

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.

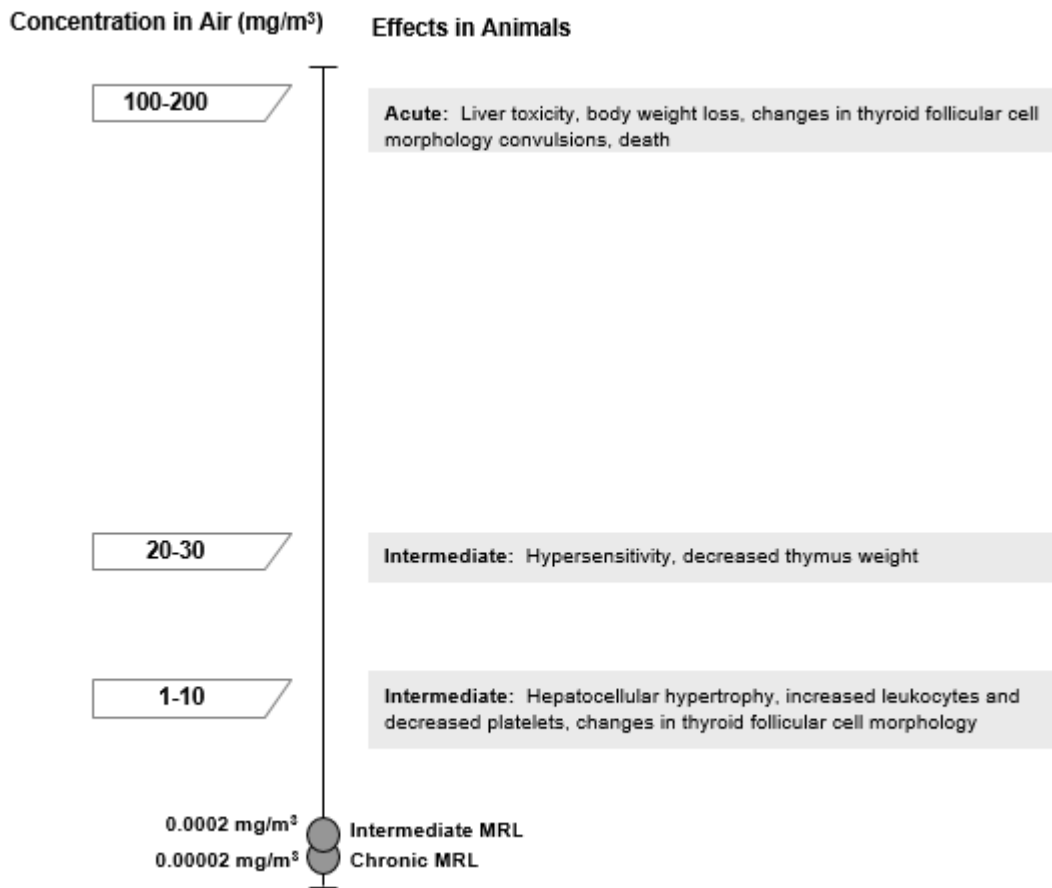
The most likely source of exposure of the general population to chlordane was from living in homes that were treated with chlordane for termites. The next most likely source was from eating chlordane-contaminated food. Because chlordane uses were banned in 1988, it is not likely that current populations 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. RELEVANCE TO PUBLIC HEALTH

1.2 SUMMARY OF HEALTH EFFECTS

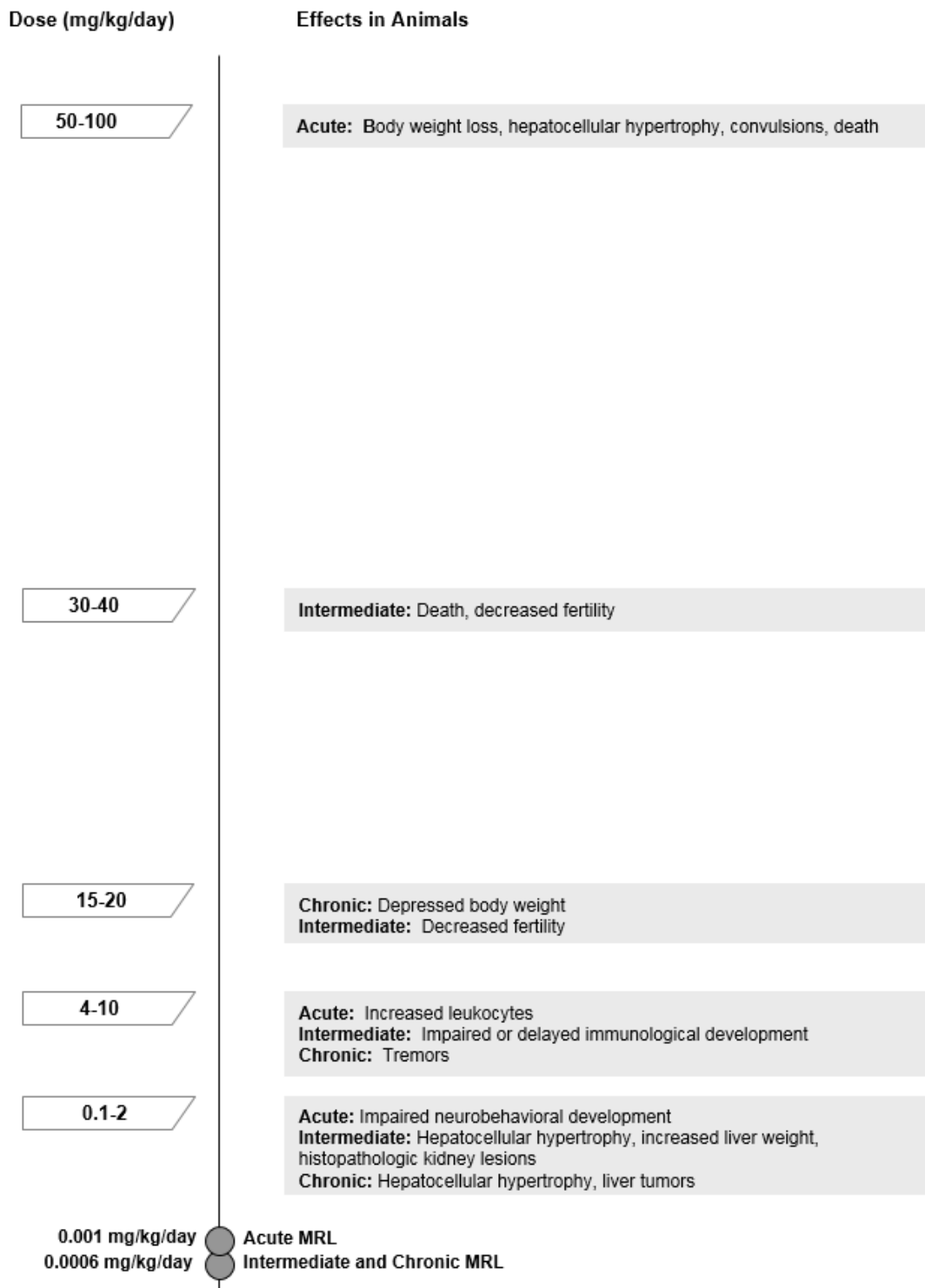
Animal studies identify hepatic, developmental, and hematological endpoints as most sensitive to chlordane toxicity. For each exposure duration, the lowest adverse effect level for each of these endpoints and others is identified in Figures 1-1 and 1-2. Oral studies in mice have consistently reported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



1. RELEVANCE TO PUBLIC HEALTH

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



1. RELEVANCE TO PUBLIC HEALTH

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/m³ (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/m³ 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

1. RELEVANCE TO PUBLIC HEALTH

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.

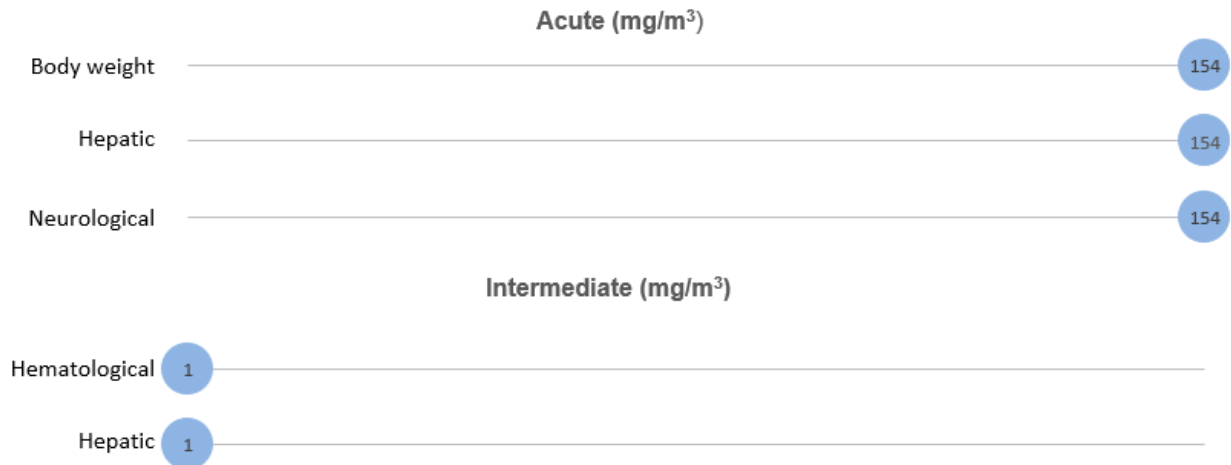
1.3 MINIMAL RISK LEVELS (MRLs)

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.

1. RELEVANCE TO PUBLIC HEALTH

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

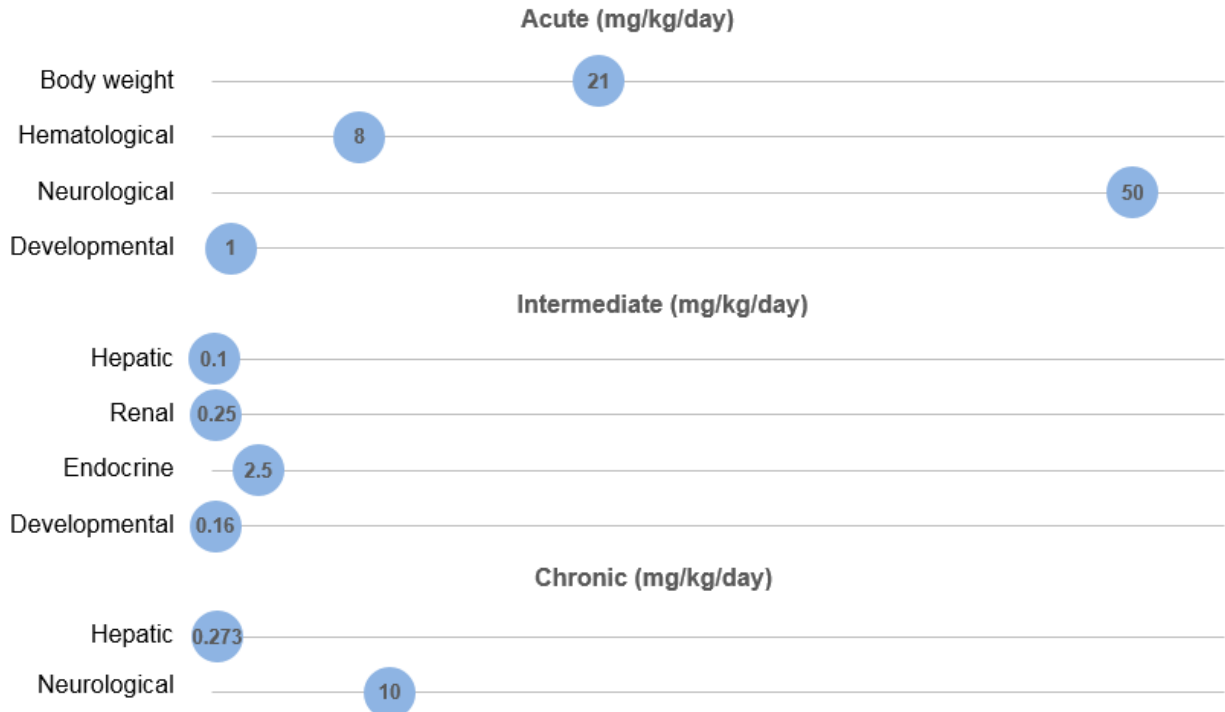
Hepatic and hematological endpoints are the most sensitive targets of chlordane.
Numbers in circles are the lowest LOAELs (ppm) for all health effects in animals; no exposure-response data were identified for humans.



1. RELEVANCE TO PUBLIC HEALTH

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.



1. RELEVANCE TO PUBLIC HEALTH

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/m³)					
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

^aSee Appendix A for additional information.

^bRat NOAEL of 0.1 mg/m³ adjusted for intermittent exposure 5 days/7 days and 8 hours/24 hours = 0.024 mg/m³.

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