376.

*Carter FL, Stringer CA. 1971. Soil persistence of termite insecticides. Pestic Contr 39:13, 14, 16, 18, 20, 22.

*CAS. 1987. Chemical Abstracts Vol. 107 Chemical Substance Index, Bi-D July-December, 1987. Columbus, OH: Chemical Abstract Service.

*CAS. 1988. CAS Registry File. Chemical Abstract Service, Columbus, OH. August, 1988.

*CAS. 1992. Chemical Abstracts Service, Columbus, Oh. March 24, 1992.

*Cassidy RA, Hastings L, Vorhees CV. 1992. Effects of chronic pre- and postnatal chlordane exposure, food deprivation and caffeine on neurobehavioral indices in the rat [Abstract]. Teratology 45:535.

*Cassidy RA, Vorhees CV, Minnema DJ, et al. 1994. The effects of chlordane exposure during pre- and postnatal periods at environmentally relevant levels on sex steroid-mediated behaviors and functions in the rat. Toxicol Appl Pharmacol 126(2):326-337. 10.1006/taap.1994.1123.

*Casterline JL, Williams CH. 1971. The effects of 28-day pesticide feeding on serum and tissue enzyme activities of rats fed diets of varying casein content. Toxicol Appl Pharmacol 18:607-618.

*CDC. 1976. Chlordane contamination of a municipal water system -Tennessee. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control. Morbidity and Mortality Weekly Report 25:117.

*CDC. 1981. Chlordane contamination of a public water supply-Pittsburgh, Pennsylvania. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control. Morbidity and Mortality Weekly Report 30:571-572.

*CDC. 2009. Fourth national report on human exposure to environmental chemicals. Atlanta, GA: Centers for Disease Control and Prevention, Department of Health and Human Services. http://www.cdc.gov/exposurereport. August 28, 2017.

*CDC. 2017. Fourth national report on human exposure to environmental chemicals. Updated tables, January 2017, Volume two. Atlanta, GA: Centers for Disease Control and Prevention, Department of Health and Human Services. https://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Volume2_Jan2017.pdf. August 28, 2017.

*CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary and immune systems. Atlanta, GA: CDC/ATSDR Subcommittee on Biomarkers of Organ Damage and Dysfunction, Centers for Disease Control, Agency for Toxic Substances and Disease Registry. Summary report, August 27, 1990.

*CELDS. 1992. Computer-Aided Environmental Legislative Data System. University of Illinois, Urbano. March 1992.

*Chadwick RW, Chadwick CJ, Freal JJ, et al. 1977. Comparative enzyme induction and lindane metabolism in rats pre-treated with various organochlorine pesticides. Xenobiotica 7:235-246.

*Chambers C, Dutta SK. 1976. Mutagenic tests of chlordane on different microbial tester strains [Abstract]. Genetics 3:13.

*Chan CH, Perkins LH. 1989. Monitoring of trace organic contaminants in atmospheric precipitation. J Great Lakes Res 15:465-475.

*Chernoff N, Kavlock RJ. 1982. An *in vivo* teratology screen utilizing pregnant mice. J Toxicol Environ Health lo:541-550.

*Chuang LF, Liu Y, Killam K Jr, et al. 1992. Modulation by the insecticides heptachlor and chlordane of the cell-mediated immune proliferative responses of Rhesus monkeys. In vivo 6:29-32.

*Clark Jr DR, Krynitsky AJ. 1985. DDE residues and artificial incubation of loggerhead sea turtle eggs. Bull Environ Contam Toxicol 34:121-125.

*Clark Jr DR, Lamont TG. 1976. Organochlorine residues in females and nursing young of the big brown bat (*Eptesicusfuscus*). Bull Environ Contam Toxicol 15:1-8.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Cohen SZ, Nickerson S, Maxey R, et al. 1990. A ground water monitoring study for pesticides and nitrates associated with golf courses on Cape Cod. Ground Water Monit Rev 10:160-173.

*Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. J Water Pollut Control Fed 56:898-908.

*Colt JS, Davis S, Severson RK, et al. 2006. Residential insecticide use and risk of non-Hodgkin's lymphoma. Cancer Epidemiol Biomarkers Prev 15(2):251-257. 10.1158/1055-9965.epi-05-0556.

*Cook MB, Trabert B, McGlynn KA. 2011. Organochlorine compounds and testicular dysgenesis syndrome: Human data. Int J Androl 34(4 Pt 2):e68-84; discussion e84-65. 10.1111/j.1365-2605.2011.01171.x.

*Corneliussen PE. 1970. Residues in food and feed. Pesticide residues in total diet samples. V. Pestic Monit J 4:89-105.

*Corneliussen PE. 1972. Residues in food and feed: Pesticide residues in total diet samples. VI. Pestic Monit J 5:313-330.

*Cortes DR, Basu I, Sweet CW, et al. 1998. Temporal trends in gas-phase concentrations of chlorinated pesticides measured at the shores of the Great lakes. Environ Sci Technol 32:1920-1927.

*Cotham Jr WE, Bidelman TF. 1991. Estimating the atmospheric deposition of organochlorine contaminants to the Arctic. Chemosphere 22:165-188.

*Cox S, Niskar AS, Narayan KM, et al. 2007. Prevalence of self-reported diabetes and exposure to organochlorine pesticides among Mexican Americans: Hispanic Health and Nutrition Examination Survey, 1982-1984. Environ Health Perspect 115(12):1747-1752. 10.1289/ehp.10258.

*Cram RL, Juchau MR, Fouts JR. 1956. Stimulation by chlordane of hepatic drug metabolism in the squirrel monkey. J Lab Clin Med 66:906-911.

*Cranmer JM, Cranmer MF, Goad PT. 1984. Prenatal chlordane exposure: Effects on plasma corticosterone concentrations over the lifespan of mice. Environ Res 35:204-210.

*Cueto Jr C, Biros FJ. 1967. Chlorinated insecticides and related materials in human urine. Toxicol Appl Pharmacol 1:261-269.

*Curley A, Garrettson LK. 1969. Acute chlordane poisoning. Clinical and chemical studies. Arch Environ Health 18:211-215.

*Dadey JL, Kammer AG. 1953. Chlordane intoxication. J Am Med Assoc 153:723.

*Dai K-S, Hasan ZA, Woolley DE. 1989. Effects of RO-5-4864 and chlordane on limbic evoked potentials in the freely behaving female rat [Abstract]. Society for Neuroscience 15:669.

*Datta KK, Gupta PC, Dikshith TSS. 1977. Effect of chlordane on the skin of male guinea pigs. In: Zaida SH, ed. Environmental pollution and human health. Lucknow, India: Industrial Toxicology Research Centre, 608-611.

*Dearth MA, Hites RA. 1991a. Chlordane accumulation in people. Environ Sci Technol 25:1279-1285.

*Dearth MA, Hites RA. 1991b. Depuration rates of chlordane compounds from rat fat. Environ Sci Technol 25:1125-1128.

*Dearth MA, Hites RA. 1991c. Complete analysis of technical chlordane using negative ionization mass spectrometry. Environ Sci Technol 25:245-254.

*Deichmann WB, Keplinger ML. 1970. Protection against the acute effects of certain pesticides by pretreatment with aldrin, dieldrin and DDT. Toxicol Occup Med 6:121-123.

*Delaplane KS, LaFage JP. 1990. Variable chlordane residues in soil surrounding house foundations in Louisiana, USA. Bull Environ Contam Toxicol 45:675-680.

*Demers A, Ayotte P, Brisson J, et al. 2000. Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Cancer Epidemiol Biomarkers Prev 9(2):161-166.

*Den Tonkelaar EM, Van Esch GJ. 1974. No-effect levels of organochlorine pesticides based on induction of microsomal liver enzymes in short-term toxicity experiments. Toxicology 2:371-380.

*Derbes VJ, Dent JH, Forrest W, et al. 1955. Fatal chlordane poisoning. J Am Med Assoc 158:1367-1369.

*Dewailly E, Mulvad G, Pedersen HS, et al. 1999. Concentration of organochlorines in human brain, liver, and adipose tissue autopsy samples from Greenland. Environ Health Perspect 107(10):823-828.

*Ditraglia D, Brown DP, Namekata T, et al. 1981. Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand J Work Environ Health 7:140-146.

*DOE. 2016a. Table 3: Protective Action Criteria (PAC) Rev. 29 based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. May 2016. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/teel/Revision_29_Table3.pdf. February 28, 2017.

*DOE. 2016b. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29 for Chemicals of Concern - May 2016. Oak Ridge, TN: U.S. Department of Energy. https://energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-29-chemicals-concern-may-2016. February 28, 2017.

*Dougherty RCMJ, Whitaker LM, Smith LM, et al. 1980. Negative chemical ionization studies of human and food chain contamination with xenobiotic chemicals. Environ Health Perspect 36:103-l18.

*Dowd PF, Mayfield GU, Coulon DP, et al. 1985. Organochlorine residues in animals from three Louisiana watersheds in 1978 and 1979. Bull Environ Contam Toxicol 34:832-841.

*Dragun J. 1991. Geochemistry and soil chemistry reactions occurring during *in situ* vitrification. J Hazard Mater 26:343-364.

*Drummond L, Chetty KN, Desaiah D. 1983. Changes in brain ATPases in rats fed on chlordane mixed with iron-sufficient and deficient diet. Drug Chem Toxicol 6:259-266.

Duggan RE, Barry HC, Johnson LY. 1966. Pesticide residues in total-diet samples. Science 151:101-104.

*Duggan RE, Barry HC, Johnson LY. 1967. Residues in food and feed. Pesticide residues in total diet samples. II. Pestic Monit J 1:2-12.

*Duggan RE, Corneliussen PE, Duggan MB, et al. 1983. Pesticide residue levels in foods in the United States from July 1, 1969 to June 30, 1976. Washington, DC: Food and Drug Administration, Division of Chemical Technology.

*Eichelberger JW, Lichtenberg JJ. 1971. Persistence of pesticides in river water. Environ Sci Technol 5:541-544.

*Eichelberger JW, Kerns EH, Olynyx P, et al. 1983. Precision and accuracy in the determination of organics in water by fused silica capillary column gas chromatography/mass spectrometry and packed column gas chromatography/mass spectrometry. Anal Chem 55:1471-1479.

*Eisenberg M, Topping JJ. 1985. Organochlorine residues in finfish from Maryland Waters, 1976-1980. J Environ Sci Health B 20:729-742.

*Elder JF, Mattraw HC. 1984. Accumulation of trace elements, pesticides, and polychlorinated biphenyls in sediments and the clam *Corbiculu manilensis* of the Apalachicola River, Florida. Environ Contam Toxicol 13:453-469.

*Elia VJ, Clark CS, Majeti VA, et al. 1983. Hazardous chemical exposure at a municipal wastewater treatment plant. Environ Res 32:360-371.

*Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier Press, 1078-1080.

*EPA. 1977. Manual of analytical methods for the analysis of pesticide residues in human and environmental samples. Revisions by the Association of Official Analytical Chemists. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division.

*EPA. 1978. OPP-68004; FRL 871-3. Consolidated heptachlor/chlordane cancellation proceedings, Velsicol Chemical Co., et al. Fed Regist 43:12372-12379.

*EPA. 1980a. Summary of reported pesticide incidents involving chlordane. Pesticide Incident Monitoring System Report No. 360. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs.

*EPA. 1980b. Ambient water quality criteria for chlordane. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. PB81117384.

*EPA. 1982a. Test methods for organic chemical analysis of municipal and industrial wastewater. Method No. S608 and S625. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory.

*EPA. 1982b. U.S. Environmental Protection Agency. Code of Federal Regulations (CFR), 40CFR261.32, 261.33. July 1, 1982.

*EPA. 1982c. Safe methods for estimating solid wastes. Method 8080, SW-846. U.S. Environmental Protection Agency.

*EPA. 1983. Analysis of the risks and benefits of seven chemicals used for subterranean termite control. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

*EPA. 1984. Analytical reference standards and supplemental data: The pesticides and industrial chemicals repository. Las Vegas, NV: U.S. Environmental Protection Agency, Office of Research and Development. EPA6001484082.

*EPA. 1985a. Memorandum. 6(a)(2) Data on chlordane. Chronic mouse and rat studies for oncogenicity testing. Act. Nos. 252267, 254665, 251815, Review No. 004635. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

*EPA. 1985b. Exposure Analysis Modeling System: Reference Manual for EXAMS II. EPA600385038. Environ Res Lab, Athens, GA.

*EPA. 1986a. Test methods for evaluating solid wastes. SW-846, Method no. 8080, Volume 1B: Laboratory manual: Physical/chemical methods, 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1986b. Graphical Exposure Modeling System (GEMS). CLOGP Computer Program, Version PC 1,2, August 1, 1986.

*EPA. 1986c. Carcinogenicity assessment of chlordane and heptachlor, heptachlor epoxide. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. PB87208757.

*EPA. 1986d. Guidance for the reregistration of pesticide products containing chlordane as the active ingredient. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. PB87175816.

*EPA. 1987a. U.S. EPA contract laboratory program. Statement of work for organic analysis. Washington, DC: U.S. Environmental Protection Agency.

*EPA. 1987b. OPP-60011; FRL-3286-8. Chlordane and heptachlor termiticides; cancellation order. Fed Regist 52:42145-42149.

*EPA. 1987c. 40 CFR Parts 117 and 302. Reportable quantity adjustments. Proposed rule. Fed Regist 52:8140-8151.

*EPA. 1987d. 40 CFR Parts 300 and 355. Extremely hazardous substances list and threshold planning quantities; emergency planning and release notification requirements. Final Rule. Fed Regist 52:13378-13410.

*EPA. 1987e. Drinking water criteria document for heptachlor, heptachlor epoxide, and chlordane. Final. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Drinking Water.

*EPA. 1987f. Memorandum. Transmittal of 90-day chlordane inhalation study conducted in rats and monkeys. Act. No. 254322. Review No. 006331. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

*EPA. 1987g. Chlordane, heptachlor, aldrin, and dieldrin technical support document (Draft). July 1987. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs and Office of Pesticides and Toxic Substances.

*EPA. 1988a. Analysis of clean water act effluent guidelines pollutants. Summary of the chemicals regulated by Industrial Point Source Category. 40 CFR Parts 400-475. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards.

*EPA. 1988b. Memorandum. Review of pathology working group slide reevaluation of livers of rats in a 30-month oral exposure to chlordane. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

*EPA 1988c. Chlordane/heptachlor termiticides; notification of cancellation and amendment of existing stocks determination. Fed Regist 53:11798-l 1805.

*EPA. 1988d. Determination of chlordane in soil by enzyme immunoassay. U.S. Environmental Protection Agency. EPA6OOD89.

*EPA. 1990a. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency. EPA600890066A.

*EPA. 1990b. Nonoccupational Pesticide Exposure Study (NOPES). Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600390003. PB90152224.

*EPA. 1991. Burning of hazardous waste in boilers and industrial furnaces. Fed Regist 56:7134-7239.

*EPA. 1993. Standards for the use and disposal of sewage sludge. Fed Regist 58:9248-9415.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA 816-F-09-0004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. February 28, 2017.

*EPA. 2012. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA 822-S-12-001. https://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf. February 28, 2017.

*EPA. 2016. Acute Exposure Guideline Levels (AEGLs) Values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2016-03/documents/compiled_aegl_update_.pdf. July 26, 2017.

*Epstein SS. 1976. Carcinogenicity of heptachlor and chlordane. Sci Total Environ 6:103-154.

*Epstein SS, Ozonoff D. 1987. Leukemias and blood dyscrasias following exposure to chlordane and heptachlor. Teratogen Carcinogen Mutagen 7:527-540.

*Epstein SS, Arnold E, Andrea J, et al. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol Appl Pharmacol 23:288-325.

*Ercegovich CD, Rashid KA. 1977. Mutagenesis induced in mutant strains of *Salmonella typhimurium* by pesticides [Abstract]. Am Chem Soc 174:43.

Erstfeld KM, Simmons MS, Atallah TH. 1989. Determination of chlordane in laboratory-generated environmental fate samples. Int J Environ Anal Chem 37:119-211.

*Everett CJ, Matheson EM. 2010. Biomarkers of pesticide exposure and diabetes in the 1999-2004 National Health and Nutrition Examination Survey. Environ Int 36(4):398-401. 10.1016/j.envint.2010.02.010.

*Ewing AD, Kadry AM, Dorough HW. 1985. Comparative disposition and elimination of chlordane in rats and mice. Toxicol Lett 26:233-239.

*Fabacher DL, Kulkarni AP, Hodgson E. 1980. Pesticides as inducers of hepatic drug-metabolizing enzymes. I. Mixed function oxidase activity. Gen Pharmacol 11:429-435.

*Falck F, Ricci A, Wolff MS, et al. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Environ Health 47:143-146.

*FAO/WHO. 1973. 1972 Evaluations of some pesticide residues in food. Rome: Food and Agriculture Organization of the United Nations. (Cited in WHO 1984)

*FAO/WHO. 1978. 1977 Evaluations of some pesticide residues in food. Rome: Food and Agriculture Organization of the United Nations. (Cited in WHO 1984)

*FDA. 1989a. Food and Drug Administration. Pesticide program - residues in foods - 1988. J Assoc Off Anal Chem 72:133A-152A.

*FDA. 1989b. Chlordane. Compliance policy guide 7141.01. U.S. Food and Drug Administration, Washington, DC.

*FDA. 1990. Food and Drug Administration. Pesticide program - residues in foods - 1989. J Assoc Off Anal Chem 73:127A-146A.

*FDA. 1991. Food and Drug Administration. Pesticide program - residues in foods - 1990. J Assoc Off Anal Chem 74:121A-141A.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. February 28, 2017.

*FDA. 2016. Subpart B - Requirements for specific standardized beverages. Section 165.110 - Bottled water. Food and Drug Administration. Code of Federal Regulations 21 CFR 165.110 https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol2/pdf/CFR-2016-title21-vol2-sec165-110.pdf. July 26, 2017.

*Fendinger NJ, Glotfelty DE, Freeman HP. 1989. Comparison of two experimental techniques for determining air/water Henry's law constants. Environ Sci Technol 23:1528-1531.

*Fenske RA, Sternbach T. 1987. Indoor air levels of chlordane in residences in New Jersey. Bull Environ Contam Toxicol 39:903-910.

*Fenster L, Eskenazi B, Anderson M, et al. 2006. Association of *in utero* organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ Health Perspect 114(4):597-602.

*Feroz M, Kagan J, Ramesh S, et al. 1981. Photolysis of *cis*-chlordane: Identification of two isomers of *cis*-photochlordane. J Agric Food Chem 29:272-276.

*Fishbein WI, White JV, Isaacs HJ. 1964. Survey of workers exposed to chlordane. Ind Med Surg 10:726-727.

*Fishman BE, Gianutsos G. 1985. Inhibition of 4-aminobutyric acid (GABA) turnover by chlordane. Toxicol Lett 26:219-223.

*Foreman WT, Bidleman TF. 1987. An experimental system for investigating vapor-particle partitioning of trace organic pollutants. Environ Sci Technol 21:869-875.

*Foreman WT, Bidleman TF. 1990. Semivolatile organic compounds in the ambient air of Denver, Colorado. Atmos Environ, 24A:2405-2416.

*Frank R, Braun HE, Stonefield KI, et al. 1990. Organochlorine and organophosphorus residues in the fat of domestic farm animal species, Ontario, Canada 1986-1988. Food Addit Contam 7:629-636.

*Fricke C, Clarkson C, Lomnitz E, et al. 1985. Comparing priority pollutants in municipal sludges. BioCycle 26:35-37.

*Frings H, O'Tousa JE. 1950. Toxicity to mice of chlordane vapor and solutions administered cutaneously. Science 111:658-660.

*Gaines TB. 1960. The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol 2:88-90.

*Gak JC, Graillot C, Truhaur R. 1976. Use of the golden hamster in toxicology. Lab Anim Sci 26(2), Part II:274-280.

*Gammon MD, Wolff MS, Neugut AI, et al. 2002. Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. Cancer Epidemiol Biomarkers Prev 11(8):686-697.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1985a. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1979-September 1980. J Assoc Off Anal Chem 68:1184-1197.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1985b. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1979-September 1980. J Assoc Off Anal Chem 68:1163-l183.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1985c. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1978-September 1979. J Assoc Off Anal Chem 68:862-875.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1985d. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1978-September 1979. J Assoc Off Anal Chem 68:842-861.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986a. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69:146-161.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986b. Chemical contaminants monitoring. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69:123-145.

*Gauthier M, Girard D. 2001. Activation of human neutrophils by chlordane: Induction of superoxide production and phagocytosis but not chemotaxis or apoptosis. Hum Exp Toxicol 20(5):229-235. 10.1191/096032701678227695.

*Gentile JM, Gentile GJ, Bultman J, et al. 1982. An evaluation of the genotoxic properties of insecticides following plant and animal activation. Mutat Res 101:19-29.

*Gilliom RJ. 1984. Pesticides in rivers of the United States. National Water Summary 1984 - Water Quality Issues, Hydrologic Perspectives, 85-92.

*Gladen BC, Shkiryak-Nyzhnyk ZA, Chyslovska N, et al. 2003. Persistent organochlorine compounds and birth weight. Ann Epidemiol 13(3):151-157

*Glotfehy DE, Schomburg CJ. 1989. Volatilization of pesticides from soil. In: Reactions and movement of organic chemicals in soils. Soil Science Society of America and American Society of Agronomy. SSSA Special Publication 22, 181-207.

*Glotfelty DE, Taylor AW, Turner BC, et al. 1984. Volatilization of surface-applied pesticides from fallow soil. J Agric Food Chem 32:638-644.

*Glynn AW, Michaelsson K, Lind PM, et al. 2000. Organochlorines and bone mineral density in Swedish men from the general population. Osteoporosis Int 11(12):1036-1042. 10.1007/s001980070025.

*Gobas FAPC, Muir DCG, Mackay D. 1988. Dynamics of dietary bioaccumulation and faecal elimination of hydrophobic organic chemicals in fish. Chemosphere 17:943-962.

*Goldberg MC. 1982. A method of calculating the pesticide partition between sediment and water for environmental systems. Sci Total Environ 24:73-84.

Gowen JA, Wiersma GB, Tai H, et al. 1976. Pesticide levels in hay and soils from nine states. Pestic Monit J 10:114-l16.

*Griffin DE, Hill WE. 1978. *In vitro* breakage of plasmid DNA by mutagens and pesticides. Mutat Res 52:161-169.

*Griffith FD, Blanke RV. 1974. Microcoulometric determination of organochlorine pesticides in human blood. J Assoc Off Anal Chem 57:595-603.

*Grimes GJ, Morrison SM. 1975. Bacterial bioconcentration of chlorinated hydrocarbon insecticides from aqueous systems. Microbial Ecol 2:43-59.

*Grutsch JF, Khasawinah A. 1991. Signs and mechanisms of chlordane intoxication. Biomed Environ Sci 4:317-326.

*Gunderson EL. 1988. FDA total diet study April 1982- April 1984, dietary intakes of pesticides, selected elements, and other chemicals. J Assoc Off Anal Chem 71:1200-1209.

*Gustafson DI. 1989. Groundwater ubiquity score: A simple method for assessing pesticide leachability. Environ Toxicol Chem 8:339-357.

*Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: WB Saunders Co., 1084-1085.

*Hall RJ, Kaiser TE, Robertson Jr WB, et al. 1979. Organochlorine residues in eggs of the endangered American crocodile (*Crocodylus acutus*). Bull Environ Contam Toxicol 23:87-90.

*Haque R, Freed VH. 1974. Behavior of pesticides in the environment: Environmental chemodynamics. Res Rev 52:89-l16.

Harbison RD. 1975. Comparative toxicity of some selected pesticides in neonatal and adult rats. Toxicol Appl Pharmacol 32:443-446.

*Hardell L, Andersson SO, Carlberg M, et al. 2006. Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. J Occup Environ Med 48(7):700-707. 10.1097/01.jom.0000205989.46603.43.

*Hardell L, Carlberg M, Hardell K, et al. 2007. Decreased survival in pancreatic cancer patients with high concentrations of organochlorines in adipose tissue. Biomed Pharmacother 61(10):659-664. 10.1016/j.biopha.2007.04.006.

*Hardell L, Liljegren G, Lindstrom G, et al. 1996. Increased concentrations of chlordane in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. Int J Oncol 9(6):1139-1142.

*Hardell L, van Bavel B, Lindstrom G, et al. 2003. Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. Environ Health Perspect 111(7):930-934.

*Hardell L, van Bavel B, Lindstrom G, et al. 2005. *In utero* exposure to persistent organic pollutants in relation to testicular cancer risk. Int J Androl 29:228-234.

*Hargrave BT, Harding GC, Vass WP, et al. 1992. Organochlorine pesticides and polychlorinated biphenyls in the Arctic Ocean food web. Arch of Environ Contam Toxicol 22:41-54.

*Harrington JM, Baker Jr EL, Folland DS, et al. 1978. Chlordane contamination of a municipal water system. Environ Res 15:155-159.

*Harris CR, Sans WW. 1976. Persistence of Velsicol HCS-3260 (Ag-Chlordane) in mineral and organic soil. Proceedings of the Entomological Society of Ontario 106:34-38.

*Hart LG, Shultice RW, Fouts JR. 1963. Stimulatory effects of chlordane on hepatic microsomal drug metabolism in the rat. Toxicol Appl Pharmacol 5:371-386.

*Hartley D, Kidd H, eds. 1983. The agrochemicals handbook. United Kingdom: The Royal Society of Chemistry.

*Hasan Z, Woolley D, Dai K-S, et al. 1989. Chlordane alters limbic evoked potentials [Abstract]. Proceedings of the Society of Toxicology, 28th Annual Meeting. Atlanta, GA. February 27, 1989-March 3, 1989.

*Hassoun E, Baggchi M, Bagchi D, et al. 1993. Comparative studies on lipid peroxidation and DNA-single strand breaks induced by lindane, DDT, chlordane and endrin in rats. Comp Biochem Physiol C Comp Pharmacol Toxicol 104(3):427-431.

*Hawley GG. 1981. The condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co., 229.

*Heinz GH, Swineford DM, Katsma DE. 1984. High PCB residues in birds from the Sheboygan River, Wisconsin. Environ Monit Assess 4:155-161.

*Hernandez HF, Lopez BFJ, Medina EJ, et al. 1987. Sulfuric acid cleanup and potassium hydroxide ethanol treatment for confirmation of organochlorine pesticides and polychlorinated biphenyls: Application to wastewater samples. J Assoc Off Anal Chem 70:727-733.

*Hinckley DA, Bidleman TF. 1991. Atmospheric organochlorine pollutants and air-sea exchange of hexachlorocyclohexane in the Bering and Chukchi Seas. J Geophys Res 96:7201-7213.

*Hinman ML, Klaine SJ. 1992. Uptake and translocation of selected organic pesticides by rooted aquatic plant *Hydrilh verticillatu* Royle. Environ Sci Technol 26:609-613.

*Hirasawa F, Takizawa Y. 1989. Accumulation and declination of chlordane congeners in mice. Toxicol Lett 47:109-117.

*Hirai Y, Tomokuni K. 1991a. Levels of chlordane, oxychlordane and nonachlor in human adipose tissues. Bull Environ Contam Toxicol 47:173-176.

*Hirai Y, Tomokuni K. 1991b. Levels of chlordane oxychlordane and nonachlor in human blood. Bull Environ Contam Toxicol 46:670-676.

*Hirai Y, Tomokuni K. 1993. Levels of chlordane, oxychlordane, and nonachlor on human skin and in human blood. Bull Environ Contam Toxicol 50:316-324.

*Hirano T, Ishida T, Oh K, et al. 2007. Biodegradation of chlordane and hexachlorobenzenes in river sediment. Chemosphere 67(3):428-434.

*Hodgson E, Kulkami AP, Fabacher DL, et al. 1980. Induction of hepatic drug metabolizing enzymes in mammals by pesticides: A review. J Environ Sci Health B 15:723-754.

*Hoff RM, Muir DCG, Grift, NP. 1992. Annual cycle of polychlorinated biphenyls and organohalogen pesticides in air in southern Ontario. 1. Air concentration data. Environ Sci Technol 26:266-275.

*Hopper ML. 1982. Automated gel permeation system for rapid separation of industrial chemicals and organophosphate and chlorinated pesticides from fats. J Agric Food Chem 30:1038-1041.

*Houk VS, DeMarini DM. 1987. Induction of prophage lambda by chlorinated pesticides. Mutat Res 182:193-202.

*Hrdina PD, Peters DA, Singhal RL. 1974. Role of noradrenaline, 5-hydroxytryptamine and acetylcholine in the hypothermic and convulsive effects of α-chlordane in rats. Eur J Pharmacol 26:306-312.

*HSDB (Hazardous Substance Data Base). 1988. Record No. 802, On-line computer database, August 14, 1988. National Library of Medicine (NLM).

*Hsu JP, Wheeler Jr HG, Camann DE, et al. 1988. Analytical methods for detection of non-occupational exposure to pesticides. J Chromatogr Sci 26:181-189.

*Huang JC. 1970. Fate of organic pesticides in the aquatic system. Engineering Extension Series (Purdue University), 449-457.

*Hung H, Halsall CJ, Blanchard P, et al. 2002. Temporal trends in organochlorine pesticides in the Canadian arctic atmosphere. Environ Sci Technol 36:862-868.

*Hunter RG, Carroll JH, Randolph JC. 1980. Organochlorine residues in fish of Lake Texoma, October 1979. Pestic Monit J 14:102-107.

Hyde KM, Falkenberg RL. 1976. Neuroelectrical disturbance as indicator of chronic chlordane toxicity. Toxicol Appl Pharmacol 37:499-515.

Hyde KM, Crandall JC, Kortman KE, et al. 1978. EEG, ECG and respiratory response to acute insecticide exposure. Bull Environ Contam Toxicol 19:47-55.

*IARC. 1987. IARC monographs on the evaluation of carcinogenic risks to humans. Update for volume 1 to 42. Lyon, France: World Health Organization.

*IARC. 2001. Chlordane and heptachlor. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 79. Some thyrotropic agents. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Monographs/vol79/mono79-17.pdf. July 26, 2017.

*IARC. 2017. Agents classified by the IARC Monographs, Volumes 1–119. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf. July 26, 2017.

*Infante P, Epstein SS, Newton Jr WA. 1978. Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. Scand J Work Environ Health 4:137-150.

*Ingle L. 1952. Chronic oral toxicity of chlordane to rats. Arch Ind Hyg Occup Med 6:357-367.

*Ingle L. 1953. The toxicity of chlordane vapors. Science 118:213-214.

*Ingle L. 1965. A monograph on chlordane toxicological and pharmacological properties. University of Illinois, Urbana, Illinois.

*Inoue K, Fujimori K, Nakazawa K, et al. 1989. The mechanism of action of chlordane a termiticide. Proceedings of the Japanese Pharmacological Society 62nd General Meeting, Kyoto, Japan, March 25-28, 1989.

*IRDC. 1973. (International Research and Development Corp.) Unpublished report to Velsicol Chemical Corporation, eighteen month oral carcinogenic study in mice. December 14. (Cited in Epstein, 1976).

*IRIS. 1992. Integrated Risk Information System. Cincinnati, OH: U.S. Environmental Protection Agency. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. February 25, 1992.

*IRIS. 2002. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0142_summary.pdf. July 26, 2017.

*Isnard P, Lambert S. 1988. Estimating bioconcentration factors from octanol-water partition coefficient and aqueous solubility. Chemosphere 17:21-34.

*Ivie GW, Knox JR, Khalifa S, et al. 1972. Novel photoproducts of heptachlor epoxide, trans-chlordane, and trans-nonachlor. Bull Environ Contam Toxicol 7:376-382.

*Iyengar L, Prabhakara Rao AVS. 1973. Metabolism of chlordane and heptachlor by *Aspergillus niger*. J Gen Appl Microbial 19:321-324. (Tokyo)

*Jaffe PR, Parker FL, Wilson DJ. 1982. Distribution of toxic substances in rivers. J Environ Eng 108:639-649.

Jang H, Talamantes F. 1977. Effects of chlordane on ova implantation in the mouse. Bull Environ Contam Toxicol 17:559-563.

*Jansson B, Wideqvist U. 1983. Analysis of toxaphene (PCC) and chlordane in biological samples by NCI mass spectrometry. Int J Environ Anal Chem 13:309-321.

*Jantunen LMM, Bidleman TF, Harner T, et al. 2000. Toxaphene, chlordane, and other organochlorine pesticides in Alabama air. Environ Sci Technol 34:5097-5105.

*Jensen AA. 1983. Chemical contaminants in human milk. Residue Rev 89:1-128.

*Johnson RD, Manske DD. 1976. Residues in food and feed. Pesticide residues in total diet samples. IX. Pestic Monit J 9:157-169.

Johnson RD, Manske DD. 1977. Pesticides in food and feed. Pesticide and other chemical residues in total diet samples. XI. Pestic Monit J 11:116-131.

*Johnson KW, Holsapple MP, Munson AE. 1986. An immunotoxicological evaluation of γ-chlordane. Fundam Appl Toxicol 6:317-326.

*Johnson KW, Kaminski NE, Munson AE. 1987. Direct suppression of cultured spleen cell responses by chlordane and the basis for differential effects on *in vivo* and *in vitro* immunocompetence. J Toxicol Environ Health 22:497-515.

Johnson RD, Manske DD, New DH, et al. 1979. Food and feed. Pesticides and other chemical residues in infant and toddler total diet samples. I. August 1974-July 1975. Pestic Monit J 13:87-98.

*Johnson RD, Manske DD, New DH, et al. 1981b. Food and feed. Pesticide, heavy metal, and other chemical residues in infant and toddler total diet samples. II. August 1975-July 1976. Pestic Monit J 15:39-50.

*Johnson RD, Manske DD, New DH, et al. 1984a. Pesticide, heavy metal, and other chemical residues in infant and toddler total diet samples. III. August 1976-September 1977. J Assoc Off Anal Chem 67:145-154.

*Johnson RD, Manske DD, New DH, et al. 1984b. Pesticide, metal, and other chemical residues in adult total diet samples. XIII. August 1976-September 1977. J Assoc Off Anal Chem 67:154-166.

*Johnson RD, Manske DD, Podrebarac DS. 1981a. Pesticide, metal, and other chemical residues in adult total diet samples. XII. August 1975-July 1976. Pestic Monit J 15:54-69.

*Johnson-Logan LR, Broshears RE, Klaine SJ. 1992. Partitioning behavior and the mobility of chlordane in groundwater. Environ Sci Technol 26:2234-2239.

*Jury WA, Focht DD, Farmer WJ. 1987a. Evaluation of pesticide groundwater pollution potential from standard indices of soil-chemical adsorption and biodegradation. J Environ Qual 16:422-428.

*Jury WA, Russo D, Streile G, et al. 1990. Evaluation of volatilization by organic chemicals residing below the soil surface. Water Resources Res 26:13-20.

*Jury WA, Winer AM, Spencer WF, et al. 1987b. Transport and transformation of organic chemicals in the soil-air-water ecosystem. Rev Environ Contam Toxicol 99:119-164.

*Kacew S, Singhal R. 1973. The influence of p,p'-DDT α-chlordane, heptachlor and endrin on hepatic and renal carbohydrate metabolism and cyclic AMP-adenyl cyclase system. Life Sci 13:1363-1371.

*Kamble ST, Ogg CL, Gold RE, et al. 1992. Exposure of applicators and residents to chlordane and heptachlor when used for subterranean termite control. Arch Environ Contam Toxicol 22:253-259.

*Kang JH, Park H, Chang YS, et al. 2008. Distribution of organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) in human serum from urban areas in Korea. Chemosphere 73(10):1625-1631. 10.1016/j.chemosphere.2008.07.087.

Karel AK, Saxena SC. 1976. Chronic chlordane toxicity: Effect on blood biochemistry of *Meriones hurriume* Jerdon, the Indian desert gerbil. Pestic Biochem Physiol 6:111-114.

*Kawano M, Tatsukawa R. 1982. [Chlordane and related compounds in blood of pest control operators.] Nippon Nogeikaguku Kaishi 56:923. (Japanese)

*Kawano M, Inoue T, Wada T, et al. 1988. Bioconcentration and residue patterns of chlordane compounds in marine animals: Invertebrates, fish, mammals, and seabirds. Environ Sci Technol 22:792-797.

*Kawano M, Nishiyama N, Tatsukawa R, et al. 1989. *In vitro* degradation of *trans*-chlordane and oxychlordane by rat liver microsomes. Chemosphere 19:1829-1833.

*Kazen C, Bloomer A, Welch R, et al. 1974. Persistence of pesticides on the hands of some occupationally exposed people. Arch Environ Health 29:315-318.

*KDHE. 1988. Kansas Department of Health and Environment. A survey of pesticides in Tuttle Creek Lake, its tributaries, and the upper Kansas River, June 1988. Bureau of Water Protection, Topeka, KS.

*Kennedy DW, Aust AD, Bumpus JA. 1990. Comparative biodegradation of alkyl halide insecticides by the white rot fungus, *Phancrochaete chrysosporium* (BKM-F-1767). Appl Environ Microbial 56:2347-2353.

*Keplinger ML, Deichmann WB. 1967. Acute toxicity of combinations of pesticides. Toxicol Appl Pharmacol 10:586-595.

*Khasawinah AM. 1989. Chlordane residues in rat and monkey tissues following subchronic inhalation exposure to technical chlordane. Bull Environ Contam Toxicol 43:459-466.

*Khasawinah AM, Grutsch JF. 1989a. Chlordane thirty-month tumorigenicity and chronic toxicity test in rats. Regul Toxicol Pharmacol 10:95-109.

*Khasawinah AM, Grutsch JF. 1989b. Chlordane: 24-month tumorigenicity and chronic toxicity test in mice. Regul Toxicol Pharmacol 10:244-254.

*Khasawinah AM, Hardy CJ, Clark GC. 1989. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J Toxicol Environ Health 28:327-347.

*Kilburn KH, Thornton JC. 1995. Protracted neurotoxicity from chlordane sprayed to kill termites. Environ Health Perspect 103(7-8):690-694.

King, KA, Krynitsky, AJ. 1986. Population trends, reproductive success and organochlorine chemical contaminants in waterbirds nesting in Galveston Bay, Texas. Arch Environ Contam Toxicol 15:367-376.

Kinoshita FK, Kempf CK. 1970. Quantitative measurement of hepatic microsomal enzyme induction after dietary intake of chlorinated hydrocarbon insecticides [Abstract]. Toxicol Appl Pharmacol 17:288.

*Kinoshita FK, Frawley JP, DuBois KP. 1966. Quantitative measure of induction of hepatic microsomal enzymes by various dietary levels of DDT and toxaphene in rats. Toxicol Appl Pharmacol 9:505-513.

*Klaas EE, Belisle AA. 1977. Organochlorine pesticide and polychlorinated biphenyl residues in selected fauna from a New Jersey salt marsh: 1967 vs. 1973. Pestic Monit J 10:149-158.

*Klaas EE, Ohlendorf HM, Cromartie E. 1980. Organochlorine residues and shell thickness in eggs of clapper rail, common gallinule, purple gallinule, and limpkin (class Aves), Eastern and Southern United States, 1972-1974. Pestic Monit J 14:90-94.

*Knap AH, Binkley KS. 1991. Chlorinated organic compounds in the troposphere over the Western North Atlantic Ocean measured by aircraft. Atmos Environ 25A:1507-1516.

*Knap AH, Binkley KS, Artz RS. 1988. The occurrence and distribution of trace organic compounds in Bermuda precipitation. Atmos Environ 22:1411-1423.

Korfmacher WA, Rushing LG, Siitonen PM, et al. 1987. Confirmation of heptachlor epoxide and octachlor [chlordane] epoxide in milk via fused-silica gas chromatography negative-ion chemical ionization mass spectrometry. J High Resolut Chromatogr Commun 10:332-336.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kuehl DW, Haebler R, Potter C. 1991. Chemical residues in dolphins from the U.S. Atlantic coast including Atlantic bottlenose obtained during the 1987/88 mass mortality. Chemosphere 22:1071-1084.

*Kuehl DW, Leonard EN, Butterworth BC, et al. 1983. Polychlorinated chemical residues in fish from major watersheds near the Great Lakes, 1979. Environ Int 9:293-299.

*Kuehl DW, Leonard EN, Welch KJ, et al. 1980. Identification of hazardous organic chemicals in fish from the Ashtabula River, Ohio, and Wabash River, Indiana. J Assoc Off Anal Chem 63:1238-1244.

*Kuntz KW, Warry ND. 1983. Chlorinated organic contaminants in water and suspended sediments of the lower Niagara River. J Great Lakes Res 9:241-248

*Kutz FW. 1983. Chemical exposure monitoring. Residue Rev 85:277-292.

*Kutz FW, Strassman SC, Sperling JF. 1979. Survey of selected organochlorine pesticides in the general population of the United States. Ann N Y Acad Sci 320:60-68.

*Kutz FW, Strassman SC, Sperling JF, et al. 1983. A fatal chlordane poisoning. J Toxicol Clin Toxicol 20:167-174.

*Kutz FW, Wood PH, Bottimore DP. 1991. Organochlorine pesticides and polychlorinated biphenyls in human adipose tissues. Rev Environ Contam Toxicol 120:1-82.

*Kutz FW, Yobs AR, Strassman SC. 1976. Organochlorine pesticide residues in human adipose tissue. Bull Soc Pharmacol Environ Pathol 4:17-19.

*Lau YL, OIiver BG, Krishnappan BG. 1989. Transport of some chlorinated contaminants by the water, suspended sediments, and bed sediments in the St. Clair and Detroit Rivers. Environ Toxicol Chem 8:293-301.

*Law LM, Goerlitz DF. 1974. Selected chlorinated hydrocarbons in bottom material from streams tributary to San Francisco Bay. Pestic Monit J 8:33-36.

*Lawrence JH, Ban-on RP, Chen JYT; et al. 1970. Note on identification of a chlordane metabolite found in milk and cheese. J Assoc Off Anal Chem 53:261-262.

*Layher WG, Wood RD, Lambley D, et al. 1985. Pesticide residues in Kansas pheasants. Bull Environ Contam Toxicol 34:317-322.

*LeBel GL, Williams DT. 1986. Determination of halogenated contaminants in human adipose tissue. J Assoc Off Anal Chem 69:451-458.

*Lee DH, Steffes MW, Sjodin A, et al. 2010. Low dose of some persistent organic pollutants predicts type 2 diabetes: A nested case-control study. Environ Health Perspect 118(9):1235-1242. 10.1289/ehp.0901480.

*Lehman AJ. 1951. Chemicals in foods: A report to the association of food and drug officials on current developments. Part II. Pesticides. Association of Food and Drug Officials Quarterly Bulletin 15:122-133.

*Leidy RB, Wright CG, Dupree Jr HE, et al. 1985. Subterranean termite control: Chlordane residues in soil surrounding and air within houses. American Chemical Society Symposium Series 273:265-277.

*Leidy RB, Wright CG. 1991. Trapping efficiency of selected adsorbents for various airborne pesticides. J Environ Sci Health [B] 26:367-382.

*Leiker TJ, Rostad CE, Barnes CR, et al. 1991. A reconnaissance study of halogenated organic compounds in catfish from the lower Mississippi River and its major tributaries. Chemosphere 23:817-830.

*Lensky P, Evans M. 1952. Human poisoning by chlordane. J Am Med Assoc 149:1394.

*Leone AD, Amato S, Falconer RL. 2001. Emission of chiral organochlorine pesticides from agricultural soils in the cornbelt region of the U.S. Environ Sci Technol 35:4592-4596.

*Lewis RG, Lee Jr RE. 1976. Air pollution from pesticides: Sources, occurrence and dispersion. In: Lee RE, ed. Air pollution from pesticide and agricultural processes. Cleveland, OH: CRC Press, 551.

*Lewis RG, Bond AE, Fitz-Simons TR, et al. 1986. Monitoring for non-occupational exposure to pesticides in indoor and personal respiratory air. In: Proceedings of the Air Pollution Control Association 79th Annual Meeting.

*Lewis RG, Bond AE, Johnson DE, et al. 1988. Measurement of atmospheric concentrations of common household pesticides: A pilot study. Environ Monit Assess 10:59-73.

*Lichtenstein EP, Schulz KR. 1959. Persistence of some chlorinated hydrocarbon insecticides as influenced by soil types, rates of application, and temperature. J Econ Entomol 52:124-131.

*Livingston JM, Jones CR. 1981. Living area contamination by chlordane used for termite treatment. Bull Environ Contam Toxicol 27:406-411.

Lopez-Avila V, Schoen S, Milanes J, et al. 1988. Single-laboratory evaluation of EPA Method 8080 for determination of chlorinated pesticides and polychlorinated biphenyls in hazardous wastes. J Assoc Off Anal Chem 71:375-387.

Lopez-Avila V, Dodhiwala NS, Beckert WF. 1990a. Supercritical fluid extraction and its application to environmental analysis. J Chromatogr Sci 28:468-476.

Lopez-Avila V, Wesselman R, Edge11 K. 1990b. Gas chromatographic-electron capture detection method for determination of 29 organochlorine pesticides in finished drinking water: Collaborative study. J Assoc Off Anal Chem 73:276-286.

*Louis JB, Kisselbach Jr KC. 1987. Indoor air levels of chlordane and heptachlor following termiticide applications. Bull Environ Contam Toxicol 39:911-918.

*Lundholm CE. 1988. The effects of DDE, PCB and chlordane on the binding of progesterone to its cytoplasmic receptor in the eggshell gland mucosa of birds and the endometrium of mammalian uterus. Comp Biochem Physiol 89C:361-368.

*Lyman WJ. 1982. Adsorption coefficient for soils and sediments. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York: McGraw Hill Book Co., Chapter 4.

*Mackay D, Paterson S, Schroeder WH. 1986. Model describing the rates of transfer processes of organic chemicals between atmosphere and water. Environ Sci Technol 20:810-816.

*MacMahon B, Mason RR, Wang HH, et al. 1988. A second follow-up of mortality in a cohort of pesticide applicators. J Occup Med 30:429-432.

*Maddy KT, Johnson L, Cusick B, et al. 1979. A study in southern California in July 1979 of the potential dermal and inhalation exposure of applicators and other persons who might later enter or occupy areas treated with chlordane used against subterranean termites under houses. California Department of Food and Agriculture, Worker Health and Safety Unit, Division of Pest Management, Environmental Protection, and Worker Safety, Sacramento, CA.

*Maguire RJ, Kuntz KW, Hale EJ. 1983. Chlorinated hydrocarbons in the surface microlayer of the Niagara River. J Great Lakes Res 9:281-286.

*Mahon DC. 1977. Interactions, in rats, between carbon tetrachloride-induced liver cirrhosis and chronic treatment with the organochlorine insecticide chlordane [Abstract]. Diss Abstr Int 38(9):4012B.

*Mahon DC, Oloffs PC, Hardwick DF. 1978. Interactions, in rats, between CCl_4-induced liver cirrhosis and chronic treatment with the organochlorine insecticide chlordane. Clin Biochem 11:435-438.

*Malarkey DE, Devereux TR, Dinse GE, et al. 1995. Hepatocarcinogenicity of chlordane in B6C3F1 and B6D2F1 male mice: Evidence for regression in $B6C3F_1$ mice and carcinogenesis independent of *ras* proto-oncogene activation. Carcinogenesis 16(11):2617-2625.

Manske DD, Corneliussen PE. 1974. Residues in food and feed. Pesticide residues in total diet samples. VII. Pestic Monit J 8:110-124.

*Manske DD, Johnson RD. 1975. Residues in food and feed. Pesticide residues in total diet samples. VIII. Pestic Monit J 9:94-105.

*Manske DD, Johnson RD. 1977. Residues in food and feed. Pesticide and other chemical residues in total diet samples. X. Pestic Monit J 10:134-148.

Marcus JM, Renfrow RT. 1990. Pesticides and PCBs in South Carolina estuaries. Mar Pollut Bull 21:96-99.

*Martin RJ, Duggan RE. 1968. Pesticide residues in total diet samples. III. Pestic Monit J 1:11-20.

*Martin H, Worthing CR, Eds. 1977. Pesticide Manual. 5th ed. British Crop Protection Council, 93.

*Martinez A, Erdman NR, Rodenburg ZL, et al. 2012. Spatial distribution of chlordanes and PCB congeners in soil in Cedar Rapids, Iowa, USA. Environ Pollut 161:222-228.

*Marsalek J, Schroeter H. 1988. Annual loadings of toxic contaminants in urban runoff from the Canadian Great Lakes Basin. Water Pollut Res J Can 23:360-378.

*Maslansky CJ, Williams GM. 1981. Evidence for an epigenetic mode of action in organochlorine pesticide hepatocarcinogenicity: A lack of genotoxicity in rat, mouse, and hamster hepatocytes. J Toxicol Environ Health 8:121-130.

*Matin MA, Kar PP, Hasan MZ, et al. 1977. Comparison of the chronic effects of alpha-chlordane and pp' DDT on the level of cerebral amino acids and free ammonia in mice. Pharmacol Res Commun 9:613-619.

*McConnachie PR, Zahalsky AC. 1992. Immune alterations in humans exposed to the termiticide technical chlordane. Arch Environ Health 47:295-301.

*McEwen LC, Stafford CJ, Hensler GL. 1984. Organochlorine residues in eggs of black-crowned night herons from Colorado and Wyoming. Environ Toxicol Chem 3:367-376.

*McGlynn KA, Quraishi SM, Graubard BI, et al. 2008. Persistent organochlorine pesticides and risk of testicular germ cell tumors. J Natl Cancer Inst 100(9):663-671. 10.1093/jnci/djn101.

*McGregor DB, Brown A, Cattanach P, et al. 1988. Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen 12:85-154.

*Menconi S, Clark JM, Langenberg P, et al. 1988. A preliminary study of potential human health effects in private residences following chlordane applications for termite control. Arch Environ Health 431:349-352.

*Menna H, Barnett JB, Soderberg LSF. 1985. Influenza Type A virus infection of mice exposed *in utero* to chlordane; survival and antibody studies. Toxicol Lett 24:45-52.

*Mes J, Marchand L, Davies DJ. 1990. Organochlorine residues in adipose tissue of Canadians. Bull Environ Contam Toxicol 45:681-688.

*Mes J. 1992. Organochlorine residues in human blood and biopsy fat and their relationship. Bull Environ Contam Toxicol 48:815-820.

*Millner GC, Shaddock JG, Harbison RD, et al. 1988. A comparison between the *in vitro* DNA repair assay and the *in vivo*/*in vitro* DNA repair and DNA replicative synthesis assays for detecting hepatocarcinogens [Abstract]. Environ Mol Mutagen 11:70.

*Mills PK, Yang R. 2005. Breast cancer risk in Hispanic agricultural workers in California. Int J Occup Environ Health 11(2):123-131. 10.1179/oeh.2005.11.2.123.

*Minyard JP, Roberts WE. 1991. State findings of pesticide residues in foods - 1988 and 1989. J Assoc Off Anal Chem 74:438-452.

*Miyagi T, Lam KM, Chuang LF, et al. 1998. Suppression of chemokine-induced chemotaxis of monkey neutrophils and monocytes by chlorinated hydrocarbon insecticides. In Vivo 12(5):441-445. (Retrieval in progress)

*Miyazaki T, Yamagishi T, Matsumoto M. 1985. Isolation and structure elucidation of some components in technical grade chlordane. Arch Environ Contam Toxicol 14:475-483.

*Montgomery MP, Kamel F, Saldana TM, et al. 2008. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. Am J Epidemiol 167(10):1235-1246. 10.1093/aje/kwn028.

*Moreau-Guigon E, Motelay-Massei A, Harner T, et al. 2007. Vertical and temporal distribution of persistent organic pollutants in Toronto. 1. Organochlorine pesticides. Environ Sci Technol 41(7):2172-2177.

*Mortelmans K, Haworth S, Lawlor T, et al. 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ Mutagen 8:1-119.

*Moser GJ, Smart RC. 1989. Hepatic tumor-promoting chlorinated hydrocarbons stimulate protein kinase C activity. Carcinogenesis 10:851-856.

*Moser VC, Cheek BM, MacPhail RC. 1995. A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity. J Toxicol Environ Health 45(2):173-210. 10.1080/15287399509531988.

*Moye HA, Malagodi MH. 1987. Levels of airborne chlordane and chlorpyrifos in two plenum houses: Saranex S-15 as a vapor barrier. Bull Environ Contam Toxicol 39:533-540.

*Mullins DE Johnson RE, Starr RI. 1971. Persistence of organochlorine insecticide residues in agricultural soils in Colorado. Pestic Monit J 5:368-375.

*Muir DCG, Norstrom RJ, Simon M. 1988. Organochlorine contaminants in Arctic marine food chains: Accumulation of specific polychlorinated biphenyls and chlordane-related compounds. Environ Sci Technol 22:1071-1079.

*Murphy RS, Kutz FW, Strassman SC. 1983. Selected pesticide residues or metabolites in blood and urine specimens from a general population survey. Environ Health Perspect 48:81-86.

*Mussalo-Rauhamaa H. 1991. Partitioning and levels of neutral organochlorine compounds in human serum, blood cells, and adipose and liver tissue. Sci Total Environ 103:159-175.

*Mussalo-Rauhamaa H, Pyysalo H, Antervo K. 1988. Relation between the content of organochlorine compounds in Finnish human milk and characteristics of the mothers. J Toxicol Environ Health 25:119.

*Nagayama J, Kohno H, Kunisue T, et al. 2007. Concentrations of organochlorine pollutants in mothers who gave birth to neonates with congenital hypothyroidism. Chemosphere 68(5):972-976. 10.1016/j.chemosphere.2007.01.010.

*Nam KS, Kapila S, Viswanath DS, et al. 1989. Application of supercritical fluid extraction of biological tissue samples for the determination of polychlorinated organics. Chemosphere 19:33-38.

*Nam KS, Kapila S, Yanders AF, et al. 1990. Supercritical fluid extraction and cleanup procedures for determination of xenobiotics in biological samples. Chemosphere 20:873-880.

*Narotsky MG, Kavlock RJ. 1995. A multidisciplinary approach to toxicological screening: II. Developmental toxicity. J Toxicol Environ Health 45(2):145-171. 10.1080/15287399509531987.

*Nash RG. 1983a. Comparative volatilization and dissipation rates of several pesticides from soil. J Agric Food Chem 31:210-217.

*Nash RG. 1983b. Determining environmental fate of pesticides with microagroecosystems. Residue Rev 85:199-215.

*Nash RG, Woolson EA. 1967. Persistence of chlorinated hydrocarbon insecticides in soils. Science 157:924-927.

*NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.

*NCI. 1977. National Cancer Institute. Bioassay of chlordane for possible carcinogenicity. Technical Report Series No. 8. U.S. Department of Health, Education and Welfare. NIH publication no. 77-808.

*Nightingale HI. 1987. Organic pollutants in soils of retention and recharge basins receiving urban runoff water. Soil Sci 144:373-382.

*NIOSH. 1984a. Health hazard evaluation report HETA 83-444-1481. Georgetown University, Washington, DC. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. PB85220895.

*NIOSH. 1984b. Health hazard evaluation report HETA 83-424-1403. Ozark National Scenic Riverways, Van Buren, MO. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1988. Registry of Toxic Effects of Chemical Substances (RTECS). Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1989a. National Occupation Exposure Survey. Cincinnati, OH. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1989b. NIOSH manual of analytical methods. 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Center of Disease Control, National Institute for Occupational Safety and Health, 5510-l to 5510-4.

*NIOSH. 1992. NIOSH recommendations for occupational safety and health. Compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 60.

*NIOSH. 2014. Chlordane. Immediately Dangerous to Life or Health Concentrations (IDLH). Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/idlh/57749.html. July 26, 2017.

*NIOSH. 2016. Chlordane. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/npg/npgd0112.html. July 26, 2017.

*Nomeir AA, Hajjar NP. 1987. Metabolism of chlordane in mammals. Rev Environ Contam Toxicol 100:l-22.

*NRC. 1982. National Research Council. An assessment of the health risks of seven pesticides used for termite control. Prepared for Department of Navy, Washington, DC. PB83136374.

*NRCC. 1974. Chlordane: Its effects on Canadian ecosystems and its chemistry. Ottawa, Canada: National Research Council of Canada. NRCC no. 14094.

*NTP. 2016. Report on Carcinogens, Fourteenth Edition. CASRN Index in MS Excel. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#P. February 28, 2017.

*Nye DE, Dorough HW. 1976. Fate of insecticides administered endotracheally to rats. Bull Environ Contam Toxicol 15:29 l-296.

*Oehme M. 1991. Dispersion and transport paths of toxic persistent organochlorines to the Arctic; levels and consequences. Sci Total Environ 106:43-53.

*Offenberg JH, Naumova YY, Turpin BJ, et al. 2004. Chlordanes in the indoor and outdoor air of three U.S. cities. Environ Sci Technol 38(10):2760-2768.

*Ogata M, Izushi F. 1991. Effects of chlordane on parameters of liver and muscle toxicity in man and experimental animals. Toxicol Lett 56:327-337.

*Ogata M, Izushi F, Eto K, et al. 1989. Effect of chlordane of hepatic mitochondrial respiration. Toxicol Lett 48:67-74.

*Ohlendorf HM, Harrison CS. 1986. Mercury, selenium, cadmium and organochlorines in eggs of three Hawaiian (USA) seabird species. Environ Pollut B 11:169-192.

*Ohlendorf HM, Swineford DM, Locke LN. 1981. Organochlorine residues and mortality of herons. Pestic Monit J 14:125-135.

*OHM-TADS. 1988. Oil and Hazardous Materials Technical Assistance Data System. U.S. EPA-NIH (U.S. Environmental Protection Agency-National Institute of Health). August 12, 1988.

*Ohno Y, Kawanishi T, Takahashi A. 1986. Comparisons of the toxicokinetic parameters in rats determined for low and high dose of γ-chlordane. J Toxicol Sci 11:111-124.

*Olanoff LS, Bristow WJ, Colcolough J, et al. 1983. Acute chlordane intoxication. J Toxicol Clin Toxicol 20:29l-306.

*Oliver BG, Niimi AJ. 1985. Bioconcentration factors of some halogenated organics for rainbow trout, limitation in their use for predictions. Environ Sci Technol 19:842-849.

*Oloffs PC, Albright LJ, Szeto SY. 1972. Fate and behavior of five chlorinated hydrocarbons in three natural waters. Can J Microbial 18:1393-1398.

*Oloffs PC, Albright LJ, Szeto SY, et al. 1973. Factors affecting the behavior of five chlorinated hydrocarbons in two natural waters and their sediments. J Fish Res Board Can 30:1619-1623.

*Onuska FI, Comba ME. 1975. Isolation and characterization of the photoalteration products of *cis* and *trans*-chlordane. J Assoc Off Anal Chem 58:6-9.

Orazio CE, Kapila S, Puri RK, et al. 1990. Field and laboratory studies on sources and persistence of chlordane contamination in the Missouri aquatic environment. Chemosphere 20:1581-1588.

*Ortega P, Hayes WJ, Durham WF. 1957. Pathologic changes in the liver of rats after feeding low levels of various insecticides. AMA Arch Pathol 64:614-622.

*OSHA. 1989. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 2016a. Subpart D Occupational health and environment controls. Section 1926.55 - Gases, vapors, fumes, dusts, and mists. Appendix A to Part 1926.55 - threshold limit values of airborne contaminants for construction. Occupational Safety and Health Standards. Code of Federal Regulations. 29 CFR 1926.55. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol8/pdf/CFR-2016-title29-vol8-sec1926-55.pdf. March 6, 2017.

*OSHA. 2016b. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Standards. Code of Federal Regulations. 29 CFR 1910.1000. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol6/pdf/CFR-2016-title29-vol6-sec1910-1000.pdf. March 6, 2017.

*OSHA. 2016c. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z - Shipyards. Occupational Safety and Health Standards. Code of Federal Regulations. 29 CFR 1915.1000. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol7/pdf/CFR-2016-title29-vol7-sec1915-1000.pdf. March 6, 2017.

OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-438, April 1990.

*Pacyna JM, Oehme M. 1988. Long-range transport of some organic compounds to the Norwegian Arctic. Atmos Environ 22:243-257.

*Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15:1475-1481.

*Parlar. 1978. [Transformation of some cyclodiene pesticides on leaf surfaces by the action of sunlight.] Chemosphere 7:721-728. (German)

*Parlar H, Korte F. 1973. [Studies on ecologic chemistry. LX: Photochemistry of chlordane derivatives.] Chemosphere 2:169-172. (German)

*Parlar H, Korte F. 1977. Photoreactions of cyclodiene insecticides under simulated environmental conditions. Chemosphere 6:665-705.

*Parlar H, Korte F. 1979. Photokinetic evaluation of dechlorination reactions of cyclodiene pesticides. Chemosphere 8:873-876.

*Parlar H, Korte F. 1980. [Phototransformation products of chlordane derivatives and their pesticidal activity.] Chemosphere 9:55-58. (German)

*Parlar H, Hustert K, Gaeb S, et al. 1979. Isolation, identification, and chromatographic characterization of some chlorinated C_{10} hydrocarbons in technical chlordane. J Agric Food Chem 27:278-283.

*Patton GW, Walla MD, Bidleman TF, et al. 1991. Polycyclic aromatic and organochlorine compounds in the atmosphere of northern Ellesmere Island, Canada. J Geophys Res 96:10,867-10,877.

*Peterman PH, Delfino JJ, Dube DJ, et al. 1980. Chloro-organic compounds in the Lower Fox River, Wisconsin. Environ Sci Res 16:145- 160.

*Phillips LJ, Birchard GF. 1991. Use of STORET data to evaluate variations in environmental contamination by census division. Chemosphere 22:835-848.

*Plumb Jr RH. 1991. The occurrence of Appendix IX organic constituents in disposal site ground water. Ground Water Monit Rev 11:157-164.

*Podowski AA, Banerjee BC, Feroz M, et al. 1979. Photolysis of heptachlor and *cis*-chlordane and toxicity of their photoisomers to animals. Arch Environ Contam Toxicol 8:509-518.

*Podrebarac DS. 1984a. Pesticide, metal, and other chemical residues in adult total diet samples. XIV. October 1977-September 1978. J Assoc Off Anal Chem 67:176-185.

*Podrebarac DS. 1984b. Pesticide, heavy metal, and other chemical residues in infant and toddler total diet samples. IV. October 1977-September 1978. J Assoc Off Anal Chem 67:166-175.

*Poonawalla NH, Korte F. 1964. Metabolism of insecticides. VIII (1): Excretion, distribution and metabolism of α-chlordane-^{14}C by rats. Life Sci 3:1497-1500.

*Poonawalla NH, Korte F. 1971. Metabolism of *trans*-chlordane-^{14}C and isolation and identification of its metabolites from the urine of rabbits. J Agric Food Chem 19:467-470.

*Princi F, Spurbeck GH. 1951. A study of workers exposed to the insecticides chlordane, aldrin, dieldrin. Arch Ind Hyg Occup Med 3:64-72.

*Probst GS, Hill LE. 1981. Chemically induced DNA repair synthesis in primary rat hepatocytes: A correlation with bacterial mutagenicity. Ann N Y Acad Sci 349:405-406.

*Prouty RM, Bunck CM. 1986. Organochlorine residues in adult mallard and black duck wings, 198l-l982. Environ Monit Assess 6:49-57.

*Purdue MP, Hoppin JA, Blair A, et al. 2006. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int J Cancer 120(3):642-649.

*Puri RK, Orazio CE, Kapila S, et al. 1990. Studies on the transport and fate of chlordane in the environment. In: Kurtz DA, ed. Long range transport of pesticides. Chelsea, MI: Lewis Publishers, 271-280.

*Quintana PJ, Delfino RJ, Korrick S, et al. 2004. Adipose tissue levels of organochlorine pesticides and polychlorinated biphenyls and risk of non-Hodgkin's lymphoma. Environ Health Perspect 112(8):854-861.

*Rashid KA, Mumma RO. 1986. Screening pesticides for their ability to damage bacterial DNA. J Environ Sci Health B 21:319-334.

*Rathbun RE. 1992. Transport and degradation of organic substances in streams. U.S. Department of the Interior, U.S. Geological Survey, Water Resources Division, North-Central Colorado

*Ray LE, Murray HE, Giam CS. 1983. Organic pollutants in marine samples from Portland, Maine. Chemosphere 12:1031-1038.

*Reding R. 1987. Chromatographic monitoring methods for organic contaminants under the Safe Drinking Water Act. J Chromatogr Sci 25:338-344.

*RePORTER. 2017. Chlordane. National Institutes of Health, Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. August 30, 2017.

*Requejo AG, West RH, Hatcher PG, et al. 1979. Polychlorinated biphenyls and chlorinated pesticides in soils of the Everglades National Park and adjacent agricultural areas. Environ Sci Technol 13:931-935.

*Reuber MD. 1978. Carcinomas and other lesions of the liver in mice ingesting organochlorine pesticides. Clin Toxicol 13:231-256.

*Rhainds M, Levallois P, Dewailly E, et al. 1999. Lead, mercury, and organochlorine compound levels in cord blood in Quebec, Canada. Arch Environ Health 54(1):40-47.

*Ritchie JM, Vial SL, Fuortes LJ, et al. 2003. Organochlorines and risk of prostate cancer. J Occup Environ Med 45(7):692-702. 10.1097/01.jom.0000071510.96740.0b.

*Ritter WF. 1990. Pesticide contamination of groundwater in the United States- A review. J Environ Sci Health 25:1-31.

Rodriguez OM, Desideri PG, Lepri L, et al. 1991. Simultaneous separation and determination of hydrocarbons and organochlorine compounds by using a two-step microcolumn. J Chromatogr 555:221-228.

*Roper EM, Wright CG. 1984. Sampling efficiency of five solid sorbents for trapping air-borne pesticides. Bull Environ Contam Toxicol 33:476-483.

*Rought SE, Yau PM, Chuang LF, et al. 1999. Effect of the chlorinated hydrocarbons heptachlor, chlordane, and toxaphene on retinoblastoma tumor suppressor in human lymphocytes. Toxicol Lett 104(1-2):127-135.

*Rumack BH, Lovejoy Jr FH. 1991. Clinical toxicology. In: Amdur MO, Doull J, Klaasen CD, eds. Casarett and Doull’s toxicology: The basic science of poisons, 4th ed. New York, NY: Pergamon Press, 924-946.

*Ruth RJ, Fransson R, Flodstrom S, et al. 1990. Inhibition of hepatocyte gap junctional intercellular communication by endosulfan, chlordane and heptachlor. Carcinogenesis 11:1097-l101.

*Saiki MK, Schmitt CJ. 1986. Organochlorine chemical residues in bluegills and common carp from the irrigated San Joaquin Valley floor, California. Arch Environ Contam Toxicol 15:357-366.

*Saito I, Kawamura N, Uno K, et al. 1985. Determination of chlordane in human blood by gas chromatography. Analyst 110:263-267.

*Saito I, Kawamura N, Uno K, et al. 1986. Relationship between chlordane and its metabolites in blood of pest control operators and spraying conditions. Arch Ind Hyg Occup Med 58:91-97.

*Sanbom JR, Metcalf RL, Bruce WN, et al. 1976. The fate of chlordane and toxaphene in a terrestrial-aquatic model ecosystem. Environ Entomol 5:533-538.

*Sanders M, Haynes BL. 1988. Distribution pattern and reduction of polychlorinated biphenyls PCB in bluefish *Pomatomus-saltutrix* (*Zinnueus*) fillets through adipose tissue removal. Bull Environ Contam Toxicol 41:670-677.

*Santolucito JA, Whitcomb E. 1971. Mechanical response of skeletal muscle following oral administration of pesticides. Toxicol Appl Pharmacol 20:66-72.

*Sarkar D, Sharma A, Talukder G. 1993. Differential protection of chlorophyllin against clastogenic effects of chromium and chlordane in mouse bone marrow *in vivo*. Mutat Res 301(1):33-38.

*Sasaki K, Ishizaka T, Suzuki T, et al. 1991a. Accumulation levels of organochlorine pesticides in human adipose tissue and blood. Bull Environ Contam Toxicol 46:662-669.

*Sasaki K, Ishizaka T, Suzuki T, et al. 1991b. Organochlorine chemicals in skin lipids as an index of their accumulation in the human body. Arch Environ Contam Toxicol 21:190-l94.

*Sasaki K, Kawasaki Y, Sekita K, et al. 1992. Disposition of β-hexachlorocyclohexane, p,p'-DDT, and *trans*-chlordane administered subcutaneously to monkeys (*Mucuca-fusciculuriss*). Arch Environ Contam Toxicol 22:25-29.

*Satoh A, Kikawa H, 1992. Metabolic fate of *cis*-and *trans*-chlordane in mice. Jpn J Hyg 47:818-825.

*Sawada N, Iwasaki M, Inoue M, et al. 2010. Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: A nested case-control study. Environ Health Perspect 118(5):659-665. 10.1289/ehp.0901214.

*Sauer TC Jr, Durell GS, Brown JS, et al. 1989. Concentrations of chlorinated pesticides and PCBs in microlayer and seawater samples collected in open-ocean waters off the U.S. East Coast and in the Gulf of Mexico. Mar Chem 27:235-257.

*Savage EP, Keefe TJ, Tessari JD, et al. 1981. National study of chlorinated hydrocarbon insecticide residues in human milk, USA. Am J Epidemiol 113:413-422.

Savage EP. 1989. Termiticide use and indoor air quality in the United States. Rev Environ Contam Toxicol 110:117-130.

*Schafer ML, Peeler JT, Gardner WS, et al. 1969. Pesticides in drinking water: Water from the Mississippi and Missouri Rivers. Environ Sci Technol 3:1261-1269.

*Schattenberg HJ III, Hsu JP. 1992. Pesticide residue survey of produce from 1989-1991. J AOAC Int 75:925-933.

*Schick CT, Brennan LA, Buchanan JB, et al. 1987. Organochlorine contamination in shorebirds from Washington state and the significance for their falcon predators. Environ Monit Assess 9:115-131.

*Schmitt CJ, Zajicek JL, Peterman PH. 1990. National contaminant biomonitoring program: Residues of organochlorine chemicals in USA freshwater fish, 1976- 1984. Arch Environ Contam Toxicol 19:748-781.

*Schmitt CJ, Zajicek JL, Ribick MA. 1985. National pesticide monitoring program: Residues of organochlorine chemicals in freshwater fish, 1980-81. Arch Environ Contam Toxicol 14:225-260.

*Schop RN, Hardy MH, Goldberg, MT. 1990. Comparison of the activity of topically applied pesticides and the herbicide 2,4-D in two short-term *in vivo* assays of genotoxicity in the mouse. Fundam Appl Toxicol 15:666-675.

Schuetz EG, Wrighton SA, Safe SH, et al. 1986. Regulation of cytochrome P-450 by phenobarbital and phenobarbital-like inducers in adult rat hepatocytes in primary monolayer culture and *in vivo*. Biochemistry 25:1124-1133.

*Sears MK, Chapman RA. 1979. Persistence and movement of four insecticides applied to turfgrass. J Econ Entomol 72:272-274.

*Sericano JL, Atlas EL, Wade TL, et al. 1990. NOAA's status and trends mussel watch program: Chlorinated pesticides and PCBs in oysters (*Crassostrea virginica*) and sediments from the Gulf of Mexico, 1986-1987. Mar Environ Res 29:161-203.

*Sethunathan N. 1973. Microbial degradation of insecticides in flooded soil and in anaerobic cultures. Residue Rev 47:143-166.

*Shain SA, Shaeffer JC, Boesel RW. 1977. The effect of chronic ingestion of selected pesticides upon rat ventral prostate homeostasis. Toxicol Appl Pharmacol 40:115-130.

*Shen L, Wania F, Lei YD, et al. 2005. Atmospheric distribution and long-range transport behavior of organochlorine pesticides in North America. Environ Sci Technol 39(2):409-420.
*Shindell S, Ulrich S. 1986. Mortality of workers employed in the manufacture of chlordane: An update. J Occup Med 28:497-501.
*Simmon VF, Kauhanen K, Tardiff RG. 1977. Mutagenicity activity of chemicals identified in drinking water. Dev Toxicol Environ Sci 2:249-258.
*Singh G Higginson FR, Fenton IG, et al. 1990. Translocation of aged cyclodiene insecticide residues from soil into forage crops under optimal glasshouse conditions. J Environ Sci Health B 25:295-308.
*Singh G Kathpal TS, Spencer WF, et al. 1991. Dissipation of some organochlorine insecticides in cropped and uncropped soil. Environ Pollut 70:219-240.
*Singhal RL and Kacew S. 1976. The role of cyclic AMP in chlorinated hydrocarbon-induced toxicity. Fed Proc 35:2618-2663.
*Sipes JG, Gandolfi AJ. 1991. Biotransformation of toxicants. In: Andur MO, Doull J, Klaassen CD, eds. Casarett and Doull's toxicology. 4th ed. New York, NY: Pergamon Press, 112.
*Smith AG. 1991. Chlorinated hydrocarbon insecticides. In: Hayes Jr WJ, Laws Jr ER, eds. Handbook of pesticide toxicology, Vol. 2: Classes of pesticides. San Diego, CA: Academic Press, 731-915.
*Smith TJ, Wilcock RJ, Pridmore RD, et al. 1992. Persistence of chlordane applied to an intertidal sandflat. Bull Environ Contam Toxicol 49:129-136.
*Snyder WS, Cook MJ, Nosset ES, et al. 1981. Report of the Task Group on Reference Man ICRP Report No. 23. New York: Pergamon Press, 33-34.
*Sobti RC, Krishan A, Davies J. 1983. Cytokinetic and cytogenetic effect of agricultural chemicals on human lymphoid cells *in vitro*. II. Organochlorine pesticides. Arch Toxicol 52:221-231.
*Speidel HK, Bourquin AW, Mann JE, et al. 1972. Microbiological removal of pesticides from aqueous environments. Develop Ind Microbial 13:277-282.
*Sperling KR, Janssen D, Wulf T. 1985. Gas chromatographic-mass spectrometric investigations on lipophilic anthropogenic substances in marine organisms. I. A clean-up procedure consisting of liquid-liquid and reversed phase (octadecyl)-partitioning. Fresenius J Anal Chem 320:1-5.
*Spinelli JJ, Ng CH, Weber JP, et al. 2007. Organochlorines and risk of non-Hodgkin lymphoma. Int J Cancer 121(12):2767-2775. 10.1002/ijc.23005.
*Spyker DA, Bond RR, Jylkka M, et al. 1989. Subacute home chlordane poisoning fact or fallacy [Abstract]. Vet Hum Toxicol 31:356.
*Spyker-Cranmer JM, Barnett JB, Avery DL, et al. 1982. Immunoteratology of chlordane: Cell mediated and humoral immune responses in adult mice exposed *in utero*. Toxicol Appl Pharmacol 62:402-408.
*SRI. 1988. 1988 Directory of Chemical Producers: United States of America. Menlo Park, CA: Stanford Research Institute International.
*SRI. 1990. 1991 Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute.
*Stanley CW, Barney II JE, Helton MR, et al. 1971. Measurement of atmospheric levels of pesticides. Environ Sci Technol 5:430-435.
*Starr Jr HG, Aldrich FD, McDougall WD, et al. 1974. Contribution of household dust to the human exposure to pesticides. Pestic Monit J 8:209-212.
*State of Kentucky. 1986. New or modified sources emitting toxic air pollution. 401 KAR 63:022.
*Steffey KL, Mack J, MacMonegle CW, et al. 1984. A ten-year study of chlorinated hydrocarbon insecticide residues in bovine milk in Illinois, 1972-1981. J Environ Sci Health B 19:49-65.
*Steichen J, Koelliker J, Grosh D, et al. 1988. Contamination of farmstead wells by pesticides, volatile organics and inorganic chemicals in Kansas. Ground Water Monit Rev 8:153.
*Stenger RJ, Porway M, Johnson EA, et al. 1975. Effects of chlordane pretreatment on the hepatotoxicity of carbon tetrachloride. Exp Mol Pathol 23:144-153.
*Stevens RJJ, Neilson MA. 1989. Inter- and intralake distributions of trace organic contaminants in surface waters of the Great Lakes. J Great Lakes Res 15:377-393.

*Stewart DKR, Chisholm D. 1971. Long-term persistence of BHC, DDT, and chlordane in a sandy loam soil. Can J Soil Sci 51:379-383.

*Stewart DKR, Fox CJS. 1971. Persistence of organochlorine insecticides and their metabolites in Nova Scotian soil. J Econ Entomol 64:367-371.

*Stohlman EF, Thorp WTS, Smith MI. 1950. Toxic action of chlordane. Arch Ind Hyg Occup Med 1:13.

*Stohs SJ, Bagchi D, Bagchi M, et al. 1997. Generation of reactive oxygen species, DNA damage and lipid peroxidation in liver by structurally dissimilar pesticides. In: Liver and environmental xenobiotics. New Delhi, India: Narosa Publishing House, 102-113. (Retrieval in progress)

*Strachan WMJ. 1985. Organic substances in the rainfall of Lake Superior (USA, Canada): 1983. Environ Toxicol Chem 4:677-684.

*Strassman SC, Kutz FW. 1977. Insecticide residues in human milk from Arkansas and Mississippi, 1973-74. Pestic Monit J 10:130-133.

*Street JC, Blau SE. 1972. Oxychlordane. Accumulation in rat adipose tissue on feeding chlordane isomers or technical chlordane. J Agric Food Chem 20:395-397.

*Sun P, Blatnchard P, Brice K, et al. 2006. Atmospheric organochlorine pesticide concentrations near the Great Lakes: temporal and spatial trends. Environ Sci Technol 40(21):6587-6593.

*Suntio LR, Shiu WY, Mackay D, et al. 1988. Critical review of Henry's law constants for pesticides. Rev Environ Contam Toxicol 103:1-59.

*Suzaki E, Inoue B, Okimasu E, et al. 1988. Stimulative effect of chlordane on the various functions of the guinea pig leukocytes. Toxicol Appl Pharmacol 93:137-145.

*Swackhamer DL, Hites RA. 1988. Occurrence and bioaccumulation of organochlorine compounds in fishes from Siskiwit Lake, Isle Royale, Lake Superior. Environ Sci Technol 22:543-548.

*Szaro RC, Coon NC, Kolbe E. 1979. Pesticide and PCB of common eider, herring gull and great black-backed gull eggs. Bull Environ Contam Toxicol 22:394-399.

*Szeto SY, Price PM. 1991. Persistence of pesticide residues in mineral and organic soils in the Fraser Valley of British Columbia. J Agric Food Chem 39:1679-1684.

*Tabak HH, Quave SA, Mashni CI, et al. 1981a. Biodegradability studies for predicting the environmental fate of organic priority pollutants. In: Test protocols for environmental fate and movement of toxicants. Symposium proceedings of the Association of Official Anal Chem 94th annual meeting, Washington, DC, 267-328.

*Tabak HH, Quave SA, Mashni CI, et al. 1981b. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Control Fed 53:1503-1518.

*Tafuri F, Businelli M, Scarponi L, et al. 1977. Decline and movement of AG chlordane in soil and its residues in alfalfa. J Agric Food Chem 25:353-356.

*Taguchi S, Yakushiji T. 1988. Influence of termite treatment in the home on the chlordane concentration in human milk. Arch Environ Contam Toxicol 17:65-72.

*Takamiya K. 1987. Residual levels of plasma oxychlordane and trans-nonachlor in pest control operators and some characteristics of these accumulations. Bull Environ Contam Toxicol 39:750-755.

*Takeda M, Sekita H, Sasaki K, et al. 1984. [Distribution of chlordane components in rat tissues after daily oral administration of technical chlordane at low levels.] Eisei Shikensho Hokoku 102:113-116. (Japanese)

*Takei GH, Kauahikaua SM, Leong GH. 1983. Analysis of human milk samples collected in Hawaii for residues of organochlorine pesticides and polychlorobiphenyls. Bull Environ Contam Toxicol 30:606-613.

Talamantes F, Jang H. 1977. Effects of chlordane isomers administered to female mice during the neonatal period. J Toxicol Environ Health 3:713-720.

*Tanabe S, Falandysz J, Higaki T, et al. 1993. Polychlorinated biphenyl and organochlorine insecticide residues in human adipose tissue in Poland. Environ Pollut 79(1):45-49.

*Tanita R, Johnson JM, Chun M, et al. 1976. Organochlorine pesticides in the Hawaii Kai Marina. Pestic Monit J 10:24-29.

*Tashiro S, Matsumura F. 1977. Metabolic routes of *cis*-and *trans*-chlordane in rats. J Agric Food Chem 25:872-880.

*Tashiro S, Matsumura F. 1978. Metabolism of trans-nonachlor and related chlordane components in rat and man. Arch Environ Contam Toxicol 7:113-127.

*Telang S, Tong C, Williams GM. 1981. Induction of mutagenesis by carcinogenic polycyclic aromatic hydrocarbons but not by organochlorine pesticides in the ARL/HGPRT mutagenesis assay [Abstract]. Environ Mutagen 3:359

*Telang S, Tong C, Williams GM. 1982. Epigenetic membrane effects of a possible tumor promoting type on cultured liver cells by the nongenotoxic organochlorine pesticides chlordane and heptachlor. Carcinogenesis 3:1175.

*Theus SA, Lau KA, Soderberg LSF, et al. 1990. Macrophage protein changes associated with prenatal chlordane exposure [Abstract]. Fed Am Soc Exp Biol 4:A1750.

*Theus SA, Lau KA, Tabor DR, et al. 1992. *In vivo* prenatal chlordane exposure induces development of endogenous inflammatory macrophages. J Leukoc Biol 51:366-372.

*Thomas TC, Nishioka YA. 1985. Sampling and analytical procedures for evaluation of airborne chlordane levels in family quarters. Environ Toxicol Chem 4:143-147.

*Tojo Y, Wariishi M, Suzuki Y, et al. 1986. Quantitation of chlordane residues in mothers' milk. Arch Environ Contam Toxicol 15:327-332.

*Tong CC, Williams GM. 1988. Detection of neoplasm promoters in the hepatocyte-liver epithelial cell system. Prog Cancer Res Ther 34:161-178.

*Tong C, Fazio M, Williams GM. 1981. Rat hepatocyte-mediated mutagenesis of human cells by carcinogenic polycyclic aromatic hydrocarbons but not organochlorine pesticides. Proc Soc Exp Biol Med 167:572-575.

*Trabert B, Longnecker MP, Brock JW, et al. 2012. Maternal pregnancy levels of *trans*-nonachlor and oxychlordane and prevalence of cryptorchidism and hypospadias in boys. Environ Health Perspect 120(3):478-482. 10.1289/ehp.1103936.

*TRI90. 1992. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI16. 2017. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: U.S. Environmental Protection Agency, Office of Information Analysis and Access, Office of Environmental Information. Toxics Release Inventory. http://www.epa.gov/triexplorer/. September 29, 2017.

*Trotter WJ, Corneliussen PE, Lasaki RR, et al. 1989. Levels of polychlorinated biphenyls and pesticides in bluefish before and after cooking. J Assoc Off Anal Chem 72:501-503.

*Truhaut R Gak JC, Graillot C. 1974. [Organochlorine insecticides; research work on their toxic action (its modalities and mechanisms): I. Comparative study of the acute toxicity on the hamster and the rat.] J Eur de Toxicol 7:159-166. (French)

*Truhaut R, Graillot C, Gak JC. 1975. [The problem of selecting animal species for assessing the toxicity of organochlorine pesticide residues for extrapolation to man. Comparative study of the sensitivity of the rat, mouse and hamster.] Comm Eur Communities, (Rep) EUR 5196:477-498. (French)

*Tryphonas H, Bondy G, Hodgen M, et al. 2003. Effects of *cis*-nonachlor, *trans*-nonachlor and chlordane on the immune system of Sprague-Dawley rats following a 28-day oral (gavage) treatment. Food Chem Toxicol 41(1):107-118.

*Tsushimoto G, Chang CC, Trosko JE, et al. 1983. Cytotoxic, mutagenic, and cell-cell communication inhibitory properties of DDT, lindane, and chlordane on Chinese hamster cells *in vitro*. Arch Environ Contam Toxicol 12:721-729.

*Tucker WA, Preston AL. 1984. Procedures for estimating atmospheric deposition properties of organic chemicals. Water Air Soil Pollut 21:247-260.

*Usami M, Kawashima K, Nakaura S, et al. 1986. [Effects of chlordane on prenatal development of rats.] Eisei Shikenso Hokoku 104:68-73. [Japanese]

*Veith GD, Kuehl DW, Leonard EN, et al. 1979. Polychlorinated biphenyls and other organic chemical residues in fish from major watersheds of the United States, 1976. Pestic Monit J 13:1-l1.

*Venkat JA, Shami S, Davis K, et al. 1995. Relative genotoxic activities of pesticides evaluated by a modified SOS microplate assay. Environ Mol Mutagen 25(1):67-76.

*Verbrugge DA, Othoudt RA, Grzyb KR, et al. 1991. Concentrations of inorganic and organic contaminants in sediments of six harbors on the North American Great Lakes. Chemosphere 22:809-820.

*VIEW. 1988. Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, GA. October 1988.

*Vogel E. 1980. Genetical relationship between resistance to insecticides and procarcinogens in two Drosophila populations. Arch Toxicol 43:201-211.

*Vollner L, Parlar H, Klein W, et al. 1971. [Concentrations in ecological chemistry - XXXI. Photoreactions of components of technical chlordane.] Tetrahedron 27:501-509. (German).

*Wallace LA. 1991. Comparison of risks from outdoor and indoor exposure to toxic chemicals. Environ Health Perspect 95:7-13.

*Wang HH, MacMahon B. 1979a. Mortality of workers employed in the manufacture of chlordane and heptachlor. J Occup Med 21:745-748.

*Wang HH, MacMahon B. 1979b. Mortality of pesticide applicators. J Occup Med 21:741-744.

*Ward EM, Schulte P, Grajewski B, et al. 2000. Serum organochlorine levels and breast cancer: A nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev 9(12):1357-1367.

*Wariishi M, Nishiyama K. 1989. Observations on the progress of chlordane contamination in humans by blood and sebum analysis. Arch Environ Contam Toxicol 18:501-507.

*Wariishi M, Suzuki Y, Nishiyama K. 1986. Chlordane residues in normal human blood. Bull Environ Contam Toxicol 36:635-643.

*Weiderpass E, Adami HO, Baron JA, et al. 2000. Organochlorines and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev 9(5):487-493.

*Weil VL, Dure G, Quentin KE. 1974. [Water solubility of chlorinated hydrocarbon insecticides and polychlorinated biphenyls in regards to loadings of water bodies with these substances.] Wasser- und Abwasser-Forsch 7:169-175. (German)

*Welch RM, Harrison Y. 1966. Reduced drug toxicity following insecticide treatment [Abstract], Pharmacologist 8:217.

*Welch HE, Muir DCG, Billeck BN, et al. 1991. Brown snow: A long-range transport event in the Canadian Arctic. Environ Sci Technol 25:280-286.

*Welch RM, Levine W, Kuntzman R, et al. 1971. Effect of halogenated hydrocarbon insecticides on the metabolism and uterotrophic action of estrogens in rats and mice. Toxicol Appl Pharmacol 19:234-246.

*Wester RC, Maibach HI, Sedlik L, et al. 1992. Percutaneous absorption of [^{14}C]chlordane from soil. J Toxicol Environ Health 35:269-277.

*Whetstone RR. 1964. Chlorocarbons and chlorohydrocarbons. In: Standen A, ed. Kirk-Othmer encyclopedia of chemical technology, 2nd ed., vol. 5. New York, NY: John Wiley and Sons, 248-249.

*White DH. 1979. Nationwide residues of organochlorine compounds in wings of adult mallards and black ducks. Pestic Monit J 13:12-16.

*White DH, Krynitsky AJ. 1986. Wildlife in some areas of New Mexico and Texas accumulate elevated DDE residues. Environ Contam Toxicol 15:149-157.

*White DH, Mitchell CA, Stafford CJ. 1985. Organochlorine concentrations, whole body weights, and lipid content of black skimmers wintering in Mexico and in south Texas. Bull Environ Contam Toxicol 34:513-517.

*White DH, Stendell RC, Mulhem BM. 1979. Relations of wintering canvasback to environmental pollutants - Chesapeake Bay, Maryland. Wilson Bulletin 91:279-287.

*WHO. 1982. Guidelines for drinking water quality. Vol 1: Recommendations. Geneva: World Health Organization. (EFPI82.39). (Cited in WHO 1984)

*WHO. 1984. Environmental Health Criteria 34: Chlordane. Geneva: World Health Organization.

*WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. January 08, 2014.

*WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

*WHO/FAO. 1978. Data Sheets on pesticides No. 36: Chlordane. Geneva: World Health Organization. (Cited in WHO 1984)

*Whysner J, Montandon F, McClain RM, et al. 1998. Absence of DNA adduct formation by phenobarbital, polychlorinated biphenyls, and chlordane in mouse liver using the 32P-postlabeling assay. Toxicol Appl Pharmacol 148(1):14-23. 10.1006/taap.1997.8311.

*Wiemeyer SN, Lamont TG, Bunck CM, et al. 1984. Organochlorine pesticide, polychlorobiphenyl, and mercury residues in bald eagle eggs - 1969-79 - and their relationships to shell thinning and reproduction. Environ Contam Toxicol 13:529-549.

*Wiemeyer SN, Lamont TG, Locke LN. 1980. Residues of environmental pollutants and necropsy data for Eastern United States ospreys. Estuaries 3:155-167.

*Wiemeyer SN, Swineford DM, Spitzer PR, et al. 1978. Organochlorine residues in New Jersey osprey eggs. Bull Environ Contam Toxicol 19:56-63.

*Wiersma GB, Tai H, Sand PF. 1972. Pesticide residues in soil from eight cities. Pestic Monit J 6:126-129.

*Wiese III, Basson NCJ. 1966. The degradation of some persistent chlorinated hydrocarbon insecticides applied to different soil types. S Afr J Agric Sci 9:945-969.

*Williams GM. 1980. Classification of genotoxic and epigenetic hepatocarcinogens using liver culture assays. Ann N Y Acad Sci 349:273-282.

*Williams GM, Numoto S. 1984. Promotion of mouse liver neoplasms by the organochlorine pesticides chlordane and heptachlor in comparison to dichlorodiphenyltrichloroethane. Carcinogenesis 5:1689-1696.

*Williams DT, LeBel GL, Junkins E. 1988a. Organohalogen residues in human adipose autopsy samples from six Ontario municipalities. J Assoc Off Anal Chem 71:410-414.

*Williams WM, Holden PW, Parsons DW, et al. 1988b. Pesticides in groundwater data base: 1988 interim report. PB8164230AS.

*Wilson DM, Oloffs PC. 1973. Persistence and movement of α- and γ-chlordane in soils following treatment with high-purity chlordane (Velsicol HCS-3260). Can J Soil Sci 53:465-472.

*Windholz M, Ed. 1983. The Merck index. 10th ed. Rahway, NJ: Merck and Co., Inc., 291.

*Winger PV, Andreasen JK. 1985. Contaminant residues in fish and sediments from Lakes in the Atchafalaya River Basin (Louisiana). Arch Environ Contam Toxicol 14:579-586.

*Wittlinger R, Ballschmiter K. 1990. Studies of the global baseline pollution XIII. C_6-C_{l4} organohalogens (α- and γ-HCH, HCB, PCB, DDT, 4,4'-DDE, *cis*-and *trans*-chlordane, trans-nonachlor, anisols) in the lower troposphere of the Southern Indian Ocean. Fresenius J Anal Chem 336:193-200.

*Wolff MS, Berkowitz GS, Brower S, et al. 2000. Organochlorine exposures and breast cancer risk in New York City women. Environ Res 84(2):151-161. 10.1006/enrs.2000.4075.

*Wood LW, Jones PA, Richards A. 1986. Possible sediment scavenging of chlordane and contamination of the aquatic biota in Belmont Lake, New York. Bull Environ Contam Toxicol 36:159-167.

*Woods JS, Polissar L. 1989. Non-Hodgkin's lymphoma among phenoxy herbicide-exposed farm workers in western Washington state. Chemosphere 18:401-406.

*Worthing CR, Walker SB, eds. 1987. The pesticide manual, a world compendium. 8th ed. The British Crop Protection Council England, 145.

*Wright CG, Leidy RB. 1982. Chlordane and heptachlor in the ambient air of houses treated for termites. Bull Environ Contam Toxicol 28:617-623.

*Xu X, Dailey AB, Talbott EO, et al. 2010. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. Environ Health Perspect 118(1):60-66. 10.1289/ehp.0900919.

*Yess NJ, Houston MG, Gunderson EL. 1991. Food and Drug Administration pesticide residue monitoring of foods: 1978-1982. J Assoc Off Anal Chem 74:265-272.

Young SJV, Kamps LR. 1982. Gas-liquid chromatographic determination of nonpolar organochlorine pesticide residues in a crude vegetable oil and its refinery by-products. J Assoc Off Anal Chem 65:916-920.

*Young S, Clower Jr M, Roach JAG. 1984. Method for determination of organohalogen pesticide residues in vegetable oil refinery by-products. J Assoc Off Anal Chem 67:95-106.

*Zahm SH, Weisenburger DD, Babbitt PA, et al. 1988. A case-control study of non-Hodgkin's lymphoma and agricultural factors in Eastern Nebraska, USA [Abstract]. Am J Epidemiol 128:901.

*Zaroogian GE, Heltshe JF, Johnson M. 1985. Estimation of bioconcentration in marine species using structure-activity models. Environ Toxicol Chem 4:3-12.

*Zheng T, Holford TR, Tessari J, et al. 2000. Oxychlordane and trans-nonachlor in breast adipose tissue and risk of female breast cancer. J Epidemiol Biostat 5(3):153-160.

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordane
CAS Numbers: 12789-03-6 (chlordane technical)
Date: May 1994
April 2017-Updated literature search
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: An MRL has not been derived for acute-duration inhalation exposure to chlordane. Only one acute inhalation study (Khasawinah et al. 1989; Velsicol Chemical Co. 1984) was located, and this study did not sufficiently identify target organs, and serious effects (death, convulsions) occurred at the lowest concentration tested.

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017—Updated literature search
Profile Status:	Final
Route:	Inhalation
Duration:	Intermediate
MRL	0.0002 mg/m^3
Critical Effect:	Hepatocellular hypertrophy
Reference:	Khasawinah et al. 1989; Velsicol Chemical Co. 1984
Point of Departure:	$NOAEL_{ADJ}$ of 0.024 mg/m^3
Uncertainty Factor:	100
LSE Graph Key:	3
Species:	Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.0002 mg/m^3 was derived for chlordane technical. The MRL is based on a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy in rats exposed to chlordane technical for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). The NOAEL was adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Intermediate-duration inhalation exposure data in rats have identified the hematological system, liver, central nervous system, thyroid, and possibly the thymus in female rats, as the target organs (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). A NOAEL of 5.8 mg/m^3 was associated with a LOAEL of 28.2 mg/m^3 for hypersensitivity to touch and decreased thymus weight in female rats and hepatocellular hypertrophy in male and female rats exposed to chlordane technical by inhalation for 8 hours/day, 5 days/week, for 28 days. A 90-day repeated exposure study (8 hours/day, 5 days/week) identified a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy, increased leukocytes, and decreased platelets in female rats. Altered follicular cell structure was noted in male rats exposed at 10 mg/m^3. Among available intermediate-duration inhalation studies for chlordane technical, hepatocellular hypertrophy was the most common effect and occurred in male and female rats at the lowest LOAEL (1.0 mg/m^3) and was therefore selected as the critical effect for deriving an intermediate-duration inhalation MRL for chlordane technical.

Selection of the Principal Study: No adverse effects were observed among monkeys following inhalation exposure to chlordane technical at 10 mg/m^3 for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). Two rat studies (a 28-day study and a 90-day study) evaluated the effects of repeated inhalation exposure to chlordane technical. The 90-day study identified the lowest LOAEL for liver effects and was selected as the principal study for deriving an intermediate-duration inhalation MRL for chlordane (Khasawinah et al. 1989; Velsicol Chemical Co. 1984).

Summary of the Principal Study:

Khasawinah AM, Hardy CJ, Clark GC. 1989. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J Toxicol Environ Health 28:327-347.

Velsicol Chemical Co. 1984. Chlordane: A 90-day inhalation toxicity study in the rat and monkey. Unpublished study No. VCL28 conducted by Huntingdon Research Centre. (cited in EPA 1987f).

Groups of Wistar rats (35–47/sex/group) were exposed to 0, 0.1, 1.0, or 10 mg/m^3 technical chlordane for 8 hours/day, 5 days/week for 13 weeks, followed by a 13-week recovery period. Blood chemistry and urinalysis were performed prior to the beginning of exposure and at exposure weeks 5 and 13. Rats were sacrificed at 9 weeks (5/sex/group) and 13 weeks (15/sex/group). The remaining rats were sacrificed following 13 weeks of recovery. There were no exposure-related effects on mortality, clinical signs (with the exception of sensitivity to touch at the highest exposure level), food consumption, body weight, ophthalmoscopy, rectal temperature, or urinalysis. Exposure-related hematological changes (e.g., increases in total white blood cells, lymphocytes, neutrophils; decreases in hemoglobin and platelets) were of relatively small magnitude, occurred primarily in female rats, and values were within normal ranges for rats; therefore, these changes are not considered adverse. Exposure-related changes indicative of liver effects were observed at 1 mg/m^3 and included increases serum P-450 activity, globulins, total protein, and cholesterol; and decreased albumin and albumin/globulin ratio. Histopathologic examinations revealed hepatocellular hypertrophy in all rats of the 10 mg/m^3 exposure group and 5/15 males and 5/15 females of the 1 mg/m^3 exposure group (compared to 0/15/sex/group at 0 or 0.1 mg/m^3).

Selection of the Point of Departure for the MRL: The NOAEL of 0.1 mg/m^3 was selected as the basis for the MRL.

Intermittent Exposure: The NOAEL was adjusted from intermittent exposure (8 hours/day, 5 days/week) to account for continuous exposure according to the following equation:

$NOAEL_{ADJ}$ = NOAEL (0.1 mg/m^3) x 8 hours/24 hours x 5 days/7days = 0.024 mg/m^3.

Human Equivalent Concentration: The duration-adjusted $NOAEL_{ADJ}$ of 0.024 mg/m^3 was converted to a human equivalent concentration (HEC) according to the equation used to calculate a HEC for extrarespiratory effects of a Category 3 gas (EPA 1994): $NOAEL_{HEC}$ (mg/m^3) = $NOAEL_{ADJ}$ (mg/m^3) x $(H_{b/g})A/(H_{b/g})H$ (i.e., the ratio of the blood:gas [air] partition coefficient of the chemical for the laboratory animal species to the human value; the value of 1.0 is used when measured values are not available).

$NOAEL_{HEC}$ = 0.024 mg/m^3 x 1 = 0.024 mg/m^3.

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 100:

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

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Liver effects were observed in the 28-day and 90-day rat studies (Khasawinah et al. 1989; Velsicol Chemical Co. 1984).

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Inhalation
Duration:	Chronic
MRL	0.00002 mg/m^3
Critical Effect:	Hepatocellular hypertrophy
Reference:	Khasawinah et al. 1989; Velsicol Chemical Co. 1984
Point of Departure:	NOAEL of 0.1 mg/m^3
Uncertainty Factor:	1,000
LSE Graph Key:	3
Species:	Rat

MRL Summary: A chronic-duration inhalation MRL of 0.00002 mg/m^3 (0.02 $\mu g/m^3$) was derived for chlordane technical. The MRL is based on a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy in rats exposed to chlordane technical for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). The NOAEL was adjusted for intermittent exposure and converted to a human equivalent concentration (NOAEL_HEC) of 0.024 mg/m^3 and was divided by an uncertainty factor of 1,000 (10 for extrapolation from intermediate to chronic duration, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Intermediate-duration inhalation exposure data in rats have identified the hematological system, liver, central nervous system, thyroid, and possibly the thymus in female rats, as the target organs (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). A NOAEL of 5.8 mg/m^3 was associated with a LOAEL of 28.2 mg/m^3 for hypersensitivity to touch and decreased thymus weight in female rats and hepatocellular hypertrophy in male and female rats exposed to chlordane technical by inhalation for 8 hours/day, 5 days/week, for 28 days. A 90-day repeated exposure study (8 hours/day, 5 days/week) identified a NOAEL of 0.1 mg/m^3 and a LOAEL of 1.0 mg/m^3 for hepatocellular hypertrophy, increased leukocytes, and decreased platelets in female rats. Altered follicular cell structure was noted in male rats exposed at 10 mg/m^3. Among available intermediate-duration inhalation studies for chlordane technical, hepatocellular hypertrophy was the most common effect and occurred in male and female rats at the lowest LOAEL (1.0 mg/m^3) and was therefore selected as the critical effect for deriving an intermediate-duration inhalation MRL for chlordane technical.

Selection of the Principal Study: No adverse effects were observed among monkeys following inhalation exposure to chlordane technical at 10 mg/m^3 for 8 hours/day, 5 days/week for 90 days (Khasawinah et al. 1989; Velsicol Chemical Co. 1984). Two rat studies (a 28-day study and a 90-day study) evaluated the effects of repeated inhalation exposure to chlordane technical. The 90-day study identified the lowest LOAEL for liver effects and was selected as the principal study for deriving an intermediate-duration inhalation MRL for chlordane (Khasawinah et al. 1989; Velsicol Chemical Co. 1984).

Summary of the Principal Study:

Khasawinah AM, Hardy CJ, Clark GC. 1989. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J Toxicol Environ Health 28:327-347.

Velsicol Chemical Co. 1984. Chlordane: A 90-day inhalation toxicity study in the rat and monkey. Unpublished study No. VCL28 conducted by Huntingdon Research Centre. (cited in EPA 1987f).

Groups of Wistar rats (35–47/sex/group) were exposed to 0, 0.1, 1.0, or 10 mg/m^3 technical chlordane for 8 hours/day, 5 days/week for 13 weeks, followed by a 13-week recovery period. Blood chemistry and urinalysis were performed prior to the beginning of exposure and at exposure weeks 5 and 13. Rats were sacrificed at 9 weeks (5/sex/group) and 13 weeks (15/sex/group). The remaining rats were sacrificed following 13 weeks of recovery. There were no exposure-related effects on mortality, clinical signs (with the exception of sensitivity to touch at the highest exposure level), food consumption, body weight, ophthalmoscopy, rectal temperature, or urinalysis. Exposure-related hematological changes (e.g., increases in total white blood cells, lymphocytes, neutrophils; decreases in hemoglobin and platelets) were of relatively small magnitude, occurred primarily in female rats, and values were within normal ranges for rats; therefore, these changes are not considered adverse. Exposure-related changes indicative of liver effects were observed at 1 mg/m^3 and included increases serum P-450 activity, globulins, total protein, and cholesterol; and decreased albumin and albumin/globulin ratio. Histopathologic examinations revealed hepatocellular hypertrophy in all rats of the 10 mg/m^3 exposure group and 5/15 males and 5/15 females of the 1 mg/m^3 exposure group (compared to 0/15/sex/group at 0 or 0.1 mg/m^3).

Selection of the Point of Departure for the MRL: The NOAEL of 0.1 mg/m^3 was selected as the basis for the MRL.

Intermittent Exposure: The NOAEL was adjusted from intermittent exposure (8 hours/day, 5 days/week) to account for continuous exposure according to the following equation:

$NOAEL_{ADJ}$ = NOAEL (0.1 mg/m^3) x 8 hours/24 hours x 5 days/7days = 0.024 mg/m^3.

Human Equivalent Concentration: The duration-adjusted $NOAEL_{ADJ}$ of 0.024 mg/m^3 was converted to a human equivalent concentration (HEC) according to the equation used to calculate a HEC for extrarespiratory effects of a Category 3 gas (EPA 1994): $NOAEL_{HEC}$ (mg/m^3) = $NOAEL_{ADJ}$ (mg/m^3) x $(H_{b/g})A/(H_{b/g})H$ (i.e., the ratio of the blood:gas [air] partition coefficient of the chemical for the laboratory animal species to the human value; the value of 1.0 is used when measured values are not available).

$NOAEL_{HEC}$ = 0.024 mg/m^3 x 1 = 0.024 mg/m^3.

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 1000:

- 10 for extrapolation from intermediate-duration to chronic-duration exposure
- 10 for extrapolation from animals to humans
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Liver effects were observed in the 28-day and 90-day rat studies (Khasawinah et al. 1989; Velsicol Chemical Co. 1984)

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Acute
MRL	0.001 mg/kg/day
Critical Effect:	Developmental effects
Reference:	Al-Hachim and Al-Baker 1973
Point of Departure:	LOAEL of 1 mg/kg/day
Uncertainty Factor:	1,000
LSE Graph Key:	17
Species:	Mouse

MRL Summary: An acute-duration oral MRL of 0.001 mg/kg/day was derived for chlordane technical. The MRL is based on a LOAEL of 1 mg/kg/day for developmental effects (depressed conditioned avoidance response acquisition, increased exploratory activity in open field testing, and increased seizure threshold) in offspring of mice exposed to chlordane during the third trimester of gestation (7 days) (Al-Hachim and Al-Baker 1973). The LOAEL divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Acute oral data have identified the liver and the central nervous system as target organs in rats and mice; LOAELs range from 50 to 200 mg/kg/day (Ambrose et al. 1953a; Hrdina et al. 1974; Ogata and Izushi 1991; Truhaut et al. 1974, 1975). One oral study in mice identified the lowest LOAEL (1 mg/kg/day for developmental effects) associated with acute-duration oral exposure to chlordane technical (Al-Hachim and Al-Baker 1973). This study identified the lowest LOAEL; therefore, it serves as the critical effect for deriving an acute-duration oral MRL for chlordane technical.

Selection of the Principal Study: The study of Al-Hachim and Al-Baker (1973) was selected as the principal study because it provided the lowest LOAEL (1 mg/kg/day for developmental effects) among candidate acute-duration oral toxicity studies.

Summary of the Principal Study:

Al-Hachim GM, Al-Baker A. 1973. Effects of chlordane on conditioned avoidance response, brain seizure threshold and open-field performance of prentally-reated mice. Br J Pharmacol 49:311-315.

Groups of pregnant albino mice (6/group) were administered technical-grade chlordane by gavage (in olive oil) for 7 days during the third trimester) at 0, 1, or 2.5 mg/kg/day. Ten mice/litter were tested for conditioned avoidance response during postnatal days 30–37. Electroshock seizure threshold was measured at 38 days of age, and open field testing was performed during postnatal weeks 6 and 7. Offspring exhibited significantly depressed conditioned avoidance response acquisition, increased exploratory activity in open field testing, and increased seizure threshold at the lowest maternal dose level (1 mg/kg/day).

Selection of the Point of Departure for the MRL: The LOAEL of 1 mg/kg/day was selected as the basis for the MRL.

Intermittent Exposure: Not applicable.

Human Equivalent Concentration: Not applicable.

Uncertainty Factor: The LOAEL was divided by a total uncertainty factor of 1,000:

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

MRL = LOAEL ÷ UFs
1 mg/kg/day ÷ 1,000 = 0.001 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: No supporting study results.

Agency Contact (Chemical Manager): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
MRL	0.0006 mg/kg/day
Critical Effect:	Liver effects
Reference:	EPA 1985a; Khasawinah and Grutsch 1989a
Point of Departure:	LOAEL of 0.055 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	47
Species:	Rat

MRL Summary: The chronic-duration oral MRL for chlordane technical was adopted as the intermediate-duration oral MRL as well. See the MRL Worksheet for the chronic-duration oral MRL for details regarding selection of the critical effect and principal study, summary of the principal study, selection of the point of departure for the MRL, and uncertainty factors.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Centrilobular hypertrophy was also observed in rats receiving chlordane technical from the diet for up to 9 months at an estimated dose of 0.125 mg/kg/day, the lowest dose tested (Ortega et al. 1957).

Agency Contact (Chemical Manager): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordane
CAS Numbers:	12789-03-6 (chlordane technical)
Date:	May 1994 April 2017-Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Chronic
MRL	0.0006 mg/kg/day
Critical Effect:	Hepatocellular hypertrophy
Reference:	EPA 1985a; Khasawinah and Grutsch 1989a
Point of Departure:	NOAEL of 0.055 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	47
Species:	Rat

MRL Summary: A chronic-duration oral MRL of 0.0006 mg/kg/day was derived for chlordane technical. The MRL is based on a NOAEL of 0.055 mg/kg/day and a LOAEL of 0.237 mg/kg/day for hepatocellular hypertrophy in female rats administered chlordane technical in the diet for 30 months (EPA 1985a; Khasawinah and Grutsch 1989a). The NOAEL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Among available chronic-duration oral animal studies for chlordane technical, targets of toxicity include the liver and body weight (Ambrose et al. 1953; EPA 1985a; Khasawinah and Grutsch 1989a). Body weight effects were observed at 16 mg/kg/day (Ambrose et al. 1953), whereas hepatocellular hypertrophy was noted in rats at doses as low as 0.273 mg/kg/day in one rat study (EPA 1985a; Khasawinah and Grutsch 1989a) and 4 mg/kg/day in another rat study (Ambrose et al. 1953). Hepatocellular hypertrophy was also noted in male and female mice at 0.47 mg/kg/day, with a corresponding NOAEL of 0.1 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989a). NCI (1977) reported neurological effects in rats and mice administered analytical-grade chlordane in the diet at estimated doses of 7.3–12.1 mg/kg/day (corresponding NOAELs were 3.9 and 6.0 mg/kg/day for rats and mice, respectively). Among available chronic-duration oral animal data, the most sensitive effect is hepatocellular hypertrophy, which was selected as the critical effect for deriving a chronic-duration oral MRL for chlordane technical.

Selection of the Principal Study: Treatment-related liver effects were associated with chronic-duration oral exposure to chlordane technical in rats (Ambrose et al. 1953; Khasawinah and Grutsch 1989a) and mice (Khasawinah and Grutsch 1989a). The study reports that reported the lowest LOAEL for liver effects (0.273 mg/kg/day in female rats) and corresponding NOAEL (0.055 mg/kg/day in female rats) were selected to represent the principal study for deriving a chronic-duration oral MRL for chlordane technical.

Summary of the Principal Study:

EPA. 1985a. Memorandum. 6(a)(2) Data on chlordane. Chronic mouse and rat studies for oncogenicity testing. Act. Nos. 252267, 254665, 251815, Review No. 004635. Office of Pesticides and Toxic Substances, Washington, DC.

Khasawinah AM, Grutsch JF. 1989a. Chlordane thirty-month tumorigenicity and chronic toxicity test in rats. Regul Toxicol Pharmacol 10:95-109.

Groups of Fischer 344 rats (80/sex/group) were administered chlordane technical in the diet for up to 30 months at 0, 1, 5, or 25 ppm (author-calculated doses of 0, 0.045, 0.229, and 1.175 mg/kg/day, respectively, for males and 0, 0.055, 0.273, and 1.409 mg/kg/day, respectively, for females). The only reported treatment-related nonneoplastic effect was that of hepatocellular hypertrophy in females at 0.273 mg/kg/day. There were no apparent treatment-related effects on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or renal systems, or dermal/ocular or body weight effects at the highest dose tested (1.175 and 1.409 mg/kg/day for males and females, respectively).

Selection of the Point of Departure for the MRL: The NOAEL of 0.055 mg/kg/day for female rats was selected as the basis for the MRL.

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

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

MRL = NOAEL ÷ UFs
0.055 mg/kg/day ÷ 100 = 0.0006 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Hepatocellular hypertrophy was also observed in male and female mice orally exposed to chlordane technical for 24 months at 0.47 mg/kg/day; the corresponding NOAEL was 0.10 mg/kg/day (EPA 1985a; Khasawinah and Grutsch 1989a).

Agency Contact (Chemical Manager): Jennifer Przybyla

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLORDANE

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 chlordane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, and chemical interactions data for chlordane. 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 chlordane 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 chlordane are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for chlordane (ATSDR 1994), thus, the literature search was restricted to studies published between January 1990 to April 2017. The following main databases were searched in April 2017:

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

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

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance priority list (SPL) resource page, and other items as needed. Regulations applicable to chlordane 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	
04/2017	((("Chlordan"[mh]) OR ("nonachlor"[nm])) AND (1992/01/01 : 3000[mhda] OR 1992/01/01 : 3000[dp])) OR (((("1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-methyleneindane"[tw] "1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-

Table B-2. Database Query Strings

Database search date	Query string
	methanoindene"[tw] OR "1,2,4,5,6,7,8,8-Octachloro-4,7-methano-3a, 4,7,7a-tetrahydroindane"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano [Italian]"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoinden, 1,2,4,5,6,7,8,9-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "Aspon-chlordane"[tw] OR "Chlor Kil"[tw] OR "Chlordan"[tw] OR "Chlordane"[tw] OR "Chlordane, technical"[tw] OR "Chlordane-technical"[tw] OR "Chlorindan"[tw] OR "Chlorotox"[tw] OR "Clordano"[tw] OR "Corodane"[tw] OR "Cortilan-neu"[tw] OR "Dichlorochlordene"[tw] OR "Dowchlor"[tw] OR "HCS 3260"[tw] OR "Intox"[tw] OR "Kilex lindane"[tw] OR "Kypchlor"[tw] OR "Octa-klor"[tw] OR "Octachlor"[tw] OR "Octachlordane"[tw] OR "Octachloro-4,7-methanotetrahydroindane"[tw] OR "Octachlorodihydrodicyclopentadiene"[tw] OR "Oktaterr"[tw] OR "OMS 1437"[tw] OR "Ortho-Klor"[tw] OR "SD 5532"[tw] OR "Shell SD-5532"[tw] OR "Starchlor"[tw] OR "Sydane"[tw] OR "Synklor"[tw] OR "TAT chlor 4"[tw] OR "Termex"[tw] OR "Termi-ded"[tw] OR "Topichlor 20"[tw] OR "Topiclor"[tw] OR "Toxichlor"[tw] OR "Unexan-Koeder"[tw] OR "Velsicol 1068"[tw] OR "(1alpha, 2alpha, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "(1alpha, 2beta, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1-alpha, 3a-alpha, 4-beta, 5-alpha, 6a-alpha)-"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1R, 3aS, 4S, 5S, 6aS)-rel-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1-alpha, 3a-beta, 6-alpha, 7a-beta, 8R*)-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1R, 3aR, 6S, 7aR, 8R)-rel-"[tw] OR "1-exo, 2-endo, 4,5,6,7,8,8-Octachloro-2,3-exo-epoxy-2,3,3a, 4,7,7a-hexahydro-4,7-methanoindene"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-,(1aR, 1bS, 2R, 5S, 5aR, 6S, 6aS)-rel-"[tw] OR "3a, 4,7,7a-Tetrahydro-1,2-epoxy-4,5,6,7,8,8-hexachloro-4,7-methanoindan"[tw] OR "4,5,6,7,8,8-Hexachlor-delta(sup 1,5)-tetrahydro-4,7-methanoinden"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methano-1H-indene"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methanoindene"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachlor-2,3,3a, 4,7,7a-hexahydro-,(1-alpha, 2-beta, 3-alpha, 3a-alpha, 4-beta, 7-beta, 7a-alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha, 3aalpha, 4beta, 7beta, 7aalph"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3alpha, 3aalpha, 4beta, 7beta,"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2R, 3aS, 4S, 7R, 7aS)-rel-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2S, 3aS, 4S, 7R, 7aS)-rel"[tw] OR "4,7-Methano-1H-indene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3-epoxy-3a, 4,7,7a-tetrahydro-, exo, endo-"[tw] OR "4,7-Methanoindan, 1-alpha, 2-alpha, 4-beta, 5,6,7-beta, 8,8-octachloro-3a-alpha, 4,7,7a-alpha-tetrahydro-"[tw] OR "4,7-Methanoindan, 3a, 4,7,7a-tetrahydro-2,3-epoxy-1,2,4,5,6,7,8,8-octachloro-, exo,

Table B-2. Database Query Strings

Database search date	Query string
	endo-"[tw] OR "4,7-Methanoindan, 3a-beta, 4,7,7a-beta-tetrahydro-1-beta, 2-alpha, 4-alpha, 5,6,7-alpha, 8,8-octachloro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-delta(sup 1,5)-tetrahydro-"[tw] OR "c-Nonachlor"[tw] OR "Chlordene"[tw] OR "cis-Nonachlor"[tw] OR "gamma-Chlordene"[tw] OR "Nonachlor, cis-"[tw] OR "Nonachlor, trans-"[tw] OR "Oxychlordan"[tw] OR "Oxychlordane"[tw] OR "t-Nonachlor"[tw] OR "trans-Nonachlor"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] 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 "pharmacology"[sh:noexp] OR "chlordan/antagonists and inhibitors"[Mesh Terms] OR "hydrocarbons, chlorinated/antagonists and inhibitors"[Mesh Terms] OR toxicokinetics[mh:noexp])) OR (("1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-methyleneindane"[tw] OR "1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methanoindene"[tw] OR "1,2,4,5,6,7,8,8-Octachloro-4,7-methano-3a, 4,7,7a-tetrahydroindane"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano"[tw] OR "1,2,4,5,6,7,8,8-Ottochloro-3a, 4,7,7a-tetraidro-4,7-endo-metano-indano [Italian]"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoinden, 1,2,4,5,6,7,8,9-octachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "Aspon-chlordane"[tw] OR "Chlor Kil"[tw] OR "Chlordan"[tw] OR "Chlordane"[tw] OR "Chlordane, technical"[tw] OR "Chlordane-technical"[tw] OR "Chlorindan"[tw] OR "Chlorotox"[tw] OR "Clordano"[tw] OR "Corodane"[tw] OR "Cortilan-neu"[tw] OR "Dichlorochlordene"[tw] OR "Dowchlor"[tw] OR "HCS 3260"[tw] OR "Intox"[tw] OR "Kilex lindane"[tw] OR "Kypchlor"[tw] OR "Octa-klor"[tw] OR "Octachlor"[tw] OR "Octachlordane"[tw] OR "Octachloro-4,7-methanotetrahydroindane"[tw] OR "Octachlorodihydrodicyclopentadiene"[tw] OR "Oktaterr"[tw] OR "OMS 1437"[tw] OR "Ortho-Klor"[tw] OR "SD 5532"[tw] OR "Shell SD-5532"[tw] OR "Starchlor"[tw] OR "Sydane"[tw] OR "Synklor"[tw] OR "TAT chlor 4"[tw] OR "Termex"[tw] OR "Termi-ded"[tw] OR "Topichlor 20"[tw] OR "Topiclor"[tw] OR "Toxichlor"[tw] OR "Unexan-Koeder"[tw] OR "Velsicol 1068"[tw] OR "(1alpha, 2alpha, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "(1alpha, 2beta, 3aalpha, 4beta, 7beta, 7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a, 4,7,7a-hexahydro-4,7-methano-1H-indene"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1-alpha, 3a-alpha, 4-beta, 5-alpha, 6a-alpha)-"[tw] OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a, 4,5,6,6a-hexahydro-,(1R, 3aS, 4S, 5S, 6aS)-rel-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1-alpha, 3a-beta, 6-alpha, 7a-beta, 8R*)-"[tw] OR "1,6-Methano-1H-indene, 2,3,3a, 4,5,8-hexachloro-3a, 6,7,7a-tetrahydro-,(1R, 3aR, 6S, 7aR, 8R)-rel-"[tw] OR "1-exo, 2-endo, 4,5,6,7,8,8-

Table B-2. Database Query Strings

Database search date	Query string
	Octachloro-2,3-exo-epoxy-2,3,3a, 4,7,7a-hexahydro-4,7-methanoindene"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-"[tw] OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a, 7,7-octachloro-1a, 1b, 5,5a, 6,6a-hexahydro-,(1aR, 1bS, 2R, 5S, 5aR, 6S, 6aS)-rel-"[tw] OR "3a, 4,7,7a-Tetrahydro-1,2-epoxy-4,5,6,7,8,8-hexachloro-4,7-methanoindan"[tw] OR "4,5,6,7,8,8-Hexachlor-delta(sup 1,5)-tetrahydro-4,7-methanoinden"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methano-1H-indene"[tw] OR "4,5,6,7,8,8-Hexachloro-3a, 4,7,7a-tetrahydro-4,7-methanoindene"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachlor-2,3,3a, 4,7,7a-hexahydro-,(1-alpha, 2-beta, 3-alpha, 3a-alpha, 4-beta, 7-beta, 7a-alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3alpha, 3aalpha, 4beta, 7beta, 7aalph"[tw] OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3alpha, 3aalpha, 4beta, 7beta,"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2alpha, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1alpha, 2beta, 3a alpha, 4beta, 7beta, 7a alpha)-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2R, 3aS, 4S, 7R, 7aS)-rel-"[tw] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a, 4,7,7a-hexahydro-,(1R, 2S, 3aS, 4S, 7R, 7aS)-rel"[tw] OR "4,7-Methano-1H-indene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3-epoxy-3a, 4,7,7a-tetrahydro-, exo, endo-"[tw] OR "4,7-Methanoindan, 1-alpha, 2-alpha, 4-beta, 5,6,7-beta, 8,8-octachloro-3a-alpha, 4,7,7a-alpha-tetrahydro-"[tw] OR "4,7-Methanoindan, 3a, 4,7,7a-tetrahydro-2,3-epoxy-1,2,4,5,6,7,8,8-octachloro-, exo, endo-"[tw] OR "4,7-Methanoindan, 3a-beta, 4,7,7a-beta-tetrahydro-1-beta, 2-alpha, 4-alpha, 5,6,7-alpha, 8,8-octachloro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-3a, 4,7,7a-tetrahydro-"[tw] OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-delta(sup 1,5)-tetrahydro-"[tw] OR "c-Nonachlor"[tw] OR "Chlordene"[tw] OR "cis-Nonachlor"[tw] OR "gamma-Chlordene"[tw] OR "Nonachlor, cis-"[tw] OR "Nonachlor, trans-"[tw] OR "Oxychlordan"[tw] OR "Oxychlordane"[tw] OR "t-Nonachlor"[tw] OR "trans-Nonachlor"[tw]) NOT medline[sb])) AND (1992/01/01 : 3000[dp] OR 1992/01/01 : 3000[crdt] OR 1992/01/01 : 3000[edat]))
Toxline	
04/2017	"(57-74-9 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org] (5103-71-9 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org] (5103-74-2 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org] (27304-13-8 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org]

Table B-2. Database Query Strings

Database search date	Query string
	OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	(56641-38-4 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	(12789-03-6 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	(56534-02-2 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	(39765-80-5 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	(5103-73-1 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	(3734-48-3 [rn]) AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	39765-80-5 [rn] [not] PubMed [org] [not] pubdart [org]
	("4 7 methanoindan 1 2 4 5 6 7 8 8 octachloro 2 3 3a 4 7 7a hexahydro " OR "4 7 methanoindan 1 2 4 5 6 7 8 8 octachloro 3a 4 7 7a tetrahydro " OR "4 7 methanoinden 1 2 4 5 6 7 8 9 octachloro 3a 4 7 7a tetrahydro " OR "aspon chlordane" OR "chlor kil" OR "chlordan" OR "chlordane") AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("chlordane technical" OR "chlordane technical" OR "chlorindan" OR "chlorotox" OR "clordano" OR "corodane" OR "cortilan neu" OR "dichlorochlordene" OR "dowchlor" OR "hcs 3260" OR "intox" OR "kilex lindane" OR "kypchlor" OR "octa klor" OR "octachlor" OR "octachlordane" OR "octachloro 4 7 methanotetrahydroindane") AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR

Table B-2. Database Query Strings

Database search date	Query string
	RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("c nonachlor" OR "chlordene" OR "cis nonachlor" OR "gamma chlordene" OR "nonachlor cis " OR "nonachlor trans " OR "oxychlordan" OR "oxychlordane" OR "t nonachlor" OR "trans nonachlor") AND 1992:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
04/2017	(FILE 'HOME' ENTERED AT 13:26:52 ON 06 APR 2017) FILE 'TOXCENTER' ENTERED AT 13:27:06 ON 06 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 5760 SEA FILE=TOXCENTER 12789-03-6 L2 1053 SEA FILE=TOXCENTER 57-74-9 L3 4698 SEA FILE=TOXCENTER 5103-71-9 OR 5103-74-2 OR 27304-13-8 OR 56641-38-4 OR 56534-02-2 OR 39765-80-5 OR 5103-73-1 OR 3734-48-3 L4 10746 SEA FILE=TOXCENTER L1 OR L2 OR L3 L5 10719 SEA FILE=TOXCENTER L4 NOT TSCATS/FS L6 10484 SEA FILE=TOXCENTER L5 NOT PATENT/DT L7 6220 SEA FILE=TOXCENTER L6 AND PY>1991 ACT TOXQUERY/Q --------- L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L23 QUE (ENDOCRIN? AND DISRUPT?) L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L30 QUE (NEPHROTOX? OR HEPATOTOX?) L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L33 QUE 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 OR L31 OR L32 L34 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?) L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L36 QUE L33 OR L34 OR L35 L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L38 QUE L36 OR L37 --------- L39 3586 SEA FILE=TOXCENTER L7 AND L38 L40 198 SEA FILE=TOXCENTER L39 AND MEDLINE/FS L41 882 SEA FILE=TOXCENTER L39 AND BIOSIS/FS L42 2446 SEA FILE=TOXCENTER L39 AND CAPLUS/FS L43 60 SEA FILE=TOXCENTER L39 NOT (L40 OR L41 OR L42) SAVE TEMP L42 CHLORDANECA CHLORDANECA/A L44 3074 DUP REM L40 L41 L43 L42 (512 DUPLICATES REMOVED) ANSWERS '1-3074' FROM FILE TOXCENTER L*** DEL 198 S L39 AND MEDLINE/FS L*** DEL 198 S L39 AND MEDLINE/FS L45 198 SEA FILE=TOXCENTER L44

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 882 S L39 AND BIOSIS/FS
	L*** DEL 882 S L39 AND BIOSIS/FS
	L46 788 SEA FILE=TOXCENTER L44
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L47 2037 SEA FILE=TOXCENTER L44
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L48 51 SEA FILE=TOXCENTER L44
	L49 788 SEA FILE=TOXCENTER (L45 OR L46 OR L47 OR L48) AND BIOSIS/FS
	L50 643 SEA FILE=TOXCENTER L49 AND PY>1998
	L51 0 SEA FILE=TOXCENTER L49 AND CAPLUS/FS
	L*** DEL 198 S L39 AND MEDLINE/FS
	L*** DEL 198 S L39 AND MEDLINE/FS
	L52 198 SEA FILE=TOXCENTER L44
	L*** DEL 882 S L39 AND BIOSIS/FS
	L*** DEL 882 S L39 AND BIOSIS/FS
	L53 788 SEA FILE=TOXCENTER L44
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L54 2037 SEA FILE=TOXCENTER L44
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L55 51 SEA FILE=TOXCENTER L44
	L56 2037 SEA FILE=TOXCENTER (L52 OR L53 OR L54 OR L55) AND CAPLUS/FS SAVE TEMP L56 CHLORDANECA/A
	L*** DEL 198 S L39 AND MEDLINE/FS
	L*** DEL 198 S L39 AND MEDLINE/FS
	L57 198 SEA FILE=TOXCENTER L44
	L*** DEL 882 S L39 AND BIOSIS/FS
	L*** DEL 882 S L39 AND BIOSIS/FS
	L58 788 SEA FILE=TOXCENTER L44
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L*** DEL 2446 S L39 AND CAPLUS/FS
	L59 2037 SEA FILE=TOXCENTER L44
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L*** DEL 60 S L39 NOT (L40 OR L41 OR L42)
	L60 51 SEA FILE=TOXCENTER L44
	L61 51 SEA FILE=TOXCENTER (L57 OR L58 OR L59 OR L60) NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L62 694 SEA FILE=TOXCENTER L50 OR L61
	L63 2731 SEA FILE=TOXCENTER L62 OR L56 D SCAN L62 D SCAN L56

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
04/2017	Compound searched: 57-74-9 5103-71-9 5103-74-2 27304-13-8 56641-38-4 12789-03-6 56534-02-2 39765-80-5 5103-73-1 3734-48-3
NTP	
04/2017	57-74-9 5103-71-9 5103-74-2 27304-13-8 56641-38-4 12789-03-6 56534-02-2 39765-80-5 5103-73-1 3734-48-3 chlordan chlordane chlordene oxychlordane cis-Nonachlor trans-Nonachlor
NIH RePORTER	
08/2017	Text Search: "1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-methyleneindane" OR "1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene" OR "1,2,4,5,6,7,8,8-Octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-" OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-" OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-" OR "4,7-Methanoinden, 1,2,4,5,6,7,8,9-octachloro-3a,4,7,7a-tetrahydro-" OR "Aspon-chlordane" OR "Chlor Kil" OR "Chlordan" OR "Chlordane" OR "Chlordane, technical" OR "Chlordane-technical" OR "Chlorindan" OR "Chlorotox" OR "Clordano" OR "Corodane" OR "Cortilan-neu" OR "Dichlorochlordene" OR "Dowchlor" OR "HCS 3260" OR "Intox" OR "Kilex lindane" OR "Kypchlor" OR "Octa-klor" OR "Octachlor" OR "Octachlordane" OR "Octachloro-4,7-methanotetrahydroindane" OR "Octachlorodihydrodicyclopentadiene" OR "Oktaterr" OR "OMS 1437" OR "Ortho-Klor" OR "SD 5532" OR "Shell SD-5532" OR "Starchlor" OR "Sydane" OR "Synklor" OR "TAT chlor 4" OR "Termex" OR "Termi-ded" OR "Topichlor 20" OR "Topiclor" OR "Toxichlor" OR "Unexan-Koeder" OR "Velsicol 1068" OR "(1alpha,2alpha,3aalpha,4beta,7beta,7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene" OR "(1alpha,2beta,3aalpha,4beta,7beta,7aalpha)-1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene" OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	1,3a,4,5,6,6a-hexahydro-, (1-alpha,3a-alpha,4-beta,5-alpha,6a-alpha)-" OR "1,4-Ethenopentalene, 1,2,3,5,7,8-hexachloro-1,3a,4,5,6,6a-hexahydro-, (1R,3aS,4S,5S,6aS)-rel-" OR "1,6-Methano-1H-indene, 2,3,3a,4,5,8-hexachloro-3a,6,7,7a-tetrahydro-, (1-alpha,3a-beta,6-alpha,7a-beta,8R)-" OR "1,6-Methano-1H-indene, 2,3,3a,4,5,8-hexachloro-3a,6,7,7a-tetrahydro-, (1R,3aR,6S,7aR,8R)-rel-" OR "1-exo,2-endo,4,5,6,7,8,8-Octachloro-2,3-exo-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene" OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a,7,7-octachloro-1a,1b,5,5a,6,6a-hexahydro-" OR "2,5-Methano-2H-indeno(1,2-b)oxirene, 2,3,4,5,6,6a,7,7-octachloro-1a,1b,5,5a,6,6a-hexahydro-, (1aR,1bS,2R,5S,5aR,6S,6aS)-rel-" OR "3a,4,7,7a-Tetrahydro-1,2-epoxy-4,5,6,7,8,8-hexachloro-4,7-methanoindan" OR "4,5,6,7,8,8-Hexachlor-delta(sup 1,5)-tetrahydro-4,7-methanoinden" OR "4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene" OR "4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
	Text Search: "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachlor-2,3,3a,4,7,7a-hexahydro-, (1-alpha,2-beta,3-alpha,3a-alpha,4-beta,7-beta,7a-alpha)-" OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2alpha,3alpha)-" OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2alpha,3alpha,3aalpha,4beta,7beta,7aalph" OR "4,7-Methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2beta,3alpha,3aalpha,4beta,7beta," OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2alpha,3a alpha,4beta,7beta,7a alpha)-" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1alpha,2beta,3a alpha,4beta,7beta,7a alpha)-" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1R,2R,3aS,4S,7R,7aS)-rel-" OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-, (1R,2S,3aS,4S,7R,7aS)-rel" OR "4,7-Methano-1H-indene, 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-" OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-, exo,endo-" OR "4,7-Methanoindan, 1-alpha,2-alpha,4-beta,5,6,7-beta,8,8-octachloro-3a-alpha,4,7,7a-alpha-tetrahydro-" OR "4,7-Methanoindan, 3a,4,7,7a-tetrahydro-2,3-epoxy-1,2,4,5,6,7,8,8-octachloro-, exo,endo-" OR "4,7-Methanoindan, 3a-beta,4,7,7a-beta-tetrahydro-1-beta,2-alpha,4-alpha,5,6,7-alpha,8,8-octachloro-" OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-" OR "4,7-Methanoindene, 4,5,6,7,8,8-hexachloro-delta(sup 1,5)-tetrahydro-" OR "c-Nonachlor" OR "Chlordene" OR "cis-Nonachlor" OR "gamma-Chlordene" OR "Nonachlor, cis-" OR "Nonachlor, trans-" OR "Oxychlordan" OR "Oxychlordane" OR "t-Nonachlor" OR "trans-Nonachlor" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

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

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 4,696
- Number of records identified from other strategies: 27
- Total number of records to undergo literature screening: 4,723

B.1.2 Literature Screening

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

- 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.

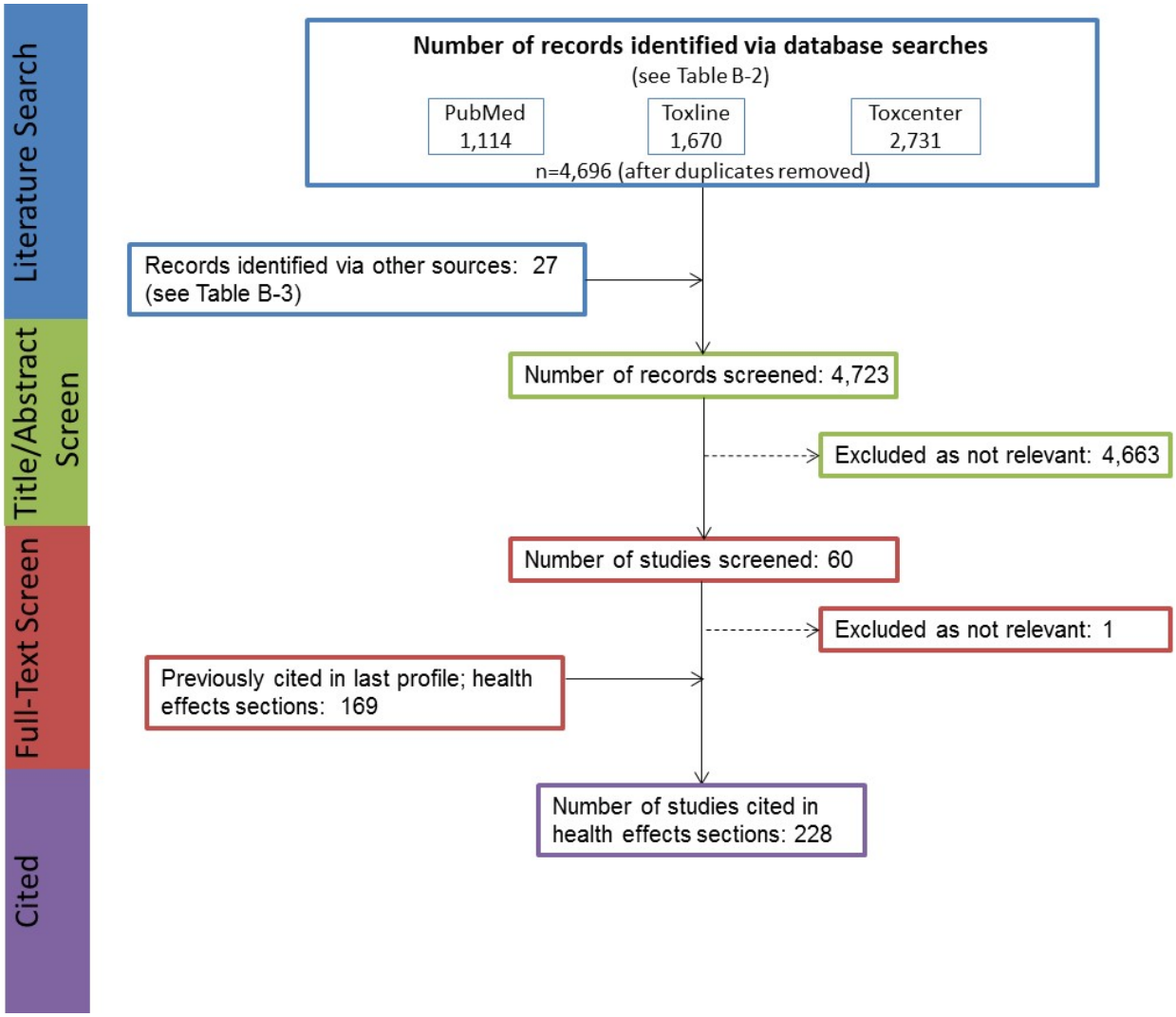
- Number of titles and abstracts screened: 4,723
- Number of studies considered relevant and moved to the next step: 60

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: 60
- Number of studies cited in the health effects sections of the existing toxicological profile (May,1994): 169
- Total number of studies cited in the health effects sections of the updated profile: 228

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

Figure B-1. April 2017 Literature Search Results and Screen for Chlordane



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] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
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									

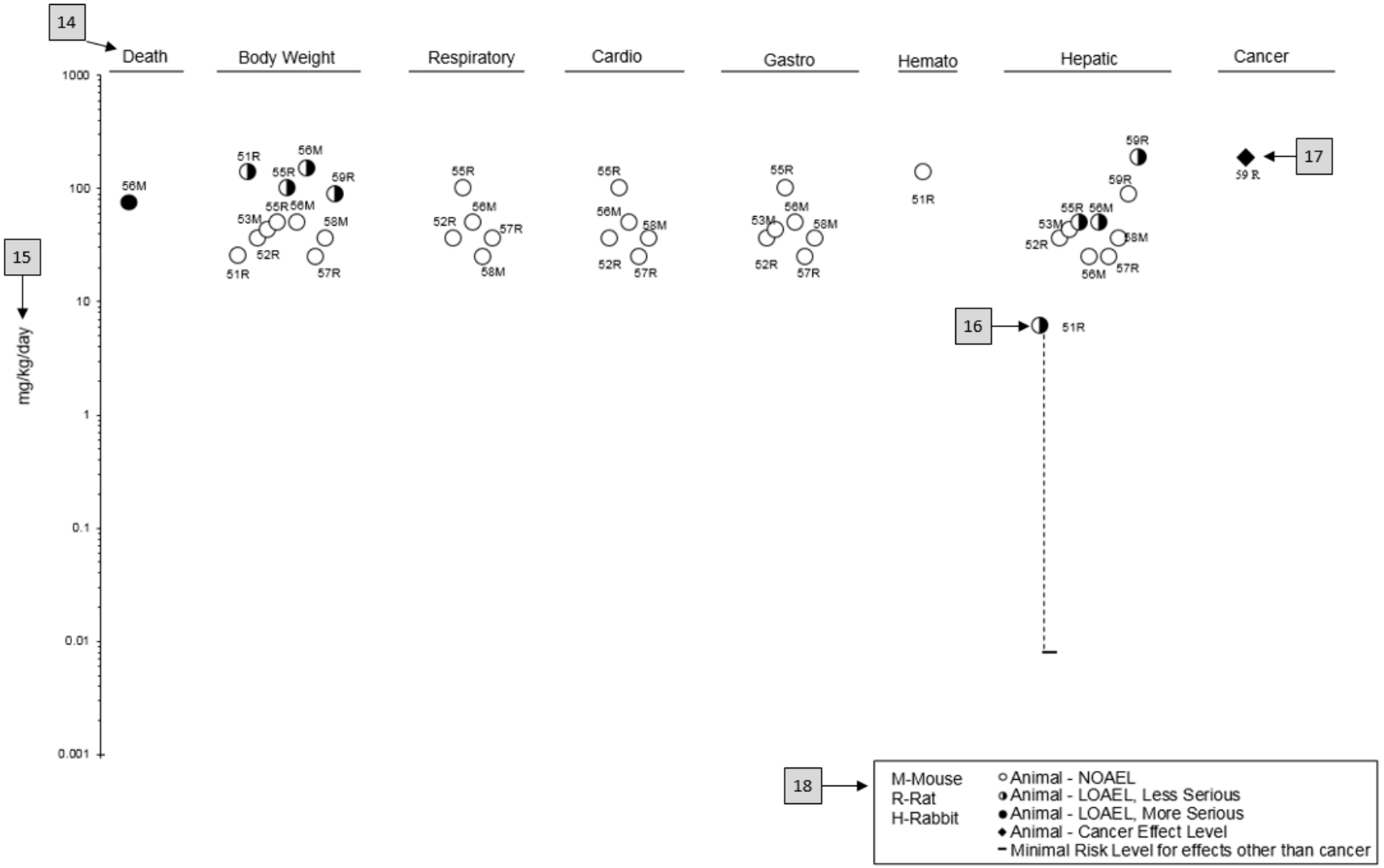
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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

13 → Chronic (≥365 days)



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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