CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Mirex and chlordecone are structurally similar highly-chlorinated derivatives of cyclopentadiene. The only structural difference between mirex and chlordecone is that mirex has two bridgehead chlorine atoms where chlordecone has a carbonyl oxygen atom. Mirex was commercially introduced in the United States in 1959 for use in pesticide formulations and as an industrial fire retardant. In the 1960s, mirex was commonly used to control fire ants in southern States. Mirex was banned for use in the United States in 1978, except for use on pineapples until stocks on hand were exhausted. Chlordecone was mainly registered for use in the United States to control banana root borer, although it was also used to control other pests. All registered products containing chlordecone were effectively canceled in 1978.

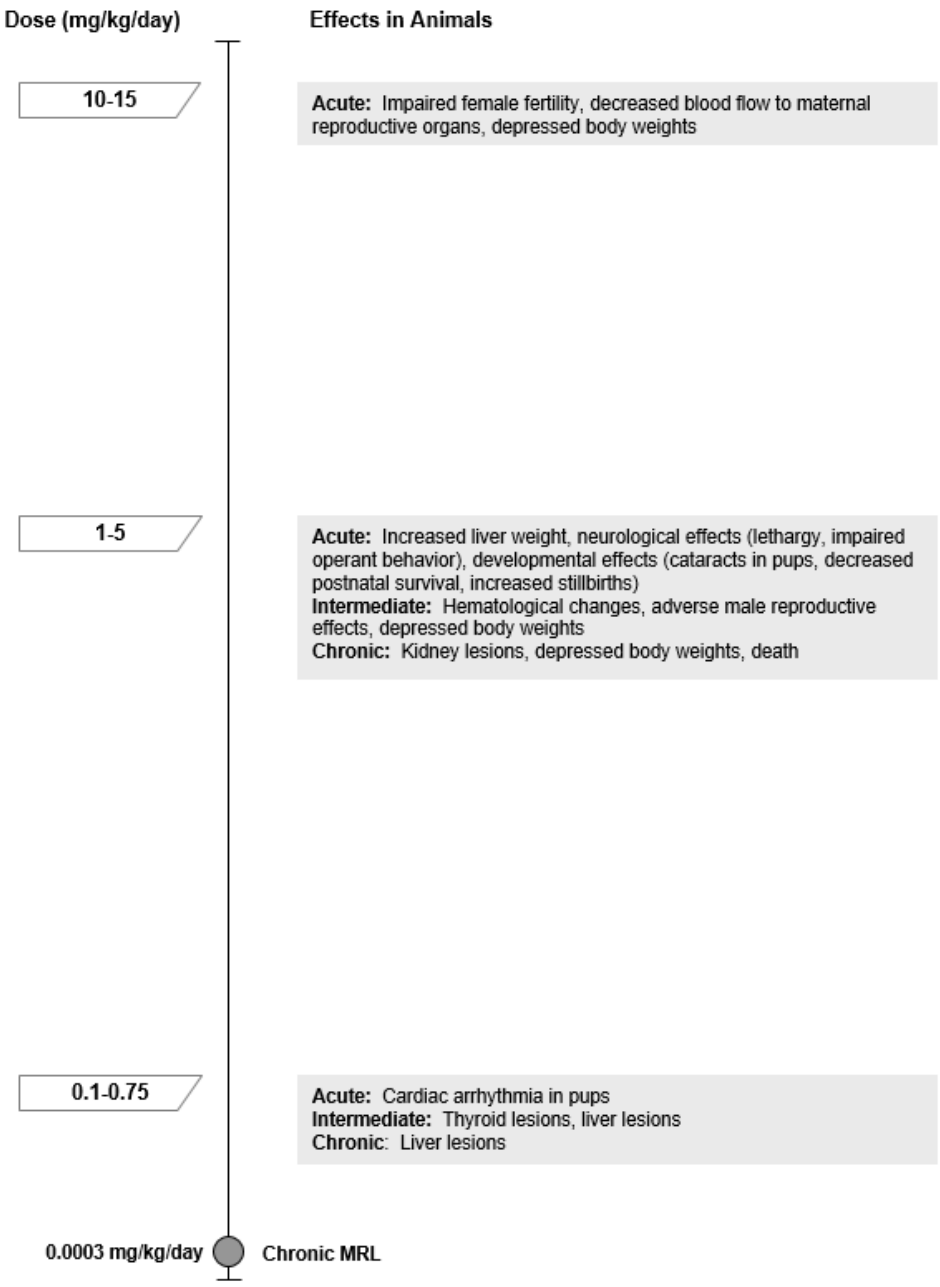
People living in areas surrounding hazardous waste sites may be exposed to mirex or chlordecone primarily via dermal contact with, or ingestion of, contaminated soil since these compounds bind to soil particles. The other major means of exposure for people living near hazardous waste sites is ingestion of indigenous wildlife since mirex and chlordecone are bioconcentrated in fish and animals. Ingestion of mirex or chlordecone from drinking water is unlikely because of their limited solubility in water (Kenaga 1980). Similarly, inhalation exposure to mirex or chlordecone following volatilization from contaminated media is not likely to be a major route of exposure since these chemicals are essentially nonvolatile. For the general population, the most likely route of exposure to mirex or chlordecone is via ingestion of contaminated food because these chemicals have been observed to persist in soil for decades following cessation of application as pesticides. Both of these chemicals are excreted very slowly and bioaccumulate in the body after exposure.

1.2 SUMMARY OF HEALTH EFFECTS

Mirex. Animal studies indicate that mirex exposure may result in a variety of adverse health effects in exposed populations. The primary organs affected by mirex in experimental animals include the liver, kidneys, selected developmental endpoints, and thyroid (see Figure 1-1). In the liver, mirex causes adaptive changes similar to those seen with other chlorinated hydrocarbon insecticides as well as decreased hepatobiliary function and decreased glycogen storage. In the kidneys, increases in glomerulosclerosis and proteinuria have been observed. Ocular lesions include the development of cataracts in the eyes of the young if exposure occurs during a critical period immediately after birth. In the thyroid, an increase in cystic follicles or a collapse of follicles has been observed. Decreased fertility

and marked developmental toxicity have been observed following exposure to mirex. Mirex exposure results in testicular atrophy and reproductive failure. Adverse developmental effects seen in fetuses and/or young animals following maternal and/or early postnatal exposure to mirex include cataracts, cardiovascular disturbances, visceral anomalies, increased resorptions, and increased stillbirths. Also, mirex is a liver carcinogen in animals.

Figure 1-1. Graph of Health Effects Found in Animals Following Oral Exposure to Mirex



Chlordecone. The primary targets of chlordecone toxicity in experimental animals include the liver, kidneys, nervous system, reproductive system, endocrine system, and selected developmental endpoints (see Figure 1-2). Studies in humans exposed occupationally to chlordecone demonstrate toxic effects on the nervous system, liver, and reproductive system. Tremors, unfounded anxiety or irritability, blurring of vision, headache, and increases in cerebrospinal fluid pressure were found in workers exposed to high levels of chlordecone during its manufacture. In addition, several workers exhibited liver effects such as hepatomegaly, evidence of increased microsomal enzyme activity, mild inflammatory changes, and fatty degeneration. Reproductive toxicity consisted of decreased sperm and sperm motility. Studies in animals have supported these findings and, in addition, have demonstrated adverse effects of chlordecone on the kidney and thermoregulation. Animal studies also show effects on the female estrous cycle, uterus, and ovaries and decreased viability and development of fetuses. Liver cancer has also been observed in animal studies. Animal studies have also demonstrated the potential for greatly potentiated hepatotoxicity of haloalkanes such as carbon tetrachloride after exposure to chlordecone. The effects observed in occupationally-exposed workers and treated animals were related to chlordecone levels much higher than environmentally-relevant levels.

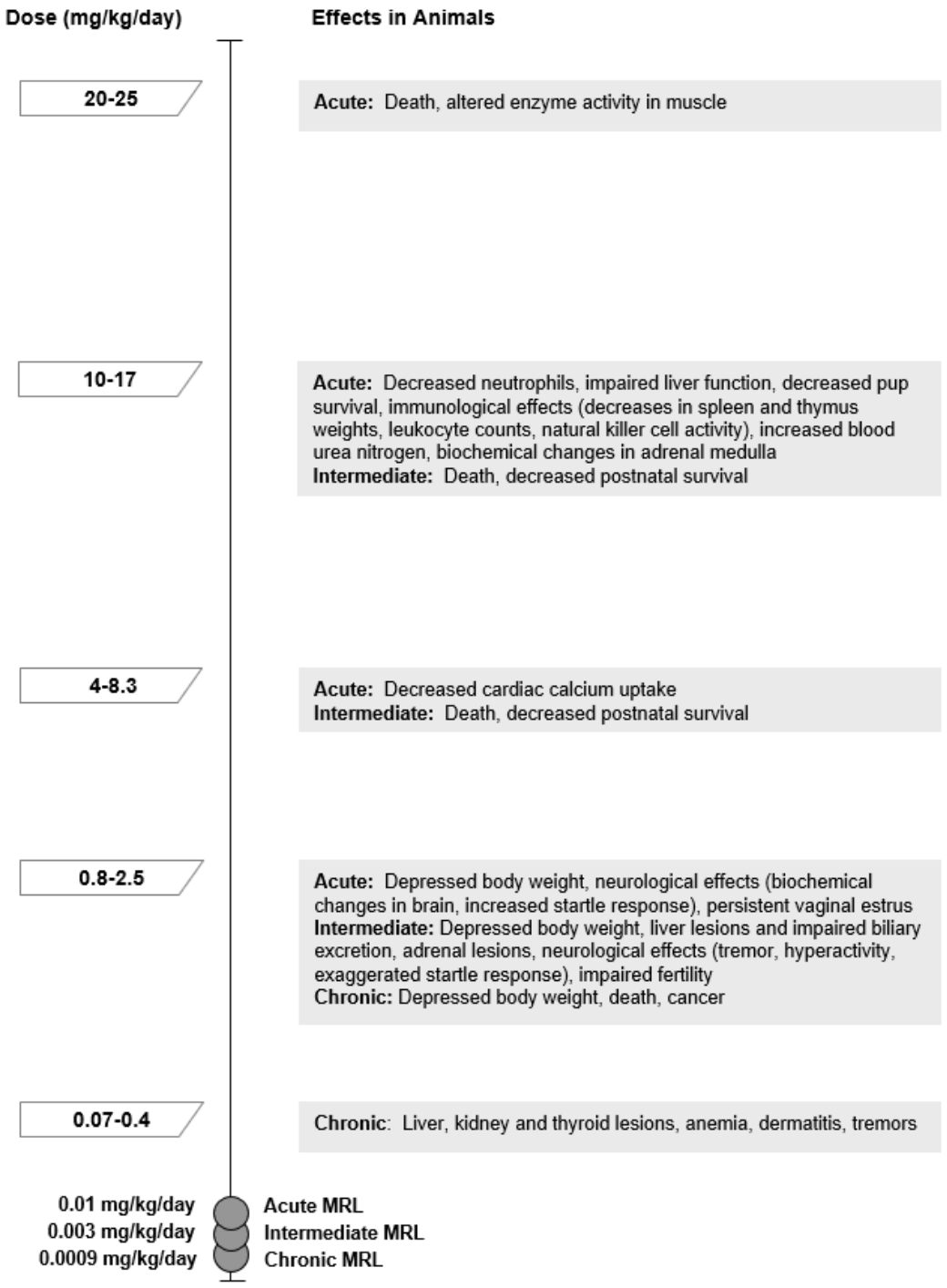
Neurological Effects

Mirex. Animal studies have demonstrated lethargy, weakness, diarrhea, hyperexcitability, tremors, and convulsions as a result of mirex exposure (Chu et al. 1981a; Curtis and Hoyt 1984; Fujimori et al. 1983; Gaines and Kimbrough 1970; Kendall 1974; Larson et al. 1979a; Mehendale 1981).

Chlordecone. Strong evidence for neurotoxicity of chlordecone has been obtained in human studies. Interviews of workers exposed to high levels of chlordecone during its manufacture revealed a high percentage of workers with histories of tremors, unfounded nervousness or anxiety, and visual difficulties (Cannon et al. 1978). The tremors were characterized as resembling intention tremors and occurred mainly in the upper extremities (Taylor 1982, 1985). In more severe cases, the lower extremities were involved and gait disturbances were apparent. Peripheral nerve biopsies of the more severely affected workers showed decreased numbers of small myelinated and unmyelinated axons in the absence of significant myelin abnormalities (Martinez et al. 1978). Although mood and memory disturbances were reported by many workers, testing revealed active encephalopathy in only one subject (Taylor 1982, 1985). Reports of blurring of vision were found to be associated with an opsoclonus-like phenomenon, in which rapid random eye movements followed horizontal saccades (Taylor 1982, 1985). This was attributed to a loss of inhibitory control of saccadic activity. Headaches were also reported by a number

of workers (Taylor 1982, 1985). Cerebrospinal fluid pressure was elevated in three of these individuals, and relief of cerebrospinal fluid pressure resulted in amelioration of the headaches (Sanborn et al. 1979).

Figure 1-2. Graph of Health Effects Found in Animals Following Oral Exposure to Chlordecone



Studies in animals have shown similar effects (tremor, exaggerated startle response, gait disturbances) (e.g., Aldous et al. 1984; Cannon and Kimbrough 1979; EPA 1986a; Klingensmith and Mehendale 1982a; Larson et al. 1979b; NCI 1976; Squibb and Tilson 1982a).

Hepatic Effects

Mirex. Although human data on the hepatic effects of mirex are minimal, animal studies have shown that the liver undergoes both adaptive and toxic changes following oral exposure. The primary toxic effects of mirex are inhibition of hepatobiliary excretion (Berman et al. 1986; Davison et al. 1976; Mehendale 1976, 1977a; Teo and Vore 1991) and depletion of hepatic glycogen stores (Elgin et al. 1990; Ervin and Yarbrough 1983; Fujimori et al. 1983; Jovanovich et al. 1987; Kendall 1979). A 28-day study in Sprague-Dawley rats reported a decrease in hepatic microsomal aniline hydroxylase. Histopathological findings in this study included fatty vacuolation, panlobular ballooning of hepatocytes, moderate lobular pattern with perinuclear clear zone, and perivenous cytoplasmic ballooning with anisokaryosis in liver (Chu et al. 1980a, 1981b). A 21-month study in Sprague-Dawley rats reported a decrease in hepatic microsomal aniline hydroxylase. Histopathological findings in this study included panlobular cytoplasmic vacuolation with loss of basophilia, fatty infiltration, and anisokaryosis in liver (Chu et al. 1981c). F344/N male and female rats fed mirex doses (males: 0.007, 0.07, 0.7, 1.8, 3.8 mg/kg/day; females: 0.007, 0.08, 0.7, 2.0, 3.9 mg/kg/day) for 2 years developed histopathological changes, which included hepatocytomegaly with eosinophilic cytoplasm observed in males and females at >0.7 mg/kg/day. Fatty metamorphosis (cytoplasmic vacuoles consistent with intracellular fat accumulation) and necrosis of hepatocytes (focal and centrilobular) were increased in males and females at >0.7 mg/kg/day. Dilation of the sinusoids (by blood or proteinaceous material) was observed in males at >0.7 mg/kg/day and in females only at the highest dose tested (NTP 1990).

Chlordecone. Guzelian et al. (1980) evaluated liver function in a group of 32 male workers involved in the manufacture of chlordecone who exhibited signs or symptoms of chlordecone toxicity and blood chlordecone levels ≥600 ng/mL. Twenty of the 32 patients exhibited liver enlargement; common histopathological findings on liver biopsy included proliferation of the smooth endoplasmic reticulum, increased microsomal enzyme activity, increased serum alkaline phosphatase, lipofuscin accumulation, mild inflammatory changes, mild portal fibrosis, fatty infiltration, and/or paracrystalline mitochondrial inclusions. Normal results were obtained for serum bilirubin, albumin, globulin, prothrombin time, cholesterol, γ-glutamyl transpeptidase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Sulfobromophthalein clearance was normal (sulfobromophthalein clearance is an indicator of

liver function). Within 2–3 years following cessation of exposure, livers appeared normal in size and ultrastructural changes had resolved. The study authors considered the hepatic changes to largely represent adaptive responses to chlordecone. The results of animal studies support these findings and indicate that oral exposure to chlordecone at doses as low as 0.5–5 mg/kg/day may also result in decreased hepatobiliary function (Curtis and Hoyt 1984; Curtis and Mehendale 1979; Curtis et al. 1979, 1981; Mehendale 1977b, 1981; Teo and Vore 1991); decreased hepatic glycogen (Fujimori et al. 1983); and increased serum nonprotein nitrogen compounds and enzymes, and decreased serum triglycerides and low-density lipoprotein (LDL) cholesterol (Chetty et al. 1993a, 1993b).

Reproductive Effects

Mirex. No studies are available to assess the reproductive effects of mirex in humans. Oral studies in animals suggest that both male and female reproductive systems are adversely affected by mirex. Reported effects in males include decreased fertility (Khera et al. 1976), decreased seminal vesicle weight (Dai et al. 2001), and decreased sperm count and testicular degeneration (Yarbrough et al. 1981). Reported effects in females include increased resorptions and failure of pregnancy (Grabowski and Payne 1980; Khera et al. 1976); decreased ovarian and uterine weights and reduced blood flow to the ovaries, uterus, and fetuses (Buelke-Sam et al. 1983); decreased numbers of litters (Gaines and Kimbrough 1970); and decreases in mating and litter size (Chu et al. 1981b). Male and female mice treated for 30 days prior to mating, and then for an additional 90 days, experienced decreased number of litters per producing pair and decreased litter size (Ware and Good 1967).

Chlordecone. Available studies involving human exposure to chlordecone suggest that adverse reproductive effects can occur in males as a result of occupational exposure to chlordecone (Guzelian 1982a; Taylor 1982, 1985; Taylor et al. 1978). Abnormal spermatogenesis has been observed among workers exposed at a chemical plant (Guzelian 1982a, 1982b). Chlordecone has demonstrated an estrogen-like action in animals (Huber 1965; Uphouse et al. 1984).

Mammalian studies indicate that testicular atrophy can occur at low doses of chlordecone in the diet for 3 months; doses were well below the level that causes overt maternal toxicity (Larson et al. 1979b). Intermediate-duration dietary exposure of female mice at chlordecone doses as low as 2–5 mg/kg/day resulted in persistent estrus (Huber 1965; Swartz et al. 1988). Chlordecone is well known for its estrogenic effects on mammalian reproductive organs when administered by oral (Hammond et al. 1978) or parenteral (Johnson et al. 1990; Pinkston and Uphouse 1988; Sierra and Uphouse 1986) routes. The

effects of neonatal exposure to chlordecone on reproductive function in rats and mice are similar to those seen with prenatal exposure. Multiple injections of chlordecone to neonatal female rats increased uterotropic response (Gellert 1978); uterine weights increased in a dose-related manner (Gellert 1978; Hammond et al. 1979). Parenteral administration of a daily dose of chlordecone to 1-day-old female mouse pups produced cellular proliferation and hypertrophy in the entire reproductive tract and keratinization of the vagina within 4 days of treatment in a dose-dependent manner (Eroschenko and Mousa 1979).

Renal Effects. Studies in animals indicated an increase in the severity of renal lesions in rats following chronic-duration oral exposures to both mirex (NTP 1990) and chlordecone (Larson et al. 1979b).

Endocrine Effects.

Mirex. Result of studies in rats indicate that mirex is toxic to the thyroid. Reversible reduction in colloid density, a thickening of follicular epithelium, and angular collapse of the follicles, but no effect on serum levels of triiodothyronine (T3) or thyroxine (T4), were reported in rats following repeated oral exposure to mirex for ≥28 days (Chu et al. 1980b, 1981a, 1981b). In other studies, ultrastructural analyses of thyroids from rats treated for 28 days showed dilation of the rough endoplasmic reticulum and increased numbers of columnar cells with irregularly-shaped lysosomal bodies, dilation of cisternae, and increased vacuolization (Singh et al. 1982, 1985). Similar effects were observed following dietary exposure for 148 days (Chu et al. 1981a). Dietary exposure for 2 years also resulted in an increase in cystic follicles in male rats (NTP 1990). Studies in animals also indicate that the adrenal gland hypertrophies and releases increased levels of corticosterone in response to mirex exposure (Ervin and Yarbrough 1985; Jovanovich et al. 1987; Williams and Yarbrough 1983). Other studies in animals have demonstrated increased adrenal weight; increased cholesterol, lipid, and protein content (Williams and Yarbrough 1983); increased adrenal weight and increased serum adrenocorticotropic hormone (Ervin and Yarbrough 1985; Jovanovich et al. 1987); and decreased body fats (Jovanovich et al. 1987).

Chlordecone. Increased relative adrenal weight was observed following a single oral dose of chlordecone in rats (Swanson and Wooley 1982). Enlargement of the adrenal gland, with hyperplasia and hypertrophy of the cortical cells, was observed in a 30-day dietary study in rats (Cannon and Kimbrough 1979); decreased adrenal lipid was observed in a 90-day dietary study in rats (Larson et al. 1979b). Consistent with a corticosterone-induced increase in lipid utilization, decreased body fat was observed following dietary exposure of rats for 15–20 days (Klingensmith and Mehendale 1982a; Mehendale et al. 1977,

1978) or exposure of mice for 33 days (Fujimori et al. 1983). In contrast to the absence of mirex-induced effects on the adrenal medulla, oral exposure to chlordecone for 8 days resulted in a decrease in the medullary content of epinephrine in rats (Baggett et al. 1980).

Developmental Effects

Mirex. One human study provides suggestive evidence that gestational exposure to mirex may disrupt reproductive hormones in boys (Araki et al. 2018). Animal studies demonstrated that prenatal exposure to mirex can induce a high incidence of dysrhythmias that can persist into the postnatal period (Grabowski 1983). These effects were sufficiently severe to cause some fetal deaths (Grabowski and Payne 1983a). Cataracts and other lesions of the lens were induced in young animals exposed to mirex during a critical period (between postpartum days 1 and 8) (Chernoff et al. 1979a; Gaines and Kimbrough 1970; Rogers and Grabowski 1984; Scotti et al. 1981).

Chlordecone. Gestational exposure of rats and mice to chlordecone resulted in increased stillbirths and decreased postnatal viability (Chernoff and Kavlock 1982; Chernoff and Rogers 1976; EPA 1986a; Gray and Kavlock 1984; Gray et al. 1983; Kavlock et al. 1985; Seidenberg and Becker 1987; Seidenberg et al. 1986), decreased fetal or neonatal weight and/or skeletal ossification (Chernoff and Kavlock 1982; Chernoff and Rogers 1976; EPA 1986a; Gray and Kavlock 1984; Kavlock et al. 1985, 1987a; Seidenberg et al. 1986), and anomalies and malformations such as enlarged renal pelvis, undescended testes, enlarged cerebral ventricles, clubfoot, fused vertebrae or ribs, and encephalocele (Chernoff and Rogers 1976; Kavlock et al. 1985). Anovulation and persistent vaginal estrus were observed in female offspring of maternal rats given chlordecone during gestation (Gellert and Wilson 1979). Gestational exposure also resulted in subtle neurological changes in the offspring later in life (Rosecrans et al. 1982; Seth et al. 1981; Squibb and Tilson 1982b).

Body Weight Effects

Mirex. Animal studies show decreases in serum glucose (Chu et al. 1981b; Ervin and Yarbrough 1983; Fujimori et al. 1983; Jovanovich et al. 1987; Robinson and Yarbrough 1978a; Williams and Yarbrough 1983; Yarbrough et al. 1981) and decreases in body weight or body weight gain (Buelke-Sam et al. 1983; Byrd et al. 1981; Chadwick et al. 1977; Chernoff et al. 1979b, 1979b; Chu et al. 1981a; Curtis and Hoyt 1984; Davison et al. 1976; Elgin et al. 1990; Fujimori et al. 1983; Jovanovich et al. 1987; Khera et al.

1976; Larson et al. 1979a; Mehendale et al. 1973; NTP 1990; Ritchie and Ho 1982; Rogers and Grabowski 1984; Villeneuve et al. 1977).

Chlordecone. Workers exposed to high levels of chlordecone at a facility where it was manufactured experienced an unexplained weight loss (Cannon et al. 1978), with losses of up to 60 pounds in 4 months in at least one individual (Taylor et al. 1978). Animal studies have also demonstrated weight loss that in some cases was quite large (Albertson et al. 1985; Cannon and Kimbrough 1979; Chernoff and Kavlock 1982; Chernoff and Rogers 1976; Curtis and Hoyt 1984; Curtis and Mehendale 1979; EPA 1986a; Fabacher and Hodgson 1976; Huang et al. 1980; Kavlock et al. 1987a; Klingensmith and Mehendale 1982a; Larson et al. 1979b; Mehendale et al. 1977, 1978; Pryor et al. 1983; Seidenberg et al. 1986; Simmons et al. 1987; Smialowicz et al. 1985; Swanson and Wooley 1982; Uzodinma et al. 1984). Consistent with the results for mirex, loss of body fat (Fujimori et al. 1983; Klingensmith and Mehendale 1982a; Mehendale et al. 1977, 1978) and decreased serum glucose levels (Fujimori et al. 1983) were seen.

Cancer. Studies in mice and rats have demonstrated the ability of mirex to cause liver tumors (Innes et al. 1969; NTP 1990; Ulland et al. 1977), adrenal gland pheochromocytomas (NTP 1990), and rare renal tumors (NTP 1990). A study in mice and rats also showed the ability of chlordecone to increase liver tumors (NCI 1976). The U.S. Department of Health and Human Services categorized both mirex and chlordecone (Kepone) as reasonably anticipated to be human carcinogens (NTP 2016a, 2016b). EPA has classified chlordecone as likely to be carcinogenic to humans (IRIS 2009). Mirex has not been assessed for carcinogenicity by EPA (IRIS 1992). The International Agency for Research on Cancer (IARC 1979) has classified mirex and chlordecone as Group 2B substances (possibly carcinogenic to humans).

1.3 MINIMAL RISK LEVELS (MRLs)

No data were available from which to derive inhalation MRLs for mirex. As presented in Figure 1-3, available data have identified the liver, developmental endpoints, reproductive endpoints, and endocrine system as sensitive targets of mirex toxicity following oral exposure. No acute- or intermediate-duration oral MRLs were derived for mirex due to inadequacy of available data (see Appendix A). The oral database was considered adequate for derivation of a chronic-duration oral MRL for mirex. The MRL value is summarized in Table 1-1 and discussed in detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Mirex – Oral

The liver, developmental endpoints, reproductive endpoints, and endocrine system are the most sensitive targets of mirex.

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.

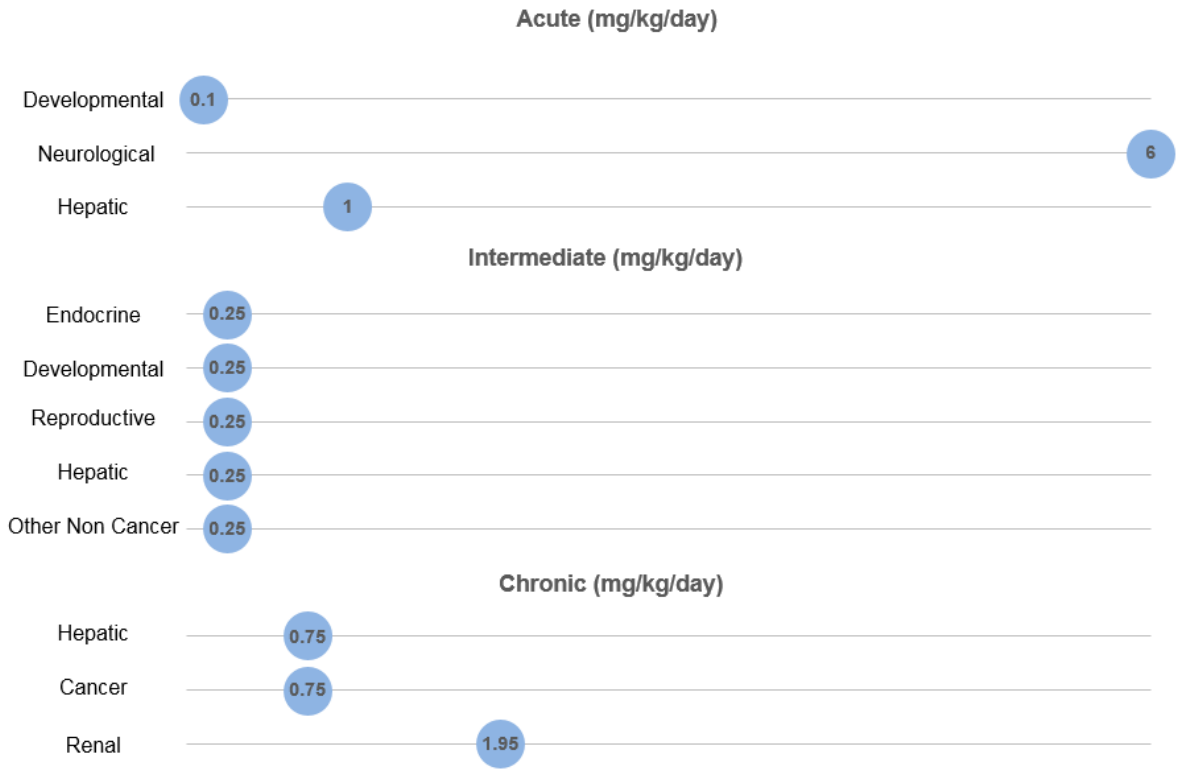


Table 1-1. Minimal Risk Levels (MRLs) for Mirex[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	0.0003	Liver lesions	NOAEL: 0.075	UF: 100 MF: 3	NTP 1990

[a]See Appendix A for additional information.

MF = modifying factor; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

No data were available from which to derive inhalation MRLs for chlordecone. As presented in Figure 1-4, available data have identified the liver, endocrine system, kidney, and neurological endpoints as sensitive targets of chlordecone toxicity following oral exposure. The oral database was considered adequate for derivation of acute-, intermediate-, and chronic-duration oral MRLs for chlordecone. The MRL values are summarized in Table 1-2 and discussed in detail in Appendix A.

Figure 1-4. Summary of Sensitive Targets of Chlordecone – Oral

The liver, endocrine system, kidney, and neurological system are the most sensitive targets of chlordecone.

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.

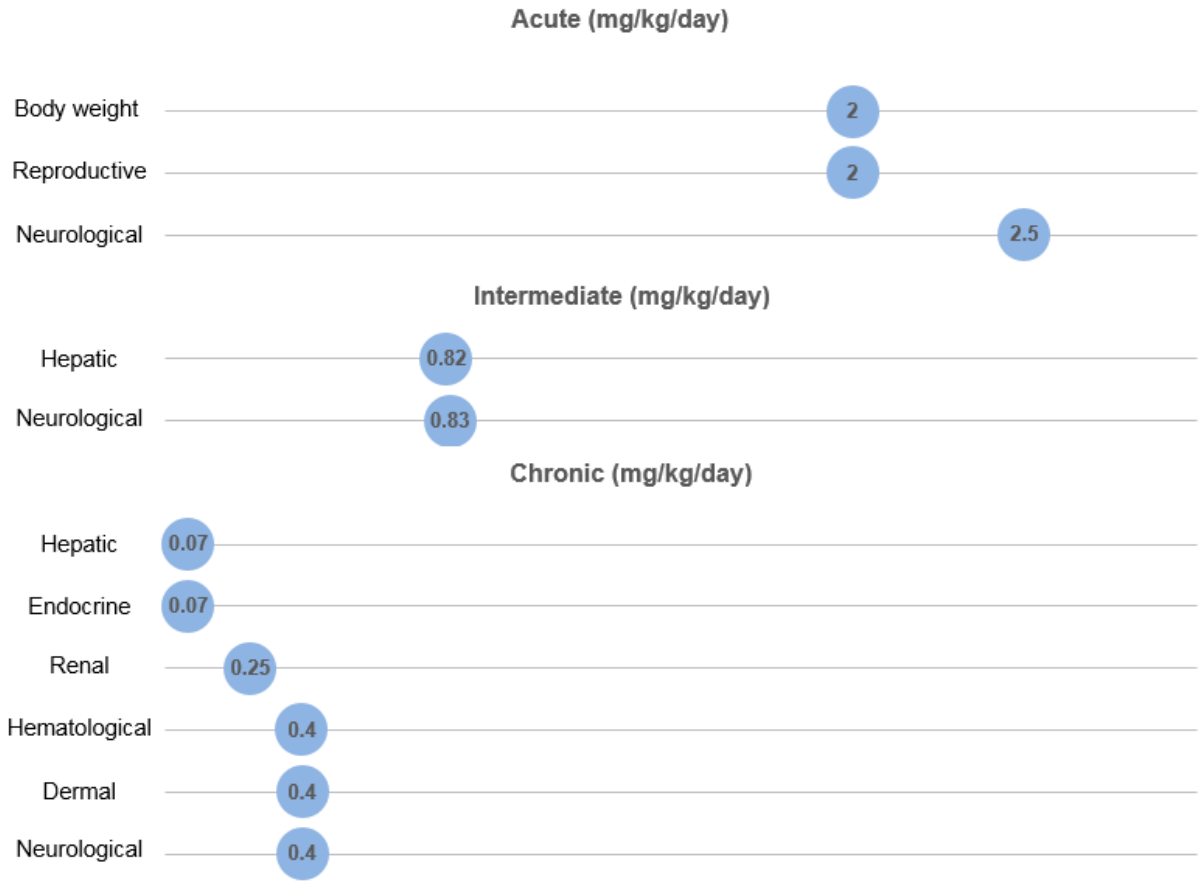


Table 1-2. Minimal Risk Levels (MRLs) for Chlordecone[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.01	Neurological effects	NOAEL: 1.25	100	EPA 1986a
Intermediate	0.003	Neurological and male reproductive effects	NOAEL: 0.26	100	Linder et al. 1983
Chronic	0.0009	Renal effects	NOAEL: 0.089	100	Larson et al. 1979b

[a]See Appendix A for additional information.

NOAEL = no-observed-adverse-effect level