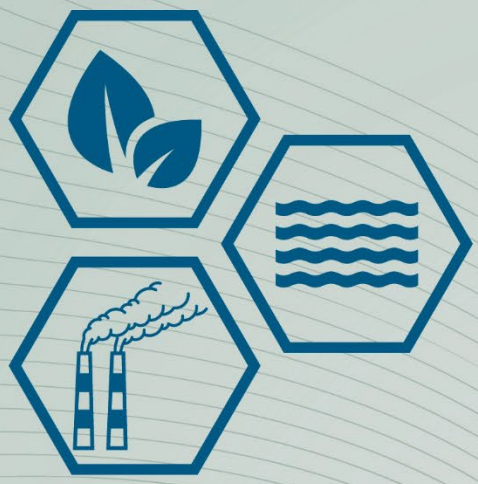

Toxicological Profile for Mirex and Chlordecone

October 2020

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

CS274127-A

DISCLAIMER

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

FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

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*Legislative Background

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

VERSION HISTORY

Date	Description
October 2020	Final toxicological profile released
May 2019	Draft for public comment toxicological profile released
August 1995	Final toxicological profile released

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

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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.

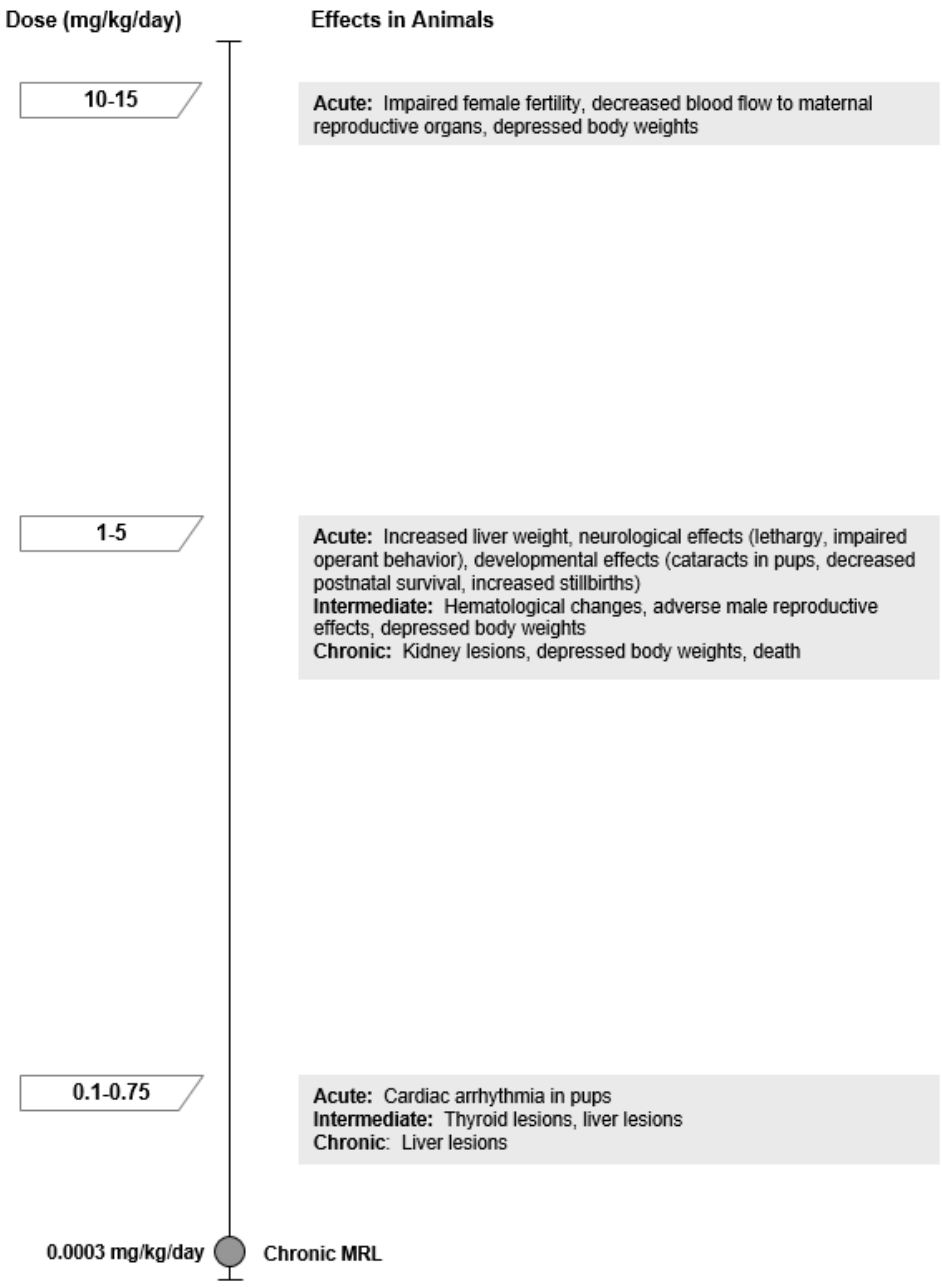
People living in areas surrounding hazardous waste sites may be exposed to mirex or chlordecone primarily via dermal contact with, or ingestion of, contaminated soil since these compounds bind to soil particles. The other major means of exposure for people living near hazardous waste sites is ingestion 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.

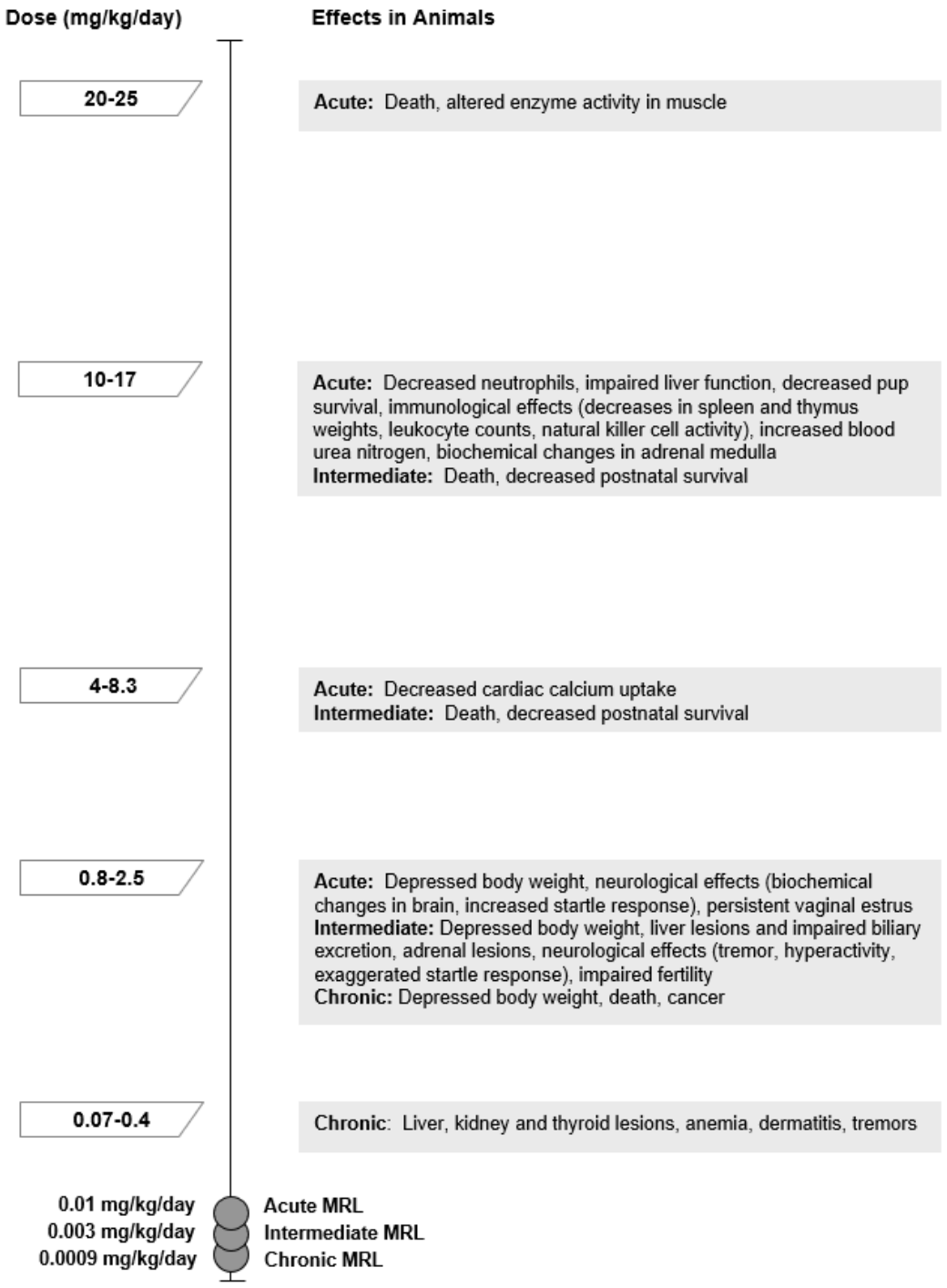
Neurological Effects

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.

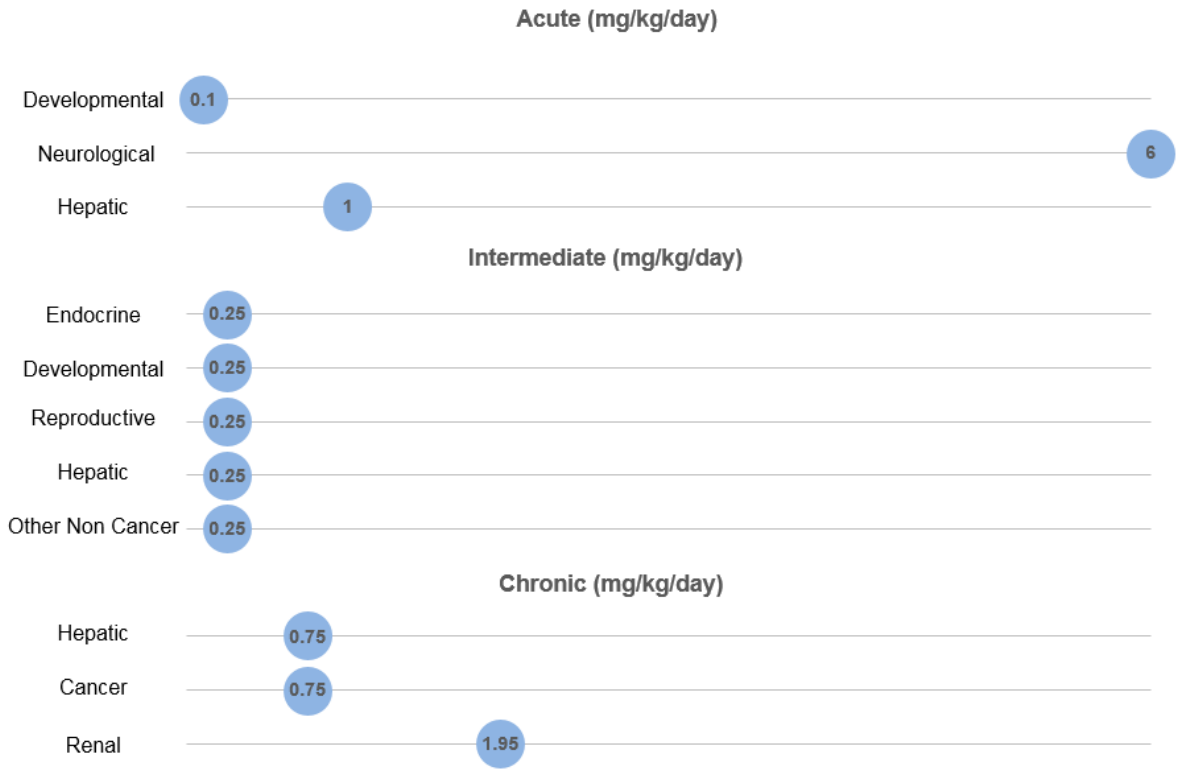


Table 1-1. Minimal Risk Levels (MRLs) for Mirex[a]

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.

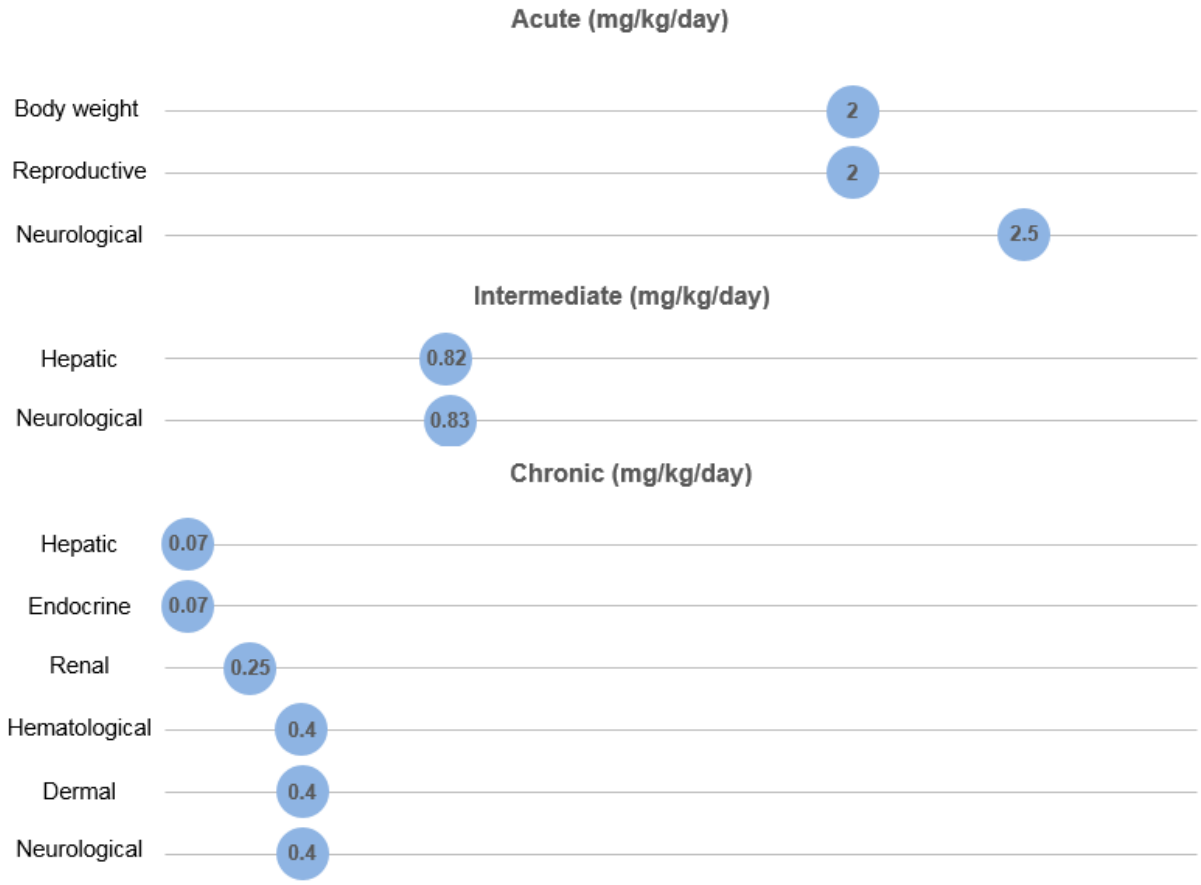


Table 1-2. Minimal Risk Levels (MRLs) for Chlordecone[a]

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

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 mirex and chlordecone. 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.

Mirex and chlordecone are structurally similar insecticides that are derivatives of cyclopentadiene. The only structural difference is that mirex has two bridgehead chlorine atoms where chlordecone has a carbonyl oxygen atom. As suggested by this similarity in structure, these two chemicals share some similarities in their toxicity profiles. However, the toxicity profiles of these two chemicals differ in a number of aspects. Therefore, each chemical will be discussed separately below.

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 for mirex and Figure 2-2 for chlordecone provide overviews 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 mirex or chlordecone, but may not be inclusive of the entire body of literature.

The epidemiological database for mirex and chlordecone consists of a small number of studies reporting effects in chlordecone workers and general population studies examining possible associations between biomarkers of mirex or chlordecone exposure (serum, cord blood, or breast milk levels) and adverse health outcomes. Occupational exposure may have involved the inhalation, oral, and dermal routes, whereas oral exposure is the presumed route of exposure for the general population observational studies. The results of the observational studies should be interpreted cautiously due to the study limitations. For a number of

studies, mirex was detected in <50% of the blood samples; in one study (Everett and Matheson 2010), mirex was only detected in approximately 8% of the blood samples. Several studies compared groups with mirex/chlordecone levels above the limit of detection to those with levels below the limit of detection. Additionally, the observational studies measured exposure at a single point in time, which may not be reflective of past exposures. Most of the studies adjusted for some potential confounders such as age, sex, body mass index, alcohol consumption, etc. A small number of studies statistically adjusted for exposure to other chlorinated pesticides (e.g., DDT and hexachlorobenzene) and polychlorinated biphenyls (PCBs). The observational studies do not establish causality between mirex/chlordecone exposure and a health outcome. In addition to these limitations, the small number of studies examining a particular health outcome limits the interpretation of the study findings. The results of the observational studies for mirex and chlordecone are presented in Tables 2-1 and 2-2, respectively.

Animal inhalation studies are not available for mirex or chlordecone. Animal oral studies are presented in Table 2-3 and Figure 2-3 for mirex and Table 2-4 and Figure 2-4 for chlordecone. Animal dermal studies are presented in Table 2-5 for mirex and Table 2-6 for chlordecone.

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) are indicated in Table 2-3 and Figure 2-3 for mirex and Table 2-4 and Figure 2-4 for chlordecone.

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.

Mirex. Human data regarding potential health effects of mirex exposure are limited to assessment of possible associations between mirex blood levels and selected health outcomes. No data were located regarding occupational exposure to mirex.

As illustrated in Figure 2-1, human studies related to mirex predominantly evaluated reproductive, developmental, and cancer endpoints, as well as diabetes. The human data do not provide exposure-response data for mirex. Available animal data suggest the following sensitive targets of mirex toxicity:

- Developmental endpoint: Particularly sensitive developmental effects following prenatal and/or early postnatal exposure to mirex in animals were cardiac dysrhythmias, cataracts, and other lesions of the lens.
- Reproductive endpoint: Studies in animals suggest that both male and female reproductive systems are adversely affected by mirex, indicated by histopathologic effects on reproductive organs and decreased fertility resulting from mirex treatment of either males or females.
- Hepatic endpoint: In the liver, mirex causes adaptive changes similar to those seen with other chlorinated hydrocarbon insecticides as well as decreased hepatobiliary function, decreased glycogen storage, and histopathologic lesions.
- Renal endpoint: Increases in glomerulosclerosis and proteinuria have been observed in the kidneys of mirex-treated animals.
- Endocrine endpoint: Adverse effects were observed in the thyroid and adrenal glands of mirex-treated animals.
- Cancer: The carcinogenicity of mirex has been demonstrated, particularly in the liver of both male and female rats and mice.

Chlordecone. Within a single cohort of 133 men exposed to chlordecone during its production in the mid-1970s, as many as 76 experienced neurological symptoms. Other effects in some workers included oligospermia and liver enlargement. There were no measurements of chlordecone levels in the working environment. Industrial hygiene was poor at the facility; therefore, chlordecone exposure may have included inhalation, oral, and/or dermal routes. Other human data regarding potential health effects is limited to assessments of possible associations between chlordecone blood levels, placental levels, and/or levels in maternal milk in studies of a population in Guadeloupe, French West Indies, where chlordecone had been used on banana plantations.

As illustrated in Figure 2-2, human studies related to chlordecone predominantly evaluated reproductive, developmental, and neurological endpoints. The human data do not provide exposure-response data for chlordecone. Available human and animal data suggest the following sensitive targets of chlordecone toxicity:

- Hepatic endpoint: Some people involved in the production of chlordecone exhibited liver effects such as hepatomegaly, evidence of increased microsomal enzyme activity, mild inflammatory changes, and fatty degeneration.

- Renal endpoint: Increased severity of selected kidney lesions have been observed in rats chronically exposed to chlordecone.

- Endocrine endpoint: Chlordecone treatment of animals resulted in effects on the adrenal gland that included increased weight, depletion of epinephrine, hyperplasia, loss of adrenal lipid, and histopathologic lesions.

- Neurological endpoint: 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.

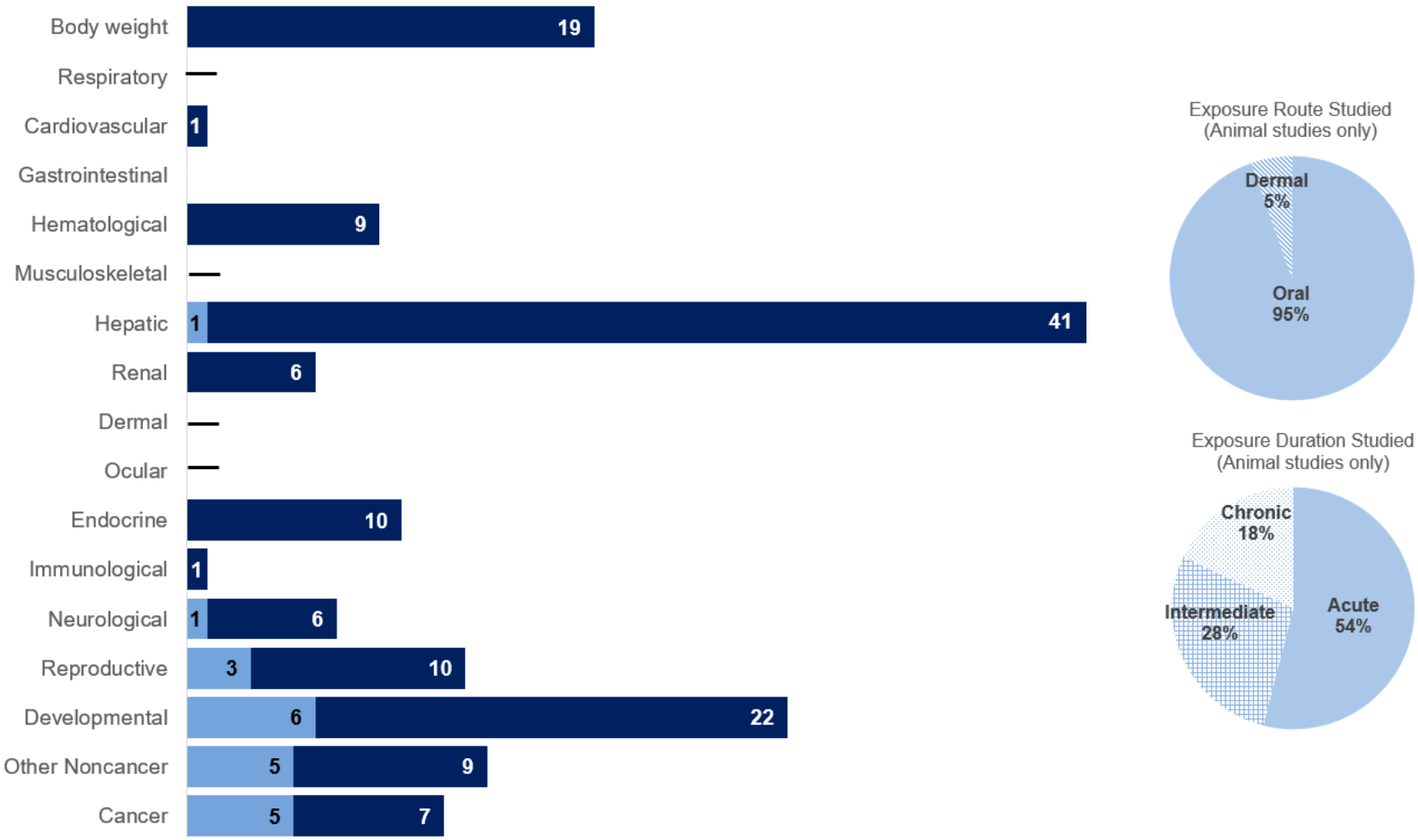
- Reproductive endpoint: Some men involved in the production of chlordecone exhibited decreases in sperm count and motility. Adverse effects on the reproductive system have been demonstrated in male and female animals exposed to chlordecone.

- Developmental endpoint: Effects such as increased stillbirths, decreased postnatal viability, delayed skeletal ossification, selected anomalies and malformations, and subtle neurological changes have been associated with gestational exposure to chlordecone in animals.

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

Most studies examined the potential body weight, hepatic, and developmental effects of mirex

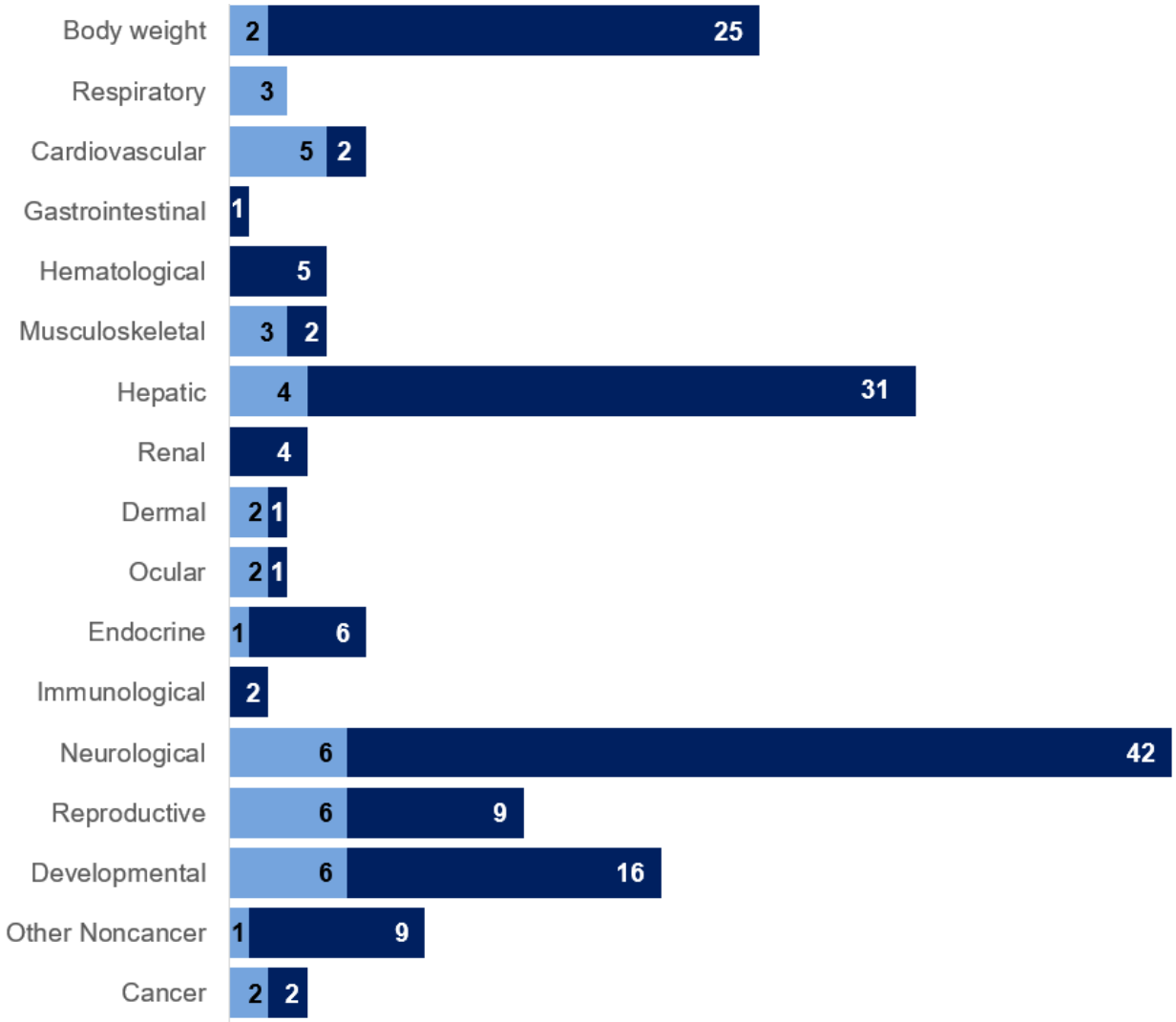
More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)

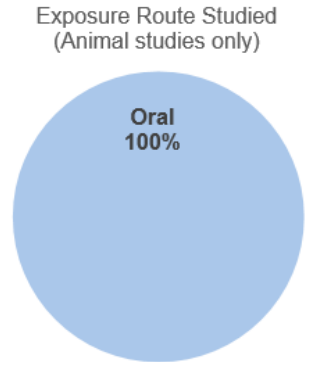


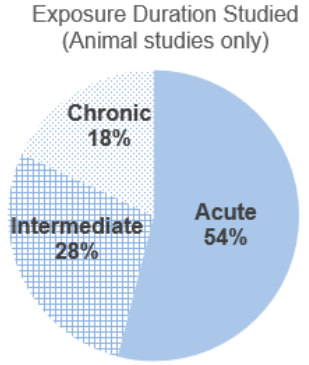
*Includes studies discussed in Chapter 2. A total of 161 studies include those finding no effect. Most studies examined multiple endpoints.

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

Most studies examined the potential body weight, hepatic, and neurological effects of chlordecone
More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 198 studies include those finding no effect. Most studies examined multiple endpoints.

Table 2-1. Results of Epidemiological Studies Evaluating Associations Between Mirex and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Endocrine Effects			
Han et al. 2019 Population-based, case-control study using 186 thyroid disease patients and 186 controls (without a history of thyroid disease) matched for age and residential area in eastern China	Serum mirex/chlordecone level (LOD ≤9.75 ng/L); median levels were 2.11 µg/kg lipid for cases and 1.55 µg/kg lipid for controls; categorized by quartile	Thyroid disease risk	↔
Reproductive Effects			
Grindler et al. 2015 Cross-sectional survey using NHANES data from 1999–2008 Primary analysis: menopausal women (>30 years of age) with a laboratory assessment of endocrine-disrupting chemicals Secondary analysis: 225 women 45–55 years of age	Serum mirex level Minimum: 0.50 ng/g Median: 3.89 ng/g 90th percentile: 9.46 ng/g Maximum: 2,960 ng/g	**Menopause in women >30 years of age**	↑
		Menopause in women 45–55 years of age	↑
Lebel et al. 1998 Case-control study of 86 women with endometriosis and 70 controls	Serum mirex level (LOD 0.02–0.03 µg/L); mirex was measurable in 56% of subjects Cases: 3.4 µg/kg lipids Controls: 3.1 µg/kg lipids	Endometriosis	↔
Upson et al. 2013 Population-based, case-control study of endometriosis among 18–49-year-old enrollees of a health care system in Washington State (248 surgically-confirmed endometriosis cases and 538 population-based controls)	Serum mirex level (LOD 10 pg/g; median mirex level 15.47 pg/g); categorized into three groups: All endometriosis: Low: ≤10 pg/g Middle: >10.0–15.47 pg/g High: >15.47 pg/g Ovarian endometriosis: Low: ≤10 pg/g Middle: >10.0–15.47 pg/g High: >15.47 pg/g	**All endometriosis**	**↑ (high group)**
		Ovarian endometriosis	↔

Table 2-1. Results of Epidemiological Studies Evaluating Associations Between Mirex and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Developmental Effects			
Araki et al. 2018 Prospective birth cohort (Hokkaido Study Sapporo Cohort) of 232 pregnant women (23–35 weeks of gestation) who presented at an obstetrics and gynecology hospital between July 2002 and October 2005, lived in the Sapporo City area, planned to deliver at the facility, and provided maternal serum and cord blood samples for analysis of maternal organochlorine pesticide levels and cord blood levels of selected steroid and reproductive hormones	Maternal serum mirex level (LOD 0.5 pg/g wet weight). Minimum: 0.88 pg/g 25th percentile: 4.11 pg/g 50th percentile: 6.04 pg/g 75th percentile: 8.53 pg/g Maximum: 30.11 pg/g	**Testosterone**	↓
		Cortisol	↓
		Cortisone	↓
		Prolactin	↓
		Testosterone-androstenedione ratio	↓
		Androstenedione – DHEA ratio	↓
		DHEA	↑
		FSH	↑
		AA-G ratio	↑
		FSH-inhibin B ratio	↑
Denham et al. 2005 Population-based cohort of 138 Akwesasne Mohawk Indian girls 10–16.9 years of age	Serum mirex level (LOD 0.02 ppb) Referent: <0.02 ppb Low: 0.02–0.03 ppb High: 0.04–1.17 ppb	Menarcheal status	↔
Fenster et al. 2006 Longitudinal birth cohort study of the health of pregnant women (n=385) and their children living in Salinas Valley, California, and enrolled in CHAMACOS; the study evaluated possible associations between *in utero* organochlorine pesticide exposure (including mirex) and fetal growth and length of gestation	Presence of detectable mirex maternal blood (LOD range 0.01–0.69 ng/g lipid) Detected in 85.9% of blood samples from 384 women (mean level of 0.3 ng/g lipid; range 0.04–15.9 ng/g lipid)	Gestation length	↔
		Birth weight	↔
		Crown-heel length	↔
Fernandez et al. 2007 Nested case-control study of 48 newborns diagnosed with cryptorchidism and/or hypospadias and 114 boys without malformations matched by gestational age, date of birth, and parity; subjects were identified at Granada University Hospital in Granada, Spain	Presence of detectable mirex in placental sample (LOD in the range of 0.1–3 ng/mL, not otherwise specified in study report) Detected in 12/48 cases (mean level of 1.4 ng/mL [SD 1.0]; range 1.0–3.0 ng/mL) and 18/114 controls (mean level of 3.7 ng/mL [SD 3.7]; range 1.0–15.0 ng/mL)	**Urogenital malformations**	↑

Table 2-1. Results of Epidemiological Studies Evaluating Associations Between Mirex and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Guo et al. 2014 A total of 81 pairs of mothers and newborns enrolled at four hospitals in four different cities in China; the study evaluated possible associations between mirex in maternal serum and birth weight and between mirex in newborn cord serum and birth weight	Maternal serum mirex detected in 47/71 samples: Mean 0.36 ng/g lipid Median 0.23 ng/g lipid Minimum <0.4 pg/Ml (LOD) Maximum 66.36 ng/g lipid)	Birth weight	↔[a]
	Cord serum mirex detected in 13/60 samples: Mean 0.27 ng/g lipid Median <LOD Minimum <LOD Maximum 23.94 ng/g lipid)	Birth weight	↔[b]
Hjermitslev et al. 2020 A total of 482 mother-child pairs from the prospective mother-child cohort study of pregnant women of the ACCEPT program in Greenland	Maternal serum mirex (LOD not reported) Median: 2.70 ng/g lipid; range: 0.45–120 ng/g lipid)	Birth weight	↔
		Gestation age at birth	↓
Puertas et al. 2010 Population-based randomly-sampled birth cohort (n=104) recruited between 2000 and 2002 in Granada, Spain, and evaluated for cognitive development at 4 years of age	Placental mirex (presence or absence, based on LOQ of 1 ng/mL) Referent: <1 ng/mL in 77/104 placentas High: ≥1 ng/mL in 27/104 placentas Median: 1.4 ng/mL; range 0.5–19.1 ng/mL	**Working memory**	↓
		Quantitative functions	↓
Other Noncancer Effects			
Aminov et al. 2016 Cross-sectional study of an adult Native-American (Mohawk) population (224 men and 377 women, 18–84 years of age; 41 men and 70 women diabetics)	Serum mirex level (MDL 0.02 ppb) Serum mirex <MDL in 16.1% of subjects (mean 0.12±0.15 ppb; range <MDL–1.67 ppb); categorization by quartile	Diabetes risk	↔
Codru et al. 2007 Cross-sectional study of an adult Native-American (Mohawk) population (352 subjects; 134 males and 218 females ≥30 years of age; 71 diabetics)	Serum mirex level (MDL 0.02 ppb) 86.4% of subjects had measurable serum mirex levels (mean 0.13±0.16 ppb)	Diabetes risk	↔

Table 2-1. Results of Epidemiological Studies Evaluating Associations Between Mirex and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Everett and Matheson 2010 Cross-sectional study of 3,364 participants in 1999–2004 NHANES survey	Serum mirex level (maximum LOD 14.6 ng/g lipid adjusted); mirex blood level was above the maximum limit of detection in 7.7% of participants	Total diabetes risk	↔
		Pre-diabetes risk	↔
Rosenbaum et al. 2017 Cross-sectional study of 548 residents of Anniston, Alabama included in the Anniston Community Health Survey (68% female; mean age 53.6±16.2 years; 56% white, 44% African American, 59% met criteria for metabolic syndrome)	**Exposure:** Serum mirex level (LOD not specified) Categorized by quintile (parts per trillion, ppt): Q1: 1.30–24.24 ppt Q2: 24.25–48.44 ppt Q3: 48.45–74.16 ppt Q4: 74.17–128.96 ppt Q5: 128.97–2,574.40 ppt	Metabolic syndrome risk	↔
Son et al. 2010 Selected participants in a community-based health survey in South Korea; included 40 subjects with fasting blood glucose level ≥126 mg/dL or who were taking antidiabetic medication (considered type 2 diabetes cases) and 40 age- and sex-matched subjects with mean fasting plasma glucose of 87.7±9.3 mg/dL; average age of 55.6 years; 52.5% males	Median serum concentration of mirex by wet weight categorized by tertile: T1: 6.6 pg/g T2: 11.7 pg/g T3: 27.8 pg/g	**Diabetes risk**	**↑ (T3)**
	Lipid-standardized median serum concentration of mirex by tertile: T1: 1.0 ng/g lipid T2: 2.0 ng/g lipid T3: 4.5 ng/g lipid	Diabetes risk	↔
Cancer Effects			
Itoh et al. 2009 Case-control study of 403 breast cancer patients and 403 matched pairs at four hospitals in Japan	Lipid-adjusted serum mirex concentration; categorized by quartile median: Q1: 1.4 ng/g lipid Q2: 1.9 ng/g lipid Q3: 2.4 ng/g lipid Q4: 3.5 ng/g lipid	**Breast cancer**	↓

Table 2-1. Results of Epidemiological Studies Evaluating Associations Between Mirex and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Koutros et al. 2015a, 2015b Nested case-control study using data from the population-based Janus Serum Bank cohort of Norway. Subjects were 149 cases of metastatic prostate cancer with no history of cancer (except nonmelanoma skin cancer) and were diagnosed at least 2 years after serum collection and 314 controls matched by region, date of blood draw, and age at blood draw	Plasma level of mirex (LOD not specified); median levels were 1.8 ng/g lipid (range 0.1–37.1 ng/g lipid) for cases and 1.7 ng/g lipid (range 0.1–18.3 ng/g lipid) for controls; categorized by quartile to approximate equal numbers of cases per quartile	Prostate cancer	↔
Moysich et al. 1998 Subset of 154 cases and 192 community controls (ages 41–85 years) from a case-control study of postmenopausal breast cancer in western New York	Serum mirex based on LOD (0.06–0.99 ng/g): <LOD >LOD	Post-menopausal breast cancer (all subjects)	↔
		Post-menopausal breast cancer (never lactated subjects)	↔
		Post-menopausal breast cancer (ever lactated subjects)	↔
Sawada et al. 2010 Nested case-control study using data from the Japan Public Health Center-based Prospective Study. Nested case-control subjects were 201 newly-diagnosed prostate cancer cases and 2 controls for each case	Plasma level of lipid-adjusted mirex (LOD 3.0 pg/g wet) categorized by quartile: Q1: <3.1 pg/g lipid-adjusted Q2: 3.1–4.0 pg/g lipid-adjusted Q3: 4.1–5.9 pg/g lipid-adjusted Q4: ≥6.0 pg/g lipid-adjusted	Prostate cancer	↔
Spinelli et al. 2007 Population-based case-control study in British Columbia, Canada, including 422 pretreatment non-Hodgkin's lymphoma cases and 460 controls	**Exposure:** Mirex in serum (lipid-adjusted) categorized by low or high concentration: Low: ≤1.43 ng/g High: >1.43–60.46 ng/g	**Non-Hodgkin lymphoma**	↑

Table 2-1. Results of Epidemiological Studies Evaluating Associations Between Mirex and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Wielsoe et al. 2017 Seventy-seven breast cancer cases and 84 controls from the general population of Inuit women from Greenland	Serum mirex (LOD 0.04 or 0.01 µg/L); median levels were 25 µg/kg lipid (range 11.15–74.92 µg/kg lipid) for cases and 22.65 µg/kg lipid (range 6.08–47.79 µg/kg lipid) for controls; categorized by tertile	**Breast cancer**	↑ **(by serum level)** ↔ (by tertile)

[a]Samples with detection rate >50%, but <80% stratified into three groups using LOD and median concentration of detected samples as cut points.
[b]Samples with detection rate >20%, but <50% stratified by the LOD value into two groups.

↑ = association; ↓ = inverse association; ↔ = no association; ACCEPT = Adapting to Climate Change, Environmental Pollution and Dietary Transition; CHAMACOS = Center for the Health Assessment of Mothers and Children of Salinas; DHEA = dehydroepiandrosterone; FSH = follicle-stimulating hormone; LOD = limit of detection or level of detection; LOQ = limit of quantitation; MDL = method detection limit; NHANES = National Health and Nutrition Examination Survey; Q = quartile; SD = standard deviation; T = tertile

Table 2-2. Results of Epidemiological Studies Evaluating Associations Between Chlordecone and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Cardiovascular Effects			
Saunders et al. 2014 Subpopulation of 779 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	Serum chlordecone level (LOD 0.06 µg/L) Q1: <0.17 µg/L; referent Q2: 0.17–0.38 µg/L Q3: 0.39–0.80 µg/L Q4: >0.80 µg/L	**Hypertensive disorders during pregnancy**	↓ **(Q3 and Q4)**
		Pre-eclampsia	↔
Endocrine Effects			
Emeville et al. 2013 Population-based, cross-sectional study using a random sample of 277 healthy, non-obese, middle-aged men from the French West Indies	Serum chlordecone level (LOD 0.06 µg/L) Geometric mean: 0.40 µg/L 90th percentile: 1.74 µg/L Maximum: 44.1 µg/L	Blood steroid hormone levels	↔
Han et al. 2019 Population-based, case-control study using 186 thyroid disease patients and 186 controls (without a history of thyroid disease) matched for age and residential area in eastern China	Serum mirex/chlordecone level (LOD ≤9.75 ng/L); median levels were 2.11 µg/kg lipid for cases and 1.55 µg/kg lipid for controls; categorized by quartile	Thyroid disease	↔
Developmental Effects			
Boucher et al. 2013 Subpopulation of 141 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	Chlordecone cord blood level (LOD 0.06 µg/L): Referent: <0.06 µg/L (LOD) Low: 0.07–0.24 µg/L High: 0.24–3.91 µg/L	**ASQ score for fine motor function**	↓ **(boys)**
Cordier et al. 2015 Subpopulation of 111 pregnant women in TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	Chlordecone cord blood level (LOD 0.06 µg/L): Referent: <0.06 µg/L (LOD) Low: 0.06–0.31 µg/L High: ≥0.31 µg/L Chlordecone in maternal milk samples at 3 months postdelivery (LOD 0.34 µg/L):	**TSH levels at 3 months of age**	↑ **(males)** ↔ (females)
		Free T3	↔ (males) ↔ (females)
		Free T4	↔ (males) ↑ **(females)**
		Fine motor development at 18 months of age	↓ **(boys)** ↔ (girls)

Table 2-2. Results of Epidemiological Studies Evaluating Associations Between Chlordecone and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
	Referent: <0.5 µg/L Low: 0.5–0.9 µg/L High: ≥0.9 µg/L		
Cordier et al. 2019 Subpopulation of 116 children (7 years of age) in TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	Chlordecone in cord blood (LOD 0.05 µg/L) Mean: 0.1 µg/L; range <LOD–7.4 µg/L (detected in 70.2% of 104 samples)	Feminine play	↔
		Masculine play	↔
	Chlordecone in 7-year-old childhood blood sample (LOD 0.02 µg/L) Mean: 0.04 µg/L; range <LOD–1.0 µg/L (detected in 70.8% of 89 samples)	Feminine play	↔
		Masculine play	↔
Costet et al. 2015 Subpopulation of 222 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	Chlordecone cord blood level (LOD 0.06 µg/L): Referent: <0.06 µg/L (LOD) Low: 0.06–0.306 µg/L High: ≥0.306 µg/L	**Body mass index in boys at 3 months**	↑
		Body mass index in girls at 3 months	↑
Dallaire et al. 2012 Subpopulation of up to 153 infants of women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) who were pregnant between November 2004 and December 2007	Chlordecone cord blood level (LOD 0.06 µg/L): Referent: <0.06 µg/L (LOD) Low: >0.06–0.31 µg/L High: >0.31 µg/L	Novelty preference on the Fagan Tests of Infant Intelligence	↑ (high group)
		Risk of obtaining low scores on the fine motor development scale	↑ (detectable chlordecone levels)
Hervé et al. 2016 Subpopulation of 593 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	Chlordecone cord blood level (LOD 0.02 µg/L): Referent: <0.08 µg/L Low: 0.08–0.20 µg/L Medium: 0.20–0.41 µg/L High: ≥0.41 µg/L	Gestational age	↔

Table 2-2. Results of Epidemiological Studies Evaluating Associations Between Chlordecone and Health Outcomes

Reference, study type, and population	Exposure	Outcome evaluated	Result
Kadhel et al. 2014 Subpopulation of 818 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	Chlordecone maternal blood level (LOD 0.06 µg/L): Q1: <0.14 µg/L; referent Q2: 0.14–0.28 µg/L Q3: 0.29–0.51 µg/L Q4: 0.52–0.97 µg/L Q5: >0.98 µg/L	**Gestation length**	↓
		Preterm birth	↑
Rouget et al. 2019 Subpopulation of pregnant women and their newborn from the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007 for whom maternal blood samples (n=843) and/or cord blood samples (n=668) were available for evaluation of chlordecone	**Exposure:** Chlordecone maternal blood level (LOD 0.02 µg/L): T1: <0.22 µg/L; referent T2: 0.22–<0.59 µg/L T3: ≥0.59 µg/L	Risk of malformations	↔
	Chlordecone cord blood level (LOD 0.02 µg/L): T1: <0.10 µg/L; referent T2: 0.10–<0.32 µg/L T3: ≥0.32 µg/L	Risk of malformations	↔
		Risk of undescended testes	↔
Other Noncancer Effects			
Saunders et al. 2014 Subpopulation of 779 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007	**Exposure:** Serum chlordecone level (LOD 0.06 µg/L) Q1: <0.17 µg/L; referent Q2: 0.17–0.38 µg/L Q3: 0.39–0.80 µg/L Q4: >0.80 µg/L	Diabetes during pregnancy	↔
Cancer Effects			
Multigner et al. 2010 Population-based case-control study of 623 prostate cancer cases and 671 controls in Guadeloupe, French West Indies	Plasma chlordecone level (LOD 0.25 µg/L): Q1: ≤0.25 µg/L (LOD); referent Q2: >0.25–0.47 µg/L Q3: >0.47–0.96 µg/L Q4: >0.96 µg/L	**Prostate cancer**	↑ **(Q4)**
		Prostate cancer (family history of prostate cancer)	↑ **(Q4)**
		Prostate cancer (past residence in western countries)	↑ **(Q4)**

↑ = association; ↓ = inverse association; ↔ = no association; ASQ = Ages and Stages Questionnaire; LOD = limit of detection or level of detection; Q = quartile or quintile; T= tertile; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone

Table 2-3. Levels of Significant Exposure to Mirex – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 36 M	8 days ad lib (F)	0, 17	BI, HP	Endocr	17			
Baggett et al. 1980									
2	Rat (Sprague-Dawley) 5–11 M	3 days 1 time/day (GO)	0, 50	OF	Hepatic		50		Impaired biliary excretion of glucuronide conjugates; increased bile flow
Berman et al. 1986									
3	Rat (CD) 6–7 F	GDs 5, 5–9, 5–14 1, 5, or 10 days 1 time/day (GO)	0, 10	BW, DX, OF, OW	Bd wt			10	35–52% decrease in maternal weight gain
					Cardio			10	Significant decrease of maternal cardiac output and heart weight
					Hepatic		10		Significant increase in maternal liver weight
					Immuno		10		32% decrease in maternal spleen weight
					Repro		10		Decreased blood flow to ovaries, uterus, and fetuses; decreased ovarian and uterine weight
					Develop		10		Decreased pup viability and pup weight; increased resorptions; fetal edema
Buelke-Sam et al. 1983									

Table 2-3. Levels of Significant Exposure to Mirex – 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
4	Rat [CRL-COBS;CD (SD)] 20–30 F	GDs 5–14 or 6–15 1 time/day (GO)	0, 10	BW, DX, LE, OW	Death			10	24–25% maternal mortality
					Bd wt			10	>30% depressed maternal body weight
					Repro			10	Decreased gravid uterine weight
					Develop			10	>59% fetuses with edema; increased prenatal mortality; >20% decrease in pup body weight
Byrd et al. 1981									
5	Rat (CD) 10–38 F	GDs 7–16 1 time/day (GO)	0, 5, 7, 9.5, 19, 38	BW, DX, LE	Death			9.5	16% maternal mortality
					Bd wt	7		9.5	36% decrease in maternal weight gain
					Develop	5	7	9.5	Delayed ossification; edematous live fetuses (7 mg/kg); enlarged cerebral ventricles and undescended testes (9.5 mg/kg)
Chernoff et al. 1979b									
6	Rat (Long-Evans) 10–45 F	PPDs 1–4 1 time/day (GO)	1, 2.5, 5, 10	BW, DX, LE, OP	Develop			10 F	35–36% mortality and cataracts in pups
Chernoff et al. 1979b									
7	Rat (Long-Evans) 3–20 F	Once GD 1, 2, 3, 4, 5, 6, 7, 8, 10, or 14 (GO)	0, 10, 15	OP	Develop			10	Cataracts in pups at postnatal days 12–14
Chernoff et al. 1979b									

Table 2-3. Levels of Significant Exposure to Mirex – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
8	Rat (Sprague-Dawley) 4 or 8 NS	14 days ad lib (F)	0, 0.6, 6	BW, OF, OW	Bd wt	6			
					Hepatic			6	Disruption of liver cord cells; focal stasis; central or midzonal hepatocellular necrosis
Davison et al. 1976									
9	Rat (Wistar) 7–29 M 7–29 F	3–7 days ad lib (F)	0, 4, 1,500, 2,000	BI, BW, OW	Bd wt	4	1,500		16–17% decrease in body weight gain
					Hepatic	4	1,500		Decreased hepatic glycogen; increased lipid accumulation
Elgin et al. 1990									
10	Rat (Sprague-Dawley) 5–20 M	Once (GO)	0, 100	BC, BI, BW, HE, OF, OW	Hemato		100		12% decreased hematocrit
					Hepatic		100		Significantly decreased hepatic glycogen
					Other noncancer		100		Decreased blood glucose
Ervin and Yarbrough 1983									
11	Rat (Sprague-Dawley) 3–11 M	Once (GO)	0, 100	BC, BW, OW	Endocr			100	88% increase in serum adrenocorticotropic hormone
Ervin and Yarbrough 1985									
12	Rat (Sherman) NS M, F	Once (GO; corn oil)	NS	LE	Death			740 M 600 F	LD_{50} LD_{50} >3,000 mg/kg with peanut oil as vehicle
Gaines 1969									

Table 2-3. Levels of Significant Exposure to Mirex – 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 (Sherman) 10 F	Once (GO)	8 dose levels; lowest dose tested: 50 mg/kg	LE	Death			365	LD_{50}
Gaines and Kimbrough 1970									
14	Rat (Long-Evans) 3–11 F	GDs 8.5–15.5 or 6.5–15.5 1 time/day (GO)	0, 5, 6, 7, 10	DX, OF	Develop			5	First-degree heart block in fetuses; decreased number of litters at 10 mg/kg/day
Grabowski and Payne 1980									
15	Rat (Long-Evans) NS F	GDs 8.5–15.5 1 time/day (GO)	0, 6	DX	Develop			6	36% edematous fetuses
Grabowski 1981									
16	Rat (Long-Evans) NS F	GDs 8.5–15.5 or 15.5–21.5 1 time/day (GO)	0, 0.1, 0.25, 0.5, 1, 1.5, 3, 6	DX, FX	Develop			0.1	Cardiac arrhythmia
Grabowski 1983									
17	Rat (Long-Evans) 8–17 F	GDs 8.5–15.5 1 time/day (GO)	0, 6	BW, DX	Develop			6	23% stillborn pups; dyspnea; cardiac rhythm blockade
Grabowski and Payne 1983a									
18	Rat (Long-Evans) 9–13 F	GDs 8.5–15.5 1 time/day (GO)	0, 6	DX	Develop			6	First degree heart block in fetuses; 14% increased fetal mortality
Grabowski and Payne 1983b									

Table 2-3. Levels of Significant Exposure to Mirex – 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
19	Rat (Sprague-Dawley) 6 M	Once (GO)	0, 50	BC, BI, OF	Hepatic		50		Increased bile flow rate
Hewitt et al. 1986a									
20	Rat (Wistar) 10–29 M 10–29 F	7 days ad lib (F)	0, 4	BC, BI, OF, OW	Hepatic		4		Two-fold increase in liver weight; increased cholesterol and triglycerides
Jovanovich et al. 1987									
21	Rat (Wistar) 7 F	4 days (F)	0, 2,100	BC, BI, BW, OW	Bd wt			2,100	30% lower mean body weight; 77% reduction in body fat
					Hepatic		2,100		Two-fold increase in liver weight and serum triglycerides; 25% decreased in liver glycogen and glucose
					Endocr			2,100	Two-fold increase in adrenal weight
					Other noncancer		2,100		Reduced food intake; 88% reduction in serum glucose
Jovanovich et al. 1987									
22	Rat (Mai-Wistar) 50 M	Once (GO)	0, 200	BI, OF	Hepatic		200		Hepatic glycogen depletion; periportal liposis; degeneration of endoplasmic reticulum
Kendall 1979									
23	Rat (Wistar) 18–20 F	GDs 6–15 1 time/day (GO)	0, 1.5, 3, 6, 12.5	LE, OF	Death			6	4/20 maternal rats died
					Repro			12.5	Pregnancy failure in 45% of dams
Khera et al. 1976									

Table 2-3. Levels of Significant Exposure to Mirex – 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 (Wistar) 20 M	10 days 1 time/day (GO)	0, 1.5, 3, 6	OF	Repro	3		6	Significantly decreased fertility
Khera et al. 1976									
25	Rat (Sprague-Dawley) 3 M	Once (GO)	0, 10	BI	Hepatic	10			
Klingensmith and Mehendale 1983a									
26	Rat (Sprague-Dawley) 3 M	Once (GO)	0, 20	BI, OF	Hepatic		20		Induction of P450b and P450e mRNAs in liver
Kocarek et al. 1991									
27	Rat (CD-1) 8 M, 8 F	5 days 1 time/day (GO)	0, 5, 10, 25, 50	LE, CS, GN	Death			50	2/8 females died
Mehendale et al. 1973									
28	Rat (Sprague-Dawley 3–4 M	3 days 1 time/day (GO)	0, 50	OF	Hepatic		50		Suppressed biliary excretion; increased bile flow
Mehendale 1977a									
29	Rat (Sprague-Dawley) 6 F	1 days 1 or 2 times (GO)	0, 1.2, 3.6, 12, 36, 60, 90, 120, 180, 240	BI, OF	Hepatic		240		Increased serum ALT
Mitra et al. 1990									
30	Rat (Sprague-Dawley) 6 M	3 days 1 time/day (GO)	0, 0.5, 2, 10	BC, BI, HP, OW	Hepatic Renal	 10	10		Swollen hepatocytes
Plaa et al. 1987									

Table 2-3. Levels of Significant Exposure to Mirex – 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
31	Rat (Sprague-Dawley) 5–12 M	Once (GO)	0, 8	BC, BI, OF, OW	Hepatic	8			
					Other noncancer		8		Decreased blood glucose
Robinson and Yarbrough 1978a									
32	Rat (Long-Evans) NS F	GDs 8–15 1 time/day (GO)	0, 6	BI, DX, HP	Develop			6 F	Cataracts in 49.6% of fetuses; 14% fetal mortality on GD 21
Rogers and Grabowski 1983									
33	Rat (Long-Evans) 3–12 F	PPDs 1–4 1 time/day (GO)	0, 10	BW HP BI	Develop			10 F	10–20% decrease in pup weight; cataracts
Rogers and Grabowski 1984									
34	Rat (Long-Evans) 5–7 F	GDs 8–15 1 time/day (GO)	0, 6	BC, DX, HE	Develop		6		Decrease in fetal hematocrit and plasma glucose
Rogers et al. 1984									
35	Rat (Sherman) NS	PPDs 1–4 1 time/day (GO)	0, 5	DX, HP, OP	Develop			5	Neonatal cortical degeneration and necrosis in lens of eye
Scotti et al. 1981									
36	Rat (Sprague-Dawley) 7–10 F	Once (GO)	0, 100	BC, BI, OF	Hepatic		100		Decreased hepatic glutathione
Sunahara and Chiesa 1992									

Table 2-3. Levels of Significant Exposure to Mirex – 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
37	Rat (Sprague-Dawley) 4–8 F	3 days 1 time/day (GO)	0, 12.5, 25, 50	BI, OF	Hepatic		12.5		Decreased hepatic ion transport
Teo and Vore 1990									
38	Rat (Sprague-Dawley) 5–8 M	3 days 1 time/day (GO)	0, 50	BI, BW, OF, OW	Hepatic		50		Decreased biliary function; decreased bile flow; decreased concentration and secretion of bile acid
Teo and Vore 1991									
39	Rat (Sprague-Dawley) 6 M	14 days 1 time/day (GO)	0, 0.1, 1.0, 10	BC, BI, BW, FI, HE, HP, OW	Bd wt			10	55% decrease in body weight gain
					Hemato	10			
					Hepatic		1		Significantly increased relative liver weight; significantly increased serum lactic dehydrogenase
Villeneuve et al. 1977									
40	Rat (Sprague-Dawley) 5–7 M	Once (GO)	0, 20, 50, 100, 150	BI, OW	Hepatic		50		Two-fold increase in liver weight
					Other noncancer		20		Increased serum corticosterone
Williams and Yarbrough 1983									
41	Mouse (CD-1) 10–25 F	PPDs 1–4 1 time/day (GO)	0, 1.5, 3.0, 6.0, 9.0	DX	Develop			6	32% pup mortality
Chernoff et al. 1979b									

Table 2-3. Levels of Significant Exposure to Mirex – 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
42	Mouse (CD-1) NS	PPDs 1–4 1 time/day (GO)	0, 1.5, 3.0, 6.0, 9.0	DX	Develop		1.5	3	11–14% lower pup weight at 1.5 mg/kg/day; cataracts in pups at 3 mg/kg/day; decreased pup viability at 6 mg/kg/day
Chernoff et al. 1979b									
43	Mouse (CD-1) 24–25 F	GDs 8–12 1 time/day (GO)	0, 7.5	BW, DX, MX	Develop			7.5	Increased mortality. Decreased pup weight on LDs 1 and 3
Chernoff and Kavlock 1982									
44	Mouse (C57BL/6) 23–32 M	2 days 1 time/day (GO)	0, 30	BC, BI	Hepatic		30		Elevated serum ALT and AST
Fouse and Hodgson 1987									
45	Mouse (ICR) 15 M	14 days 1 time/day (GO)	0, 10, 25, 50	BW, FI, LE, WI	Death			10	12/15 rats died
					Bd wt		10		>10% decrease in body weight
					Other noncancer		10		20% decrease in plasma glucose; decreased food and water consumption
Fujimori et al. 1983									
46	Mouse (ICR) 3–8 M	PPDs 54 and 58 (GO)	0, 10, 25	BC, BI	Hepatic	10	25		Decreased hepatic glycogen
					Other noncancer	10	25		Decreased serum glucose and lactate; decreased free fatty acids
Fujimori et al. 1983									
47	Mouse (CD-1) NS F	GDs 8–12 1 time/day (G)	0, 7.5	BH, BW, DX, FX, MX, OF, OW, TG	Develop			7.5	56% increased mortality in pups
Gray et al. 1983									

Table 2-3. Levels of Significant Exposure to Mirex – 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 (Swiss Webster) 6–16 M	Once (GO)	0, 10, 50, 250	HP, OW	Hepatic		50		Slight hepatocyte vacuolization and loss of basophilic staining
					Renal	50			
Hewitt et al. 1979									
49	Dog (Mongrel) 1–5 M	Once (GO)	125, 250, 500, 750, 1,000, 1,250, 1,500	LE	Death			1,250	3/5 dogs died
Larson et al. 1979a									
INTERMEDIATE EXPOSURE									
50	Rat (Sprague-Dawley) 4–5 M	15s days ad lib (F)	0, 0.95	BC, BI, HP, OW	Hepatic		0.95		Decreased hepatobiliary function
Bell and Mehendale 1985									
51	Rat (CD) 17–21 F	PPDs 1–46 ad lib (F)	0, 2	DX, OP	Develop			2	Cataracts, outlined lenses, increased still births, 10–19% decreased postnatal growth
Chernoff et al. 1979a									
52	Rat (CD) 21–24 F	GD 4–PPD 46 ad lib (F)	0, 2	DX	Develop			2	Decreased postnatal viability; increased stillbirths, cataracts, and outlined lenses
Chernoff et al. 1979a									

Table 2-3. Levels of Significant Exposure to Mirex – 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	Rat (Sprague-Dawley) 10 M	28 days ad lib (F)	0, 0.086	BC, BI, BW, CS, FI, HE, HP	Bd wt	0.086			
					Hemato	0.086			
					Hepatic	0.086			
					Renal	0.086			
					Endocr	0.086			
					Other noncancer	0.086			
Chu et al. 1980b									
54	Rat (Sprague-Dawley) 5 M, 5 F	28 days ad lib (F)	0, 6.2	BC, BW, CS, FI, HE, HP, OF, OW	Bd wt	6.2			
					Hepatic		6.2		>34% increased liver weight; histopathologic liver lesions (e.g., hepatocellular hypertrophy, anisokaryosis, fatty vacuolation)
					Endocr		6.2		Thyroid lesions (e.g., reduced colloid density with collapse of follicles, increased epithelial height)
Chu et al. 1980c									

Table 2-3. Levels of Significant Exposure to Mirex – 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
55	Rat (Sprague-Dawley) 15 M, 20 F	M: 91 days premating, 15 days mating (106 days) F: 91 days premating, 15 days mating, gestation, lactation (148 days) ad lib (F)	Premating and mating: 0, 0.49, 0.98, 2, 3	BC, BW, DX, FI, GN, HE, HP, MX, OF, OW	Hemato	2			
					Hepatic		0.49		Dose-related increased incidence and severity of histopathologic liver lesions
					Endocr		0.49		Dose-related increased incidence and severity of histopathologic thyroid lesions
					Neuro	2		3	Hypoactivity, irritability, tremors
					Repro			0.49	Dose-related decreased numbers of females exhibiting sperm in vaginal smears; dose-related decreased litter size
					Develop			0.49	Cataracts in 4/10 female pups (0/14 controls) at 0.25 mg/kg/day; significantly decreased 21-day pup survival at 1 mg/kg/day

Chu et al. 1981b

Table 2-3. Levels of Significant Exposure to Mirex – 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
56	Rat (Sprague-Dawley) 10M	28 d ad lib (F)	0, 0.25, 2.5	BC, BW, CS, EA, GN, HE, HP, LE, OW	Hemato	2.5			
					Hepatic		0.25		Liver lesions (fatty infiltration, cytoplasmic vacuolation, anisokaryosis and necrosis of hepatocytes)
					Endocr		0.25		Thyroid lesions (thickening of follicular epithelium; loss of colloid and collapse of follicles)
					Other noncancer		0.25		Decreased serum glucose
Chu et al. 1981a									
57	Rat (Sprague-Dawley) 3–11 M	15 days (F)	0, 1.6, 8.2	BW, CS, OF	Bd wt	1.6		8.2	39% decreased mean body weight gain
					Hepatic		1.6		Impaired biliary excretion
					Neuro	1.6		8.2	Lethargy
Curtis and Hoyt 1984									
58	Rat (Sprague-Dawley) 5–6 M	15 days ad lib (F)	0, 0.9	BC, BW, CS, HP, OW	Hepatic	0.9			
Curtis et al. 1981									
59	Rat (Sprague-Dawley) 5 M	15 days ad lib (F)	0, 0.88	BW, CS, EA, FI, HP, OF, OW	Bd wt	0.88			
					Hepatic	0.88			
Curtis and Mehendale 1980									

Table 2-3. Levels of Significant Exposure to Mirex – 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
60	Rat (Sprague-Dawley) 8 NS	28 days ad lib (F)	0, 0.6, 6	BW, HP, OF	Bd wt		6		15% lower mean final body weight than controls
					Hepatic			0.6	Disruption of liver cord cells; focal bile stasis; central or midzonal hepatocellular necrosis
Davison et al. 1976									
61	Rat (Zivac-Miller) 15–30 NS	NS 5–6 days/week 1 time/day (GO)	5, 12.5, 25	BH, CS	Neuro			5	Decrease in operant behavior
Dietz and McMillan 1979									
62	Rat (Sherman) 10 F	90 days ad lib (F)	5.7, 11, 17, 23, 28	LE	Death			5.7	LD_{LO}
Gaines and Kimbrough 1970									
63	Rat (Sherman) 10 M, 10 F	166 days ad lib (F)	M: 0, 0.04–0.09, 0.21–0.48, 1.3–3.1 F: 0.06–0.1, 0.31–0.49, 1.8–2.8	BI, HP, OF, OW	Hepatic	0.48	1.3		Bile stasis; decreased hepatic glycogen, multinucleation
Gaines and Kimbrough 1970									

Table 2-3. Levels of Significant Exposure to Mirex – 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
64	Rat (Sherman) 10 M, 10 F	2-generation repro ad lib (F)	M: 0, 1.3–3.1 F: 0, 1.8–2.8, 0.31–0.49	DX, OF	Repro	0.31		1.8	Decreased number of litters and number of live births from mirex-treated maternal rats only
					Develop	0.31		1.8	Cataracts, decreased live births, increased mortality through weaning among pups from mirex-treated maternal rats only
Gaines and Kimbrough 1970									
65	Rat (Charles River) 10 M, 10 F	13 weeks ad lib (F)	0, 0.43, 1.7, 6.9, 28, 110	LE, CS, BW, HE, HP	Death			110	M: 50% mortality F: 100% mortality
					Bd wt	28		110	M: 33–34% lower mean final body weight than controls
					Hemato	6.9	28		Decreased hemoglobin
					Hepatic	1.7	6.9		Hepatocellular vacuolation
					Renal	110			
					Neuro	28		110	Hyperexcitability, tremors, convulsions
Larson et al. 1979a									
66	Rat (Sprague-Dawley) 5M	<30 days ad lib (F)	0, 10	CS, OF, OW	Gastro		10		Diarrhea
					Hepatic		10		Impaired biliary excretion
					Neuro			10	Lethargy
Mehendale 1981									
67	Rat (Sprague-Dawley) 10 M	28 days ad lib (F)	0, 0.67, 6.7	HP	Endocr	0.67	6.7		Increase in large irregularly shaped lysosomes in the thyroid
Singh et al. 1982									

Table 2-3. Levels of Significant Exposure to Mirex – 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
68	Rat (Sprague-Dawley) 10 M	28 days ad lib (F)	0, 0.67, 6.7	OF	Endocr		0.67		Dilation of rough endoplasmic reticulum cisternae of thyroid in weanling rats
Singh et al. 1985									
69	Rat (Long-Evans) 3–5 M	61–113 days ad lib (F)	0, 1.2	NX	Neuro	1.2			
Thorne et al. 1978									
70	Rat (Sprague-Dawley) 10 M	28 days ad lib (F)	0, 0.043, 0.43, 4.3, 6.5	BC	Hemato	6.5			
					Hepatic	6.5			
					Endocr	0.43	4.3		Significantly decreased serum thyroid T3
					Repro	4.3		6.5	Hypocellularity of the seminiferous tubules; testicular degeneration
Yarbrough et al. 1981									
71	Mouse (CD-1) 3 M	21 days (G)	0, 5	BW, OW	Bd wt	5			
					Hepatic		5		>2-fold increase in mean absolute liver weight
					Repro		5		27% decrease in mean absolute seminal vesicle weight
Dai et al. 2001									
72	Mouse (ICR) 15 M	15 days 1 time/day (GO)	0, 10	LE	Death			10	100% mortality
Fujimori et al. 1983									

Table 2-3. Levels of Significant Exposure to Mirex – 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
73	Mouse (Swiss-Webster) 6 M	15 days ad lib (F)	0, 1.9	BW, OW, FI, HP, BC, BI	Bd wt	1.9			
					Hepatic	1.9			
Mehendale et al. 1989									
74	Mouse (BALB/c) (CFW) 43–50 M 43–50 F	120 days ad lib (F)	0, 0.94	OR	Repro	0.94			
Ware and Good 1967									
75	Mouse (BALB/c) 102–108 M, 102–108 F	120 days ad lib (F)	0, 0.65	OR	Repro	0.94			
Ware and Good 1967									
76	Dog (Beagle) 2 M, 2 F	13 weeks ad lib (F)	0, 0.19, 0.95, 4.8	HE, UR, HP, BW	Bd wt	0.95		4.8	58–74% decrease in body weight gain
					Hemato	0.95	4.8		Increased hematocrit and leukocyte count
					Hepatic	0.95	4.8		Increased serum alkaline phosphatase, impaired biliary excretion
					Renal	4.8			
Larson et al. 1979a									
77	Gerbil (Mongolian) 4–5 M	15 days ad lib (F)	0, 0.9	BC, BI	Hepatic	0.9			
Cai and Mehendale 1990									

Table 2-3. Levels of Significant Exposure to Mirex – 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									
78	Rat (Sprague-Dawley) 10 M, 10 F	21 months ad lib (F)	0, 0.073, 0.37	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd wt	0.37			
					Hemato	0.37			
					Hepatic	0.37			
Chu et al. 1981c									
79	Rat (F344/N) First study: 52 M, 52 F Second study: 52 F	2 years ad lib (F)	First study: Combined sexes: 0, 0.007, 0.075, 0.75, 1.95, 3.85 Second study: F: 0, 3.9, 7.7	BW, CS, FI, GN, HP, LE	Death			1.95	63% mortality in males
					Bd wt	1.95	3.85		Up to 17–18% lower mean body weight
					Hepatic	0.075[b]	0.75		Focal and centrilobular necrosis; fatty metamorphosis; dilation of sinusoids
					Renal	0.075	0.75		Increased incidence of epithelial hyperplasia of the renal pelvis at 0.75 mg/kg/day; increased severity of nephrotoxicity at 1.95 mg/kg/day
					Cancer			0.75	CEL: neoplastic liver nodules in males, mononuclear cell leukemia in females
NTP 1990									

Table 2-3. Levels of Significant Exposure to Mirex – 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
80	Rat (CD) 20 or 26 M 20 or 26 F	18 months followed by 6 months of recovery ad lib (F)	0, 3.6, 7.2	BW, GN, HP, LE	Death			7.2	Decreased survival of males and females after treatment week 52
					Bd wt	7.2			
					Hepatic		3.6		Megalocytosis in the liver of 14/26 males and 8/26 females; no incidences among controls
					Cancer			7.2	CEL: neoplastic nodules in the liver of 7/26 males (0/20 controls); hepatocellular carcinoma in 4/26 males

Ulland et al. 1977

Table 2-3. Levels of Significant Exposure to Mirex – 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
81	Mouse (C57BL/6 x C3H/ANF) (C57BL/6 x AKR) 18 M, 18 F	21 days by gavage, in food until terminal sacrifice at weeks 59–70	0, 4.8 (TWA)	LE	Death			4.8	100% mortality; 11% in controls
					Cancer			4.8	CEL: hepatomas in males and females of both mouse strains

Innes et al. 1969

[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 a chronic-duration oral minimal risk level (MRL) of 0.0003 mg/kg/day for mirex; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability) and modifying factor of 3 (to protect for developmental toxicity); see Appendix A for more detailed information regarding the MRL.

ad lib = ad libitum; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd wt or BW = body weight; BC = serum (blood) chemistry; BH = behavioral; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage-not specified; GD = gestation day; (GF) = gavage or diet; GN = gross necropsy; (GO) = gavage-oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD = lactation day; LD_{50} = lethal dose, 50% kill; LD_{L0} = lowest lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology;; OW = organ weight; PPD = postpartum day; Repro = reproductive; RNA = ribonucleic acid; T3 = triiodothyronine; TG = teratogenicity; TWA = time-weighted average; UR= urinalysis; WI = water intake

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

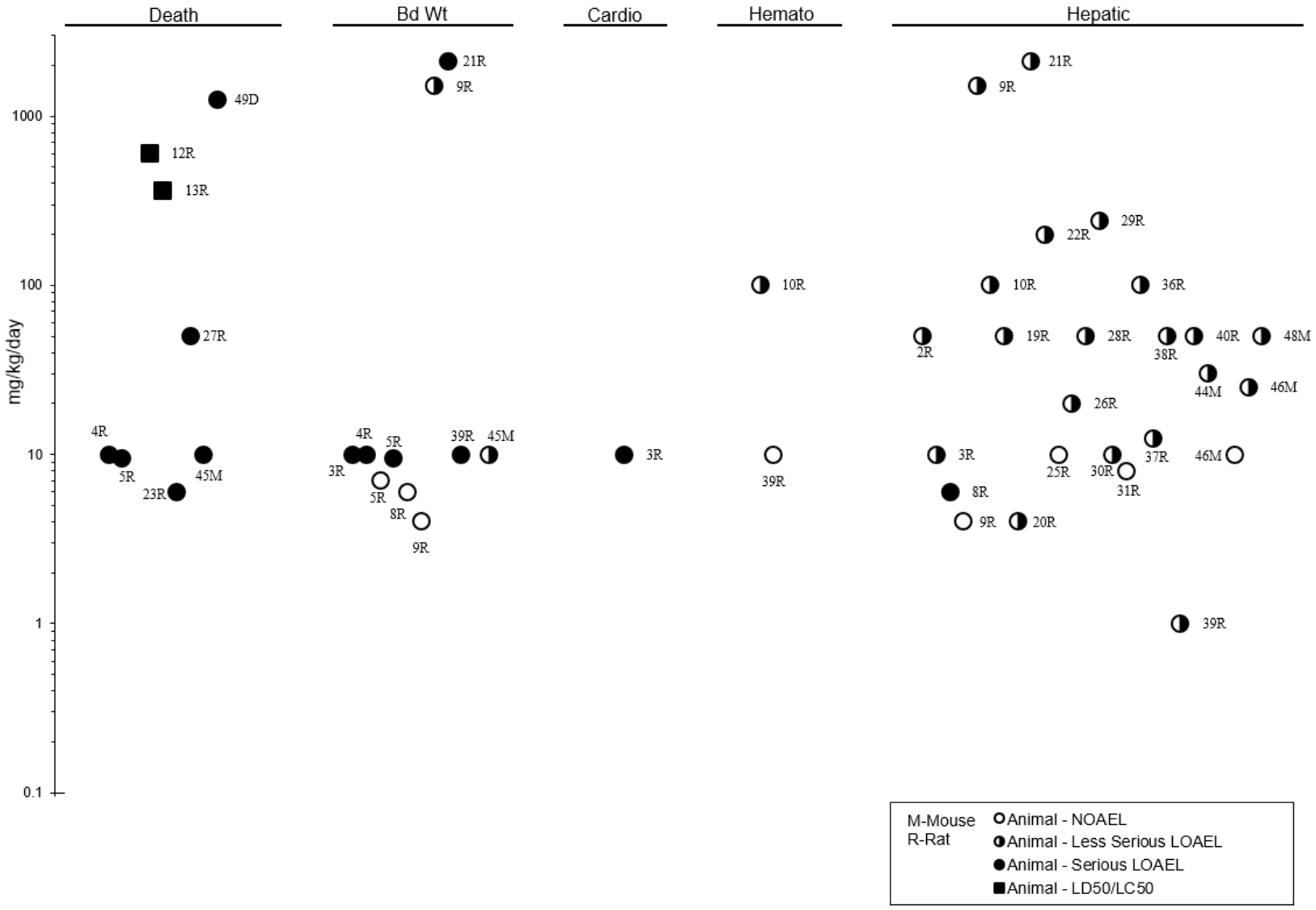


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Acute (≤14 days)

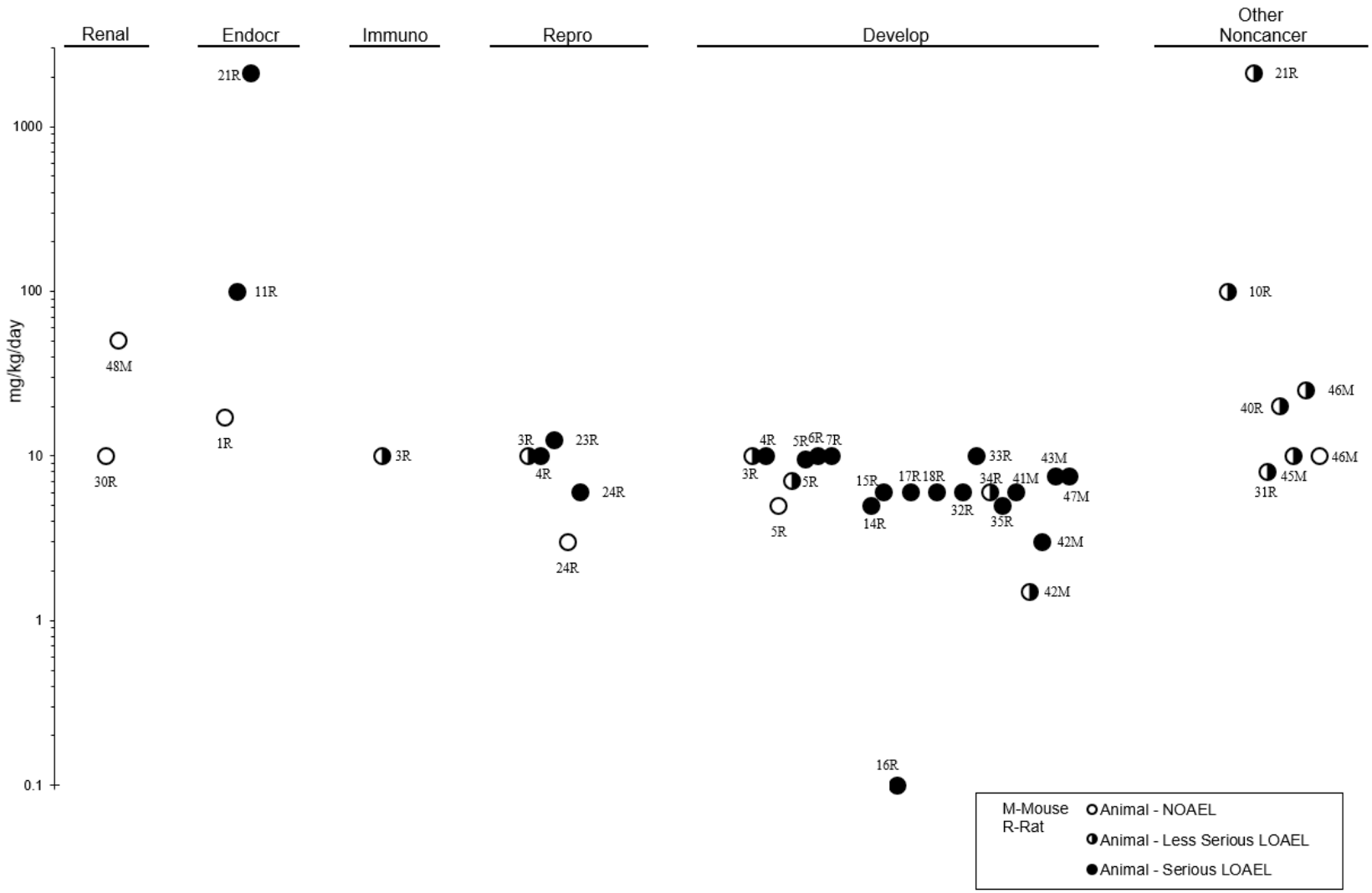


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Intermediate (15–364 days)

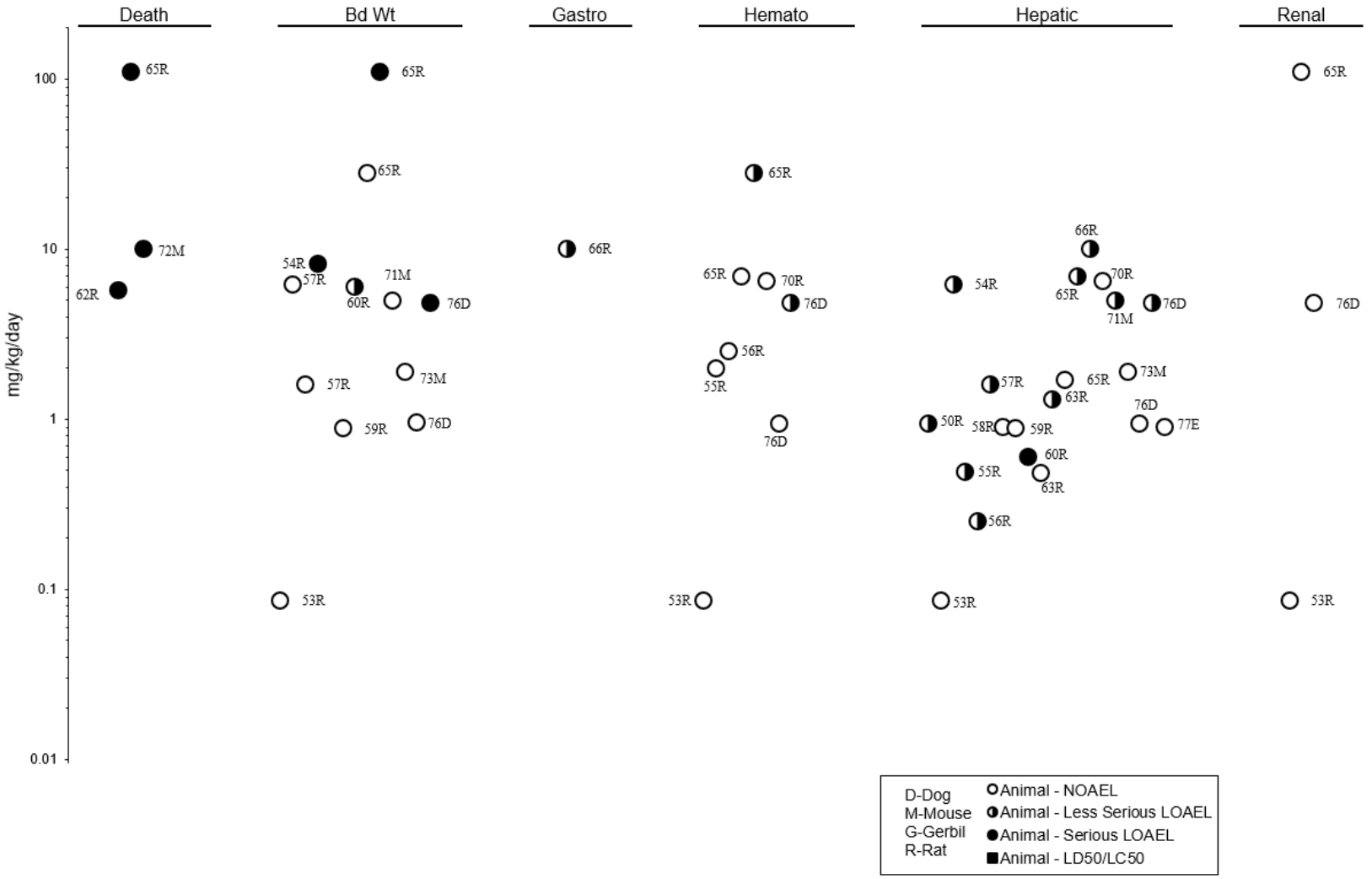


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Intermediate (15–364 days)

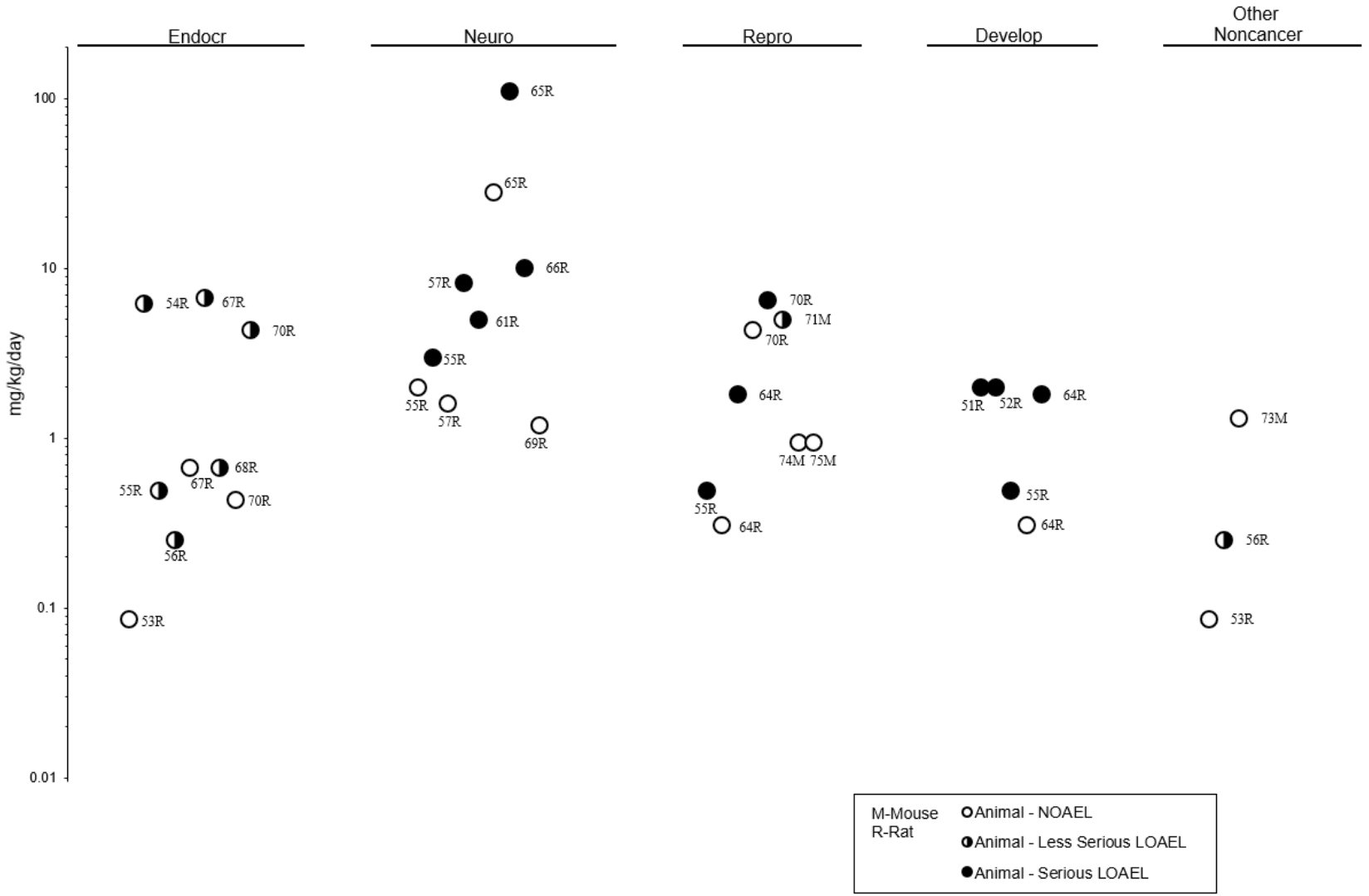


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Chronic (≥365 days)

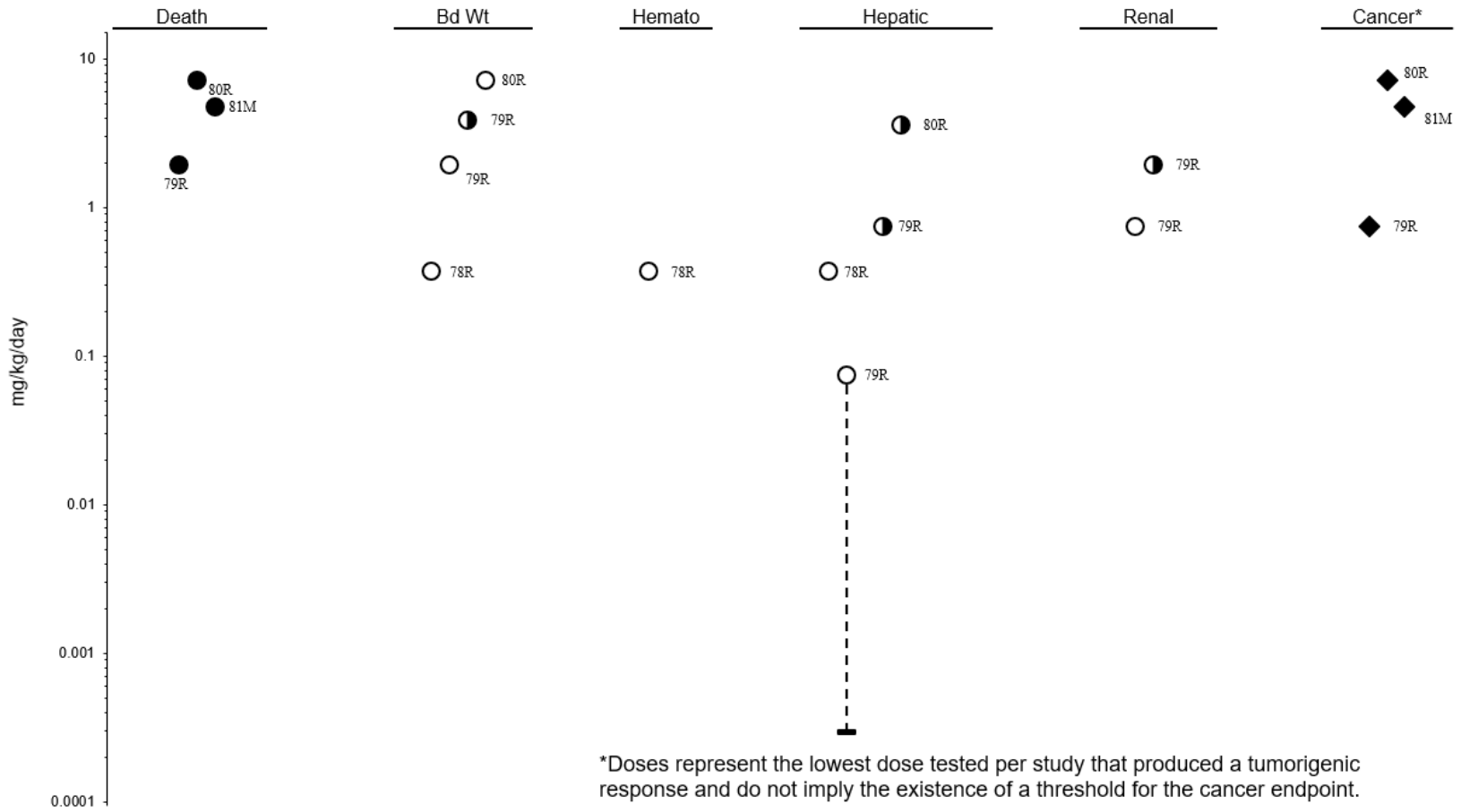


Table 2-4. Levels of Significant Exposure to Chlordecone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 14 M	Once (GO)	0, 50	BH, BW, CS	Bd wt		50		11% weight loss
					Neuro			50	Tremors; splaying of legs
Albertson et al. 1985									
2	Rat (Sprague-Dawley) 4–5 M	Once (GO)	0, 25, 50, 100	CS, BI	Neuro	50		100	Mild tremors
Aldous et al. 1984									
3	Rat (Sprague-Dawley) 3–15 M	10 days 1 time/day (GO)	0, 2.5, 5, 10	BI, CS	Neuro	5		10	Mild tremors
Aldous et al. 1984									
4	Rat (Sprague-Dawley) 15–68 M	8 days (F)	0, 17	HP, BI	Bd wt		17		Depletion of body fat
					Endocr		17		Depletion of epinephrine in adrenal medulla
					Neuro			17	Tremor, hyperexcitability
Baggett et al. 1980									
5	Rat (CD) 26–42 F	GDs 7–16 1 time/day (GO)	0, 2, 6, 10	BW, DX, LE, OW	Death			10	19% maternal mortality
					Bd wt		2		15% decrease in maternal body weight gain
					Develop	6		10	Increased number of fetuses with enlarged renal pelvis, edema, undescended testes, or enlarged cerebral ventricles; reduced fetal weight, reduced ossification
Chernoff and Rogers 1976									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
6	Rat (Long-Evans) 5 F	4 days 1 time/day (GO)	0, 15	DX, LE	Death			15	40% mortality
					Develop	15			
Chernoff et al. 1979b									
7	Rat (Sprague-Dawley) 3–7 M	Once (GO)	0, 5	BC, BI, BW, OF, OW	Hepatic	5			
Davis and Mehendale 1980									
8	Rat (Sprague-Dawley) 6 M	10 days 1 time/day (GO)	0, 2.5, 5, 10	BI	Neuro	10	25		Decreased dopamine binding and uptake; decreased norepinephrine uptake
Desaiah 1985									
9	Rat (Sprague-Dawley) 4 NS	10 days (F)	0, 2.5, 5, 10	BI	Neuro		2.5		>20% decreased total brain calmodulin
Desaiah et al. 1985									
10	Rat (Sprague-Dawley) 50 M	Once (GO)	0, 72–98	CS, OF	Musc/skel		72–98		Muscle weakness
					Neuro			72–98	Tremors; hyperexcitability; abnormal gait
Egle et al. 1979									
11	Rat (NS) 6 NS	Once (G)	0, 40	BH, BI, HP	Neuro			40	Tremors
End et al. 1981									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
12	Rat (Fischer-344) 10–14 M	10 days 1 time/day (GO)	0, 0.625, 1.25, 2.5, 5, 10	BC, BW, OF, OW	Bd wt	5		10	10% lower mean terminal body weight
					Hepatic	5	10		Increased serum alkaline phosphatase, ALT, AST
					Renal	5	10		Increased blood urea nitrogen
					Endocr	5	10		38% increased relative adrenal weight
					Immuno	5	10		Decreased spleen and thymus weights, leukocyte counts, natural killer cell activity, and Concanavalin A responsiveness
					Neuro	1.25[b]	2.5		Increased startle response
					Other noncancer	5	10		Decreased serum cholesterol and glucose
EPA 1986a									
13	Rat (Fischer 344) 24 F	GDs 7–16 1 time/day (GO)	0, 10	DX, LE	Develop			10	84% decreased PPD 3 pup survival
EPA 1986a									
14	Rat (Sherman) NS M NS F	Once (GO)	NS	CS, LE	Death			125	LD_{50}
Gaines 1969									
15	Rat (Sprague-Dawley) NS F	GDs 14–20 1 time/day (GO)	0, 15	BI, DX, OF, OW	Develop			15	Anovulation and persistent vaginal estrus in offspring
Gellert and Wilson 1979									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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 (Sprague-Dawley) 4–6 M	Once (GO)	0, 15.2	BI	Hepatic	15.2			
Glende and Lee 1985									
17	Rat (Sprague-Dawley) 3 M	3 days 1 time/day (GO)	0, 10, 25, 50	BH, BI	Neuro		25	50	Decreased Na^+-K^+ATPase; decreased oligomycin sensitive Mg^{2+}ATPase (25 mg/kg); increased activity; tremor; exaggerated startle response; abnormal gait (50 mg/kg)
Jordan et al. 1981									
18	Rat (Sprague-Dawley) 5 M	5 days (F)	0, 9.7	BC, BW, CS, FI, OF, OW	Bd wt Hepatic Neuro	9.7 9.7		 9.7	 Tremors; exaggerated startle response
Klingensmith and Mehendale 1982a									
19	Rat (Sprague-Dawley) 6 M	3 days 1x/d (GO)	0, 8.3, 16.7, 25	BI	Cardio		8.3		Decreased ^{45}Ca-uptake and Ca^{2+} ATPase activity
Kodavanti et al. 1990a									
20	Rat (Wistar) 10 M, 10 F	Once (GO)		LE	Death			132 M 126 F	LD_{50}
Larson et al. 1979b									
21	Rat (Sprague-Dawley) 4–6 M	2–3 days 1 time/day (GO)	0, 10, 25, 50	CS, HP	Musc/skel	10	25		Increased Mg^{2+} ATPase activity in muscle sarcoplasmic reticulum
					Neuro			25	Tremors
Mishra et al. 1980									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
22	Rat (Sprague-Dawley) 6 M	3 days 1 time/day (GO)	0, 0.5, 2, 10	BC, BI, HP, OW	Hepatic	10			
					Renal	10			
Plaa et al. 1987									
23	Rat (Fischer 344) 8–10 M	Once (GO)		LE	Death			91.3 M	LD_{50}
Pryor et al. 1983									
24	Rat (Fischer 344) 10 M	10 days 1 time/day	0, 0.625, 1.25, 2.5, 5, 10	BC, CS, OW	Bd wt	5	10		19% decrease in body weight
					Hemato	5	10		Decreased neutrophils
					Neuro	5		10	Tremors
Smialowicz et al. 1985									
25	Rat (Sprague-Dawley) 8–10 F	Once (GO)	0, 35, 55, 75	BW, CS, OF, OW	Bd wt		75		12% decrease in body weight
					Endocr		35		Increased relative adrenal weight
					Immuno		75		Decreased thymus weight
					Neuro			35	Tremors; exaggerated startle response
					Repro			35	Persistent estrus
					Other noncancer	35	55		Decrease in colonic temperature
Swanson and Woolley 1982									
26	Rat (Sprague-Dawley) 5–8 M	3 days 1 time/day (GO)	0, 18.75	BI, BW, OF, OW	Bd wt	18.75			
					Hepatic		18.75		Increased bile flow; decreased bile acid concentration and secretory rate
Teo and Vore 1991									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
27	Mouse (ICR) 7 M	2–4 days 1 time/day (GO)	0, 25, 50	CS	Neuro			25	Severe tremors; motor incoordination
Chang-Tsui and Ho 1979									
28	Mouse (ICR) NS M	2–3 days 1 time/day (GO)	0, 50	BI	Neuro		50		Decreased dopamine and norepinephrine uptake; decreased dopamine binding
Chang-Tsui and Ho 1980									
29	Mouse (CD-1) 25 F	GDs 8–12 1 time/day (GO)	0, 20	LE, CS	Death			20	16% mortality
					Bd wt			20	61% decrease in maternal body weight gain
					Develop			20	Decreased survival and body weight of pups on PPDs 1 and 3
Chernoff and Kavlock 1982									
30	Mouse (CD-1) 12–26 F	GDs 7–16 10 days 1 time/day (GO)	0, 2, 4, 8, 12	BW, DX, MX, OW	Develop	8		12	Increased fetal deaths; increased club foot
Chernoff and Rogers 1976									
31	Mouse (CD-1) NS F	PPDs 1–4 1 time/day (GO)	0, 6, 18, 24	DX, LE	Death			24	4 of 9 maternal mice died
					Develop			18	64% pup mortality; 100% pup mortality at 24 mg/kg/day
Chernoff et al. 1979b									
32	Mouse (ICR) 10 M	12 days 1 time/day (GO)	0, 25, 50	CS, LE	Death			25	100% mortality
					Neuro			25	Mild tremors
Desaiah et al. 1980a									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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	Mouse (C57BL/6) 13–32 M	2 days 1 time/day (GO)	0, 30	BC, BI, CS	Hepatic	30			
Fouse and Hodgson 1987									
34	Mouse (ICR) 5–9 M	1–11 days 1 time/day (GO)	0, 10, 25, 50	BH, BI	Neuro			10	Motor incoordination
Fujimori et al. 1982a									
35	Mouse (ICR) 3–8 M	4 days 1 time/day (GO)	0, 10, 25	BC, BI	Hepatic		25		Decreased hepatic glycogen
					Other noncancer		25		Decreased serum glucose and lactate
Fujimori et al. 1983									
36	Mouse (ICR) 6–12 M	5 or 8 days 1 time/day (GO)	0, 25	BH, BI	Neuro		25		Decreased striatal dopamine synthesis uptake and release
Fujimori et al. 1986									
37	Mouse (CD-1) NS F	GDs 8–12 1 time/day (G)	0, 20	BH, BW, DX, FX, MX, OF, OW, TG	Develop			20	Decreased postnatal viability
Gray et al. 1983									
38	Mouse (ICR) 4–5 M	Once (GO)	0, 25	BH, BI	Neuro		25		Increased brain calcium in mice 6–8 weeks old; decreased brain calcium in adults
Hoskins and Ho 1982									
39	Mouse (ICR) 3–4 M	8 days 1 time/day (GO)	0, 25	BH, BI	Neuro		25		Tremors
Hoskins and Ho 1982									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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 (ICR) 15 M	2–14 days 1 time/day (GO)	0, 10, 25, 50	BH, BI, CS	Bd wt		10		10–15% decrease in maternal weight gain
					Neuro			10	Decreased motor coordination; tremors
Huang et al. 1980									
41	Mouse (CD-1) 15–40 F	Once GD 8 (GO)	0, 110, 125	DX, LE	Death			110	25% mortality
					Develop			125	Increased resorptions and malformations; decreased viable litters
Kavlock et al. 1985									
42	Mouse (ICR/SIM) 27–28 F	GDs 8–12 1 time/day (GO)	0, 24	BW, DX, LE	Death			24	18% mortality
					Bd wt			24	85% decrease in maternal weight gain
					Develop			24	Decreased fetal survival and neonatal weight gain; increased still births
Seidenberg et al. 1986									
43	Mouse (CD-1) 6–15 F	2 weeks 5 days/week 1 time/day (GO)	0, 2, 4, 8	OF	Repro			2	Induction of persistent vaginal estrus
Swartz et al. 1988									
44	Rabbit (NS) NS	Once (GO)		LE	Death			71	LD_{50}
Larson et al. 1979b									
45	Dog (NS) NS	Once (GO)		LE	Death			250	LD_{50}
Larson et al. 1979b									

Table 2-4. Levels of Significant Exposure to Chlordecone – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
INTERMEDIATE EXPOSURE									
46	Rat (Sprague-Dawley) 4–5 M	15 days (F)	0, 0.95, 2.4, 4.7, 9.5	BI, CS	Neuro	2.4		4.7	Tremors
Agarwal and Mehendale 1984a									
47	Rat (Fischer-344) 25 F	105 days (F)	0, 0.11, 0.68	BI, BW	Bd wt	0.68			
					Endocr	0.68			
Ali et al. 1982									
48	Rat (Sherman) 24–25 M, 22–25 F	3 months (F)	M: 0, 1.17-1.58 F: 0, 1.62-1.71	BW, CS, DX, HP, OF, OW	Bd wt	1.62 F	1.17 M		13% lower mean body weight gain
					Hepatic		1.17 M 1.62 F		Focal necrosis
					Endocr		1.17 M 1.62 F		Reversible hyperplasia of adrenal cortex
					Neuro			1.17 M 1.62 F	Tremor, hyperactivity, exaggerated startle response
					Repro	1.17 M	1.62 F		Decreased number of litters born to control males mated to chlordecone-treated females
					Develop	1.17 M 1.62 F			
Cannon and Kimbrough 1979									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
49	Rat (Sprague-Dawley) 6 M	15 days (F)	0, 0.086, 0.86, 4.3, 8.6	BC, BI, BW, OF, OW	Hepatic	0.86	4.3		Significantly increased serum nonprotein nitrogen compounds and enzymes
					Other noncancer		8.6		Decreased serum triglycerides, LDL, and cholesterol
Chetty et al. 1993a									
50	Rat (Sprague-Dawley) 10 M	28 days (F)	0, 0.086	BC, BI, BW, CS, FI, HP	Bd wt	0.086			
					Hemato	0.086			
					Hepatic	0.086			
					Renal	0.086			
Chu et al. 1980b									
51	Rat (Sprague-Dawley) 3–11 M	15 days (F)	0, 1.6, 8.2	BH, BI, BW, CS, OF, OW	Bd wt	1.6		8.2	99% decrease in body weight gain
					Hepatic		1.6		Impaired biliary excretion Increases in liver weight, serum ALT, and AST at 5 mg/kg/day
					Neuro	1.6		8.2	Tremors and hypersensitivity to sound and touch
Curtis and Hoyt 1984									
52	Rat (Sprague-Dawley) 20 M	15 days (F)	0, 0.8, 4, 12	BI, BW, CS, FI, GN, OF, OW	Bd wt	0.8		4.	63% lower body weight gain
					Neuro	4		12	Tremors; hyperexcitability
Curtis and Mehendale 1979									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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	Rat (Zivac-Miller) 1–5 M, 3 F	90 days 5–6 days/week 1 time/day (GO)	1, 5, 10	BH, CS, LE	Neuro			1	Decrease in operant behavior; tremors
Dietz and McMillan 1979									
54	Rat (Sprague-Dawley) 4–5 M	15 days (F)	0, 0.86	BI, BW, FI, HP, OW, WI	Bd wt	0.86			
Faroon and Mehendale 1990									
55	Rat (Sprague-Dawley) 5 M	15 or 20 days (F)	0, 9.7	BH, BW, CS, FI, OW	Bd wt			9.7	48–49% decrease in body weight gain
					Hepatic	9.7			
					Neuro			9.7	Progressively increased constant tremors
					Other noncancer		9.7		36% decrease in epididymal fat
Klingensmith and Mehendale 1982a									
56	Rat (Wistar) 5 M, 5 F	3–9 months during a 2-year study (F)	M: 0, 0.083, 0.42, 0.83, 2.10, 4.2, 6.7 F: 0, 0.097, 0.48, 0.97, 2.4, 4.8, 7.8	BC, BW, CS, FI, HP, OW, UR	Bd wt	0.97 M 0.83 F	2.1 M	2.4 F	Up to 20% lower mean body weight Up to 24% lower mean body weight
					Hemato	7.8 M 6.7 F			
					Hepatic	0.97 M 0.83 F	2.4 M 2.1 F		Congestion in liver of 3/5 males and 2/5 females at 3 months
					Endocr	6.7 M 0.83 F	2.4 F		Loss of adrenal lipid in 2/5 females at 3 months

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
					Neuro	0.83 M 0.97 F		2.1 M 2.4 F	Tremors (earlier onset and increased severity with increasing dose) up to 6 months, regressing thereafter; incidences by sex not reported
					Repro	0.83 M		2.1 M	Testicular atrophy in 4/5 males at 3 months
					Other noncancer	0.83 M 2.4 F	2.1 M		Increased metabolic rate in males at 9 months
Larson et al. 1979b									
57	Rat (Sprague-Dawley) 10 M	90 days (F)	0, 0.26, 0.83, 1.67	CS, DX, OF	Neuro	0.26[c]	0.83		Hyperexcitability; mild tremors at 0.83 and 1.67 mg/kg/day
					Repro	0.26[c]	0.83		46–48% decreased sperm motility and viability; 19% decreased epididymal sperm concentration
					Develop	1.67			
Linder et al. 1983									
58	Rat (Sprague-Dawley) 4 F	16 days (F)	0, 3.95, 8.54, 11.63	BI, BW, CS, FI, OW	Bd wt			3.95	Dose-related depressed body weight gain (28–78% less than controls)
					Neuro			3.95	Tremors; hypersensitivity to noise and stress
Mehendale et al. 1978									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
59	Rat (Sprague-Dawley) 5 M	30–35 days (F)	0, 10	BH, CS, LE, OF, OW	Death			10	2/5 died
					Bd wt		10		Significantly decreased body weight gain
					Hepatic		10		Impaired biliary function
					Neuro			10	Tremors, hyperactivity, exaggerated startle response
Mehendale 1981									
60	Rat (Sprague-Dawley) 4–5 M	15 days (F)	0, 4	OF	Hepatic		4		Decreased hepatobiliary function
Mehendale 1990									
61	Rat (Sprague-Dawley) 4 M	15 days (F)	0, 0.88	BC	Hepatic	0.88			
Mehendale et al. 1991									
62	Rat (Fischer 344) 9–10 M	15 weeks 5 days/week 1 time/day (GO)	0, 2.8, 4.1, 7.1, 11.2	BH, CS, LE	Death			4.1	6/10 died
					Bd wt		2.8		>10% decrease in body weight gain
					Neuro	2.8		4.1	Increased startle response
					Other noncancer		7.1		Increased body temperature
Pryor et al. 1983									
63	Rat (Fischer-344) 8–12 M	90 days (F)	0, 1.0, 3.0	BH, CS	Neuro			1.0	Exaggerated startle response
Squibb and Tilson 1982a									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
64	Mouse (ICR) 15 M	33 days 1 time/day (GO)	0, 10, 25, 50	BI, CS, GN, LE	Death			10	100% mortality
					Gastro		NS		Mild diarrhea
					Neuro			10	Tremors; decreased motor coordination
					Other noncancer		10		Decreased adipose tissue; decreased plasma glucose
Fujimori et al. 1983									
65	Mouse (BALB/c) 24–36 M, 24–36 F	5 months (1 month premating and through production of two litters (F)	0, 0.94, 1.9	OF	Repro			0.94	36% decrease in second litters
Good et al. 1965									
66	Mouse (BALB/c) 4–70 M,F	2–12 months (F)	1.9, 5.6, 7.5, 11, 13, 15, 19	BW, HP, LE, OW	Death			11	12% mortality in adults; 100% mortality in juveniles
					Bd wt	7.5	11		Decreased body weight in juveniles and adults
					Hepatic		7.5		Focal necrosis, cellular hypertrophy, hyperplasia, congestion; liposphere formation and decreased numbers of mitochondria
					Neuro	1.9		5.6	Tremor
					Repro			7.5	Increased estrus
Huber 1965									
67	Mouse (BALB/c) 14 M,14 F	160 days (F)	0, 7.5	OF	Repro			7.5	Persistent vaginal estrus; reversible reproductive failure
Huber 1965									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
68	Mouse (BALB/c) 8 M, 8 F	130 days (F)	0, 1.9, 5.6, 7	OF	Repro			1.9	8% decrease in litter size and 19% increase in pair-days to litter; constant estrus at 3.9 mg/kg/day
					Develop	1.9		7	Decreased postnatal survival
Huber 1965									
69	Mouse (Swiss-Webster) 6 M	15 days (F)	0, 1.9	BC, BI, BW, FI, HP, OW	Bd wt Hepatic	1.9 1.9			
Mehendale et al. 1989									
70	Mouse (CD-1) 6 F	4 weeks 5 days/week 1 time/day (GO)	0, 8	BH, CS	Neuro			8	Slight tremors; increased reactivity to noise
Swartz and Schutzmann 1986									
71	Mouse (CD-1) 6–22 F	4 or 6 weeks 5 days/week 1 time/day (GO)	0, 2, 4, 8	OF	Repro			2	Increased ovulation; persistent vaginal estrus
Swartz et al. 1988									
72	Gerbil (Mongolian) 4–5 M	15 days (F)	0, 5.4	BC, BI	Hepatic	5.4			
Cai and Mehendale 1990									
73	Gerbil (Mongolian) 4–5 M	15 days (F)	0, 5.4	BI, HP	Hepatic	5.4			
Cai and Mehendale 1991a									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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									
74	Rat (Sprague-Dawley) 4–10 M	21 months (GO)	0, 0.07	BI, BW, HE, HP	Hemato	0.07			
Chu et al. 1981c									
75	Rat (Wistar) 40 M, 40 F	Up to 2 years (F)	0, 0.089, 0.45, 0.89, 2.2, 4.5, 7.1	BC, BW, CS, FI, HE, HP, OW, UR	Death			2.2	Decreased survival in females; 100% mortality in both sexes at 2.5 and 4.0 mg/kg/day treated for 25 and 17 weeks, respectively
					Bd wt	0.89	2.2		>10% decreased body weight gain at 1 and 2 years
					Cardio	2.2			No effect among survivors at 1 and 2 years
					Hemato	0.89	2.2		Depressed hematocrit levels at 1 and 2 years
					Hepatic	0.45	0.89		Fatty changes in liver at 1 and 2 years
					Renal	0.089[d]	0.45		Proteinuria and increased severity of glomerulosclerosis at 1 and 2 years
					Neuro	0.89		2.2	Tremor; observed as early as weeks 2–3 at the two highest dose levels
Larson et al. 1979b									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
76	Rat (Osborne-Mendel) 44–50 M 45–49 F	80 weeks (F)	M: 0, 0.56, 1.7 F: 0, 1.4, 2.0	CS, HE, HP, LE	Death			1.7 M 2.0 F	Decreased survival among males and females
					Hemato		0.56 M 1.4 F		Anemia
					Hepatic		0.56 M 1.4 F		Fatty infiltration and liver degeneration
					Dermal		0.56 M 1.4 F		Dermatitis
					Neuro			0.56 M 1.4 F	Tremors
					Cancer			1.7 M 2.0 F	CEL: hepatocellular carcinoma
NCI 1976									
77	Mouse (B6C3F1) 48–49 M 49–50 F	80 weeks (F)	M: 0, 3.4, 3.9 F: 0, 3.5, 6.9	CS, LE	Death			3.4 M	Decreased survival in males
					Hepatic		3.4M 3.5 F		Hepatocellular hyperplasia
					Neuro		3.4M 3.5 F		Tremors
					Cancer			3.4M 3.5 F	CEL: hepatocellular carcinoma
NCI 1976									

Table 2-4. Levels of Significant Exposure to Chlordecone – 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
78	Dog (beagle) 2 M, 2 F	124–128 weeks (F)	0, 0.047, 0.24, 01.2	BC, BW, HP, OW	Neuro	1.2			
Larson et al. 1979b									

[a]The number corresponds to entries in Figure 2-4; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an acute-duration Minimal Risk Level (MRL) of 0.01 mg/kg/day for chlordecone; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive an intermediate-duration MRL of 0.003 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[d]Used to derive a chronic-duration MRL of 0.0009 mg/kg/day for chlordecone; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATPase = adenosinetriphosphatase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BH = behavioral; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage, not specified; Gastro = gastrointestinal; GD = gestation day; (GO) = gavage, oil; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose, 50% kill; LDL = low-density lipoprotein; 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; PPD = post-partum day; Repro = reproductive; TG = teratogenicity; UR = urinalysis; WI = water intake

Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral
Acute (≤14 days)

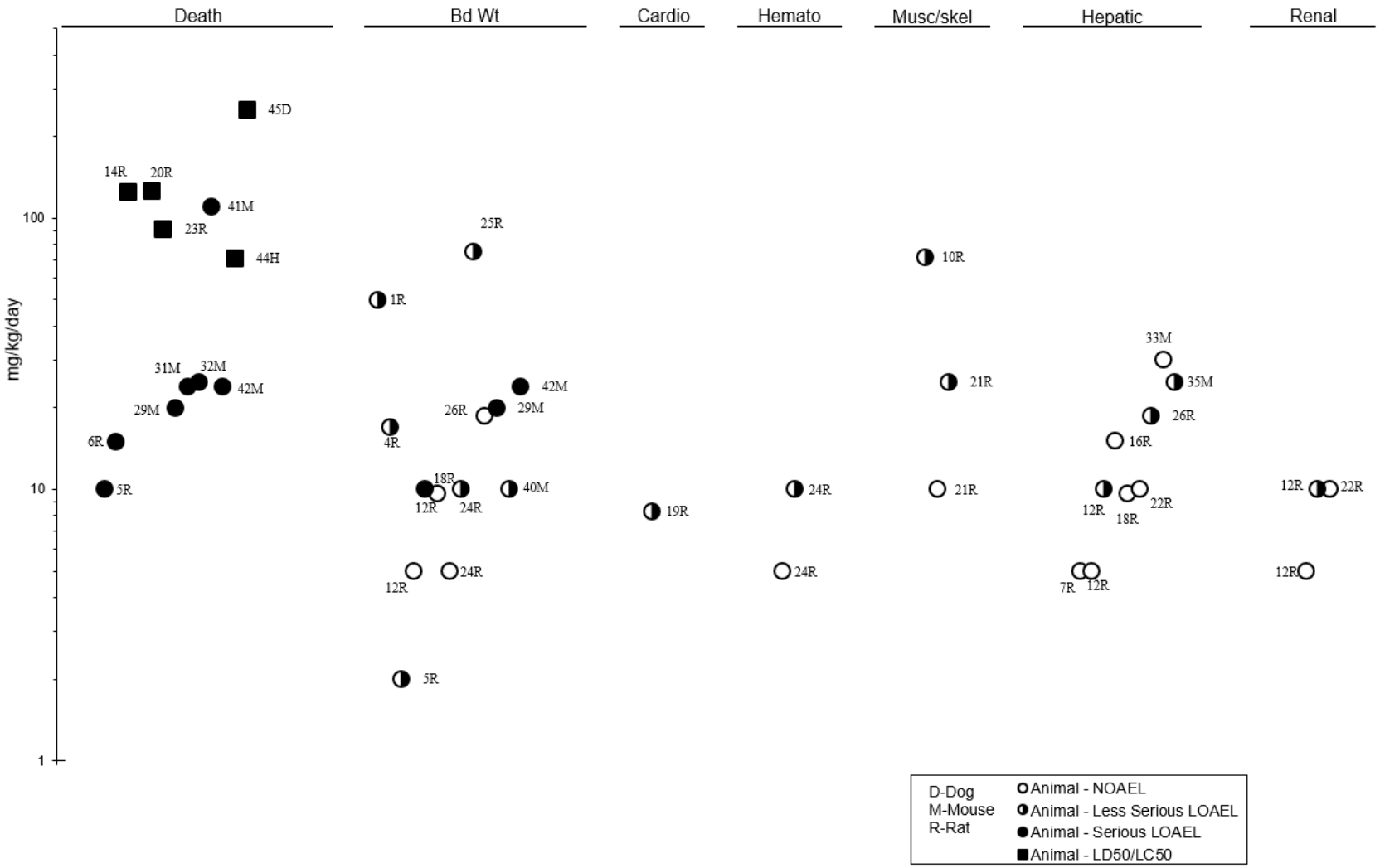


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral
Acute (≤14 days)

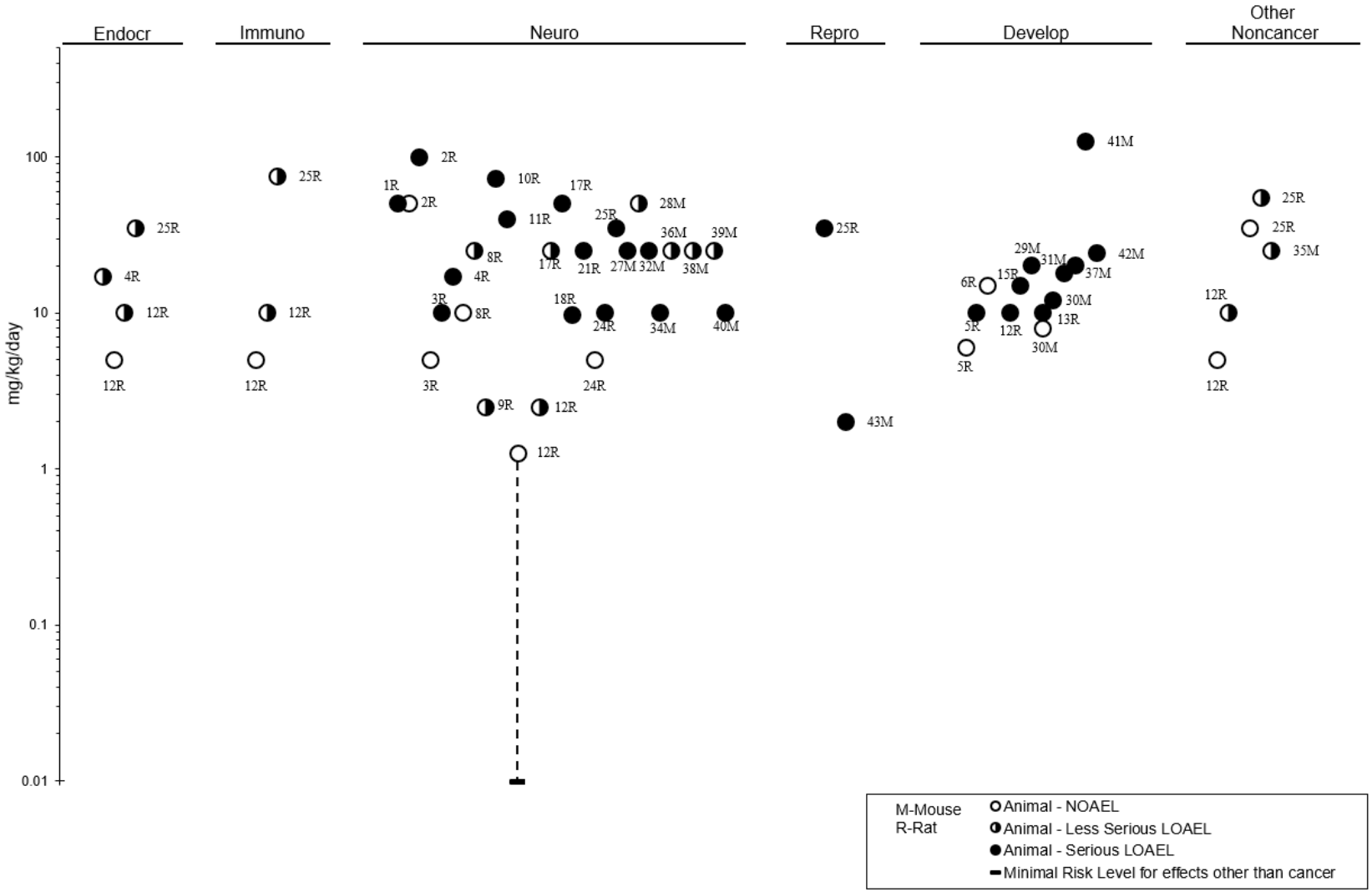


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral
Intermediate (15–364 days)

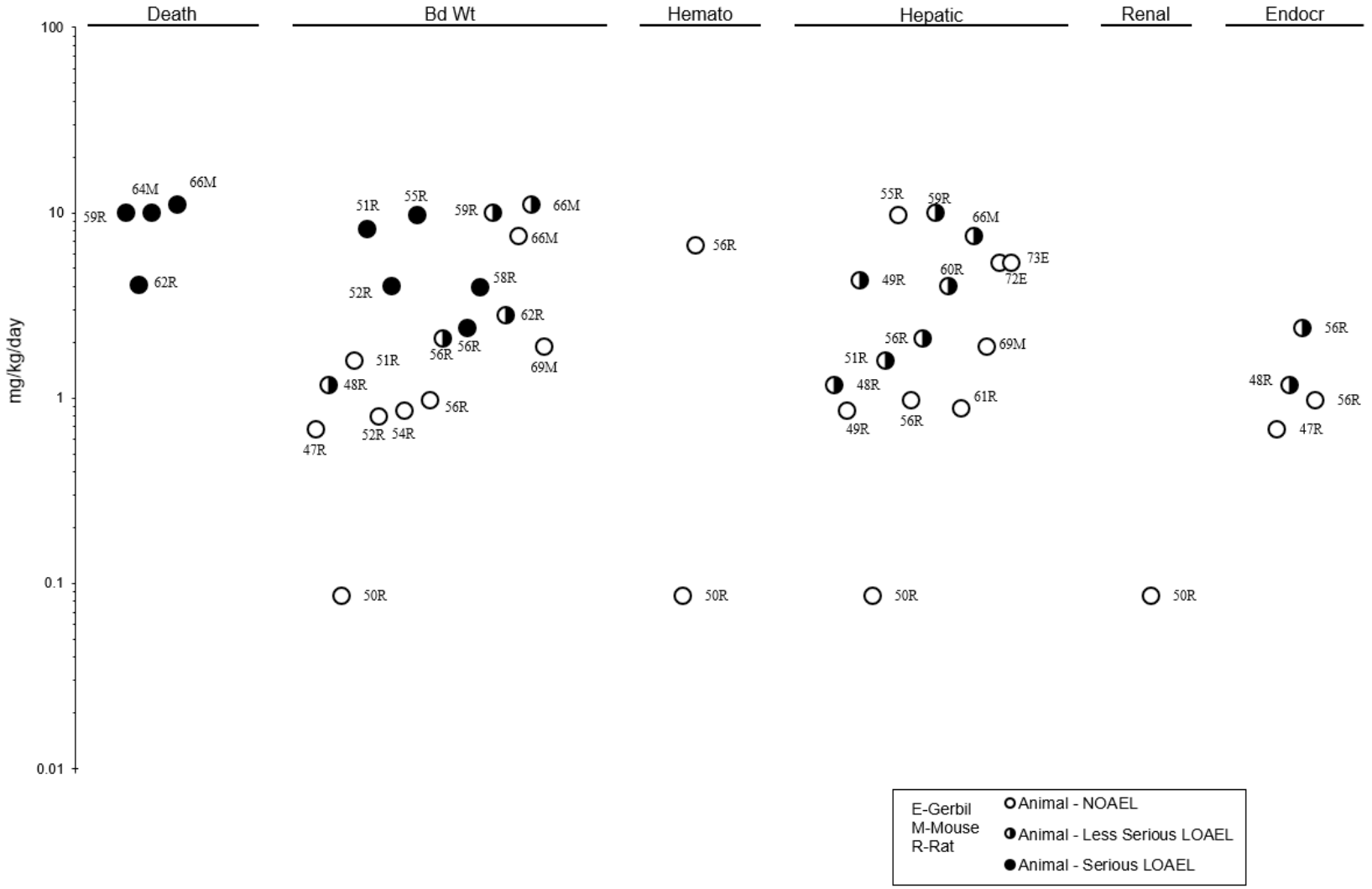


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral
Intermediate (15–364 days)

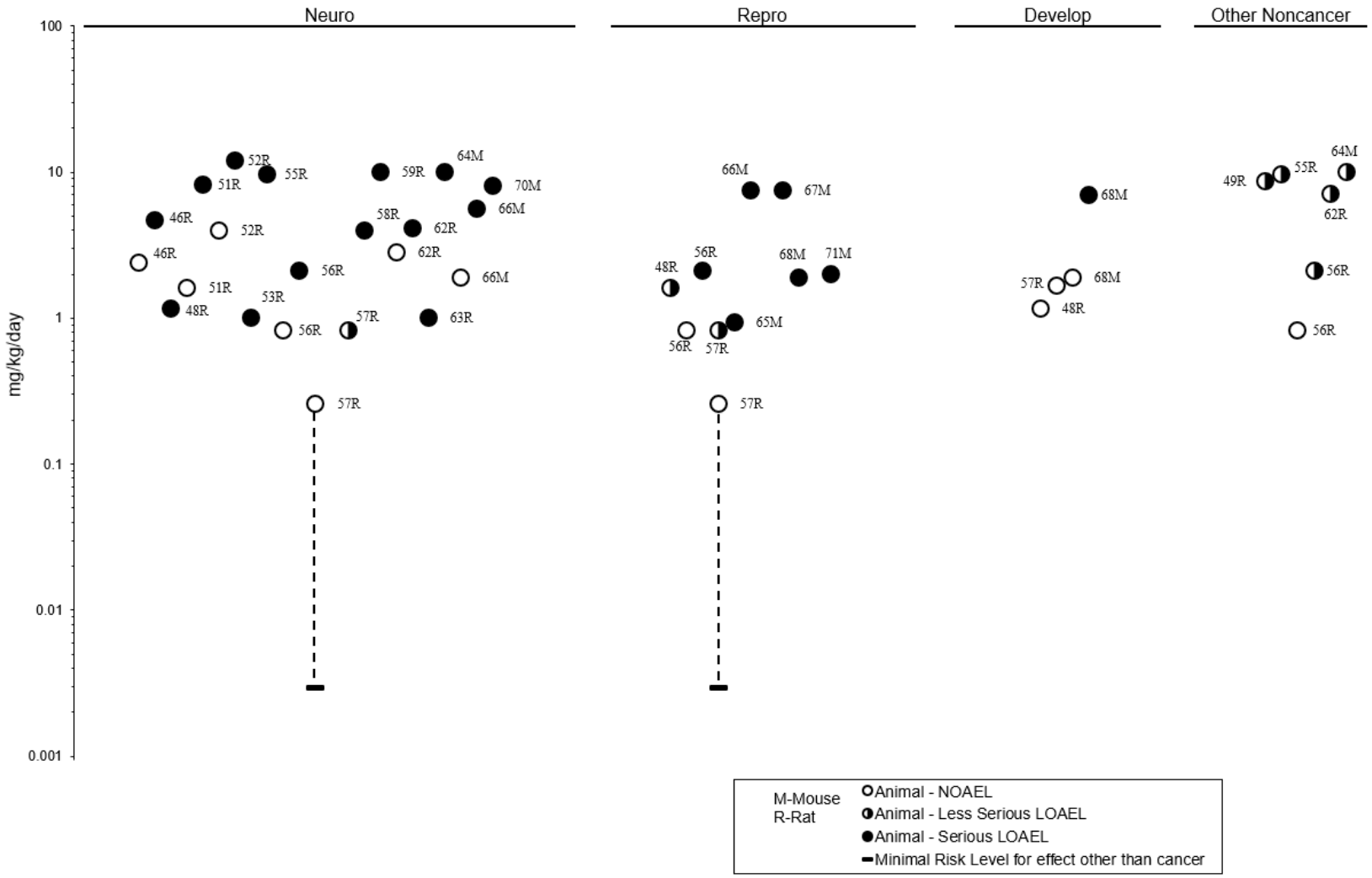


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral

Chronic (≥365 days)

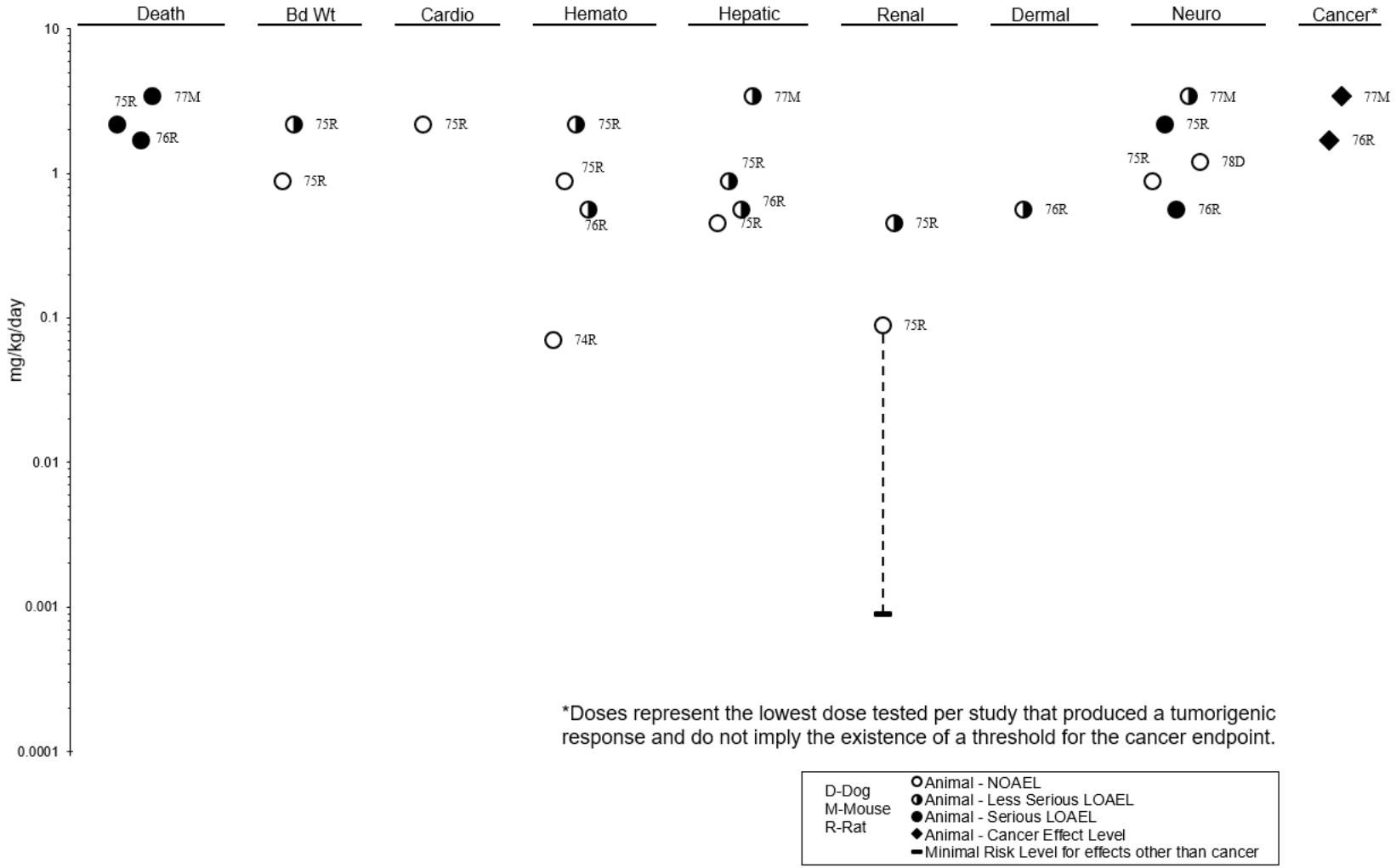


Table 2-5. Levels of Significant Exposure to Mirex – Dermal

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 (Sherman) 10 M,10 F	NS	NS	LE	Death			>2,000	LD_{50}
Gaines 1969								
INTERMEDIATE EXPOSURE								
Mouse (CD-1) 30 F	4 weeks 3 times/week (paint)	0, 3.6	BI, HP	Cancer			3.6 F	Skin tumor promotion
Meyer et al. 1993								
Mouse (CD-1) 30 F	20 weeks 2 times/week (paint)	0, 3.6	BI, HP	Cancer			3.6 F	Skin tumor promotion
Meyer et al. 1994								
Mouse (CD-1) 30 F	4 weeks 3 times/week (paint)	0, 3.6	HP	Cancer		3.6 F		Mild epidermal hyperplasia
Moser et al. 1992								
Mouse (CD-1) 30 F	20 or 34 weeks 3 times/week (paint)	0, 0.45, 0.9, 1.8, 3.6	BI, HP	Cancer			0.45 F	Skin tumor promotion
Moser et al. 1992								
Mouse (CD-1) 30 M, 30 F	20 weeks 3 times/week (paint)	0, 3.6	CS, GN, HP	Cancer			0.45 F	Skin tumor promotion
Moser et al. 1993								

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

Table 2-6. Levels of Significant Exposure to Chlordecone – 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 (Sherman) 10 M,10 F	NS	NS	LE	Death			>2,000	LD_{50}
Gaines 1969								
Rabbit (NS) 10 M	NS	20	LE	Death			410 M	LD_{50}
Larson et al. 1979b								

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

2.2 DEATH

Mirex. Oral LD_{50} values for mirex obtained in rats have been somewhat variable. In one study, administration of mirex in corn oil resulted in an LD_{50} value in females of 365 mg/kg (Gaines and Kimbrough 1970), whereas in another study, the LD_{50} values in male and female rats were 740 and 600 mg/kg, respectively, after administration of mirex in corn oil, but in excess of 3,000 mg/kg after administration in peanut oil (Gaines 1969). Mehendale et al. (1973) reported death of 2/5 female rats during a 5-day period of mirex gavage dosing at 50 mg/kg/day. Pregnant rats appear to be somewhat more sensitive to the lethal effect of mirex. Although a single oral dose of mirex at 25 mg/kg resulted in no mortality in nonpregnant females (Mehendale et al. 1973), 16–25% mortality in pregnant rats occurred at doses ranging from 6 to 10 mg/kg/day over a 10–11-day period during gestation (Byrd et al. 1981; Chernoff et al. 1979a; Khera et al. 1976) and mortality rates of 32–36% were observed in rat and mouse pups exposed through the milk during the first 4 days of lactation at these doses (Chernoff et al. 1979a). Four of 20 maternal rats died during oral exposure to mirex at 6 mg/kg/day on gestation days 6–15 (Khera et al. 1976). Twelve of 15 mice died during a 14-day study that employed oral dosing with mirex at 10 mg/kg/day (Fujimori et al. 1983). In male dogs, a single oral dose of mirex at 1,250 mg/kg was lethal to three of five treated animals; there were no deaths among five dogs similarly treated at 1,000 mg/kg (Larson et al. 1979a).

Several studies evaluated mortality in laboratory animals orally exposed to mirex for intermediate durations. Mortality was increased in adult male rats at doses as low as 5 mg/kg/day for 30 days (Mehendale 1981), in adult female rats at doses as low as 5.7 mg/kg/day for 90 days (Gaines and Kimbrough 1970; Larson et al. 1979a), and in rat pups at 1.8–2.8 mg/kg/day for the duration of lactation (Gaines and Kimbrough 1970). In mice, 100% mortality occurred following 1.3 mg/kg/day for 60 days and 0–25% mortality occurred at 0.65 mg/kg/day for 120 days (Ware and Good 1967). Death occurred in one of two dogs treated orally with mirex at 4.8 mg/kg/day for 13 weeks (Larson et al. 1979a). In a 2-year study in rats, males exhibited mirex treatment-related increased mortality at 1.8 mg/kg/day (63 versus 15% in controls), but females exhibited no mirex-related decrease in survival at as much as 7.7 mg/kg/day (NTP 1990). In an 18-month oral study of mice, unscheduled death was observed among all mice at 4.8 mg mirex/kg/day (Innes et al. 1969). In a 15-month study, Wolfe et al. (1979) reported 20 and 92% mortality among mice ingesting mirex at 0.24 and 2.4 mg/kg/day, respectively.

The dermal LD_{50} value for mirex in rats was reported to be in excess of 2,000 mg/kg (Gaines 1969).

Chlordecone. Single-dose oral LD_{50} values in rats for chlordecone were reported to be 126 mg/kg in females (Larson et al. 1979b) and 91.3 mg/kg (Pryor et al. 1983) and 132 mg/kg (Larson et al. 1979b) in males. An oral LD_{50} for male and female rats was 125 mg/kg (Gaines 1969). LD_{50} values for male rabbits and dogs (sex not specified) were 71 and 250 mg/kg, respectively (Larson et al. 1979b). A single oral dose of 110 mg/kg resulted in the death of 5/20 pregnant mice; at 125 mg/kg, death occurred in 17/40 pregnant mice (Kavlock et al. 1985). No mortality was observed in male rats dosed with chlordecone at approximately 10 mg/kg/day for 10 days (Simmons et al. 1987), but 8/42 pregnant mice died during oral treatment with chlordecone at 10 mg/kg/day on gestation days 7–16 (Chernoff and Rogers 1976). Gavage dosing of 24 mg chlordecone/kg/day during gestation days 8–12 resulted in the death of 5/27 pregnant mice (Seidenberg et al. 1986). Ingestion of milk from dams given 18 mg chlordecone/kg/day during the first 4 days of lactation resulted in 64% mortality in mouse pups (Chernoff et al. 1979a). Daily oral administration of chlordecone to male mice at 25 or 50 mg/kg/day resulted in 100% mortality by treatment days 12 and 6, respectively (Desaiah et al. 1980b).

In intermediate-duration studies of male rats, 2/5 rats died during 5 weeks of oral exposure to chlordecone at 8.6 mg/kg/day (Mehendale 1981) and 6/10 rats died during 15 weeks of treatment at 4.1 mg/kg/day (Pryor et al. 1983). In mice of both sexes, at a dose of 11 mg/kg/day for up to 12 months, only 12% mortality was observed among adult mice, whereas all four treated juvenile mice died, indicating a greater sensitivity in immature mice (Huber 1965). All 15 male mice exposed orally with chlordecone at 10 mg/kg/day died during a scheduled 33-day dosing period (Fujimori et al. 1983). Survival was decreased in female rats receiving chlordecone from the diet at 2.2 mg/kg/day for up to 2 years (Larson et al. 1979b), both male and female rats receiving chlordecone from the diet at 1.7–2.0 mg/kg/day for up to 80 weeks (NCI 1976), and male mice receiving chlordecone from the diet at 3.4 mg/kg/day for up to 80 weeks (NCI 1976).

The dermal LD_{50} value for chlordecone in rats was reported to be in excess of 2,000 mg/kg (Gaines 1969). In male rabbits exposed dermally to chlordecone in corn oil, an LD_{50} value of 410 mg/kg was reported (Larson et al. 1979b).

2.3 BODY WEIGHT

Mirex. No studies were located regarding body weight effects in humans exposed to mirex. Decreases >10% in body weight or body weight gain have been observed in studies of laboratory animals following acute-, intermediate-, and chronic-duration oral exposure to mirex (Buelke-Sam et al. 1983; Byrd et al.

1981; Chadwick et al. 1977; Chernoff et al. 1979a, 1979b; Chu et al. 1981b; 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. Weight loss was reported among 27 of 133 workers examined as a result of intermediate- or chronic-duration occupational exposures to chlordecone (Cannon et al. 1978). Weight loss (up to 60 pounds in 4 months) was reported in 10 of 23 workers with blood chlordecone levels in excess of 2 µg/L (Taylor et al. 1978). Decreases >10% in body weight or body weight gain have also been observed in studies of laboratory animals following acute-, intermediate-, and chronic-duration oral exposure to chlordecone (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, 1978b; Pryor et al. 1983; Seidenberg et al. 1986; Simmons et al. 1987; Smialowicz et al. 1985; Swanson and Wooley 1982). In the report by Larson et al. (1979b), the decreases in body weight were observed in the presence of increases in food consumption, indicating a decrease in food utilization efficiency and/or increased stress to the animals.

2.4 RESPIRATORY

Mirex. No studies were located regarding respiratory effects in humans or animals exposed to mirex.

Chlordecone. Pleuritic chest pains were reported by 32 of 133 workers examined for toxicity following intermediate- or chronic-duration occupational exposure at a chlordecone-manufacturing facility (Cannon et al. 1978); pleuritic chest pains were reported by 18 of 23 workers with blood levels in excess of 2 µg/L. Further examination of these workers did not reveal any dyspnea, and chest x-rays revealed no lung pathology (Taylor 1982, 1985). Extremely limited information was located regarding respiratory effects in animals following oral exposure to chlordecone. Routine histopathological examination of the lungs of rats in both 90-day and 2-year feeding studies with doses as high as 4 mg/kg/day showed no adverse effects. Also, routine histopathological examination of the lungs of dogs exposed to doses as high as 0.625 mg/kg/day in a 2-year feeding study showed no effects (Larson et al. 1979b). It is unclear how many lung tissue samples were actually examined; the dog study used only two animals/sex/dose.

2.5 CARDIOVASCULAR

Mirex. No studies were located regarding cardiovascular effects in humans exposed to mirex. Limited information was located regarding cardiovascular effects of mirex in animals. Changes in blood flow patterns were seen in pregnant rats given gavage doses of mirex at 10 mg/kg/day for varying periods during pregnancy (Buelke-Sam et al. 1983). In this study, a single oral dose resulted in a decrease in blood flow to the stomach, while 5 and 10 daily doses resulted in decreased blood flow to other essential internal organs (lungs, liver, spleen, or kidneys). Five days of exposure also resulted in decreased cardiac output, but this effect had disappeared by day 10 of exposure. There was also a significant decrease in the heart weight of the maternal rats. Another study showed that rats given mirex at 100 mg/kg/day by gavage for 3 days experienced a slight inhibition of Na+K+ATPase in myocardial membranes (Desaiah 1980). The biological significance of this effect is unknown. There was no gross or histopathological evidence of mirex-related adverse cardiac effects among rats ingesting mirex for 13 weeks at doses as high as 64 mg/kg/day (Larson et al. 1979a).

Chlordecone. Symptoms associated with the cardiovascular system were not commonly reported by 133 workers exposed for intermediate or chronic durations to unspecified levels of chlordecone at a chlordecone-manufacturing facility (Cannon et al. 1978; Taylor 1982, 1985; Taylor et al. 1978). Furthermore, results from electrocardiography of 23 workers with active symptoms of chlordecone intoxication were normal (Taylor 1982, 1985). Maternal serum chlordecone was not associated with hypertensive disorders or preeclampsia in pregnant women (Saunders et al. 2014). See Table 2-2 for additional study details.

Available information regarding the cardiovascular effects of chlordecone in animals is also limited. Acute-duration studies have primarily examined biochemical parameters. For example, gavage dosing of rats with chlordecone (≥10 mg/kg/day for 3 days) resulted in inhibition of myocardial Na^+K^+ATPase (Desaiah 1980). At ≥25 mg/kg/day, inhibition of mitochondrial Mg^{2+}ATPase occurred; decreased norepinephrine and dopamine binding to myocardial membranes was observed at 50 mg/kg/day. Similarly, inhibition of calcium uptake, Ca^{2+}ATPase activity, and protein phosphorylation was observed in rat cardiac sarcoplasmic reticulum following gavage doses of chlordecone at 8.3 mg/kg/day for 3 days (Kodavanti et al. 1990a). Because of the importance of calcium regulation in all phases of the cardiac cycle, this might indicate a decrease in cardiac effectiveness.

Vasodilation of tail vessels has been observed in rats following oral administration of chlordecone for 90 days at 4 mg/kg/day (Larson et al. 1979b). The cause of the vasodilation was not investigated, but was suggested to have been associated with altered thermoregulatory mechanism.

Routine histopathological analyses of heart samples have not shown significant changes following oral exposure of rats to chlordecone for 2 years at 2.2 mg/kg/day or dogs for 124–128 weeks at 0.625 mg/kg/day (Larson et al. 1979b). However, these studies are limited in that it is unclear how many heart samples were actually examined, and the dog study employed only two animals/sex/dose.

2.6 GASTROINTESTINAL

Mirex. No studies were located regarding gastrointestinal effects in humans exposed to mirex. Limited information was located regarding gastrointestinal effects in animals following oral exposure to mirex; however, the available data indicate that diarrhea is a relatively common result of high-dose mirex exposure. Several acute- and intermediate-duration studies have identified diarrhea in treated animals, but few of these studies presented sufficient information to assign a LOAEL for this effect. Diarrhea was identified as a predominant sign in female rats that died during a l0-day gavage study, but the mirex doses at which this was observed were not specified (6 or 12.5 mg/kg/day) (Khera et al. 1976). Similarly, diarrhea was noted as one of the clinical signs seen in rats after a single gavage dose, but it was unclear whether this effect occurred at the lowest dose (100 mg/kg) at which clinical signs were observed (Gaines and Kimbrough 1970). Diarrhea was observed in rats fed a total of 365 mg/kg over 12 days, but the daily dose was not specified (Kendall 1974). Mild diarrhea was observed in treated rats (10 mg/kg/day) starting on the 8th day of exposure and continuing over the duration of a 30-day dietary study (Mehendale 1981). Diarrhea was also observed in a 90-day gavage study of rats, but the dose (5, 12.5, or 25 mg/kg/day) at which it was observed was not reported (Dietz and McMillan 1979). Severe diarrhea was reported in mice following gastric intubation with mirex for up to 15 days, but the report did not state which of the doses (10, 25, or 50 mg/kg/day) caused this effect (Fujimori et al. 1983). Necropsy showed hemorrhagic intestines, indicating a gastrointestinal origin for the diarrhea rather than a neurally mediated response.

Chlordecone. No studies were located regarding gastrointestinal effects in humans exposed to chlordecone. Mild diarrhea has also been observed in a 33-day gavage study of mice receiving chlordecone at 10 mg/kg/day; however, necropsy revealed no evidence of treatment-related effects on stomach or intestines (Fujimori et al. 1983). Likewise, routine histopathological analyses of

gastrointestinal tissues showed no compound-related effects in rats after 2 years of oral exposure to chlordecone at 1.25 mg/kg/day or in dogs after 124–128 weeks of exposure at 0.625 mg/kg/day (Larson et al. 1979b). Both of these studies are limited in that it is unclear whether tissues from all exposed animals were examined and only two animals/sex/group were included in the dog study.

2.7 HEMATOLOGICAL

Mirex. No studies were located regarding hematological effects in humans exposed to mirex. Adverse hematological effects have not been reported to be a prominent feature of mirex toxicity in animals. No effects on standard hematological parameters were observed in male rats after 14 days of gavage administration to mirex at 10 mg/kg/day (Villeneuve et al. 1977). However, a single oral dose of 100 mg/kg mirex to rats resulted in a 12% increase in hematocrit (Ervin and Yarbrough 1983). The hematocrit was increased 26–27% in adrenalectomized rats. The significance of this effect is unclear. Most intermediate-duration studies have shown no effect of mirex on hematological parameters. No effect on routine hematological parameters occurred in rats treated for 28 days at oral doses as high as 6.5 mg/kg/day (Chu et al. 1980b; Yarbrough et al. 1981). In addition, no effects were observed among rats receiving mirex from the food for 148 days at 3 mg/kg/day (Chu et al. 1981a). In contrast, oral exposure of rats to mirex for 13 weeks resulted in decreased hemoglobin at 28 mg/kg/day and increased leukocytes at 64 mg/kg/day (Larson et al. 1979a). Increased hematocrit was reported for a male dog that died during a 13-week study in which the dog received mirex from the food at 4.8 mg/kg/day (Larson et al. 1979a). There was no evidence of mirex treatment-related hematological effects among rabbits following repeated dermal application (unspecified amount) of mirex for 9 weeks (Larson et al. 1979a).

Chlordecone. No studies were located regarding hematological effects in humans exposed to chlordecone. Studies examining the hematological effects of chlordecone in experimental animals have also given predominantly negative results. In intermediate-duration studies in rats, no effect on any hematological parameters occurred following 28 days of dietary exposure to chlordecone at 0.086 mg/kg/day (Chu et al. 1980b) or 90 days of dietary exposure at doses up to 7.8 or 6.7 mg/kg/day for males and females, respectively (Larson et al. 1979b). Similarly, in chronic-duration studies, no effects were seen during routine hematology in rats receiving chlordecone from the food for 2 years at up to 2.2 mg/kg/day or in dogs receiving chlordecone from the food for 124–128 weeks at doses up to 0.625 mg/kg/day (Larson et al. 1979b).

2.8 MUSCULOSKELETAL

Mirex. No studies were located regarding musculoskeletal effects in humans or animals exposed to mirex.

Chlordecone. Skeletal muscle biopsies obtained from six workers who had experienced tremors, muscle weakness, gait ataxia, and incoordination as a result of intermediate- or chronic-duration occupational exposure to high concentrations of chlordecone revealed a predominance of fiber grouping characteristic of myopathic conditions, and a slight increase in lipochrome content (Martinez et al. 1978); the biological significance of this effect is unknown. It is unclear whether the myopathy was a direct toxic effect of chlordecone on the muscle or whether the myopathy was a consequence of neuronal dysfunction. Arthralgia in the proximal joints was reported by 4 of 23 workers with active symptoms of chlordecone intoxication (Taylor 1982, 1985); no cause for the joint pain could be determined.

Studies examining the effects of acute-duration oral exposure to large amounts of chlordecone suggest that direct toxic effects of chlordecone on muscle occur. A single gavage dose of chlordecone to rats at between 72 and 98 mg/kg resulted in increasing muscle weakness (Egle et al. 1979). Weakness was observed on the first day of treatment and continued to increase throughout a 49-day observation period. Following 2–3 days of oral exposure to chlordecone (25 and 50 mg/kg/day), inhibition of Mg^{2+}ATPase was observed in sarcoplasmic reticulum of treated rats (Mishra et al. 1980). There was no histopathologic evidence of chlordecone-related effects on skeletal muscle among laboratory animals treated for longer durations at lower dose levels. For example, no compound-related effects were reported among rats receiving chlordecone from the diet for 90 days at up to 7.37 and 8.21 mg/kg/day (males and females, respectively), other rats treated for or 2 years at up to 1.25 mg/kg/day, or dogs treated for 124–128 weeks at up to 0.625 mg/kg/day (Larson et al. 1979b).

2.9 HEPATIC

Mirex. The hepatotoxicity of mirex in humans has not been demonstrated. One study of human subjects (sex and number not specified) from a chronically-exposed cohort in southeast Ohio assessed the potential for mirex to induce cytochrome P4501A2 (CYP1A2) using a breath test that measures caffeine metabolism. The mirex-exposed subjects had elevated caffeine metabolism as compared to negative control individuals (subjects with no known exposure to mirex or polyhalogenated biphenyls or other related chemicals) in which the metabolism did not increase (Lambert et al. 1992). However, the study did not assess liver function.

Mirex-related hepatic effects have been well characterized in experimental animals. The changes observed in livers include both adaptive and toxic effects. The adaptive effects observed are those generally produced by halogenated hydrocarbons and include the following:

- Increased liver weight or size (Abston and Yarbrough 1976; Byard et al. 1975; Chadwick et al. 1977; Chambers and Trevethan 1983; Chu et al. 1980a, 1981a, 1981b; Curtis and Hoyt 1984; Dai et al. 2001; Davison et al. 1976; Elgin et al. 1990; Ervin and Yarbrough 1983; Fujimori et al. 1983; Fulfs et al. 1977; Gaines and Kimbrough 1970; Hewitt et al. 1979; Jovanovich et al. 1987; Karl and Yarbrough 1984; Larson et al. 1979a; Mehendale 1981; Mehendale et al. 1973; Pittz et al. 1979; Plaa et al. 1987; Purushotham et al. 1988; Ritchie and Ho 1982; Robacker et al. 1981; Robinson and Yarbrough 1978a, 1978b; Teo and Vore 1991; Thottassery and Yarbrough 1991; Villeneuve et al. 1977; Warren et al. 1978; Williams and Yarbrough 1983; Wilson and Yarbrough 1988; Yarbrough et al. 1981, 1984, 1986a, 1986b, 1992)

- Hepatocellular hypertrophy (Davison et al. 1976; Fulfs et al. 1977; Gaines and Kimbrough 1970; Ulland et al. 1977; Yarbrough et al. 1981)

- Cytoplasmic eosinophilia with migration of basophilic granules (Chu et al. 1981a; NTP 1990; Yarbrough et al. 1981)

- Increased smooth endoplasmic reticulum content (Baker et al. 1972; Curtis et al. 1981; Davison et al. 1976; Fulfs et al. 1977; Gaines and Kimbrough 1970; Mehendale et al. 1989)

- Increased microsomal protein content (Chambers and Trevethan 1983; Davison et al. 1976; Elgin et al. 1990; Karl and Yarbrough 1984; Klingensmith and Mehendale 1983a; Pittz et al. 1979; Villeneuve et al. 1977; Yarbrough et al. 1981, 1986a)

- Increased CYP450 content (Baker et al. 1972; Chambers and Trevethan 1983; Cianflone et al. 1980; Curtis et al. 1981; Davison et al. 1976; Fujimori et al. 1983; Iverson 1976; Klingensmith and Mehendale 1983a; Kocarek et al. 1991; Peppriell 1981; Robacker et al. 1981; Robinson and Yarbrough 1978a; Yarbrough et al. 1981, 1986a)

- Increased NADPH2-cytochrome c reductase (Chambers and Trevethan 1983; Fujimori et al. 1983; Robacker et al. 1981; Yarbrough et al. 1986a), accompanied or unaccompanied by an increase in microsomal enzyme activity (Byard et al. 1975; Chadwick et al. 1977; Chambers and Trevethan 1983; Chu et al. 1981a, 1981b; Cianflone et al. 1980; Curtis et al. 1981; Fabacher and Hodgson 1976; Iverson 1976; Mehendale et al. 1973; Robacker et al. 1981; Stevens et al. 1979; Villeneuve et al. 1977; Warren et al. 1978; Yarbrough et al. 1981, 1986a)

Marked hepatic toxicity has been observed in laboratory animals orally exposed to mirex. The primary form of hepatotoxicity observed in rats is hepatobiliary toxicity, typically expressed as decreased hepatobiliary excretion of selected substances often in the presence of increased bile flow (e.g., Bell and Mehendale 1985; Berman et al. 1986; Curtis and Mehendale 1979; Dahlstrom-King et al. 1992; Hewitt et al. 1986a; Larson et al. 1979a; Mehendale 1976, 1977a, 1979; Teo and Vore 1991). Decreased uptake of

substances into rat hepatocytes was observed after gavage dosing, suggesting that transport of substances into hepatocytes may contribute to the decrease in their biliary excretion (Teo and Vore 1990).

Other evidence of generalized mirex-related hepatic toxicity in orally-exposed laboratory animals includes:

- Increases in serum ALT and/or AST (Fouse and Hodgson 1987; Mitra et al. 1990)
- Periportal liposis and degeneration of the endoplasmic reticulum (Kendall 1979)
- Increased hepatic lipids or decreased hepatic glutathione or glucocorticoid receptors (Ervin and Yarbrough 1983; Sunahara and Chiesa 1992; Thottassery and Yarbrough 1991)
- Swollen hepatocytes or megalocytosis (NTP 1990; Plaa et al. 1987; Ulland et al. 1977)
- Increased hepatic lipid (Fulfs et al. 1977)
- Increased serum triglycerides (Jovanovich et al. 1987)
- Hepatic glycogen depletion in rats (Elgin et al. 1990; Ervin and Yarbrough 1983; Jovanovich et al. 1987; Kendall 1974, 1979) and mice (Fujimori et al. 1983)
- Vacuolation, necrosis, and/or degeneration (Chu et al. 1981b; Davison et al. 1976; Gaines and Kimbrough 1970; Hewitt et al. 1979; Larson et al. 1979a; NTP 1990)

Chlordecone. Mild hepatomegaly (occasionally with splenomegaly) was noted in 9 of 23 workers with chlordecone blood levels in excess of 2 μg/L, but there were no observed changes in organ function and only slight increases in serum alkaline phosphatase in several of the men (Taylor 1982, 1985; Taylor et al. 1978). When liver function and structure were evaluated in 32 men exposed to high concentrations of chlordecone while employed for 1–22 months (5.6 months average) in the production of chlordecone, hepatomegaly was reported in 20 of the workers, 10 of whom exhibited minimal splenomegaly as well (Guzelian et al. 1980). In the exposed workers, urinary excretion of glucaric acid was significantly increased and the half-life of orally administered antipyrine in the blood was significantly decreased, indicating increased microsomal enzyme activity. Needle biopsies of hepatic tissue from 12 of the 32 workers showed marked proliferation of smooth endoplasmic reticulum in several samples. All of these are considered to be adaptive changes. Limited evidence of hepatic toxicity in these workers included small increases in serum alkaline phosphatase in 7 of the 32 workers. In addition, liver biopsies showed lipofuscin accumulation in 11 of 12, mild inflammatory changes in 5 of 12, vacuolization of nuclei in 3 of 12, mild portal fibrosis in 3 of 12, fatty infiltration in 3 of 12, and paracrystalline mitochondrial inclusions in 4 of 12 individuals tested. Retention of sulfobromophthalein (intravenously administered to evaluate

liver function) was normal; serum levels of bilirubin, albumin, globulin, ALT and AST activity, and γ-glutamyl transferase activity were also normal (Guzelian et al. 1980).

Chlordecone causes both adaptive and toxic changes in the livers of experimental animals. Adaptive responses of the liver seen after oral exposure of rats, mice, or gerbils to chlordecone include the following:

- Increased liver size or weight (Cannon and Kimbrough 1979; Chernoff and Rogers 1976; Curtis and Mehendale 1979; EPA 1986a; Fabacher and Hodgson 1976; Fujimori et al. 1983; Huber 1965; Larson et al. 1979b; Mehendale 1981; Mehendale et al. 1977, 1978; Purushotham et al. 1988; Simmons et al. 1987; Swartz and Schutzmann 1986, 1987)
- Hepatocellular hypertrophy (Cannon and Kimbrough 1979)
- Increased smooth endoplasmic reticulum content (Curtis et al. 1981; Lockard et al. 1983a, 1983b; Mehendale et al. 1989)
- Increased microsomal protein content (Chambers and Trevethan 1983; Klingensmith and Mehendale 1982b, 1983b; Mehendale et al. 1977, 1978)
- Increased CYP450 content (Agarwal and Mehendale 1984b; Britton et al. 1987; Cai and Mehendale 1990; Chambers and Trevethan 1983; Chaudhury and Mehendale 1991; Fabacher and Hodgson 1976; Fujimori et al. 1983; Kitchin and Brown 1989; Klingensmith and Mehendale 1982b, 1983b; Kocarek et al. 1991; Mehendale et al. 1977, 1978)
- Increased NADPH2-cytochrome c reductase (Chambers and Trevethan 1983; Fujimori et al. 1983; Mehendale et al. 1977, 1978); and/or microsomal enzyme activity (Chaudhury and Mehendale 1991; Cianflone et al. 1980; Curtis et al. 1981; Fabacher and Hodgson 1976; Klingensmith and Mehendale 1982b; Mehendale et al. 1977, 1978)

Indicators of chlordecone-induced liver toxicity in orally-exposed laboratory animals include:

- Decreased bile acid concentration, decreased bile acid secretion, and increased bile flow (Teo and Vore 1991)
- Decreased serum triglycerides and LDL cholesterol (Chetty et al. 1993a, 1993b)
- Increased serum alkaline phosphatase and ALT (EPA 1986a)
- Increased mannitol recovery (indicates decreased permeability of the canalicular membrane) or increased lysosomal fragility (Hewitt et al. 1986a, 1990)
- Decreased hepatic glycogen (Fujimori et al. 1983)

- Vacuolation, necrosis, and/or degeneration (Cannon and Kimbrough 1979; Hewitt et al. 1979; Huber 1965; NCI 1976)
- Hepatocellular hyperplasia (NCI 1976)

Several studies reported decreased biliary excretion of selected xenobiotics following repeated oral exposure to chlordecone (e.g., Curtis and Hoyt 1984; Curtis and Mehendale 1979; Curtis et al. 1979, 1981; Faroon and Mehendale 1990; Faroon et al. 1991; Mehendale 1977b). These effects were observed in the absence of biochemical or histopathological evidence of chlordecone treatment-related adverse liver effects. The altered biliary excretion of selected xenobiotics is not considered of itself representative of an adverse liver effect; therefore, the results are not summarized in Table 2-4 or plotted in Figure 2-4.

Ultrastructural changes in livers from rats receiving chlordecone from the diet for 15 days at 0.86 mg/kg/day included fragmentation of, and/or a decrease in rough endoplasmic reticulum, minute vacuolation of the cytoplasm, and/or tortuous bile canaliculi and deformed and swollen microvilli (Curtis et al. 1981; Faroon and Mehendale 1990; Faroon et al. 1991). These ultrastructural changes were observed in the absence of light microscopic evidence of histopathological liver effects. Furthermore, similar ultrastructural effects were not observed in another study that employed similar exposure of the same strain of rats (Lockard et al. 1983a, 1983b). Therefore, these ultrastructural changes are not considered evidence of chlordecone treatment-related adverse liver effects and are not summarized in Table 2-4 or plotted in Figure 2-4.

2.10 RENAL

Mirex. No data were located regarding renal effects in humans exposed to mirex. No effect on rat kidney weight or blood urea nitrogen and no adverse histopathological findings were reported following a single oral dose at 50 mg/kg or three daily doses at 10 mg/kg/day (Plaa et al. 1987). No effect on kidney weight, blood urea nitrogen, or ion exchange in the kidneys and no adverse histopathological findings were reported in mice following a single oral dose at 50 mg/kg (Hewitt et al. 1979). No treatment-related histopathological renal effects or changes in urinalysis parameters were observed in 13-week oral studies of rats receiving mirex from the diet at doses as high as 110 mg/kg/day or dogs receiving mirex from the diet at doses as high as 2.5 mg/kg/day (Larson et al. 1979a). Chu et al. (1980b) reported moderate focal lymphoid aggregates and multiple focal interstitial mononuclear infiltrates in the kidneys of 2/10 rats following dietary exposure to mirex for 28 days at 0.086 mg/kg/day. However, the significance of these findings is limited by the low number of animals with these findings and the use of only a single dose, precluding determination of the presence or absence of a dose-response relationship. Nephropathy

increased in severity in rats following 2 years of dietary exposure to mirex at 20.7 mg/kg/day among males and ≥2 mg/kg/day among females (NTP 1990).

Chlordecone. No data were located regarding renal effects in humans exposed to chlordecone. Increases in blood urea nitrogen and kidney weight were observed following a 10-day oral exposure of rats to chlordecone at 10 mg/kg/day (EPA 1986a). An increase in eosinophilic inclusions in the proximal tubules was observed in 2 of 10 rats examined following oral exposure to chlordecone for 28 days at 0.05 mg/kg/day (Chu et al. 1980b). However, the biological significance of this finding is unknown based on the small number of animals with this lesion and the use of only one dose, precluding the determination of a dose-response relationship. Renal pathology was observed in rats following intermediate- and chronic-duration exposures to relatively small oral doses of chlordecone. At 9 months of a 2-year oral study of rats receiving chlordecone from the diet, higher concentrations of urinary protein were reported in all groups of chlordecone-treated males and in females treated ≥0.48 mg/kg/day compared to controls (Larson et al. 1979b). At most time points ≥1 year, higher concentrations of urinary protein were observed in males and females at all treatment levels. However, statistical comparisons were not performed and only 5 males and 5 females per group were evaluated, thus precluding meaningful conclusions regarding adverse effect levels. At 12- and 24-month sacrifices, relative kidney weights among chlordecone-treated groups were not significantly different from those of controls. At 12-month sacrifice, there was no evidence of treatment-related kidney lesions. At 2-year terminal sacrifice, the severity of observed glomerulosclerosis was increased in both males and females at doses ≥0.45 mg/kg/day. No increases in urinary protein or adverse histopathological changes were seen in the kidneys of dogs receiving chlordecone from the diet for 124–128 weeks at 0.625 mg/kg/day (Larson et al. 1979b).

2.11 DERMAL

Mirex. No data were located regarding dermal effects in humans exposed to mirex. Hair loss in the very young is the primary dermal effect observed in animals as a result of oral exposure to mirex. Hair loss was reported in an acute-duration exposure study in which rats were given a total of 365 mg/kg in the diet over a 12-day period (Kendall 1974), but a LOAEL could not be determined because the daily dose was not reported. Hair loss was also reported in a 90-day gavage study in rats (5, 12.5, and 25 mg/kg/day) (Dietz and McMillan 1979), but the specific dose associated with this effect was not specified, precluding determination of LOAEL for this effect. Mild epidermal proliferation was reported among mice administered dermal application of mirex at 3.6 mg/kg, 3 times/week for 4 weeks (Moser et al. 1992).

Application of an unspecified amount of mirex to the skin of rabbits for 6–7 hours/day, 5 days/week for 9 weeks, resulted in slight erythema and scaling after day 5 (Larson et al. 1979a). This effect was reversible after 2 days without treatment.

Chlordecone. Eighty-nine of 133 workers interviewed as a result of intermediate- or chronic-duration occupational exposure to high concentrations of chlordecone during its manufacture reported skin rashes of an erythematous, macropapular nature at some time during occupational exposure to high concentrations of chlordecone during its manufacture (Cannon et al. 1978). Among 23 of these workers with blood chlordecone levels in excess of 2 μg/L, 6 men reported rashes following exposure (Taylor et al. 1978). It is likely that these rashes were the direct result of dermal exposure. However, insufficient information was given to eliminate a systemic effect resulting from inhalation and/or oral exposure.

No signs of dermal irritation were observed in rabbits following dermal application of a 20% solution of chlordecone in corn oil of chlordecone (Larson et al. 1979b). No effects on the skin were observed during routine histopathological analyses of the skin of rats receiving chlordecone from the diet for 90 days at doses as high as 7.37–8.21 mg/kg/day or for 2 years at doses as high as 4 mg/kg/day, or in dogs exposed for 124–128 weeks at doses as high as 0.625 mg/kg/day (Larson et al. 1979b). Increased dermatitis was reported in an 80-week dietary cancer bioassay of rats receiving chlordecone from the diet at doses as low as 0.56 mg/kg/day (NCI 1976).

2.12 OCULAR

Mirex. No data were located regarding ocular effects in humans exposed to mirex.

Production of cataracts in the very young was observed in rats receiving mirex orally during 12 days at a total dose of 365 mg/kg (Kendall 1974); a LOAEL could not be determined because the daily dose was not reported. Cataracts were produced in other newborn rats and mice following early postnatal oral exposure (Chernoff et al. 1979a; Rogers and Grabowski 1984; Scotti et al. 1981). Cataracts were characterized as diffuse anterior corneal opacities, and lenses were found to have increased water and sodium content relative to potassium content (Rogers and Grabowski 1984). Histopathological analyses showed increased vacuoles, pyknotic nuclei, swollen fibers, and/or degeneration. Cataracts were produced in newborn rodents that received mirex indirectly through the mother's milk (Chernoff et al. 1979a; Rogers and Grabowski 1984). Administration of mirex directly to the newborn by gavage at 5 mg/kg/day starting on postpartum day 1 resulted in swelling of the lens fibers as early as postpartum

day 7, with degeneration and necrosis of the lenses apparent with increasing duration of exposure (Scotti et al. 1981). Dietary exposure of maternal animals to mirex at doses as low as 1.25 mg/kg/day during postpartum days 1–4 or to doses as low as 1.8–2.8 mg/kg/day throughout the period of lactation (Gaines and Kimbrough 1970) also resulted in cataracts in rat pups. Exposure during the first few days of life appears to be critical to the development of cataracts. A single oral dose resulted in cataracts only if administered on or before postpartum day 6 and resulted in outlined lenses if administered on or before postpartum day 8 (Chernoff et al. 1979a). Eye irritation was also reported in a 90-day gavage study of rats (5, 12.5, and 25 mg/kg/day), but the specific dose associated with this effect was not specified, thus precluding determination of a LOAEL (Dietz and McMillan 1979).

Chlordecone. Vision was blurred in 15 of 23 workers with chlordecone blood levels in excess of 2 µg/L; the workers were occupationally exposed during the manufacture of chlordecone (Taylor 1982, 1985). Other effects on vision are discussed in Section 2.15 (Neurological).

There was no indication of treatment-related ocular effects on the offspring of maternal rats or mice orally exposed to chlordecone during the first 4 days of lactation at doses as high as 10 and 24 mg/kg/day, respectively (Chernoff et al. 1979b).

2.13 ENDOCRINE

Thyroid

Limited information was located regarding mirex or chlordecone and thyroid status in humans. Han et al. (2019) reported an inverse association between serum mirex/chlordecone levels and incidence of thyroid disease in a case-control study in eastern China (see Tables 2-1 and 2-2 for additional information).

Mirex. Studies in rats indicate that mirex is toxic to the thyroid (Chu et al. 1981a, 1981b; NTP 1990; Singh et al. 1982, 1985). Doses of 0.49 mg/kg/day mirex in the diet for 28 days resulted in a reversible reduction in colloid, a thickening of follicular epithelium, and angular collapse of the follicles, but no effect on serum levels of T3 or T4 (Chu et al. 1980a, 1981a, 1981b). Ultrastructural analyses of thyroids from rats treated for 28 days showed dilation of the rough endoplasmic reticulum at 0.67 mg/kg/day and increased columnar cells with irregularly shaped lysosomal bodies, dilation of cisternae, and increased vacuolization at 6.7 mg/kg/day (Singh et al. 1982, 1985). Similar effects were observed following dietary exposure to 0.25 mg/kg/day for 148 days (Chu et al. 1981a) and for 28 days (Chu et al. 1981b). Dietary

exposure to 0.7 mg/kg/day and above for 2 years also resulted in an increase in cystic follicles in male rats (NTP 1990).

Chlordecone. No studies were located regarding thyroid effects in animals exposed to chlordecone.

Adrenal

Mirex. No studies were located regarding adrenal gland effects in humans exposed to mirex. Studies in animals 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). Single gavage doses of 20 mg/kg resulted in an increased level of serum corticosterone in rats (Williams and Yarbrough 1983); 100 mg/kg resulted in increases of adrenal weight, cholesterol, lipid, and protein content (Williams and Yarbrough 1983) and increased serum adrenocorticotropic hormone (Ervin and Yarbrough 1985). Seven days of exposure at 2,100 mg/kg/day also increased adrenal weight in rats (Jovanovich et al. 1987). Consistent with the ability of corticosterone to mobilize fatty acids for energy, a decrease in body fats was observed in this study. No effects on the adrenal medulla were observed following 8-day dietary exposure of rats to mirex at 17 mg/kg/day (Baggett et al. 1980).

Chlordecone. Emeville et al. (2013) found no association between serum chlordecone and blood levels of steroid hormones in a population-based cross-sectional study; see Table 2-2 for additional study details.

Limited information is available regarding the effects of chlordecone on the adrenal glands of animals. Increased relative adrenal weight was observed in rats following a single oral dose of 35 mg/kg (Swanson and Wooley 1982) and following 10 days of gavage dosing at 10 mg/kg/day (EPA 1986a). An enlarged adrenal gland with hyperplasia and hypertrophy of the cortical cells was observed in rats receiving chlordecone from the diet for 3 months at 1.17 mg/kg/day (Cannon and Kimbrough 1979). Decreased adrenal lipid was reported for rats receiving chlordecone from the diet for 90 days at 2.4 mg/kg/day (Larson et al. 1979b). Consistent with a corticosterone-induced increase in lipid utilization, decreased body fat was observed in rats receiving chlordecone from the diet for 16 days at 2.5 or 5 mg/kg/day (Mehendale et al. 1977, 1978), 15 or 20 days at 9.7 mg/kg/day (Klingensmith and Mehendale 1982a), or in mice treated for 33 days at 10 mg/kg/day (Fujimori et al. 1983). In contrast to the absence of mirex-related noncancer effects on the adrenal medulla, chlordecone induced a decrease in the medullary content of epinephrine of rats orally treated for 8 days at 17 mg/kg/day (Baggett et al. 1980).

2.14 IMMUNOLOGICAL

Mirex. No studies were located regarding immunological effects in humans exposed to mirex. Available information regarding potential for mirex-induced immunological effects in animals is limited to a single account of 32% decreased spleen weight among maternal rats gavaged with mirex at 10 mg/kg/day for up to 10 days during gestation (Buelke-Sam et al. 1983). Oral administration of chlordecone in corn oil to male Fischer 344 rats did not cause dose-related changes in lymphoproliferative responses of splenic lymphocytes to the T-cell mitogens, phytohemagglutinin or pokeweed mitogen; it did cause decreases in the proliferative response to the T-cell mitogen, concanavalin A, and the B-cell mitogen, *Salmonella typhimurium* mitogen, but only at a dose (10 mg/kg/day for 10 days) that also resulted in impaired overall health of the rats (EPA 1986a; Smialowicz et al. 1985). Statistically significant reductions in spleen and thymus weights, and in natural killer cell activity of splenocytes against allogeneic (W/Fu-Gl rat lymphoma) and xenogeneic (YAK-1 mouse lymphoma) tumor cell lines (EPA 1986a; Smialowicz et al. 1985), were observed in rats only at a dose (10 mg/kg/day) producing generalized toxicity. Also, a slight decrease in total leukocyte count (EPA 1986a) and a 49% decrease in neutrophils (Smialowicz et al. 1985) were observed at toxic doses. The authors suggested that these effects were associated with the compromised health status of the animals and were not due to selective toxicity toward the immune system. The limitations of these studies include lack of information on cell-mediated functions, such as alloantigen reactivity and cytotoxicity, and on humoral immunity in the treated animals. However, as part of a study evaluating the effects of calcium deficiency on the toxicity of chlordecone in male rats, an increase in plaque-forming cells was observed at the lowest chlordecone dose tested (0.86 mg/kg/day) (Chetty et al. 1993c).

Chlordecone. No studies were located regarding immunological effects in humans exposed to chlordecone. A significant reduction of thymus weight was observed in rats 3 weeks after a single oral dose of chlordecone at 75 mg/kg (Swanson and Wooley 1982). It is likely that this effect may have been associated with generalized toxicity in the experimental animals.

2.15 NEUROLOGICAL

Mirex. No studies were located regarding neurological effects in humans exposed to mirex. Clinical signs indicative of neurotoxicity have not been widely reported in animals treated with mirex. However, a number of studies did note some abnormal behavior following oral administration of mirex. Following acute-duration exposures of rats to large doses (12.5–>365 mg/kg) of mirex, lethargy, weakness,

hyperexcitability, and/or tremors have been observed (Gaines and Kimbrough 1970; Kendall 1974). Although the precise doses associated with specific neurotoxic effects were not specified in these studies, single oral doses at ≥100 mg/kg were necessary. Juvenile rats showed a high sensitivity to acute exposure to mirex immediately after birth. Lactational exposure via dams treated with mirex at 2.5 mg/kg/day on lactation days 1–4 caused no behavioral abnormalities at the time of exposure, but resulted in increased activity when the offspring reached adulthood (Reiter 1977).

Intermediate-duration exposures to mirex generally resulted in lethargy as the predominant clinical sign at lower exposures and hyperexcitability at higher doses. Lethargy was observed at a mirex dose level of 8.2–10 mg/kg/day during both 15- and 30-day dietary studies in rats (Curtis and Hoyt 1984; Mehendale 1981). Decreased operant responding was also observed in rats gavaged for 90 days at 5 mg/kg/day (Dietz and McMillan 1979). Mirex had no effect on motor coordination of mice gavaged for 15 days at 10 mg/kg/day, but some mice were observed to become too weak to balance on a glass rod during the 15-day treatment period (Fujimori et al. 1983). In a 13-week dietary study of rats, mirex treatment at 28 mg/kg/day did not affect behavior, but at 110 mg/kg/day, rats became hyperexcitable and developed tremors and convulsions (Larson et al. 1979a). Longer-duration exposures also resulted in increased excitability. Hypoactivity, irritability, and tremors were observed in rats receiving mirex from the diet for up to 148 days at 3 mg/kg/day (Chu et al. 1981a).

Chlordecone. Examinations of 133 workers occupationally exposed to chlordecone during its production revealed 61 cases of tremors, 58 cases of nervousness or unfounded anxiety, and 42 cases of visual difficulties (Cannon et al. 1978). Tremors were observed in all 23 workers with blood chlordecone levels in excess of 2 µg/L (Taylor et al. 1978). The tremors were characterized as intention tremors or as occurring with a fixed posture against gravity (Taylor 1982, 1985). The tremors were most apparent in the upper extremities, but were also detectable in the lower extremities. In the more severe cases, gait was affected. Mental disturbances consisting of irritability and poor recent memory were reported by 13 of the 23 workers. Standard tests of memory and intelligence showed clear evidence of an encephalopathy in 1 of the 13 workers (Taylor 1982, 1985). The worker with encephalopathy reported auditory and visual hallucinations and demonstrated whole-body myoclonic jerks in response to loud noises. In 15 of the 23 workers, vision was blurred (Taylor 1982, 1985). Other effects on vision were characterized by a disruption of ocular motility by a brief series of rapid multidirectional eye movements at the end of a saccade (a quick, simultaneous movement of both eyes between two or more phases of fixation in the same direction). Visual acuity and smooth pursuit eye movements were unaffected. The rapid eye movements were considered to conform to the usual description of opsoclonus (a saccadic

oscillation without intersaccadic intervals, consisting of conjugate multidirectional saccades occurring in random directions with varying amplitudes). Headaches of mild-to-moderate severity were reported by 9 of the 23 workers. Three of these nine workers had increased cerebrospinal fluid pressure and papilledema (Sanborn et al. 1979; Taylor 1982, 1985). Nerve conduction velocity tests, electroencephalography, radioisotope brain scans, computerized tomography, and analyses of cerebral spinal fluid content were normal. Sural nerve biopsies obtained from five workers with detectable tremor, mental disturbances consisting of irritability and poor recent memory, rapid random eye movements, muscle weakness, gait ataxia, incoordination, or slurred speech revealed a greatly decreased number of small myelinated and unmyelinated axons (Martinez et al. 1978). Ultrastructural analyses of the nerves showed increased interstitial collagen, redundant folds in the Schwann cell cytoplasm, and the presence of occasional crystalloid inclusions suggesting that chlordecone exerted a direct toxic effect on the Schwann cell. Examination of 16 of the 23 affected individuals from 5 to 7 years after cessation of exposure and after body levels of chlordecone had been substantially reduced showed that 9 were asymptomatic, 5 had persistent tremor or nervousness, and 3 had emotional problems (Taylor 1982, 1985).

The neurotoxicity of chlordecone, which includes tremoring and/or a time-dependent exaggerated startle response, has been widely studied in experimental animals. Single oral doses of chlordecone resulted in increased tremoring and/or an exaggerated response to audio or tactile stimuli (Albertson et al. 1985; Aldous et al. 1984; Egle et al. 1979; End et al. 1981; Huang et al. 1980; Hwang and van Woert 1979; Maier and Costa 1990; Swanson and Wooley 1982). Following single oral doses as low as 3.5 mg/kg in rats, increased tremoring during handling was observed for up to 1 week (Swanson and Wooley 1982). In mice, tremors, decreased motor coordination, and hyperexcitability were observed following a single oral dose of chlordecone at 10 mg/kg (Huang et al. 1980). In these studies, the tremors were apparent at earlier times when higher doses were used than when lower doses were used. Abnormal gait was also apparent after single oral doses of 72–98 mg/kg (Egle et al. 1979). Slightly lower multiple oral doses given over several days produced increased tremors, exaggerated startle responses, and/or abnormal gait (Aldous et al. 1984; Baggett et al. 1980; Chang-Tsui and Ho 1979; Desaiah et al. 1980b; Fujimori et al. 1982a; Hoskins and Ho 1982; Huang et al. 1980; Jordan et al. 1981; Klingensmith and Mehendale 1982b; Mishra et al. 1980; Smialowicz et al. 1985). In rats, tremors and an exaggerated startle response were observed at oral doses as low as 9.7 mg/kg/day over 5 days (Klingensmith and Mehendale 1982b). An increased startle response without visible tremoring was observed at doses as low as 2.5 mg/kg/day over 10 days (EPA 1986a). This study was part of a toxicity screen performed at EPA in which male Fischer-344 rats received gavage doses of chlordecone at 0.625–10 mg/kg/day for 10 consecutive days. At a dose of 2.5 mg/kg/day, the amplitude of the acoustic startle response was significantly increased with the

highest decibel stimulus (80 decibels). At 5 and 10 mg/kg/day, the amplitude of the acoustic startle response was significantly increased with all intensities of stimulus (50, 65, and 80 decibels). Motor activity in a figure-8 maze was decreased at 10 mg/kg/day.

Tremoring, accompanied or unaccompanied by increased responsiveness to touch and noise, have also been observed in a number of intermediate-duration studies of chlordecone (Agarwal and Mehendale 1984a; Cannon and Kimbrough 1979; Curtis and Hoyt 1984; Curtis and Mehendale 1979; Dietz and McMillan 1979; Fujimori et al. 1983; Huber 1965; Klingensmith and Mehendale 1982a; Larson et al. 1979b; Linder et al. 1983; Mehendale 1981; Mehendale et al. 1978; Pryor et al. 1983; Squibb and Tilson 1982a; Swartz and Schutzmann 1986, 1987). Mild tremors were observed in rats receiving chlordecone from the diet for up to 90 days at doses as low as 0.83 mg/kg/day (Linder et al. 1983). Squibb and Tilson (1982a) reported increased startle response among rats receiving chlordecone from the diet at an estimated dose of 1.0 mg/kg/day, but no tremoring or effects on reflexes such as the tail flick response or the negative geotaxis test were observed, indicating that the startle response may be a sensitive indicator of chlordecone-induced neuronal dysfunction (Squibb and Tilson 1982a). Chronic-duration studies in rats have also demonstrated increased tremoring. Tremoring was observed at 2.2 mg/kg/day but not at 0.89 mg/kg/day in a 2-year rat dietary study (Larson et al. 1979b). Tremoring was also observed in rats and mice receiving chlordecone from the diet for up to 80 weeks at doses as low as 0.56 and 3.4 mg/kg/day, respectively (NCI 1976). No tremors or other behavioral abnormalities were observed in dogs receiving chlordecone from the diet for up to 2 years at 1.2 mg/kg/day (Larson et al. 1979b).

Several acute-duration studies have attempted to correlate the tremoring with underlying neurochemical changes. However, in many cases, it has been difficult to determine whether the effects observed were causative or the result of other underlying effects. Inhibition of brain Na^+K^+ATPase and Mg^{2+}ATPases has been correlated with the onset and diminution of tremoring in both rats and mice (Bansal and Desaiah 1985; Desaiah et al. 1980b; Jordan et al. 1981). However, other studies have not produced similar results (Maier and Costa 1990; Mishra et al. 1980). In rats, mixed results have been obtained regarding changes in norepinephrine and dopamine levels in brains from treated animals. Some studies have reported that norepinephrine uptake and dopamine uptake and binding were decreased (Chang-Tsui and Ho 1980; Desaiah 1985) and striatal dopamine synthesis, uptake, and release were inhibited (Fujimori et al. 1986) at tremorgenic doses; other studies have found no effect on norepinephrine or on dopamine content (Aldous et al. 1984; End et al. 1981) or synthesis (End et al. 1981) at equally tremorgenic doses. Effects on calcium have also been observed in treated rats and mice. Decreased calcium uptake occurred in rats following a single oral dose of 40 mg/kg (End et al. 1981), and decreased brain calcium content was

observed in adult mice following a single oral dose of 25 mg/kg (Hoskins and Ho 1982). Decreased brain calmodulin was observed in rats at 2.5 mg/kg/day for 10 days (Desaiah et al. 1985).

2.16 REPRODUCTIVE

Mirex. Possible associations between serum mirex and selected reproductive health outcomes were evaluated in three studies. In a cross-sectional study of women, 45–55 years of age, participating in the National Health and Nutrition Examination Survey (NHANES), serum mirex was associated with being menopausal (Grindler et al. 2015). In a case-control study, there was no significant difference in geometric mean mirex level (lipid-standardized) between endometriosis cases controls (Lebel et al. 1998). A borderline association was reported for mirex serum level and risk of endometriosis in a population-based case-control study; however, no association was found when cases were limited to ovarian endometriosis (Upson et al. 2013). See Table 2-1 for additional study details.

Studies in animals suggest that both male and female reproductive systems are adversely affected by mirex. Gavage treatment of male rats to 6 mg/kg/day mirex daily for 10 days decreased their fertility significantly. Although residues of mirex were found in the testes, this did not affect reproduction parameters in subsequent mating trials. The authors attributed the observed decrease in the incidence of pregnancy in females mated with males in this dose group in the first trial to a subclinical toxic effect as suggested by reduction in body weight gain in the dosed males (Khera et al. 1976). Gestational exposure of female rats with higher dosages (12.5 mg/kg/day; gestation days 6–15) of mirex resulted in increased resorptions and failure of pregnancy in 45% of dams (Grabowski and Payne 1980; Khera et al. 1976). Gestational gavage treatment of female rats at 10 mg/kg/day for 5 days resulted in decreased ovarian and uterine weights and reduced blood flow to the ovaries, uterus, and fetuses (Buelke-Sam et al. 1983). This effect was not observed if the duration of exposure during gestation was shortened to 1 day or lengthened to 10 days; thus, the significance of this effect is unknown.

Gavage administration of mirex to adult male CD-1 mice at 5 mg/kg/day for 21 days resulted in approximately 27% decreased mean absolute seminal vesicle weight; the mean body weight of mirex-treated mice was not significantly different from controls (Dai et al. 2001). In a 28-day dietary study, decreased sperm count was noted in male rats at dosages as low as 0.043 mg/kg/day (Yarbrough et al. 1981); the significance of this finding is unclear because the decreases were not dose-related and was not observed at the highest dose (6.5 mg/kg/day) tested. The study also reported testicular degeneration at 6.5 mg/kg/day. However, there was no evidence of treatment-related effects on fertility when mirex was

fed to male rats at 1.3–3.1 mg/kg/day for 2 generations (Gaines and Kimbrough 1970). In contrast, females given 1.8–2.8 mg/kg/day for 2 generations produced decreased numbers of litters (Gaines and Kimbrough 1970). Administration of 0.49 mg/kg/day to male and female rats for 91 days prior to mating and then through lactation resulted in decreases in mating and litter size (Chu et al. 1981b). Male and female mice treated at 0.94 mg/kg/day for 30 days prior to mating, and then for an additional 90 days, experienced reduced fecundity and reduced litter size and number of offspring (Ware and Good 1967); however, only one dosage level was tested. Dietary exposure of wild mice to 2.4 mg/kg/day mirex for 15 months inhibited reproduction (Wolfe et al. 1979). However, this study was limited in that few reproductive parameters were measured and mice of unknown genetic background were used.

Chlordecone. The available human data on chlordecone provide qualitative evidence to support the conclusion that intermediate- or chronic-duration exposures to high concentrations of chlordecone in the workplace causes oligospermia and decreases sperm motility among male workers (Guzelian 1982a, 1982b; Taylor 1982, 1985; Taylor et al. 1978). The threshold for abnormally low sperm counts was considered to be approximately 1 μg chlordecone per liter of serum, and the number of motile sperm cells increased as the serum chlordecone concentration decreased (Guzelian 1982a). Despite loss of sperm motility in some of the workers, there were no reported difficulties with fertility (Taylor 1982, 1985). These studies, however, can only be used as suggestive evidence of chlordecone-induced male reproductive toxicity because the airborne concentrations of chlordecone and the frequency of exposure were not quantified and effects on sperm morphology were not examined.

Chlordecone produced reproductive toxicity in both male and female animals. Gavage dosing of male rats at 0.625, 1.25, or 5 mg/kg/day for 10 days resulted in decreased sperm count; however, increased sperm count was observed at 2.5 and 10 mg/kg/day and increased relative testes weight was noted at 10 mg/kg/day (EPA 1986a). In a dominant lethality study, male rats were administered chlordecone by gavage for 5 days at 11.4 mg/kg/day, followed 2 days later by a 14-week mating period whereby the males were mated with naive, nulliparous females each week for 14 consecutive weeks (Simon et al. 1986). There was no effect on male fertility under the conditions of the study. Persistent vaginal estrus was reported in female mice administered chlordecone by gavage for 2 weeks at 2 mg/kg/day (Swartz et al. 1988).

Effects observed after intermediate-duration exposure of male and female mice to chlordecone include decreases in numbers of litters, litter size, and frequency of litter production (Good et al. 1965; Huber

1965). These effects were observed at dietary doses as low as 1.87 mg/kg/day for 130 days (Huber 1965) and 0.94 mg/kg/day for 6 months (Good et al. 1965).

Dietary exposure of male rats to ≥0.83 mg/kg/day of chlordecone for 90 days resulted in decreased sperm motility and viability; at ≥1.67 mg/kg/day, decreases in seminal vesicle and prostate weights were observed (Linder et al. 1983). Despite these effects, the fertility, litter size, sperm morphology, sperm count, and histopathology of male gonads were unaffected. In a reproductive toxicity study, Cannon and Kimbrough (1979) evaluated the effects of chlordecone on fertility of male and female rats receiving chlordecone from the diet for 3 months at 0 or 1.17–1.58 mg/kg/day (males) and 0 or 1.62–1.71 mg/kg/day (females). During a 4.5-month recovery period, mating of untreated females to chlordecone-treated males, chlordecone-treated females to untreated males, chlordecone-treated males to chlordecone-treated females, and untreated males to untreated females were performed twice. There were no apparent effects on fertility in pairings of control females with chlordecone-treated males; however, no litters were produced from matings of chlordecone-treated females to untreated males. In mice treated at higher doses (5.2 mg/kg/day chlordecone for 160 days), no effect on spermatogenesis occurred, but a decrease in litter size was observed when treated males were mated with control females (Huber 1965). Testicular atrophy was reported for adolescent rats receiving chlordecone from the diet for 90 days at 2.1 mg/kg/day as part of a 2-year study (Larson et al. 1979b).

Intermediate-duration oral exposure of female animals indicates that chlordecone may cause effects such as persistent vaginal estrus, decreased ovulation, and reproductive failure. Persistent vaginal estrus was observed in female mice receiving chlordecone for 3–6 weeks at doses as low as 1.87–2 mg/kg/day (Huber 1965; Swartz and Mall 1989; Swartz et al. 1988). Increased atresia of follicles (Swartz and Mall 1989), decreased ovulation (Swartz et al. 1988), and small- and medium-sized follicles (Swartz and Mall 1989) were observed in mice after 4 weeks of exposure to 8 mg/kg/day of chlordecone. Similarly, decreased numbers of corpora lutea were observed in mice receiving chlordecone from the diet for 130 days at 1.87 mg/kg/day (Huber 1965). Decreased numbers of litters or complete reproductive failure were observed among female rats receiving chlordecone from the diet for 3 months at 1.62 mg/kg/day (Cannon and Kimbrough 1979) and female mice receiving chlordecone from the diet for 160 days at 7.5 mg/kg/day for 160 days (Huber 1965).

The only animal study that referred to reproductive effects following dermal exposure to chlordecone was conducted in rabbits by Allied Chemical. This study was not available for review. A published review of the study (Epstein 1978) indicated that chlordecone applied to shaved skin for 8 hours/day, 5 days/week,

for 3 weeks induced testicular atrophy in two of six rabbits following application at 5 mg/kg and in one of six rabbits following application at 10 mg/kg. No other toxic effects were noted. This study is limited by the lack of dose response and lack of a NOAEL for the effect observed.

2.17 DEVELOPMENTAL

Mirex. Several epidemiological studies have evaluated potential associations between maternal mirex exposure and alterations in birth outcome and development of the reproductive and neurological systems; a summary of these studies is presented in Table 2-1. No associations between maternal blood or cord blood mirex levels and birth weight (Fenster et al. 2006; Guo et al. 2014; Hjermitslev et al. 2020), crown-heel length (Fenster et al. 2006), gestation age at birth (Hjermitslev et al. 2020), or gestation length (Fenster et al. 2006) were observed. A birth cohort study reported inverse associations between maternal serum mirex levels and cord blood levels of testosterone, prolactin, cortisol, cortisone, androstenedione/ dehydroepiandrosterone, and testosterone/androstenedione in male infants (Araki et al. 2018). The study also found associations between maternal serum mirex and male cord blood dehydroepiandrosterone, follicle-stimulating hormone (FSH), adrenal androgen/glucocorticoid, and FSH/inhibin B. Additionally, a case-control study found an association between the presence of mirex in the placenta and the risk of urogenital malformations in male infants (Fernandez et al. 2007). However, the mean concentration of mirex in placentas from the control group was 3.7±3.37 ng/g of lipid, compared to only 1.4±1.1 ng/g of lipid in placentas from the group with urogenital malformations, a finding that underscores the fact that this association could not be attributed to mirex *per se*, but only to a combination of mirex and other mirex-like compounds. No association was found between serum mirex and menarcheal status in a population-based cohort of girls 10–16.9 years of age (Denham et al. 2005). A cross-sectional study found an inverse association between the presence of mirex in placental tissues and cognitive development in boys at 4 years of age, specifically reductions in working memory and quantitative function compared to unexposed children of the same age and sex (Puertas et al. 2010).

Exposure of maternal rats and mice to mirex during gestation resulted in increases in resorptions and stillbirths and decreases in postnatal viability at doses as low as 6–10 mg/kg/day when administered during periods of gestation (Buelke-Sam et al. 1983; Byrd et al. 1981; Grabowski 1983; Grabowski and Payne 1980, 1983a, 1983b; Gray et al. 1983; Rogers and Grabowski 1983). Examination of fetuses at the end of gestation showed increases in the incidence of edematous fetuses and fetuses with cardiac arrhythmias (primarily first-degree heart block) (Buelke-Sam et al. 1983; Byrd et al. 1981; Chernoff et al. 1979b; Grabowski 1981, 1983; Grabowski and Payne 1980, 1983a, 1983b; Kavlock et al. 1982; Khera et

al. 1976). The final trimester appeared to be the most sensitive period for induction of cardiac dysrhythmias; the incidence was slightly increased at doses as low as 0.1 mg/kg/day during gestation days 15.5–21.5 (Grabowski 1983). These effects were generally seen at lower doses than the increases in mortality. Other visceral anomalies were not widely reported, but instances of anomalies such as enlarged cerebral ventricles, undescended testes, ectopic gonads, hydrocephaly, scoliosis, cleft palate, fleshy heart, enlarged atrium, or short tail were reported in a few studies (Chernoff et al. 1979b; Kavlock et al. 1982; Khera et al. 1976). Additional effects observed in fetuses included decreased skeletal ossification (Chernoff et al. 1979b), decreased fetal weight (Buelke-Sam et al. 1983; Byrd et al. 1981; Chernoff and Kavlock 1982; Gray and Kavlock 1984; Gray et al. 1983; Kavlock et al. 1982; Khera et al. 1976), decreased serum glucose and hematocrit (Rogers et al. 1984), decreased serum plasma proteins (Grabowski 1981), decreased fetal liver weight and glycogen content (Kavlock et al. 1982), decreased renal protein and alkaline phosphatase (Kavlock et al. 1982), decreased kidney weights at postpartum day 250 (Gray and Kavlock 1984; Gray et al. 1983), increased dyspnea (Grabowski and Payne 1983a), and increased liver and thyroid lesions (Chu et al. 1981a). Cataracts were also observed in offspring in several studies (Chernoff et al. 1979b; Chu et al. 1981a; Gaines and Kimbrough 1970; Rogers and Grabowski 1983; Rogers et al. 1984); however, cataracts also resulted from early postnatal exposure (Chernoff et al. 1979a; Rogers and Grabowski 1984; Scotti et al. 1981).

Chlordecone. Several human studies were designed to evaluate possible associations between cord blood chlordecone levels and risk of developmental effects in participants in the TIMOUN prospective mother-child cohort study in Guadeloupe, French West Indies, where pesticides (including chlordecone) were extensively used on banana plantations. Kadhel et al. (2014) reported that maternal blood chlordecone levels were inversely associated with gestation length and associated with risk of preterm birth. Hervé et al. (2016) found no association between cord blood chlordecone level and gestational weight. No associations were observed between maternal blood chlordecone or cord blood chlordecone levels and risk of malformations or undescended testes (Rouget et al. 2019). Another study found that cord blood chlordecone level was positively associated with increased thyroid-stimulating hormone (TSH) level in male infants evaluated at 3 months of age and with free thyroxine levels in female infants at 3 months of age (Cordier et al. 2015). Cord blood chlordecone level was positively associated with increased body mass index in boys evaluated at 3 months of age and in girls at 8 months of age (Costet et al. 2015). Four studies evaluated possible associations between maternal chlordecone levels and neurodevelopment. Cord blood chlordecone level was associated with signs of neurodevelopmental delay in 7-month-old infants (Dallaire et al. 2012). Boucher et al. (2013) and Cordier et al. (2015) reported inverse associations between cord blood chlordecone level and fine motor function among 18-month-old boys; no association

was found in girls. Among 7-year-old children, no association was observed between chlordecone in cord blood samples (taken at birth) or blood samples (taken at 7 years of age) and sex-typed toy preference (Cordier et al. 2019).

Although impaired spermatogenesis among male workers occupationally exposed to chlordecone did not appear to affect their fertility (Guzelian 1982a, 1982b; Taylor 1982, 1985; Taylor et al. 1978), it is unclear whether abnormalities in their sperm may have resulted in developmental effects in offspring.

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; Huber 1965; Kavlock et al. 1985; Seidenberg and Becker 1987; Seidenberg et al. 1986). The increase in fetal/pup mortality was observed at doses as low as 10 mg/kg/day when administered to rats during gestation days 7–16 (EPA 1986a) and at doses as low as 12 mg/kg/day when administered to mice during gestation days 7–16 (Chernoff and Rogers 1976). Edema was reported in rat fetuses at doses of 10 mg/kg/day during gestation days 7–16 (Chernoff and Rogers 1976), but this effect was not noted in other developmental toxicity studies with chlordecone. Other indicators of developmental toxicity included 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, 1987b; Seidenberg et al. 1986) and a few instances of 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 15 mg/kg/day of chlordecone on gestation days 14–20 (Gellert and Wilson 1979). However, no effects on vaginal patency or fertility were observed in female offspring of maternal mice gavaged at 20 mg/kg/day during gestation days 8–12 or 14–18 (Gray and Kavlock 1984).

Exposure of female rats to chlordecone for 60 days prior to mating through lactation day 12 showed subtle neurological changes in the offspring later in life (Rosecrans et al. 1982; Seth et al. 1981; Squibb and Tilson 1982b). Although major reflexes were unaltered, the offspring of dams exposed to 0.3 mg/kg/day showed increased serotonin turnover and decreased dopamine in response to stress (Rosecrans et al. 1982). Offspring of mice exposed to 0.075 mg/kg/day in this exposure paradigm showed an increased reactivity to apomorphine (a dopamine agonist) (Squibb and Tilson 1982b). These studies suggest that perinatal exposure to low doses of chlordecone may affect dopaminergic function in

adult offspring; however, none of these studies demonstrated a treatment-related effect on neurological function. Therefore, the results are not summarized in Table 2-4 or plotted in Figure 2-4.

Squibb and Tilson (1982b) also noted significantly depressed mean body weight in the male and female offspring at postpartum day 100 from mothers receiving chlordecone from the diet at 0.45 and ≥0.075 mg/kg/day, respectively. However, the toxicological significance of this finding is uncertain because there was no effect on offspring body weight at postpartum day 30. Therefore this result is not summarized in Table 2-4 or plotted in Figure 2-4.

Laessig et al. (2007) administered chlordecone (5 mg/kg) in a single intraperitoneal dose to pregnant Sprague-Dawley rats on gestation day 16 and assessed its effect on sexually-differentiated behavior of the adult offspring. The offspring were gonadectomized on postnatal day (PND) 50 to eliminate effects of circulating hormones and were sequentially tested for sex-typic spontaneous behaviors in open field (PND 60) and elevated plus maze (PND 61–63) tests to assess the effects of prenatal exposure to chlordecone on sexually differentiated behavior in Sprague-Dawley rats. Gonadectomized male and female offspring were also assessed for reproductive behavior following sex-specific steroid treatment. On PND 68 or 69, male and female offspring were treated with a chemical paradigm that induces lordosis (a female sexual behavior). On PND 70, male offspring received a testosterone implant; these males were assessed 6 weeks later for mounting behavior with a sexually-responsive female. On PND 120, blood was collected from male and female offspring for assessment of serum testosterone levels. There were no apparent chlordecone treatment-related effects on time to parturition, litter size, sex ratio, or growth indices of offspring compared to controls. Chlordecone-exposed (*in utero*) gonadectomized female offspring exhibited significantly increased ratio of inner to total crossings in the open field; significant increases in lordosis response with steroid priming and mounting with prolonged testosterone administration were observed in both male and female offspring. These results suggest that chlordecone may interfere with estrogen-dependent events during sexual differentiation of the brain that impact later activation of hormone-dependent behavior.

Gely-Pernot et al. (2018) administered chlordecone to pregnant female mice by daily gavage at 0.1 mg/kg/day during gestation days 6.5–15.5. The study authors reported decreased numbers of spermatogonia and spermatozoa among F1 and/or F3 progeny; meiotic defects in spermatocytes; and altered expression of genes associated with chromosome segregation, cell division, and DNA repair (note only the parental [F0] dams were administered chlordecone). In a similarly-designed study (Legoff et al. 2019), increased numbers of meiotic double-strand breaks were reported in oocytes from mouse fetuses.

Adult progeny of the chlordecone-treated maternal mice exhibited delayed puberty, decreased numbers of primordial follicles, and increased numbers of atretic follicles; these changes were associated with altered epigenetic features. Both studies only tested a single dose; thus, dose-response relationships cannot be evaluated. Study weaknesses include the lack of examination for potential maternal toxicity, although the study authors stated that the selected dose level (0.1 mg/kg/day) "has no effect on murine health;" lack of information regarding numbers of pregnant mice/group, numbers of litters produced, numbers of litters contributing to the quantitative data reported; and use of only four progeny/group in some of the analyses. Based on these limitations, the reported results from these studies are not included in Table 2-4 or Figure 2-4.

2.18 OTHER NONCANCER

Diabetes

Mirex. Possible associations between mirex serum levels and risk of diabetes were evaluated in several population-based human studies (Aminov et al. 2016; Codru et al. 2007; Everett and Matheson 2010; Son et al. 2010). There was no convincing evidence of mirex-related increased risk of diabetes. Refer to Table 2-1 for individual study details. Serum glucose levels were decreased uniformly in all studies that examined this parameter following oral exposure of animals to high doses of mirex (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). Decreases were observed following single oral doses as low as 8 mg/kg in rats (Robinson and Yarbrough 1978a) and dietary doses as low as 0.25 mg/kg/day for 28 days in rats (Chu et al. 1981b).

Chlordecone. No association was found between maternal serum chlordecone and risk of diabetes mellitus in pregnant women participating in a prospective mother-child cohort study (Saunders et al. 2014). Reports of chlordecone-induced effects on serum glucose in animals were limited to a single report of decreased serum glucose in mice exposed for 4 days at doses as low as 25 mg/kg/day or for 33 days at doses as low as 10 mg/kg/day (Fujimori et al. 1983).

Thermoregulation

Mirex. No studies were located regarding thermoregulatory effects in humans or animals exposed to mirex.

Chlordecone. No data were located regarding thermoregulatory effects in humans exposed to chlordecone. Chlordecone was shown to cause a decrease in core temperature following ingestion of a single dose of 55 or 75 mg/kg in rats (Swanson and Wooley 1982). The core temperatures were depressed for up to 12 days after administration of 75 mg/kg of chlordecone. Slight hyperthermia occurred after the body temperature recovered. Slight hyperthermia was also observed in rats after 12 weeks of exposure at 7.1 mg/kg/day (Pryor et al. 1983).

Metabolic Syndrome

Mirex. Rosenbaum et al. (2017) found no association between serum mirex level and occurrence of metabolic syndrome in a cross-sectional study. See Table 2-1 for additional study details.

2.19 CANCER

Mirex. Six epidemiological studies evaluated possible associations between mirex and cancer outcomes in the general population; additional information on these studies is presented in Table 2-1. Mixed results were found in three case-control studies evaluating breast cancer. One study reported an inverse association between lipid-adjusted median serum mirex concentration and risk of breast cancer (Itoh et al. 2009), a second study found no association between blood mirex level and risk of postmenopausal breast cancer (Moysich et al. 1998), and the third study reported an association between serum mirex level and risk of breast cancer (Wielsoe et al. 2017). Two case-control studies found no evidence of a positive association between lipid-adjusted serum mirex concentration and risk of prostate cancer (Koutros et al. 2105a, 2015b; Sawada et al. 2010). A positive association between mirex blood level and risk of non-Hodgkin lymphoma (NHL) was reported in a population-based, case-control study (Spinelli et al. 2007).

The carcinogenicity of mirex has been demonstrated in animal studies. An increase in the incidence of neoplastic liver nodules (described as nonencapsulated, circumscribed areas of parenchyma usually occupying the space of several lobules) was observed in male CD rats receiving mirex from the diet for 18 months at 7.2 mg/kg/day (Ulland et al. 1977). NTP (1990) fed mirex in the diet to F344/N rats (52/sex) for 2 years at 0, 0.1, 1.0, 10, 25, or 50 ppm. Based on absence of observable toxic effects in female rats, other groups of females were similarly treated at 0, 50, or 100 ppm mirex in the diet. Estimated average mirex doses to the males and females (combined) in the initial portion of the study were 0, 0.007, 0.075, 0.75, 1.95, and 3.85 mg/kg/day, respectively. In the second portion of the study,

estimated doses to the 0, 50, and 100 ppm females were 0, 3.9, and 7.7 mg/kg/day, respectively. Significantly increased incidences of neoplastic liver nodules (usually consisting of enlarged hepatocytes with eosinophilic or clear cytoplasm arranged in irregular distorted cords one or two cell layers thick, but some consisting of cells with basophilic cytoplasm) were observed among male rats at doses ≥0.75 mg/kg/day (incidences of 14/52, 15/52, and 26/52 for 0.75, 1.95, and 3.85 mg/kg/day dose groups, respectively, versus 3/52 among controls) and among female rats in the second portion of the study at 3.9 and 7.7 mg/kg/day (incidences of 23/52 and 30/52, respectively, versus 2/52 among controls). Incidences of hepatocellular carcinoma among mirex-treated male and female rats were not significantly different from that of controls. Incidences of benign or malignant pheochromocytoma (combined) in the adrenal gland of male rats occurred with a significant positive dose-related trend; incidences at 1.95 mg/kg/day (18/51) and 3.85 mg/kg/day (20/51) were significantly higher than that of controls (10/51). Most adrenal gland pheochromocytomas were benign. Transitional cell papillomas of the renal pelvis of male rats occurred with a significant positive dose-related trend, although the tumor was only observed in 1/51 and 3/52 males at the dose levels of 1.95 and 3.85 mg/kg/day, respectively. Female rats exhibited significantly increased incidence of mononuclear cell leukemia at doses ≥0.075 mg/kg/day (14/52, 18/52, 27/104, and 14/52 at 0.075, 0.75, 1.95, 3.85–3.9, and 7.7 mg/kg/day, respectively, versus 14/104 among controls; incidences from the two portions of the study combined). NTP concluded that under the conditions of the study, there was clear evidence of carcinogenic activity among the high-dose male and female F344/N rats. An audit summary of this report states that because of an apparent disproportionate number of liver tissue samples taken from the high-dose groups, additional and comparative liver sections were made for control groups of both sexes and the high-dose male group after the initial Pathology Working Group (PWG) review of this study. A second PWG, convened to review the liver sections, concluded that any discrepancies noted during the review of the pathology materials were minor in nature and not clustered in any one group of study animals. Consequently, the NTP considered the data produced from this study supportive of the conclusion of clear evidence of carcinogenic activity for mirex in F344/N rats.

Both male and female mice (18/sex/dose) of the (C57BL/6 x C3H/Anf)F1 or (C57BL/6 x AKR)F1 strains showed a significant increase in the incidence of hepatomas in a screening study in which mirex was administered first by gavage from 7 until 28 days of age at 10 mg/kg/day and then in the diet at 28 ppm (estimated dose of 4.5 mg/kg/day) until terminal sacrifice at weeks 59–70 (estimated time-weighted average dose of 4.8 mg/kg/day) (Innes et al. 1969).

Chlordecone. Plasma chlordecone level was positively associated with risk of prostate cancer in a population-based, case-control study (Multigner et al. 2010). The positive association appeared to be strongest among subjects with family history of prostate cancer and among subjects with past residence in western countries. See Table 2-2 for additional study details.

Liver biopsy samples taken from 12 workers with hepatomegaly resulting from intermediate or chronic-duration exposures to unspecified high levels of chlordecone showed no evidence of cancer (Guzelian et al. 1980). However, conclusions from this study are limited by the very small number of workers sampled, the relatively brief duration of exposures, and the absence of a sufficient latent period for tumor development. The average exposure of the subjects was 5–6 months and they were examined immediately after exposure.

Chlordecone was shown to be carcinogenic in rats and mice. The results of NCI (1976) bioassays in mice and rats clearly suggest that chlordecone induces hepatocellular carcinomas in both sexes of rats and mice. Administration of chlordecone to Osborne-Mendel rats via the diet for 80 weeks resulted in a significant increase in the incidence of hepatocellular carcinomas over pooled controls in both males and females at time-weighted average doses of 1.7 mg/kg/day in males and 2.0 mg/kg/day in females (NCI 1976). In the NCI (1976) bioassay of rats, the incidence of hepatocellular carcinomas was significantly increased ($p<0.05$) in both sexes with a dose-related trend. The incidence of hepatocellular carcinomas in high-dose males and females were 7 and 22% for males and females, respectively. Nevertheless, this study had several limitations. Initial doses were not well tolerated because the Maximum Tolerated Dose (MTD) was exceeded, as indicated by excessive deaths. Doses were reduced 17–33% from initial doses once or twice during the experiment. During the final 75 days of treatment, high-dose males received chlordecone on alternative weeks only. Doses above the MTD were used for 42–386 days. An unusually high mortality rate occurred in control animals, and only pooled controls were used in this bioassay.

Administration of chlordecone to B6C3F1 mice for 80 weeks also resulted in significantly increased incidences of hepatocellular carcinomas in both males and females at doses as low as 3.4-3.5 mg/kg/day (NCI 1976). In the NCI (1976) bioassay in mice, the incidence of hepatocellular carcinomas was significantly increased ($p<0.05$) in both males and females with a dose-related trend. The incidences of hepatocellular carcinomas were 81 and 88% in low- and high-dose males, respectively, and 52 and 47% in low-and high-dose females, respectively. In addition, a decrease of latency time of tumor appearance was observed in treated mice, as compared to controls. Nevertheless, this study had several limitations. An abnormally high incidence (32%) of hepatocellular carcinomas was found in the matched control

group of male mice. In addition, initial doses were not well tolerated because of exceedance of the MTD, as indicated by excessive deaths. Doses were reduced 25–50% from initial doses once or twice during the experiment. Doses above the MTD were used for 90–134 days. An unusually high mortality rate occurred in control animals as well.

In its evaluations, the Department of Health and Human Services (DHHS) has determined that both mirex and chlordecone may reasonably be anticipated to be carcinogenic on the basis of sufficient evidence of carcinogenicity in animals (NTP 2016a, 2016b). The Integrated Risk Information System (IRIS) of EPA does not include a carcinogenicity evaluation for mirex (see IRIS 1992). EPA (IRIS 2009) evaluated available human and animal data for chlordecone and determined that chlordecone is likely to be carcinogenic to humans, based on increased incidence of hepatocellular carcinomas in both sexes of rats and mice (NCI 1976).

Mirex has been shown to be a nonmutagenic hepatocarcinogen in animals. Mirex was tested at a dermal dose of 3.6 mg/kg for 4 weeks in female CD-1 mice to evaluate tumor promoter activity and evidence of epidermal hyperplasia after initiation with 7,12-dimethyl-benz[a]anthracene (DMBA) at 200 nmol/day for 1 week (Meyer et al. 1993; Moser et al. 1992, 1993). Positive control mice were treated with 2 nmol/day of the phorbol ester tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), following initiation with DMBA. A third group of mice was treated with both 3.6 mg/kg mirex and 2 nmol/day TPA for 4 weeks following initiation with DMBA. Multiple applications of mirex for 4 weeks to the DMBA-initiated mice resulted only in minimal increases in the number of nucleated epidermal cell layers. In contrast, a definitive hyperplastic response of 6–7 cell layers was observed after repeated application with TPA to the DMBA-initiated mice. Mice that were promoted with mirex or TPA without DMBA initiation did not develop tumors. At 20 weeks, DMBA-initiated mice promoted with 3.6 mg/kg mirex developed an average of 14.2 tumors. Mice promoted with 2 nmol/day TPA bore 4.7 tumors per mouse. Mice co-promoted with 3.6 mg/kg mirex and 2 nmol TPA gave a greater-than-additive response (35.4 tumors per mouse). The tumor incidence was also greater than additive in mice co-promoted with 3.6 mg/kg mirex and 2 nmol/day TPA. The tumors consisted mainly of papillomas with some squamous cell carcinomas. The study also found a 90% incidence (activation) of the c-Ha-ras tumor gene in these co-promoted tumors. Under conditions where both 3.6 mg/kg/day mirex and 2 nmol/day gave a similar tumor yield, only the TPA response was associated with biochemical markers of enhanced cell proliferation, induction of epidermal ornithine decarboxylase activity and increased DNA synthesis, and hyperplasia. On the basis of the data, the authors concluded that there is evidence for a dual effect of mirex during co-

promotion: first, as an independent tumor promoter with a mechanism different than that of phorbol esters and, second, as a compound that also potentiates skin tumor promotion by TPA.

A second study examined the effects of DMBA initiated mirex-promoted tumors in female mice on ovarian hormones. This study found that the loss of ovary (OVX) protected the female mice (40%) from mirex tumor promotion. Tumor promotion was unaffected in DMBA-initiated OVX mice promoted with TPA. Based on the data, the authors concluded that there is a structural specificity in the tumor-promoting ability of mirex in mouse skin and that mirex is a much more effective skin tumor promoter in female CD-1 mice than in male CD-1 mice or OVX mice (Meyer et al. 1994).

2.20 GENOTOXICITY

Available data suggest that neither mirex nor chlordecone are genotoxic.

Limited information is available regarding the potential for mirex- or chlordecone-induced genotoxicity *in vivo* (Table 2-7). Mirex did not induce dominant lethal mutations following gavage treatment of male rats at 1.5–6.0 mg/kg/day for 10 consecutive days (Khera et al. 1976). Single gavage dosing of female Sprague-Dawley rats with mirex at 90 or 120 mg/kg resulted in no evidence of significant damage to DNA as measured by alkaline elution (Mitra et al. 1990). Oral administration of mirex to male mice at 86.8 mg/kg/day for 5 days did not induce DNA strand breaks in hepatocytes (Umegaki et al. 1993). Miyagawa et al. (1995) reported 4–9.5-fold increases in replicative DNA synthesis within hepatocytes of 8-week-old male B6C3F1 mice at 24–39 hours following gavage administration of mirex at 60 mg/kg. Marked disturbances in the distribution of ploidy (diploid and tetraploid nuclei) were observed in livers from male Sprague-Dawley rats fed 100 ppm mirex (equivalent to ≈5 mg/kg/day) for 13 months (Abraham et al. 1983). Mirex selectively reduced the number of tetraploids with the most significant reduction noted in hepatocellular carcinomas; however, nuclei in the areas adjacent to these tumors were also primarily composed of diploids. These data should be interpreted with caution since isolation of nuclei from tumors is difficult and because “of the fantastic variety of forms that tumor nuclei assume” (Smuckler et al. 1976). Additionally, the relevance to humans is not clear since human liver is mainly composed of diploid cells (99%) and contains few tetraploids (Adler et al. 1981).

Table 2-7. *In Vivo* Genotoxicity of Mirex and Chlordecone in Orally-Exposed Animals

Species	Endpoint	Results	Reference
Mirex			
Male rat germinal cells	Dominant lethal mutations	–	Khera et al. 1976
Rat hepatocytes	DNA damage (alkaline elution)	–	Mitra et al. 1990
Mouse hepatocytes	DNA strand breaks	–	Umegaki et al. 1993
Mouse hepatocytes	DNA synthesis	+	Miyagawa et al. 1995
Rat hepatocytes	Selective reduction of polyploid cells	+	Abraham et al. 1983
Chlordecone			
Male rat germinal cells	Dominant lethal mutations	–	Simon et al. 1986
Rat hepatocytes	DNA damage (alkaline elution)	–	Kitchin and Brown 1989
Rat hepatocytes	Unscheduled DNA synthesis/DNA strand breaks	+/–	Ikegwuonu and Mehendale 1991

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

Chlordecone did not induce dominant lethal mutations following gavage treatment of male rats for 5 days at 3.6 or 11.4 mg /kg/day (Simon et al. 1986). There was no evidence of chlordecone-induced DNA damage following gavage treatment of female Sprague-Dawley rats at 19 or 57 mg/kg both 21 and 4 hours prior to sacrifice (Kitchin and Brown 1989). Chlordecone induced a low level of unscheduled DNA synthesis in hepatocytes from male Sprague-Dawley rats gavaged at 10 mg/kg (Ikegwuonu and Mehendale 1991). However, the response (≈1.2-fold over control) was too marginal to conclude a positive effect. The comparative evaluation of chlordecone effects on adenosine diphosphate-ribosyltransferase (ADPRT) activity and DNA strand breaks provided inconsistent results. Although the data suggest that chlordecone treatment increased DNA strand breaks, ADPRT activity was suppressed rather than stimulated; stimulation would be expected when DNA strand breaks occur.

Results from genotoxicity testing of mirex and chlordecone *in vitro* are summarized in Table 2-8. Mirex was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 either with or without exogenous metabolic activation (Mortelmans et al. 1986; Probst et al. 1981; Schoeny et al. 1979). Probst et al. (1981) found no evidence of a mutagenic response in *S. typhimurium* strains TA1538, C3076, D3052, or G46 or *Escherichia coli* strains WP2 or WP2 uvrA either with or without exogenous metabolic activation. Mirex was also negative for the induction of prophage in *E. coli* either with or without exogenous metabolic activation (Houk and DeMarini 1987). Mirex was not mutagenic to human foreskin fibroblasts (Detroit-550) either with or without exogenous metabolic activation (Tong et al. 1981).

Table 2-8. Genotoxicity of Mirex and Chlordecone *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Mirex				
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Mortelmans et al. 1986
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Schoeny et al. 1979
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, C3076, D3052, G46	Gene mutation	–	–	Probst et al. 1981
Escherichia coli WP2, WP2uvrA	Gene mutation	–	–	Probst et al. 1981
E. coli $WP2_s$ (λ), SR714	λ Prophage induction	–	–	Houk and DeMarini 1987
Human foreskin fibroblasts (Detroit-550 cells)	Gene mutation	–	–	Tong et al. 1981
Mouse hepatocytes	Preferential binding to polyploid cells	NA	+	Rosenbaum and Charles 1986
Rat, mouse, and/or hamster hepatocytes	Unscheduled DNA synthesis	NA	–	Maslansky and Williams 1981; Probst et al. 1981; Williams 1980
Chinese hamster lung fibroblasts (V79)	Inhibition of metabolic cooperation	NA	+	Tsushimoto et al. 1982
Chlordecone				
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Mortelmans et al. 1986
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Schoeny et al. 1979
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, C3076, D3052, G46	Gene mutation	–	–	Probst et al. 1981
E. coli WP2, WP2uvrA	Gene mutation	–	–	Probst et al. 1981
Rat liver epithelial cells	Gene mutation	–	–	Williams 1980
Testicular cells from human organ transplant donors	Single-stranded DNA breaks	NA	+	Bjorge et al. 1996
Rat testicular cells	Single-stranded DNA breaks	NA	+	Bjorge et al. 1996
Chinese hamster ovary cells	Structural chromosome aberrations	–	–	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	–	+	Galloway et al. 1987
Chinese hamster M3-1 cells	Structural chromosome aberrations	NR	+/–	Bale 1983
Rat, mouse, and/or hamster hepatocytes	Unscheduled DNA synthesis	NA	–	Maslansky and Williams 1981; Probst et al. 1981

Table 2-8. Genotoxicity of Mirex and Chlordecone *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Chinese hamster lung fibroblasts (V79)	Inhibition of metabolic cooperation	NA	+	Tsushimoto et al. 1982

DNA = deoxyribonucleic acid; NA = not applicable; NR= not reported; – = negative result; + = positive result; +/– = inconclusive results

Rosenbaum and Charles (1986) provided evidence that mirex preferentially binds to freshly prepared polyploid mouse hepatocytes; the response was partially Na^+ dependent and completely Ca^{2+} dependent. Subcytotoxic doses of mirex did not induce unscheduled DNA synthesis in primary hepatocytes recovered from rats, mice, or hamsters (Maslansky and Williams 1981; Williams 1980). Similar results were obtained by Probst et al. (1981) using primary rat hepatocytes exposed to 1,000 µmol/L mirex. Metabolic cooperation between 6-thioguanine-resistant (6-TGr) mutants ($HGPRT^-$) and 6-thioguanineinsensitive (6-TGs) wild-type ($HGPRT^+$) Chinese hamster lung fibroblasts (V79) was inhibited by mirex (Tsushimoto et al. 1982).

In agreement with the findings from microbial gene mutation studies with mirex, there is no evidence that chlordecone is a mutagen for *S. typhimurium* or *E. coli* (Mortelmans et al. 1986; Probst et al. 1981; Schoeny et al. 1979). Williams (1980) found no evidence of mutagenicity in chlordecone-treated rat liver epithelial cells either with or without exogenous metabolic activation. Chlordecone (≥300 µM) induced significantly increased frequencies of single-stranded DNA (ssDNA) breaks in testicular cells from human organ transplant donors and from Wistar rats (Bjorge et al. 1996). Chlordecone did not increase the frequency of Chinese hamster ovary cells with abnormal chromosome morphology over a nonactivated concentration range of 10–20 mg/L or an activated concentration range of 5–15 mg/L (Galloway et al. 1987). Chlordecone (1.67–10.00 mg/L) did increase the frequency of sister chromatid exchange in Chinese hamster ovary cells, but only without exogenous metabolic activation and only in the presence of cell-cycle delay (Galloway et al. 1987). Evidence of a clastogenic effect reported by Bale (1983) for Chinese hamster M3-1 cells exposed to 2, 4, or 6 mg/L chlordecone was inconclusive. The significant ($p<0.05$) increase in the aberration yield at 6 mg/L could not be fully assessed because chromatid and chromosome gaps (the predominant type of aberration) were included in the statistical analysis and there was a high background frequency of cells treated with solvent (dimethyl sulfoxide) that had abnormal values. Subcytotoxic doses of chlordecone did not induce unscheduled DNA synthesis in

primary hepatocytes recovered from rats, mice, or hamsters (Maslansky and Williams 1981; Williams 1980). Similar results were obtained by Probst et al. (1981) using primary rat hepatocytes exposed to 1,000 µmol/L chlordecone. Metabolic cooperation between 6-thioguanine-resistant (6-TGr) mutants ($HGPRT^-$) and 6-thioguanineinsensitive (6-TGs) wild-type ($HGPRT^+$) Chinese hamster lung fibroblasts (V79) was inhibited by chlordecone (Tsushimoto et al. 1982).

2.21 MECHANISMS OF ACTION

Pharmacokinetic Mechanisms. The specific mechanism by which mirex is transferred from the gut, lungs, or skin to the blood is not known. However, mirex is a highly stable, lipophilic compound that is resistant to metabolism. It has a high lipid:water partition coefficient, so it partitions readily to fat and demonstrates a very high potential for accumulation in tissues (Chambers et al. 1982; Ivie et al. 1974a).

The specific mechanism by which chlordecone is transferred from the gut, lungs, or skin to the blood is not known. However, the preferential distribution of chlordecone to the liver rather than the fat tissues suggests that it may be transported in the plasma differently from other organochlorine compounds (Soine et al. 1982). *In vitro* and *in vivo* studies of human, rat, and pig plasma showed that chlordecone is preferentially bound by albumin and high-density lipoproteins (HDL), which may explain its tissue distribution. Other organochlorine pesticides such as aldrin and dieldrin bind to very-low-density lipoproteins (VLDL) and LDL and distribute preferentially to fat (Soine et al. 1982).

Hepatotoxicity. Several studies have attempted to define the mechanism by which mirex and chlordecone inhibit hepatobiliary excretion. At very high levels, both mirex (Chetty et al. 1983a; Desaiah 1980) and chlordecone (Bansal and Desaiah 1985; Chetty et al. 1983a; Curtis and Mehendale 1979; Desaiah et al. 1980b, 1991; Jinna et al. 1989; Jordan et al. 1981; Kodavanti et al. 1990a; Mehendale 1979) depress ATPase activity or cellular energy utilization at moderate to relatively high doses (2.5–100 and 50–100 mg/kg/day, respectively), thereby inhibiting the biliary excretion of substances. The inhibition does not appear to be due to inhibition of metabolism of the substance to be excreted in the bile or to decreased bile flow (Mehendale 1977a). Possible explanations for the decreased excretion of metabolites in the bile include decreased uptake of substances by the hepatocyte (Teo and Vore 1990), a decreased transfer of chemicals from the hepatocyte to the bile (Berman et al. 1986), and leaking of metabolites from the bile duct via a paracellular pathway (Curtis and Hoyt 1984). The decrease in transfer may be due to decreased permeability of the canalicular membrane (Hewitt et al. 1986a) resulting from inhibition of the Mg^{2+}ATPase activity of the bile canaliculi (Bansal and Desaiah 1985; Curtis 1988; Curtis and Mehendale

1981) or perturbations of plasma membrane (Rochelle et al. 1990). Although the precise mechanism for the hypothermia induced by chlordecone is unknown, data suggest a role of central nervous system dopaminergic or α-noradrenergic activity in expression of hypothermia. The decrease in body temperature produced by chlordecone was mimicked by intracisternal norepinephrine (Cook et al. 1988a, 1988b) and was blocked by administration of α-noradrenergic antagonists and by 6-hydroxydopamine, a treatment that depletes noradrenergic neurons in the brain (Cook et al. 1988b). Pretreatment with the dopamine antagonist, haloperidol, was also capable of blocking the hypothermia (Hsu et al. 1986). It has been suggested that the decrease in body temperature is the result of centrally mediated vasodilation (Cook et al. 1988a, 1988b), but direct evidence for this has not yet been obtained.

Mitochondrial oligomycin-sensitive Mg^{2+}ATPase is thought to play a major role in oxidative phosphorylation (Boyer et al. 1977). It has been suggested that impairment of mitochondrial energy metabolism by chlordecone may contribute to the decreases in body weight observed following exposure to this chemical (Desaiah 1981).

Carpenter et al. (1996) examined ultrastructural, protein, and lipid profiles in the livers of chlordecone-treated mice. Male C57BL/6N mice were administered chlordecone intraperitoneally, followed 3 days later by intraperitoneal injection of radiolabeled chlordecone. Livers and kidneys were subsequently removed for assessment of radioactivity. Livers were examined for histological and ultrastructural changes and total lipid content and fatty acid profiles in livers and kidneys were determined. Pretreatment with unlabeled chlordecone resulted in dose-dependent decreased accumulation of chlordecone in the liver; renal accumulation was not affected. Chlordecone induced marked hepatic mitochondrial swelling, decreased the number of cytoplasmic lipid droplets in hepatocytes, induced proliferation and vesiculation of smooth endoplasmic reticulum, and increased the number of intracellular peroxisome-like structures. Chlordecone did not alter the total lipid content of the liver or kidney. The changes in the liver suggest that chlordecone caused alterations in hepatocellular transport, storage, and metabolism pathways via increased hepatocyte secretory activity.

Neurotoxicity. Several studies have been undertaken in an attempt to define the mechanism of the neurotoxic effects of chlordecone. No single mechanism has been identified that readily explains the neurotoxic effects of chlordecone. However, studies have revealed substantial information regarding the effects of chlordecone on the nervous system. Chlordecone does not appear to act through a mechanism similar to other chlorinated hydrocarbon insecticides such as dieldrin or lindane. Chlordecone has a different profile of neurotoxicity in that it primarily causes hyperexcitability and tremors, but no

convulsions, and appears to lack activity at the γ-aminobutyric acid (GABA) receptor in mammals (Bloomquist et al. 1986; Chang-Tsui and Ho 1979; Lawrence and Casida 1984; Seth et al. 1981). Chlordecone has been shown to be a potent antagonist of the picrotoxinin binding site on the GABA receptor in cockroaches (Matsumura 1985). However, this finding is difficult to interpret based on the poor binding at a comparable site in mammalian tissues.

The hyperexcitability and tremor induced by chlordecone are similar to that produced by dichloro-diphenyldichloroethane (DDT). However, it has been suggested that the mechanism of these tremors is different; diphenylhydantoin exacerbates chlordecone-induced tremor but suppresses tremor induced by DDT (Hong et al. 1986; Tilson et al. 1985, 1986). The tremors induced by chlordecone appear to be initiated in the central nervous system above the level of the spinal cord, since transection of the spinal cord resulted in elimination of the tremors below the level of transection (Hwang and van Woert 1979).

Several pharmacological studies indicate that α-noradrenergic and serotonergic transmitter systems in the central nervous system are the primary neurotransmitter systems involved in the expression of the tremor and enhanced startle response produced by chlordecone (Gerhart et al. 1982, 1983, 1985; Herr et al. 1987; Hong et al. 1984; Hwang and van Woert 1979). These conclusions are supported by a number of studies examining brain neurochemistry following administration of tremorgenic doses of chlordecone (Brown et al. 1991; Chen et al. 1985; Hong et al. 1984; Tilson et al. 1986; Uphouse and Eckols 1986). However, dopamine (Desaiah 1985; Fujimori et al. 1982a) and acetylcholine (Aronstam and Hong 1986; Gerhart et al. 1983, 1985) have also been implicated.

At the cellular level, chlordecone causes spontaneous neurotransmitter release (End et al. 1981) and increases in free intracellular calcium in synaptosomes (Bondy and Halsall 1988; Bondy and McKee 1990; Bondy et al. 1989; Komulainen and Bondy 1987). This appears to be due, at least in part, to increased permeability of the plasma membrane (Bondy and Halsall 1988; Bondy and McKee 1990; Bondy et al. 1989; Komulainen and Bondy 1987), activation of voltage-dependent calcium channels (Komulainen and Bondy 1987), and inhibition of brain mitochondrial calcium uptake (End et al. 1979, 1981).

Chlordecone also decreased the activity of calmodulin-stimulated enzymes (Kodavanti et al. 1988, 1989a; Vig et al. 1990, 1991) and of enzymes integral to maintenance of neuronal energy and ionic gradients; Na^+K^+ATPase (Bansal and Desaiah 1982; Chetty et al. 1983b; Desaiah 1981; Desaiah et al. 1980b; Folmar 1978; Jinna et al. 1989; Singh et al. 1984), oligomycin-sensitive Mg^{2+}ATPase (Chetty et al.

1983b; Desaiah et al. 1980b; Jinna et al. 1989; Mishra et al. 1980), and Ca^{2+}ATPase (Desaiah et al. 1991; Jinna et al. 1989; Mishra et al. 1980) activities in brain tissues have been shown to be decreased by exposure to chlordecone both *in vivo* and *in vitro*. It is unclear whether inhibition of these enzymes is directly responsible for the effects of chlordecone on intracellular calcium or whether these changes are coincidental with the changes in intracellular calcium.

Reproductive Toxicity. Mechanisms underlying many of the adverse effects of chlordecone on reproductive function may be related to the estrogenic properties of chlordecone. Following both *in vitro* (Bulger et al. 1979; Hammond et al. 1979) and parenteral administration (Williams et al. 1989a), chlordecone was shown to bind to estrogen receptors and to cause translocation of the receptor from the cytoplasm to the nuclear fraction. When the activity of chlordecone was compared in uterine and brain tissues, the effect was greater in the uterine tissue (Williams et al. 1989a). Chlordecone caused the translocation of estrogen receptors from the cytosolic to the nuclear fraction in both isolated rat uteri and ovariectomized immature rats (Bulger et al. 1979; Williams et al. 1989a). These results indicate that chlordecone may act directly on the uterus. Johnson (1996) found that chlordecone-induced uterine effects (hypertrophy, hyperplasia) observed in ovariectomized immature rats were enhanced by coadministration of estradiol. These results suggest that both the estrogen and xenoestrogen are influencing uterine hypertrophy and hyperplasia by a single mechanism. Chlordecone demonstrated fairly high affinity for recombinant human estrogen receptors (Bolger et al. 1998; Scippo et al. 2004). Chlordecone exhibited approximately equal affinity for both subtypes of human estrogen receptors (ERα and ERβ) (Kuiper et al. 1998); the binding affinity was on the order of 1,000-fold less than that of estradiol. In a study by Johnson et al. (1995), uterine levels of adenosine 3'5'-cyclic monophosphate (cAMP) decreased with increasing uterine weight following repeated exposure to chlordecone in ovariectomized immature rats. Levels of cAMP were not decreased in similarly treated rats that were also given the antiestrogen (ICI-182,780), indicating that the chlordecone-induced effect on cAMP is estrogen receptor-dependent.

The affinity of chlordecone for estrogen appears to be tissue-dependent. Although competition between [^{3}H]estradiol and chlordecone was comparable in magnitude within estrogen receptor preparations from brain or uterine tissues of rats, *in vivo* binding of chlordecone in the brain of ovariectomized rats was much less than that observed in the uterus (Williams et al. 1989b). The basis for this may result, at least in part, from a greater time requirement for chlordecone to reach a concentration in the brain that could result in a significant estrogenic effect. Although chlordecone may mimic the effect of estrogen in uterine

tissue, chlordecone appears to function as an estrogen antagonist in central nervous tissue (Huang and Nelson 1986; Uphouse et al. 1986).

Chlordecone has been evaluated for its potential to bind to receptors other than the estrogen receptor and was found to have relatively high affinity for recombinant human progesterone receptors (Scippo et al. 2004). In ovariectomized (NBZ x NZW) F1 mice, both estradiol (an estrogen) and chlordecone were shown to accelerate development of the autoimmune disorder, systemic lupus erythematosus (Wang et al. 2007a). However, it was found that chlordecone was not simply mimicking estrogen, based on contrasting effects on splenic B-cells populations. In a follow-up a study, also in ovariectomized (NBZ x NZW) F1 mice, Wang et al. (2007b) compared the effects of chlordecone and estradiol treatment on serum levels of the autoimmune-accelerating hormone, prolactin. In chlordecone-treated mice, they found a dose-dependent decrease in prolactin levels (compared to controls). However, in estradiol-treated mice, prolactin levels were 10–20 fold higher than controls. In a related study, chlordecone exhibited characteristics of a partial androgen antagonist, based on reduced inhibition of 5α-dihydroxytestosterone-mediated activation of luciferase activity by 6.9 μM chlordecone in the human PC-3 prostate carcinoma cell line (Schrader and Cooke 2000).

Results from a study by Das et al. (1997) indicate that chlordecone-induced uterine effects may also be induced via a pathway other than that which includes the estrogen receptor. Chlordecone upregulated uterine expression of an estrogen-responsive gene, lactoferrin, in ERα knockout mice, whereas these effects were not elicited by 17β-estradiol. Neither the estrogen receptor antagonist ICI-182,780 nor 17β-estradiol inhibited the chlordecone-induced uterine expression of lactoferrin in these mice.

Substantially less is known about the mechanism by which mirex causes reproductive toxicity. Mirex does not, however, appear to produce its reproductive toxicity by mimicking estrogen (Gellert 1978; Hammond et al. 1979). Dai et al. (2001) hypothesized that modulation of testosterone metabolism via induction of specific CYP isoforms may be a contributing factor in mirex-induced antiandrogenic effects. Evidence includes significantly increased (3.1-fold greater than controls) total CYP contents in homogenated livers of adult male CD-1 mice administered mirex by gavage at 5 mg/kg/day for 21 days (Dai et al. 2001). Western blot analysis indicated that CYP2E1 and CYP3A were the isoforms induced to the greatest extent. Incubation of testosterone with microsomes from the treated mice resulted in an approximately 2.5-fold increase in testosterone hydrolase activity.

Developmental Toxicity. No information was located regarding possible mechanisms of mirex developmental toxicity. Laessig et al. (2007) administered chlordecone (5 mg/kg) in a single intraperitoneal dose to pregnant Sprague-Dawley rats on gestation day 16 and assessed its effect on sexually-differentiated behavior of the adult offspring. The offspring were gonadectomized on PND 50 to eliminate effects of circulating hormones and were sequentially evaluated for sex-typic spontaneous behaviors in open field (PND 60) and elevated plus maze (PND 61–63) performance. Gonadectomized male and female offspring were also assessed for reproductive behavior following sex-specific steroid treatment. On PND 68 or 69, male and female offspring were treated with a chemical paradigm that induces lordosis (a female sexual behavior). On PND 70, male offspring received a testosterone implant; these males were assessed 6 weeks later for mounting behavior with a sexually-responsive female. On PND 120, blood was collected from male and female offspring for assessment of serum testosterone levels. There were no apparent chlordecone treatment-related effects on time to parturition, litter size, sex ratio, or growth indices of offspring compared to controls. Chlordecone-exposed (*in utero*) gonadectomized female offspring exhibited a significantly increased ratio of inner to total crossings in the open field; significant increases in lordosis response with steroid priming and mounting with prolonged testosterone administration were observed in both male and female offspring. These results suggest that chlordecone may interfere with estrogen-dependent events during sexual differentiation of the brain that impact later activation of hormone-dependent behavior.

Tumor Promotion. There is convincing evidence that mirex and chlordecone interfere with cell-to-cell communication. Tsushimoto et al. (1982) demonstrated that metabolic cooperation between 6-thioguanine-resistant (6-TG^r) mutants (HGPRT$^-$) and 6-TG^r wild-type (HGPRT$^+$) Chinese hamster lung fibroblasts (V79) was inhibited by both mirex and chlordecone. In this assay system, the ability of HGPRT$^+$ cells to transport a lethal substrate (formed from the metabolism of 6-thioguanine) to HGPRT cells (6-TG^r) is evaluated. Transport of the mononucleotide of thioguanine from the HGPRT$^+$ to the HGPRT$^-$ cells occurs presumably through gap junctions and results in the killing of heretofore 6-TG^r cells. Therefore, increased survival of the HGPRT$^-$ cells in the presence of a test material indicates an interference with metabolic cooperation. Mirex doses ranging from 3 to 12 mg/L induced a dose-related increase in the recovery of 6-TG^r colonies. The maximum percentage recovery of 6-TG^r cells (≈70%) was noted at 12 mg/L. Chlordecone also inhibited metabolic cooperation at concentrations well below the cytotoxic level. However, in contrast to the mirex data, chlordecone produced a much steeper dose-response between 1 and 4 mg/L with the maximum percentage of 6-TG^r cell recovery (70%) occurring at 4 mg/L. While it is tempting to speculate that chlordecone is a more potent inhibitor of metabolic cooperation, the differences observed may be explained by differences in solubility. Chlordecone also

reversibly disrupted gap junctional communication in human embryonic palatal mesenchyme cells when tested by assessing Lucifer yellow dye transfer (Caldwell and Loch-Caruso 1992).

Starcevic et al. (2001) designed an experiment to test whether chlordecone disrupts adherens junctions in human breast epithelial cells cultured on Matrigel. When exposed to chlordecone, MCF-10ATG3B human breast epithelial cells exhibited significantly decreased E-cadherin and beta-catenin protein levels; desmoglein and α- and γ-catenin levels did not vary significantly from control levels. Chlordecone also caused disruption in E-cadherin-γ-catenin association. These results indicate that chlordecone disrupts cellular architecture, which may ultimately play a role in development of neoplastic lesions. Chlordecone in combination with other xenobiotic chemicals such as carbon tetrachloride and ether reduced the threshold values of toxicity by several fold for those chemicals and decreased the aromatase activity by 50% in some cases. Prolonged exposures to low doses of xenobiotics amplified aromatase inhibition by 50 times. Because chlordecone is known to bioaccumulate, chronic, low-level exposures may result in body burden levels that could also affect cell signaling mechanisms (Benachour et al. 2007).

Collectively, results from several studies provide evidence that mirex acts as a tumor promoter with a mechanism different from that of phorbol esters and that mirex potentiates skin tumor promotion by TPA in DMBA-initiated mice (Meyer et al. 1993, 1994; Moser et al. 1992, 1993). Twenty weeks of thrice weekly dermal application of mirex (200 nmole) to DMBA-initiated mice resulted in 96% skin tumor incidence with an average of 4 tumors/mouse; similar treatment of other mice with TPA (2 nmole) resulted in 78% tumor incidence with 14 tumors/mouse. TPA-treated (but not mirex-treated) mice exhibited a hyperplastic response; this result indicates that mechanisms of mirex tumor promotion differ from those of TPA. Co-application of 200 nmole mirex and 2 nmole TPA on DMBA-initiated mouse skin yielded 28 tumors/mouse (compared to 14 tumors/mouse after mirex treatment separately and 4 tumors/mouse after TPA treatment separately). In addition, co-treatment with mirex and TPA resulted in earlier tumor development; after 8 weeks of promotion, 90% of cotreated mice bore tumors compared to 47% of mice treated with mirex separately and 17% of mice treated with TPA separately. Mirex-promoted skin tumors in DMBA-initiated mice were 3 times more prevalent in female than male mice and 3 times less prevalent in ovariectomized mice, suggesting that ovarian hormones may influence mirex-tumor promotion sensitivity.

Kim and coworkers (Kim and Smart 1995; Kim et al. 1997) reported that mirex promoted the development of papillomas involving a Ha-ras mutation in DMBA-initiated mice. The ovarian hormone 17β-estradiol may be involved in mirex skin tumor promotion in mice. Porter et al. (2002) assessed the

role of 17β-estradiol in mirex skin tumor promotion by applying topical mirex to ovariectomized mice that had subcutaneous implants either with or without the hormone. Ovariectomized mice with implanted 17β-estradiol exhibited normal physiological levels of serum 17β-estradiol throughout the treatment period. The 17β-estradiol implants restored approximately 80% of the mirex tumor promoting response of intact mice. 17β-Estradiol implants in male mice increased sensitivity to mirex tumor promotion as well, but not to the level of response seen in intact female mice.

There are convincing data from a metabolic cooperation assay (Tsushimoto et al. 1982) and a dye transfer assay (Caldwell and Loch-Caruso 1992) indicating that mirex and chlordecone interfere with intracellular communication. Inhibition of cell-to-cell communication is a property exhibited by numerous promoters (Williams 1980). Similarly, the data indicating that both agents probably induce liver tumors in rodents through epigenetic/promoter mechanisms are supported by the striking similarities that these test materials share with many established promoters: (1) tumors induced by mirex or chlordecone are found predominantly in rat or mouse livers; (2) neither agent is genotoxic; (3) both agents induce ornithine decarboxylase activity; (4) there is no evidence of covalent binding to DNA; and (5) both agents lack reactive functional groups. Mirex has not been evaluated for promoter activity *in vivo*; however, chlordecone was shown to be a tumor promotor in a two-stage assay in which the initiator, diethylnitrosamine, was given orally to partially hepatectomized Sprague-Dawley rats followed by subcutaneous doses of chlordecone. The treatment resulted in hyperplastic liver nodules in seven of eight initiated males and hepatocellular carcinomas in five of six initiated females.

The weight of evidence from *in vivo* and *in vitro* genetic toxicology tests, *in vivo* liver function studies, and the two-stage tumor promotion assay is adequate to conclude that chlordecone is a promotor rather than an initiator of carcinogenesis. While the evaluation of mirex in an *in vivo* tumor promoter assay is desirable, it is, nevertheless, concluded that there is sufficient evidence to consider mirex a probable promoter.

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

3.1 TOXICOKINETICS

Mirex. Mirex is absorbed from the digestive tract of animals. Following exposure to mirex, an initial rapid excretion of the majority of the ingested mirex occurs via the feces within the first 48 hours postdosing. This fecal mirex represents unabsorbed compound. Once absorbed, mirex is widely distributed throughout the body, but is sequestered in the fat. It has a long retention time in the body. Mirex is not metabolized in humans, rodents, cows, or minipigs. The parent compound is the only radiolabeled compound that has been found in the plasma, fat, and feces. In animals, mirex is excreted unchanged mainly in the feces; urinary excretion is negligible. Mirex is also excreted in human milk. Only a very limited number of studies were located regarding the toxicokinetics of mirex via inhalation or dermal routes. Limited data indicate that mirex is absorbed by rats following exposure to the compound in cigarette smoke.

Chlordecone. Occupational studies indicate that chlordecone is absorbed via the inhalation and oral routes. Chlordecone is readily absorbed from the gastrointestinal tract of humans and animals. Chlordecone is widely distributed throughout the body and concentrates in the liver of humans and animals. It has a long retention time in the body. Chlordecone is metabolized to chlordecone alcohol in humans, gerbils, and pigs. Rats, guinea pigs, and hamsters cannot convert chlordecone to chlordecone alcohol. Chlordecone, chlordecone alcohol, and their glucuronide conjugates are slowly excreted in the bile and eliminated in the feces. However, a substantial enterohepatic recirculation of chlordecone exists that curtails its excretion in the feces. Chlordecone is also excreted in saliva and mother's milk. Only a very limited number of studies were located regarding the toxicokinetics of chlordecone via inhalation or dermal routes. Occupational studies indicate that chlordecone can be absorbed via inhalation and oral routes. Limited animal data indicate that dermal absorption of chlordecone is low.

3.1.1 Absorption

Mirex. Very limited data show that inhaled mirex can be rapidly absorbed into the blood of rats (Atallah and Dorough 1975; Dorough and Atallah 1975). The fate of [^{14}C] mirex in cigarette smoke was assessed in rats with the aid of a smoking device (Atallah and Dorough 1975; Dorough and Atallah 1975). Eight 5-mL puffs were administered to the trachea of rats at 15-second intervals. At 2–4 minutes after

inhalation, 47% of the radiolabel was exhaled, 36% was found in the lung, 11% was found in the blood, and 1% was found in the heart.

Several studies in rats indicate that mirex is absorbed from the digestive tract following gavage administration with a corn oil vehicle (Byrd et al. 1982; Gibson et al. 1972; Mehendale et al. 1972). Experiments with rats given single oral doses of mirex ranging from 0.2 to 10 mg/kg showed that an initial rapid excretion of mirex occurs in the feces within the first 48 hours post-dosing (Byrd et al. 1982; Gibson et al. 1972; Mehendale et al. 1972). The excretion of mirex in the feces within this time period is attributed to unabsorbed mirex. A majority (85–94%) of the total quantity excreted after 7 days is eliminated in this first rapid excretion phase (Gibson et al. 1972; Mehendale et al. 1972). Other data provided an absorption estimate of 69%, which occurred with female rats given a single oral dose of 10 mg/kg (Byrd et al. 1982). Similarly, most of the fecal mirex was recovered within the first 48 hours. This was attributed to the elimination of unabsorbed mirex (Byrd et al. 1982). Intestinal absorption of mirex was slightly decreased by the presence of an existing body burden (Gibson et al. 1972). For example, rats fed 12.5 mg/kg of unlabeled mirex before administration of a single dose (0.2 mg/kg) of mirex excreted 25% of the administered dose in the feces, as compared with 18% excretion for the animals given only a single dose (Gibson et al. 1972).

Orally administered mirex is rapidly absorbed by rats and monkeys. Peak plasma concentrations of ^{14}C-mirex occurred within 4–7 hours after female rats were given a single gavage dose of 10 mg/kg mirex in corn oil (Byrd et al. 1982) and within 2 hours after male rats were administered a single oral dose of 100 mg/kg (Brown and Yarbrough 1988). ^{14}C-Mirex levels in plasma peaked 5 hours after oral administration of 1 mg/kg mirex administered via a capsule to a female rhesus monkey (Wiener et al. 1976). Thereafter, the decline in plasma ^{14}C concentration continued at a much slower rate and paralleled that in the intravenously-dosed monkeys (Wiener et al. 1976).

Mirex rapidly entered the maternal bloodstream of pregnant rats following gavage administration of 5 mg/kg mirex in corn oil on gestation days 15, 18, or 20 (Kavlock et al. 1980). Four hours after oral dosing on gestation day 15, the plasma concentration of mirex was 13 ppm. Mirex plasma concentrations were significantly affected by both the time of administration and the hour of observation. Higher plasma concentrations were found at older gestation ages (13 ppm on gestation day 15, compared to 23 ppm on gestation day 20; measured 4 hours after administration). Plasma concentrations declined with time after dosing (Kavlock et al. 1980).

Mirex concentrations in plasma of pregnant goats receiving daily doses of 1 mg/kg, administered via capsule, for 61 weeks stabilized after 15 weeks (Smrek et al. 1977). An increase in the dose from 1 to 10 mg/kg at the end of the study resulted in an increase in the plasma level of mirex. Females dosed for 18 weeks starting at the first day postpartum had plasma levels that were similar to females that were started on mirex in early pregnancy (Smrek et al. 1977).

Chlordecone. Chlordecone is absorbed after occupational exposure; however, due to extremely poor workplace hygiene in available sources of human data, relative contributions from inhalation, oral, and dermal exposure routes are not available (Cannon et al. 1978; Cohn et al. 1978; Taylor 1982, 1985). Mean blood levels of workers exposed to chlordecone at a manufacturing plant in Hopewell, Virginia were 2.53 ppm for workers manifesting illness (nervousness or unfounded anxiety; pleuritic chest pain; weight loss of up to 60 pounds in 4 months; visual difficulties; skin rashes of an erythematous, macropapular nature) and 0.6 ppm for workers with no illness (Cannon et al. 1978). Two months following cessation of exposure, blood levels in workers were in excess of 2 ppm (Taylor 1982, 1985). Following exposure in humans, mean half-lives of 96 days (range of 63–148 days) (Adir et al. 1978) and 165 days (Cohn et al. 1978) in blood have been reported for chlordecone. This relatively long half-life may be due to the high degree of lipid solubility and limited metabolism of chlordecone.

Chlordecone is readily absorbed (90%) from the gastrointestinal tract of rodents and has a long half-life (Egle et al. 1978). In rats exposed to a single gavage dose of 40 mg/kg chlordecone in corn oil, the blood half-lives at 4, 8, and 14 weeks posttreatment were 8.5, 24, and 45 days, respectively (Egle et al. 1978). Chlordecone is also rapidly absorbed by pregnant rats (Kavlock et al. 1980). Four hours after gavage dosing (5 mg/kg mirex in corn oil) on gestation day 15, the plasma concentration of chlordecone was 6 ppm.

Chlordecone in acetone is absorbed to a limited extent following dermal exposure in rats (Hall et al. 1988; Shah et al. 1987). The percent of dose absorbed was determined by dividing the radioactivity in the body (carcass) and in the excreta by the total radioactivity recovered (in carcass, excreta, treated skin, and washes of the application materials). The results showed that fractional absorption decreased as the dose of chlordecone increased. At 72 hours after exposure to 0.29, 0.54, or 2.68 μmol ^{14}C-chlordecone/cm^2, skin penetration of chlordecone in young rats was 10.17, 7.23, and 1.93%, respectively, of the applied dose. Skin penetration of chlordecone in adult rats at 72 hours was 9.2, 5.96, and 1.03% for the low-, middle-, and high-dose groups, respectively. The area of application when expressed as the percentage of the total surface area (≈2.3%) was the same in both young and adult rats. The actual amount of

chlordecone absorbed (0.03 pmol/cm^2) was similar for all dose groups, suggesting that saturation occurred at the low dose. No significant age-dependent differences in dermal absorption were seen.

3.1.2 Distribution

Mirex. Mirex has been detected in a variety of human samples. Mirex levels of 0.16–5.94 and 0.3–1.13 ppm (males and females, respectively) were found in adipose tissue samples taken either from postmortem examinations or during surgery (Kutz et al. 1974). The adipose tissue samples came from individuals who lived in areas in which mirex was used extensively in a program to control fire ants. Adipose tissue levels of mirex ranging from 0.03 to 3.72 ppm have been found in residents living near a dump site in Tennessee (Burse et al. 1989). Mirex has also been detected in human serum samples (e.g., Butler Walker et al. 2003; Fenster et al. 2006; Greizerstein et al. 1999; Schell et al. 2003; van Oostdam et al. 2004), milk samples from lactating women (Fitzgerald et al. 2001; Greizerstein et al. 1999; Mes et al. 1978; Newsome and Ryan 1999; Newsome et al. 1995), and placental tissue and umbilical cord blood (Butler Walker et al. 2003; Lopez-Espinosa et al. 2007).

Only very limited animal data were located regarding the distribution of absorbed mirex following inhalation exposure. Mirex was found in the lungs (36%), blood (11%), and hearts (1%) of rats exposed to mirex in cigarette smoke (Atallah and Dorough 1975; Dorough and Atallah 1975).

Following oral dosing in animals, mirex is distributed to various tissues and sequestered in fat. Females generally accumulated greater amounts than males. Mirex demonstrated an affinity for lipids in male and female rats given a single oral dose of mirex (0.2 mg/kg); highest concentrations were found in fat (Chambers et al. 1982; Gibson et al. 1972). The levels in fat of females were approximately 2 times higher than levels in fat of males (Chambers et al. 1982). For females, mirex levels in the fat ranged from 338 to 944 ng/g at 7 days and increased to 483–1,043 ng/g at 14 days. For males, mirex levels in fat ranged from 161 to 479 ng/g at 7 days and from 419 to 530 ng/g at 14 days. Mirex also accumulated in nervous tissue, with females accumulating higher amounts than males (Chambers et al. 1982). Mirex concentrations in the nervous tissue in males and females at 7 days posttreatment were 13.228 ng/g and 40–59 ng/g, respectively; concentrations declined during posttreatment days 7–14. Mirex accumulated in various other tissues of both males and females, including gastrointestinal tract, liver, lung, heart, kidney, adrenals, brain, skeletal muscle, spleen, and thymus (Chambers et al. 1982; Gibson et al. 1972).

Seven days after a single administration of mirex (6 mg/kg) to rats, 34% of the total dose was retained in the tissues and organs; 27.8% was stored in the fat, 3.2% was stored in the muscle, and 1.75% was stored in the liver (Mehendale et al. 1972). The remaining tissues each retained <1% of the total dose. No metabolite of mirex was detected in the tissues. The repetitive administration of 10 mg/kg mirex to rats resulted in an accumulation of mirex in several tissues (plasma, liver, kidney, fat), with more accumulating in fat tissue (Plaa et al. 1987). Following oral administration of 1 mg/kg ^{14}C-mirex to a female rhesus monkey, the highest tissue levels of radioactivity were found in fat, followed by large intestine, adrenal glands, liver, ovaries, and peripheral nerves (Wiener et al. 1976). The administered dose of radioactivity was distributed as follows: 55.3% was recovered in fat and ≤2% was recovered in the remaining tissues. Mirex was the only labeled compound identified in fat. Mirex fed to minipigs for 7 consecutive days (3–4.5 mg/kg/day) was distributed to backfat (41.5 ppm), liver (1.24 ppm), kidney (0.44 ppm), plasma (0.04 ppm), and red blood cells (0.01 ppm) at 9 days after dosing (Morgan et al. 1979).

Mirex was detected in brains from male rats within 0.5–2 hours after a single oral dose of 100 mg/kg mirex (Brown and Yarbrough 1988). By 96 hours, the following concentrations (in μmol ^{14}C-mirex/g) were measured in the brain regions: cerebral cortex (0.47), cerebellum (0.50), brain stem (0.73), and spinal cord (0.75). Mirex was also distributed to the liver, kidneys, testes, and omental fat. Peak tissue concentrations of mirex in the kidneys, testes, liver, and omental fat occurred 12, 48, 48, and 96 hours postdosing, respectively. Following a single oral dose of 50 mg/kg mirex to mice, mirex was distributed to the brain; mirex levels in the striatum and medulla/pons were significantly higher than in the cortex, midbrain, or cerebellum at 48 hours postdosing (Fujimori et al. 1982b). However, at 6, 12, and 96 hours postdosing, discrete brain area levels of mirex did not differ significantly. Mirex levels in whole brain and plasma were 3–40 times lower than levels found in chlordecone-treated mice, and mirex showed less-specific distribution in discrete areas of the brain than did chlordecone (Fujimori et al. 1982b). Samples of brain tissue from rats fed 0, 0.089, or 0.89 mg mirex/kg/day for 34–49 days showed that mirex accumulates in rat brain tissue in a dose-dependent manner; mirex levels in brain tissue were 7–8 times higher in the high-dose group than in the low-dose group (Thorne et al. 1978).

Mirex accumulates in maternal tissues, readily crosses the placenta of animals, and accumulates in fetal tissues. Maximum concentrations of mirex found in the placenta of rats ranged from 3.5 to 4 ppm at 4 hours postdosing (Kavlock et al. 1980). Mirex levels in the placenta at 48 hours postdosing were <50% of the 4-hour level. The uptake of mirex by fetal organs was in the order of liver > brain = heart > kidney in a ratio of 3:2:2:1. Fetal mirex concentrations remained low at 4 hours postdosing, increased slightly at

24 hours, and decreased thereafter. The decline noted in the second 24-hour period was due to both organ growth and mirex elimination. Mirex accumulated in maternal and fetal tissues at all dose levels (1.5, 3, 6, 12.5 mg/kg given on gestation days 6–15) (Khera et al. 1976). At the 12.5 mg/kg/day dose level, fetal brain levels were >3 times higher (31.5 ppm) than mean maternal brain levels (8.87 ppm). All other mean fetal tissue values were lower than mean maternal values. The highest maternal levels of mirex were found in the fat, indicating the potential for long-term sequestering of the compound.

In a study in which dams were dosed with 1 or 10 mg/kg of mirex on days 2–5 postpartum, mirex was found in the stomach milk of pups (Kavlock et al. 1980). Mirex appeared in the milk in direct proportion to the dose. Mirex was also distributed to the liver, brain, and eyes of the pups in the approximate ratio of 40:4:1. Mirex tissue levels paralleled milk levels.

Mirex concentrations in adipose tissues of goats fed daily doses of 1 mg/kg did not reach a steady state, but continued to increase throughout a 61-week exposure period and did not seem to be affected by pregnancy or lactation (Smrek et al. 1977). When the dose was increased from 1 to 10 mg/kg, the adipose tissue levels did not increase dramatically. Twenty-eight days postdosing, the following residue levels were found in tissues of lactating cows given daily doses of 0.005 mg/kg/day for 28 days: 0.21 ppm in fat, 0.03 ppm in liver, and 0.02 ppm in kidney (Dorough and Ivie 1974). Muscle and brain contained no detectable residues. Mirex was the only compound identified in the fat. Analyses of the composition of residues in liver and kidney were not performed.

There was a dose-related increase in the levels of mirex in fat of rats fed 0.02, 0.2, or 1.5 mg/kg/day for 16 months (Ivie et al. 1974a). Mirex levels in fat were 120-fold higher than corresponding dietary intakes. Mirex levels increased in tissues throughout the exposure period, with fat accumulating the highest amounts of mirex. No plateau of residue accumulation occurred in any tissue during the feeding period. Removal of animals from treatment after 6 months resulted in a decline of residue levels in all tissues.

Mirex is rapidly absorbed and distributes to plasma and liver after intraperitoneal injection. Peak concentrations were seen at 3 hours postdosing in plasma and 6 hours postdosing in the liver following single or multiple doses of mirex (4 mg/kg) injected into mice (Charles et al. 1985). Significant amounts were rapidly taken up by the liver (21–29%) within the first 3–6 hours postdosing. Plasma-to-liver ratios were low (<1), indicating an increased influx of the chemical into tissue. Mirex decay curves for plasma and liver during 72 hours postdosing showed a biphasic pattern that consisted of a rapid phase (up to

24 hours) and a slow phase (24–72 hours). For plasma, the half-lives were 9.2 and 62.8 hours for the rapid and slow phases, respectively. For liver, the half-lives for the rapid and slow phases were 12.1 and 62.4 hours, respectively (Charles et al. 1985).

Mirex was rapidly cleared from the blood of rats following intravenous injection of 10 mg/kg (Byrd et al. 1982). Mirex blood levels at 8 hours postinjection were <4% of the levels seen 2 minutes postinjection. Pharmacokinetic modeling predicted that intravenously administered mirex was quickly cleared from the blood into a rapidly equilibrating compartment. Over the next several weeks, mirex was redistributed to a slowly equilibrating compartment, which acted as a depot for mirex storage (Byrd et al. 1982). The biological half-life of mirex was estimated to be 435 days (Byrd et al. 1982).

Following a single intravenous dose of 1 mg/kg to female rhesus monkeys, 86–87% of the administered dose was recovered in fat, 3.7–10% in skin, 0.6–1.7% in skeletal muscle, and <0.5% in other tissues (Wiener et al. 1976). Mirex was the only compound identified in fat.

Chlordecone. In humans, chlordecone is absorbed and distributed to various tissues and has a long retention time in the body (Cannon et al. 1978; Cohn et al. 1978; Taylor 1982, 1985). Chlordecone was eliminated slowly from the blood (half-life of 165 days) and fat (half-life of 125 days) of industrial workers (Cohn et al. 1978). Tissue-to-blood ratios for liver, fat, muscle, and gallbladder bile were 15, 6.7, 2.9, and 2.5, respectively (Guzelian et al. 1981). The relatively higher partition of chlordecone to blood (fat-to-blood concentration ratio of 1:7) compared to that of other organochlorine pesticides (e.g., DDT with a fat-to-blood concentration ratio of 300:1) may be explained by the fact that chlordecone is bound specifically by the proteins in plasma, particularly high-density lipoproteins (HDLs), unlike most organochlorine pesticides, which distribute among tissues in direct proportion to the concentration of tissue fat (Guzelian et al. 1981).

In rats, chlordecone was absorbed and distributed to various tissues, with the highest concentrations in liver (Egle et al. 1978; Hewitt et al. 1986b; Plaa et al. 1987). Chlordecone was detected in liver (125.8 mg/kg), adipose tissue (27.3 mg/kg), kidney (25.2 mg/kg), and plasma (4.9 mg/L) of rats 8 days following a single oral dose of 50 mg/kg (Hewitt et al. 1986b). Chlordecone was detected in liver, kidney, and fat of rats following single or repetitive dosing (0.5, 1, 2, 2.5, 5, 10, or 25 mg/kg) (Plaa et al. 1987). For all dose groups, the liver contained the highest concentration, followed by kidney, then fat. The ratios of tissue levels in animals that received multiple doses to levels in animals that received single doses were as follows: 4.27 (plasma), 3.27 (liver), 3.74 (kidney), and 3.42 (fat). These ratios show an

even accumulation of chlordecone in the tissues. Rats given four daily doses of 10 mg/kg chlordecone had tissue-to-blood distribution ratios for fat, liver, muscle, and skin of 15, 55, 5, and 6, respectively (Bungay et al. 1981).

Studies show that pretreatment with an inducer (phenobarbital) or inhibitor (SKF-525A) of CYP450 causes an alteration in the distribution of chlordecone in rats (Aldous et al. 1983). Following a single oral dose of chlordecone alone, the liver had the highest chlordecone level, followed by adrenal gland, lung, kidney, and spinal cord (Aldous et al. 1983). Pretreatment with phenobarbital (particularly with multiple phenobarbital doses) caused an increase in the accumulation of chlordecone in the liver compared to animals given no pretreatment. This hepatic increase resulted in a significant decrease of chlordecone levels in other tissue (e.g., brain, kidney, muscle) as well as significantly reduced excretion. Pretreatment with SKF-525A caused a nonsignificant reduction in chlordecone levels in the liver and significant increases in digestive system tissues. The results of the chlordecone distribution following SKF-525A pre-dosing must be interpreted with caution, since the effects may have resulted partly from SKF-525A-mediated decreases in absorption of chlordecone (Aldous et al. 1983).

Following a single oral dose of 50 mg/kg chlordecone to male mice, chlordecone was distributed to the brain (Fujimori et al. 1982b; Wang et al. 1981). The results showed that the striatum and medulla/pons had significantly higher levels of chlordecone than the cortex, midbrain, or cerebellum (Fujimori et al. 1982b). Mice similarly treated with mirex did not exhibit marked differences in distribution among these brain areas. Chlordecone levels were 3–40 times higher than mirex levels in plasma and brain. Following repeated oral doses of chlordecone (10 mg/kg/day) for 12 days, the compound was rapidly absorbed and distributed to the brain (Wang et al. 1981). Plasma levels of chlordecone increased during the 12-day treatment period. Brain levels of chlordecone increased linearly for the first 8 days and reached a plateau of 90 µg/g on the 10th day (Wang et al. 1981).

Chlordecone is well distributed throughout the reproductive tract of male rats and appears in the ejaculate. In rats given a single oral dose of 40 mg/kg chlordecone, the descending order of concentration was vas deferens (81.6) > seminal vesicular fluid (19.7) > unwashed sperm (14.6) > prostate (11.3) > seminal vesicle (6.2) > washed sperm (1.97). This relationship persisted as levels declined over the 21-day observation period (Simon et al. 1986).

Chlordecone accumulates in maternal tissues, readily crosses the placenta of rats, and accumulates in fetal tissues (Chernoff et al. 1979b; Kavlock et al. 1980). Four hours following a single oral dose of 5 mg/kg,

maximal concentrations of chlordecone in the placenta ranged from 3.5 to 4 ppm (Kavlock et al. 1980). Concentrations of chlordecone in the placenta remained steady for up to 48 hours postdosing. Chlordecone levels in the fetus were generally highest in the liver, followed by the brain, heart, and kidney. Concentrations increased during the first 24 hours after dosing and declined in the second 24-hour period, regardless of gestation age at the time of dosing (Kavlock et al. 1980). Chlordecone levels found in maternal and fetal tissues were slightly higher than the levels of mirex following administration of equal doses (Kavlock et al. 1980). The livers of weanling rats fed diets of 0.05 mg/kg chlordecone or mirex for 28 days accumulated higher levels of chlordecone (6.1 ppm) than mirex (0.89 ppm) (Chu et al. 1980b). Possible explanations for this are that mirex is more poorly absorbed from the feed than is chlordecone or that the absorbed dose of mirex accumulates in the liver to a lesser extent than absorbed chlordecone (Chu et al. 1980b).

In a study in which lactating rat dams were dosed with 1 or 10 mg/kg chlordecone on days 2–5 postpartum, chlordecone was found in the stomach milk of pups (Kavlock et al. 1980). Chlordecone appeared in the milk in direct proportion to the dose. Chlordecone was distributed to the liver, brain, and eyes of the pups in the approximate ratio of 16:4:1 (Kavlock et al. 1980).

3.1.3 Metabolism

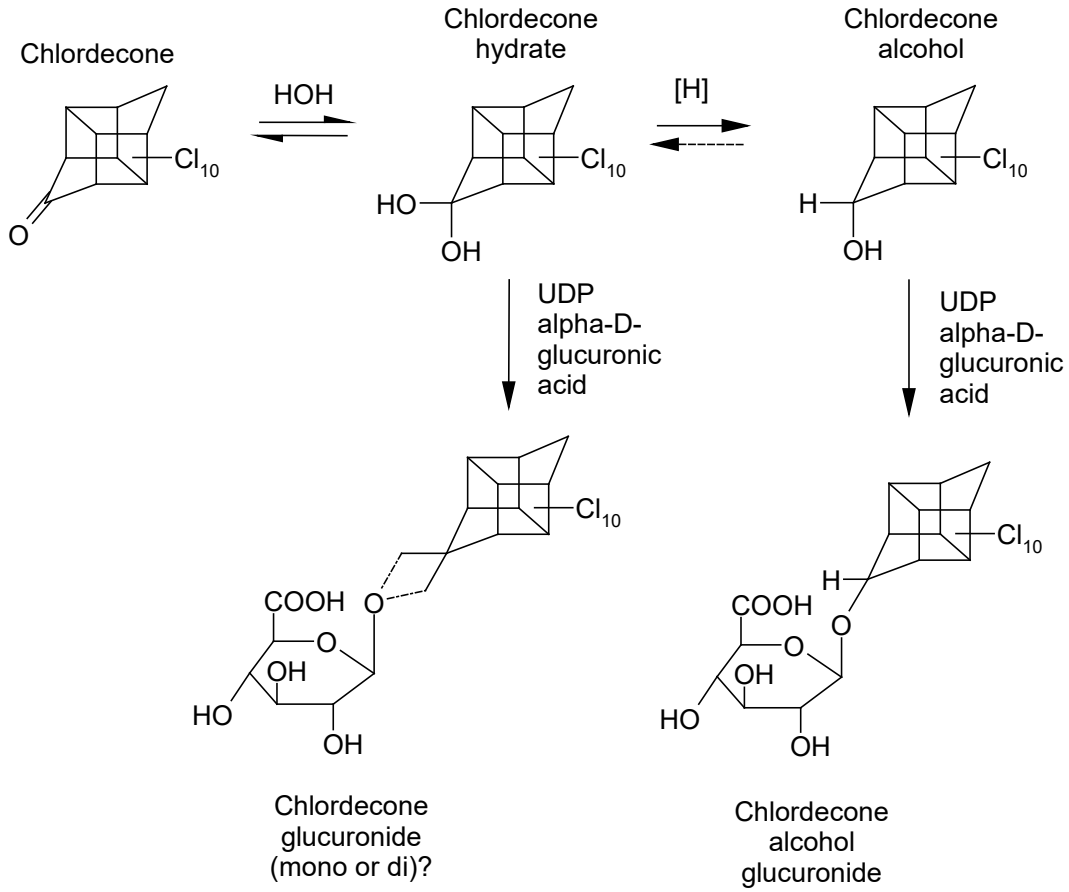
Mirex. Radiolabeling experiments showed that mirex is not metabolized in humans, rodents, cows, or minipigs; the parent compound was the only radiolabeled compound present in the plasma, fat, and feces (Dorough and Ivie 1974; Gibson et al. 1972; Kutz et al. 1974; Mehendale et al. 1972; Morgan et al. 1979). However, a monohydro derivative of mirex was identified in the feces, but not the fat or plasma, of rhesus monkeys given an oral or intravenous dose of mirex (Pittman et al. 1976; Stein et al. 1976; Wiener et al. 1976). It is believed that the suspected metabolite may have arisen as a result of bacterial action in the lower gut or feces (Stein et al. 1976).

The potential for *in vivo* conversion of mirex to chlordecone was also examined (Morgan et al. 1979). Mirex was found in a variety of tissues from minipigs administered mirex in the feed for 7 days; however, chlordecone was not detected in any tissues (Morgan et al. 1979). This result indicates that significant *in vivo* conversion of absorbed mirex to chlordecone is not likely.

Chlordecone. The fate of chlordecone in humans involves uptake by the liver, enzymatic reduction to chlordecone alcohol, conjugation with glucuronic acid, partial conversion to unidentified polar forms, and

excretion of these metabolites mainly as glucuronide conjugates into bile (Fariss et al. 1980; Guzelian et al. 1981) (see Figure 3-1). Of the total chlordecone measured in bile of occupationally exposed workers, the predominant portion (72%) was unconjugated, with only a small portion conjugated with glucuronic acid or sulfate (9%) (Fariss et al. 1980). The remaining fraction (19%) of total chlordecone measured in the bile was stable polar metabolites, which were resistant to β-glucuronidase. Following treatment of bile with β-glucuronidase plus sulfatase, the ratio of total chlordecone to total chlordecone alcohol was 1:3 in human bile (Fariss et al. 1980). Bioreduction of chlordecone to chlordecone alcohol is species-specific since rats treated orally or intraperitoneally with chlordecone produced no chlordecone alcohol in the feces, bile, or liver (Fariss et al. 1980; Guzelian et al. 1981; Houston et al. 1981). Following treatment of bile with β-glucuronidase plus sulfatase, the ratio of total chlordecone to total chlordecone alcohol in rat bile was in excess of 150:1 for orally exposed rats (Fariss et al. 1980; Guzelian et al. 1981). Guinea pigs and hamsters given an intraperitoneal dose of 20 mg/kg chlordecone also did not convert chlordecone to chlordecone alcohol, as indicated by the fact that no chlordecone alcohol was detected in the feces, bile, or liver (Houston et al. 1981). Therefore, rats, guinea pigs, and hamsters are not good animal models for predicting chlordecone metabolism in humans because they do not convert chlordecone to chlordecone alcohol. Gerbils were found to be the most suitable animal model of chlordecone metabolism in humans because only gerbils converted chlordecone to its alcohol (Houston et al. 1981). Reduction of chlordecone is catalyzed in gerbil liver by a species-specific reductase, chlordecone reductase. This chlordecone reductase was characterized in gerbil liver cytosol *in vitro* and determined to be of the "aldo-keto reductase" family (Molowa et al. 1986). It is specific to gerbils and humans (Molowa et al. 1986). Like humans, chlordecone-treated gerbils excreted chlordecone alcohol exclusively in the stool and not in the urine (Houston et al. 1981). Following intraperitoneal dosing of 20 mg/kg ^{14}C-chlordecone, the ratio of chlordecone to chlordecone alcohol in the bile of gerbils was approximately 2.5:1. No quantitative estimate of the extent to which chlordecone was metabolized was given. Following treatment of bile with β-glucuronidase plus acid hydrolysis, the ratio of chlordecone to chlordecone alcohol in the bile was 1:2, indicating that chlordecone is present in the bile largely in the form of its glucuronide conjugate (Houston et al. 1981). Incubation of chlordecone with the cytosolic fraction of gerbil liver homogenate in the presence of NADPH produced chlordecone alcohol (Houston et al. 1981). Intraperitoneally-injected chlordecone was biotransformed in pigs to conjugated chlordecone, chlordecone alcohol, and conjugated chlordecone alcohol, which were excreted in the bile and eliminated in the feces (Soine et al. 1983). Relatively high levels of chlordecone alcohol and conjugated chlordecone alcohol in the bile and the absence of these metabolites in the plasma and liver suggest that chlordecone alcohol is formed and conjugated in the liver and excreted into the bile (Soine et al. 1983).

Figure 3-1. Proposed Metabolic Pathways for Chlordecone



Source: Fariss et al. 1980

3.1.4 Excretion

Mirex. Available information regarding mirex-related excretion in humans is limited. Mirex was detected in milk samples from lactating women (Fitzgerald et al. 2001; Greizerstein et al. 1999; Mes et al. 1978; Newsome and Ryan 1999; Newsome et al. 1995).

In animals, mirex is excreted unchanged mainly in the feces; urinary excretion is negligible (Byrd et al. 1982; Chambers et al. 1982; Gibson et al. 1972; Ivie et al. 1974a). Female rats receiving a single oral dose of ^{14}C-mirex (0.2 mg/kg) excreted 18% of the total administered dose in the feces during a 7-day posttreatment period; very little was excreted in the urine (0.3% of the total dose) (Gibson et al. 1972). Of the total quantity eliminated, 85% was excreted in the feces within the first 48 hours. This percentage represents unabsorbed material. The virtual lack of urinary excretion and the fact that fecal excretion was

only about 3% of the administered dose after the initial 48 hours suggest that mirex is not metabolized in rats and that the absorbed portion is only slowly excreted. In female rats administered a single oral dose of 10 mg/kg mirex, cumulative fecal excretion of mirex during 21 days posttreatment was 18–45% (Byrd et al. 1982). Most of the fecal mirex was excreted within 48 hours and represented unabsorbed mirex. A biological half-life of mirex was estimated to be 460 days by a model developed to simulate mirex pharmacokinetics after oral administration (Byrd et al. 1982). Male rats receiving a single oral dose of mirex at 6 mg/kg excreted 58.5% of the administered dose in the feces during 7 days posttreatment (Mehendale et al. 1972). Fifty-five percent of the administered dose was excreted in the feces within the first 48 hours post-dosing and probably represented unabsorbed dose from the gut. Only 0.69% of the administered dose was excreted in the urine. Mirex was the only treatment-related compound identified in the urine or feces. A half-life of 38 hours was estimated based on the first rapid elimination. A second half-life was projected to be >l00 days, indicating a very slow rate of elimination from the body.

Following oral administration of 1 mg/kg ^{14}C-mirex to a female rhesus monkey, 25% of the radioactivity was recovered in the feces within 48 hours, with a cumulative excretion of 26.5% over 23 days. Less than 1% was recovered in the urine over 23 days (Wiener et al. 1976). A monohydro derivative of mirex was identified in the feces of rhesus monkeys given daily doses of 1 mg/kg mirex; the exact duration of dosing was not specified (Stein and Pittman 1977).

The secretion of mirex in milk was a major route of elimination for nursing rat dams given either 1 or 10 mg/kg/day of mirex via gavage on postpartum days 2–5 (Kavlock et al. 1980). Mirex entered the milk supply more quickly than chlordecone. Greater amounts of mirex were excreted via the milk as compared with chlordecone because of the octanol-water partition coefficient. Mirex was also excreted in the milk of lactating goats given daily doses of 1 mg/kg for 18 or 61 weeks followed by daily doses of 10 mg/kg for 4 weeks (Smrek et al. 1977). The concentration of mirex in colostrum fat ranged from 16 to 20 ppm. Colostrum, which is fluid secreted for the first few days after parturition, is characterized by high protein and antibody content. Over 8 weeks, the levels of mirex in milk fat decreased to less than half the amount excreted in colostrum immediately after birth of the kids. The goats eliminated more mirex in colostrum than in regular milk. A lactating Jersey cow given a daily dose equivalent to 0.005 mg/kg/day in the diet for 28 days, excreted 50% of the administered dose in the feces during the 28-day exposure period (Dorough and Ivie 1974). Only approximately 3% of the administered dose of mirex was excreted in the feces in the 28 days after treatment ended. These results show that the radioactivity in the feces represents unabsorbed mirex, and that the turnover rate of mirex stored in the tissues is very low. In this study, mirex was also found in cow's milk. About 10% of the administered dose was excreted in the milk

10 days after treatment began. Cumulative excretion in the milk was 13% after 28 days of exposure. Only 2% of the administered dose was excreted in the milk during the entire 28-day post-treatment period. The levels of mirex in milk equilibrated after 1 week of treatment, with the concentration in whole milk being 0.058 ppm. One week after treatment ended, the residues in the milk dropped to 0.006 ppm and then declined to 0.002 ppm after 28 days (Dorough and Ivie 1974). Mirex was the only treatment-related compound identified in the feces and cow's milk.

Mirex has a long retention time in the body and is excreted slowly. Cumulative fecal excretion was 7% of the administered dose 21 days following intravenous dosing of 10 mg/kg in rats (Byrd et al. 1982). Cumulative urinary excretion was <1% of the administered dose (Byrd et al. 1982). The biological half-life of mirex was estimated to be 435 days (Byrd et al. 1982). Cumulative fecal excretion was 4.69 and 6.91% of the dose after 106 and 388 days, respectively, following a single intravenous dose of 1 mg/kg to female monkeys (Wiener et al. 1976). Cumulative urinary excretion accounted for 0.18–0.37% of the administered dose by the end of 1 week. Mirex was the only labeled compound identified in the feces. An unidentified substance found in the feces was thought to be a decomposition product of mirex, not a metabolite (Wiener et al. 1976). Mirex and an unidentified metabolite, a nonpolar derivative, were found in the feces of rhesus monkeys given an intravenous dose of 1 mg/kg of mirex (Stein et al. 1976). It is believed that the suspected metabolite may have arisen as a result of bacterial action in the lower gut or feces (Stein et al. 1976).

Chlordecone. Chlordecone, chlordecone alcohol, and their glucuronide conjugates were excreted in the bile and eliminated via the feces of humans occupationally exposed to chlordecone (Blanke et al. 1978; Boylan et al. 1979; Cohn et al. 1978; Guzelian et al. 1981). In the study of Guzelian et al. (1981), most of the total chlordecone measured in bile was unconjugated (72%), a small amount (9%) was conjugated with glucuronic acid, and the final portion (19%) was present as an uncharacterized "acid releasable" form. Only a minor amount of chlordecone alcohol (<10%) was present in bile as the free metabolite; the remainder was conjugated with glucuronide. A substantial enterohepatic recirculation of chlordecone exists that curtails its excretion (Boylan et al. 1979; Cohn et al. 1978; Guzelian et al. 1981). Only 5–10% of the biliary chlordecone entering the lumen of the duodenum appeared in the feces (Cohn et al. 1978; Guzelian et al. 1981). Similarly, the rate of chlordecone excretion in the bile was, on average, 19 times greater than the rate of elimination of chlordecone in the stool (Cohn et al. 1978). Chlordecone was not detected in the sweat and was detected in only minor quantities in urine, saliva, and gastric juice (Cohn et al. 1978). Similarly, stool contained 11–34% of the quantities excreted in bile for workers exposed for 6 months (Boylan et al. 1979). When biliary contents were diverted, fecal excretion of chlordecone

alcohol fell to low or undetectable levels; however, chlordecone excretion in feces persisted, suggesting a nonbiliary mechanism for the excretion of chlordecone into the intestine and feces (Boylan et al. 1979). Analogous experiments with rats gave similar results (Boylan et al. 1979). With no bile in the gut, the average amount of chlordecone in the human stool in two 72-hour collections was eight times as great as with the biliary circuit intact (Boylan et al. 1979). This suggests that bile may suppress nonbiliary excretion of chlordecone. When bile was completely diverted from the intestines of rats, however, fecal excretion of radiolabel was unchanged (Boylan et al. 1979).

In rats, chlordecone is slowly eliminated in the feces (Egle et al. 1978). Rats given a single oral dose of 40 mg/kg ^{14}C-chlordecone excreted 65.5% of the administered dose in the feces and 1.6% of the dose in the urine by 84 days (Egle et al. 1978). Less than 1% of the administered dose was expired as radiolabeled carbon dioxide (^{14}C-CO_2) (Egle et al. 1978). Rats fed ^{14}C-chlordecone (0.2 mg/kg/day for 3 days) excreted 52.16% of the radioactivity in the feces and 0.52% in the urine 25 days postdosing (Richter et al. 1979).

Chlordecone was excreted in the saliva of rats following administration of 50 mg/kg (Borzelleca and Skalsky 1980; Skalsky et al. 1980). Peak levels of chlordecone in saliva were reached 6–24 hours postdosing (Borzelleca and Skalsky 1980; Skalsky et al. 1980). The saliva-to-plasma ratios were <1 throughout the study period, indicating that chlordecone is not actively concentrated by the salivary glands (Borzelleca and Skalsky 1980). Thus, chlordecone enters the salivary tissue (submaxillary, parotid, and sublingual tissues) and saliva by passive diffusion (Borzelleca and Skalsky 1980; Skalsky et al. 1980).

Chlordecone is also excreted in the milk of nursing rats (Kavlock et al. 1980). When compared with mirex-treated rats, chlordecone entered the milk supply more slowly than mirex. More mirex was excreted via the milk than chlordecone because of a higher octanol-water partition coefficient.

Chlordecone was detected in the bile and feces of rats, guinea pigs, hamsters, gerbils, and pigs given intraperitoneal doses of 20 mg/kg chlordecone (Houston et al. 1981; Soine et al. 1983). Rats given intraperitoneal injections of chlordecone had a fecal excretion half-life of 40 days (Pore 1984). Chlordecone alcohol was detected in the bile and feces of gerbils and pigs only (Houston et al. 1981; Soine et al. 1983).

Chlordecone appeared in the bile within 1–3 hours after intravenous dosing of rats (0.1, 1, or 10 mg/kg) (Bungay et al. 1981). The average concentration of chlordecone in the bile varied linearly with dose: 0.051, 0.50, and 5 μg/g in the low-, middle-, and high-dose groups, respectively (Bungay et al. 1981). Rats given a single intravenous dose of 1 mg/kg had a chlordecone excretion rate in the bile of 0.22% of the dose per hour (Bungay et al. 1981).

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.

PBPK models for mirex have not been developed. Several models were developed for chlordecone. Bungay et al. (1979) developed a model to predict the kinetics of chlordecone in the gastrointestinal tract by comparing excretion following oral administration to intact rats and intravenous administration to bile-cannulated rats. Heatherington et al. (1998) used experimental data from chlordecone-treated young and adult rats to predict percutaneous absorption and disposition. El-Masri et al. (1995) evaluated interactions between chlordecone and carbon tetrachloride in the rat liver using pharmacokinetic and pharmacodynamic modeling. Belfiore et al. (2007) developed a model to describe sequestration of chlordecone in the rat liver. None of the models are useful for predicting the toxicokinetic behavior or target concentrations of chlordecone in humans.

3.1.6 Animal-to-Human Extrapolations

The toxicokinetics of mirex has been widely studied in experimental animals (Atallah and Dorough 1975; Brown and Yarbrough 1988; Byrd et al. 1982; Chambers et al. 1982; Dorough and Atallah 1975; Gibson et al. 1972; Ivie et al. 1974a; Kavlock et al. 1980; Mehendale et al. 1972; Morgan et al. 1979; Plaa et al. 1987; Smrek et al. 1977; Wiener et al. 1976). Available data demonstrate that mirex accumulates in tissues (particularly fat), is not metabolized, and is slowly excreted in feces. Most animal studies were conducted using rats. A few studies using monkeys, goats, or cows yielded results generally similar to

those reported for rats. Limited human data have not identified or quantified the toxicokinetics of mirex (Burse et al. 1989; Kutz et al. 1974; Mes et al. 1978). No information was located to indicate that the toxicokinetics of mirex in humans would be significantly different from that observed in experimental animals.

Toxicokinetic studies have been performed using multiple animal species; the data indicate that rats, guinea pigs, and hamsters may not represent appropriate models for extrapolation to humans because these animal species do not convert chlordecone to chlordecone alcohol (Fariss et al. 1980; Guzelian et al. 1981; Houston et al. 1981). Gerbils and pigs may be more appropriate species to study animal-to-human extrapolation because these species convert chlordecone to chlordecone alcohol (Houston et al. 1981; Soine et al. 1983). Limited human toxicokinetic data are available for chlordecone (Adir et al. 1978; Blanke et al. 1978; Boylan et al. 1978; Cannon et al. 1978; Cohn et al. 1978; Guzelian et al. 1981; Taylor 1982, 1985). It does not appear that sufficient data exist to provide meaningful extrapolation from animals to humans with respect to chlordecone toxicokinetics.

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 mirex or chlordecone are discussed in Section 5.7, Populations with Potentially High Exposures.

Review of the literature regarding toxic effects of mirex and chlordecone did not reveal any human populations that are known to be unusually sensitive to mirex or chlordecone. However, based on

knowledge of the toxicities of mirex and chlordecone, some populations can be identified that may demonstrate unusual sensitivity to these chemicals. Those with potentially high sensitivity to mirex include the very young. Those with potentially high sensitivity to chlordecone include juvenile and elderly persons as well as persons being treated with some antidepressants or the anticonvulsant, diphenylhydantoin.

In experimental animals, mirex administered within the week after birth causes a high incidence of cataracts and other lesions of the lens (Chernoff et al. 1979a; Gaines and Kimbrough 1970; Rogers and Grabowski 1984; Scotti et al. 1981). These effects were observed whether the neonatal animals received mirex through the milk of lactating dams or directly by gavage. Although it is unclear whether the lens of humans also undergoes a similar period of susceptibility, the possibility exists that newborn children may also develop cataracts if exposed to mirex shortly after birth.

Studies in rats have demonstrated that certain treatments exacerbate the tremors associated with chlordecone exposure. These include pretreatment with the anticonvulsant, diphenylhydantoin (Hong et al. 1986; Tilson et al. 1985, 1986), and treatment with the non-selective serotonergic receptor agonist, quipazine (Gerhart et al. 1983). Therefore, persons being treated with diphenylhydantoin for epilepsy or quipazine for depression may be likely to experience more severe tremors upon exposure to high levels of chlordecone. Extrapolating from the effects seen in animals with quipazine, it might be likely that persons taking the prescription drug Prozac®, a selective serotonin reuptake inhibitor (SSRI) used to treat depression, may also experience more severe tremors. Furthermore, the elderly may be a susceptible population because serotonin metabolism is increased during aging (Walker and Fishman 1991).

Studies in animals have also shown that juvenile animals experience a higher death rate than adults following exposure to chlordecone at equivalent mg/kg doses (Huber 1965). No explanation was given for these findings, but similar sensitivities may exist in children. Furthermore, although inhibition of Na^+K^+ATPase, Mg^{2+}ATPase, and Ca^{2+}ATPase activities have not been definitively shown to be the mechanism underlying chlordecone toxicity, sufficient evidence exists to suggest that their inhibition may be involved in a number of adverse effects. Neonatal rats have shown a greater inhibition of these enzymes than adult rats (Jinna et al. 1989). This provides additional support for the suggestion that infants and young children may represent a susceptible population to the toxic effects of chlordecone.

In contrast, a recent study of developing postnatal rats has shown that the young may be less susceptible to at least one of the toxic effects of chlordecone. Young and adolescent rats show less potentiation of

carbon tetrachloride toxicity than adult rats (Cai and Mehendale 1993). This may be due to a combination of incomplete development of the microsomal enzyme systems and a higher level of hepatic regenerating activity in the very young rats. In adolescent rats (35 and 45 days old), the microsomal enzyme activity is comparable to adult levels, but the level of damage is still less than in adult rats (60 days old). This may be due to that fact that hepatic regenerating activity remained higher in the adolescents than in the adults.

Several studies (Dalu and Mehendale 1996; Dalu et al. 1995, 1998; Murali et al. 2004) provide additional insight to earlier findings of age-related differences in the lethality and hepatotoxicity induced by exposure of rats to nontoxic levels of chlordecone and subsequent exposure to otherwise nonlethal levels of carbon tetrachloride. Results of Blain et al. (1999) indicate both sex- and age-dependent influences on chlordecone-carbon-tetrachloride-induced hepatotoxicity in rats.

In studies performed by Sobel and coworkers (Sobel et al. 2005, 2006; Wang et al. 2008), chronic exposure of systemic lupus erythematosus-prone female (NZB x NZW) F_1 mice to chlordecone via subcutaneously-implanted pellets significantly shortened the time to onset of elevated autoantibody titers and renal disease in a dose-related manner. These effects were not seen in nonlupus-prone BALB/c mice. These results indicate that humans with lupus may be particularly sensitive to chlordecone toxicity.

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 mirex or chlordecone 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 mirex or chlordecone 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 mirex or chlordecone 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

The primary biomarkers of exposure to mirex include mirex concentrations in blood (Butler Walker et al. 2003; Byrd et al. 1982; Fenster et al. 2006; Greizerstein et al. 1999; Kavlock et al. 1980; Schell et al. 2003; Smrek et al. 1977; van Oostdam et al. 2004; Wiener et al. 1976), fat (Burse et al. 1989; Kutz et al. 1974), feces (Byrd et al. 1982; Chambers et al. 1982; Gibson et al. 1972; Ivie et al. 1974a), or breast milk (Dorough and Ivie 1974; Fitzgerald et al. 2001; Greizerstein et al. 1999; Kavlock et al. 1980; Mes et al. 1978; Newsome and Ryan 1999; Newsome et al. 1995; Smrek et al. 1977). Since mirex is not metabolized, it is the only biomarker to be measured in these biological media. Since mirex is retained in the body for long periods of time and only slowly excreted, its measurement is useful as a biomarker of acute-, intermediate-, or chronic-duration exposures to both low and high levels. Biomonitoring levels for mirex are presented in Section 5.6.

The biomarkers of exposure to chlordecone include blood or saliva concentrations of chlordecone, and fecal or bile concentrations of chlordecone, chlordecone alcohol, and/or their glucuronide conjugates. Blood samples are the most useful tool for epidemiological studies of exposure to chlordecone (Guzelian et al. 1981). The unusually high concentration of chlordecone in blood compared with its concentration in fat (1:7 in humans), which is due to chlordecone’s association with plasma proteins, and its long half-life, make chlordecone in blood (a readily sampled tissue) a good biomarker of exposure. The blood

concentration of chlordecone serves as an accurate reflection of total body content of chlordecone. Blood is the best biological material to monitor and to use for determining acute, intermediate, and chronic exposures to both low and high levels of chlordecone.

Blood is a better indicator of exposure to chlordecone than saliva (Borzelleca and Skalsky 1980; Skalsky et al. 1980). Chlordecone has been detected in saliva of humans only in trace amounts and in rats at concentrations 3–4 times lower than in blood (Guzelian et al. 1981; Skalsky et al. 1980). Peak chlordecone concentrations occurred within the first 24 hours of exposure; therefore, the period of utility of saliva as a biomarker is limited. The movement of chlordecone from blood into saliva is one of passive diffusion and is not concentration dependent (Borzelleca and Skalsky 1980; Skalsky et al. 1980). Thus, blood is a better biological material than saliva for monitoring chlordecone exposure.

Other biomarkers of exposure include tissue concentrations of chlordecone (Bungay et al. 1981; Cannon et al. 1978; Cohn et al. 1978; Egle et al. 1978; Hewitt et al. 1986b; Plaa et al. 1987; Taylor 1982, 1985) and fecal or bile concentrations of chlordecone, chlordecone alcohol, and their glucuronide conjugates (Blanke et al. 1978; Boylan et al. 1979; Cohn et al. 1978; Guzelian et al. 1981). These can be measured and are reliable indicators of exposure to chlordecone.

3.3.2 Biomarkers of Effect

Microsomal enzyme induction has been shown to be increased by both mirex and chlordecone in humans and/or experimental animals. Serum levels of chlordecone associated with enzyme induction in exposed workers were estimated to range from 100 to 500 µg/L (Guzelian 1985). Urinary D-glucaric acid levels have been shown to be a sensitive indicator of microsomal enzyme induction in workers exposed to chlordecone (Guzelian 1985). However, other substances such as barbiturates, phenytoin, chlorbutanol, aminopyrine, phenylbutazone, and contraceptive steroids as well as other organochlorinated pesticides also cause microsomal enzyme induction and cause changes in urinary D-glucaric acid (Morgan and Roan 1974).

Studies in experimental animals suggest that biliary excretion of chemicals from the liver may be impaired by mirex or chlordecone (Berman et al. 1986; Curtis and Hoyt 1984; Curtis and Mehendale 1979; Curtis et al. 1979, 1981; Davison et al. 1976; Mehendale 1976, 1977a, 1977b, 1981; Teo and Vore 1991). Measurement of serum bile acid levels may provide information regarding biliary excretory function.

Studies in experimental animals have also shown increased urinary protein accompanied or unaccompanied by histopathological changes of the kidneys following exposure to mirex (NTP 1990) or chlordecone (Larson et al. 1979b). Although these changes are not specific for mirex or chlordecone, measurement of these parameters may provide information about renal damage in exposed populations.

Chlordecone causes a number of neurotoxic responses in humans and animals exposed to sufficiently high levels. Tremor accentuated by intentional acts, sustained postural movement, anxiety, and/or fatigue have been observed in workers exposed to high levels of chlordecone. Tremorograms have been used to objectively assess tremors associated with chlordecone exposure in humans (Taylor et al. 1978). An infrared reflection technique and oculography have been used to assess oculomotor disturbances caused by chlordecone (Taylor et al. 1978). Standard tests for memory and intelligence can be used to determine the presence of encephalopathy, but in the absence of baseline preexposure levels for individuals, subtle changes may be difficult to detect.

Decreased sperm count has been observed following exposure to mirex or chlordecone in humans and/or experimental animals. Clinically, the most straightforward biomarker would be examination of sperm in the ejaculate. However, testicular biopsies may also be helpful. Both procedures have been used to assess the male reproductive toxicity of chlordecone in exposed persons (Taylor et al. 1978).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Limited data are available regarding interactions with other chemicals that affect the toxicity of mirex or chlordecone. Selected agents have been shown to exacerbate or suppress chlordecone-induced tremors in laboratory animals. Pretreatment of rats with diphenylhydantoin resulted in exacerbation of chlordecone-induced tremors (Hong et al. 1986; Tilson et al. 1985, 1986). The mechanism for the exacerbation of the tremors is unknown. Therefore, if persons receiving diphenylhydantoin treatment for epilepsy were exposed to sufficiently high concentrations of chlordecone, increased tremor severity may be likely to occur. Treatment with quipazine (a nonselective serotonergic receptor agonist) was shown to potentiate chlordecone-induced tremors in rats (Gerhart et al. 1983). Therefore, it is possible that persons being treated for depression with quipazine or with SSRIs such as Prozac® may experience enhanced tremors.

A number of pharmacological agents have been shown to decrease the tremors produced by chlordecone in rats (Gerhart et al. 1983, 1985; Herr et al. 1987). Agents shown to be effective in at least one study

include yohimbe or phenoxybenzamine (α-noradrenergic antagonists), mecamylamine (a nicotinic antagonist), chlordiazepoxide (α benzodiazepine), muscimol (a GABA agonist), and mephenesin (a centrally acting muscle relaxant). Persons being treated therapeutically with any of these drugs are likely to experience diminished tremors following exposure to chlordecone.

Pretreatment of rats with difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase, prior to exposure to a tremorgenic dose of chlordecone, also resulted in inhibition of the tremor (Tilson et al. 1986). DFMO was more effective if given 5 hours prior to the chlordecone than if given 24 hours prior to exposure. The DFMO was ineffective if given 19 hours after chlordecone exposure. These results suggest an interaction of the polyamine synthetic pathway with tremors produced by chlordecone. The mechanism of the interaction is unclear, but may involve effects of polyamines on intracellular calcium homeostasis. Persons being treated with DFMO for cancer or protozoal infections would be likely to have reduced tremor severity after exposure to chlordecone.

Cholestyramine, a chelating agent, binds chlordecone present in the gastrointestinal tract and limits its enterohepatic recirculation (Boylan et al. 1978; Cohn et al. 1978). This interaction leads to increased excretion of chlordecone and decreased toxicity. Thus, persons being treated with cholestyramine to lower plasma cholesterol may experience increased excretion of chlordecone and decreased toxicity.

A number of animal studies have focused on effects of chlordecone on toxicity produced by other agents. Although these studies do not address the issue of interactions that affect chlordecone toxicity, results are summarized below.

By far, the most extensively studied interaction of mirex or chlordecone is the ability of chlordecone to markedly potentiate the hepatotoxicity of halomethanes such as carbon tetrachloride (Agarwal and Mehendale 1983a; Bell and Mehendale 1985; Chaudhury and Mehendale 1991; Curtis et al. 1979, 1981; Davis and Mehendale 1980; Klingensmith and Mehendale 1981, 1982b, 1983a, 1983b; Klingensmith et al. 1983; Kodavanti et al. 1989b, 1990a, 1991; Lockard et al. 1983a, 1983b; Mehendale and Klingensmith 1988; Soni and Mehendale 1993; Tabet et al. 2016), bromotrichloromethane (Agarwal and Mehendale 1982; Faroon and Mehendale 1990; Faroon et al. 1991; Klingensmith and Mehendale 1981), and chloroform (Cianflone et al. 1980; Hewitt et al. 1979, 1983, 1986a, 1986b, 1990; Iijima et al. 1983; Mehendale et al. 1989; Purushotham et al. 1988). For example, pretreatment of rats with 5 mg/kg chlordecone resulted in a 67-fold increase in carbon tetrachloride-induced lethality due to liver failure (Klingensmith and Mehendale 1982b). The increase in hepatotoxicity is characterized by increased serum

enzymes, extensive necrosis, increased destruction of CYP450 isozymes, and decreased biliary function. The potentiation of hepatotoxicity does not appear to be due solely to increased metabolism of the haloalkanes to toxic intermediates (CCl_3, free radical and phosgene) and, as such, is distinct from the potentiation of halomethane toxicity by phenobarbital (Agarwal and Mehendale 1984a, 1984d; Bell and Mehendale 1987; Klingensmith and Mehendale 1983b; Mehendale and Klingensmith 1988; Mehendale 1990) or mirex (Bell and Mehendale 1985; Cianflone et al. 1980; Hewitt et al. 1979, 1986a; Mehendale and Klingensmith 1988; Mehendale et al. 1989; Purushotham et al. 1988).

Several studies (Dalu and Mehendale 1996; Dalu et al. 1995, 1998; Murali et al. 2004) provide additional insight to findings of age-related differences in the lethality and hepatotoxicity induced by exposure of rats to nontoxic levels of chlordecone and subsequent exposure to otherwise nonlethal levels of carbon tetrachloride (Cai and Mehendale 1993). Results of Blain et al. (1999) indicate both sex- and age-dependent influences on chlordecone-carbon tetrachloride induced hepatotoxicity in rats.

The primary mechanism for potentiation of hepatotoxicity may be the suppression of the early tissue regenerative response normally seen in livers of rats and mice exposed to low doses of halomethanes (Mehendale 1992, 1994). The dramatic increase in mitotic activity that normally occurs soon after halomethane exposure does not occur in chlordecone-pretreated animals (Faroon and Mehendale 1990; Lockard et al. 1983b). Gerbils, which do not exhibit early hepatocellular regeneration following halomethane exposure (and thus are more susceptible to the toxic and lethal effects of halomethanes), do not exhibit potentiation following chlordecone pretreatment (Cai and Mehendale 1990, 1991a). Experiments performed with partially hepatectomized animals provide further evidence for the role of suppressed regeneration following carbon tetrachloride exposure (Cai and Mehendale 1991b). Partial hepatectomy, which stimulates tissue regeneration, afforded partial protection from the potentiating effects of chlordecone in rats (Bell et al. 1988; Rao et al. 1989; Young and Mehendale 1989). Similarly, Cai and Mehendale (1993) have shown that young rats with greater hepatocellular regenerative activity than adult rats also experience less hepatocellular damage following exposure to both chlordecone and carbon tetrachloride. Cellular changes that may facilitate the chlordecone-induced suppression of regeneration include marked depletion of hepatocellular glycogen (Bell and Mehendale 1987; Faroon et al. 1991; Lockard et al. 1983a, 1983b), depletion of ATP (Faroon et al. 1991; Kodavanti et al. 1990b), and disruptions in the regulation of intracellular calcium (Agarwal and Mehendale 1984a, 1984c, 1984d, 1986; Hegarty et al. 1986; Kodavanti et al. 1991). It has been demonstrated that suppression of cell division due to glycogen depletion results in decreased ATP availability and, consequently, suppressed cellular regeneration (Soni and Mehendale 1993, 1994).

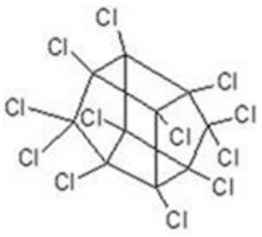
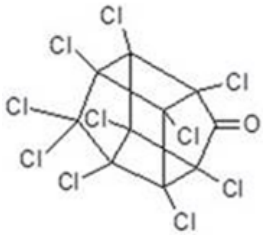
Both mirex and chlordecone are microsomal enzyme inducers, and as such, enhance the metabolism of compounds oxidized or reduced by the mixed function oxygenase system. For example, the metabolism of lindane was enhanced in rats previously exposed to chlordecone (Chadwick et al. 1979). For chemicals that undergo a loss of activity with metabolism, a decrease in effectiveness would be likely in mirex- or chlordecone-exposed persons. For example, pretreatment of rats with chlordecone reduced the cholinesterase inhibition produced by a subsequent dose of methyl parathion (Tvede et al. 1989). In this study, methyl parathion was apparently metabolized to its active metabolite, methyl paraoxon, and the methyl paraoxon was further metabolized to an inactive metabolite. For chemicals that undergo a transformation to an active or toxic metabolite, enhanced activity/toxicity would be likely in mirex- or chlordecone-exposed persons. An example of this type of interaction was shown in the enhancement of acetaminophen toxicity by 30 mg/kg of mirex or chlordecone (Fouse and Hodgson 1987). Acetaminophen causes hepatic necrosis as the result of the binding of the reactive intermediate, postulated to be N-acetylquinoneimine, formed by the microsomal CYP450 dependent monooxygenase system. Mirex and chlordecone increased the activity of this system, and as a result, the toxicity of the acetaminophen was increased.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of mirex and chlordecone is located in Table 4-1.

Table 4-1. Chemical Identity of Mirex and Chlordecone[a]

	Information	
Characteristic	Mirex	Chlordecone
Chemical name	1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodeca-chlorooctahydro-1,3,4-metheno-1H-cyclobuta[cd]- pentalene	1,1a,3,3a,4,5,5,5a,5b,6-Deca-chlorooctahydro-1,3,4- metheno-2H-cyclobuta[cd] pentalen-2-one
Synonym(s) and registered trade name(s)	1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene dimer[b]; dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta[cd] pentalene[b] CG-1283; Dechlorane; ENT 25719[d]	Decachloroketone[c]; decachloro-octahydro-1,3,4-metheno-2H-cyclobuta[cd]pentalen-2-one[c] GC 1189; Kepone; Merex[c]
Chemical formula	$C_{10}Cl_{12}$	$C_{10}Cl_{10}O$
Chemical structure		
CAS Registry Number	2385-85-5	143-50-0

[a]All information obtained from Budavari et al. 1989, except where noted.
[b]IARC 1979.
[c]IARC 1979.
[d]NLM 2020.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of mirex and chlordecone is located in Table 4-2.

Table 4-2. Physical and Chemical Properties of Mirex and Chlordecone

	Information	
Property	Mirex	Chlordecone
Molecular weight	545.59	490.68
Color	Snow-white	Tan-white[b]
Physical state	Crystalline solid	Crystalline solid
Melting point	485°C (decomposes)	350°C (decomposes)[b]
Boiling point	No data	No data
Density at 25°C	No data	No data
Odor	Odorless	Odorless[c]
Odor threshold	5.0667 mg/m^3 [d]	
Solubility:		
Water	Practically insoluble 0.60 mg/L[e] insoluble[f] 0.2 mg/L at 24°C (practical grade)[f]	Slightly soluble 3.0 mg/L[e] practically insoluble[b]
Organic solvents	Dioxane (15.3%); xylene (14.3%); benzene (12.2%); CCl_4 (7.2%); methyl ethyl ketone (5.6%)	Soluble in hydrocarbon solvents, alcohols, ketones
Partition coefficients:		
Log K_{ow}	5.28[g]	4.50[h]
Log K_{oc}	3.763[f]	3.38–3.415[h]
Vapor pressure at 25°C	3x10^{-7} mm Hg[f]	<3x10^{-7} mm Hg[b]
Henry's law constant:		
at 20°C	839.37 Pa m^3/mole[i]	2.50x10^{-8} atm
At 22°C	5.16x10^{-4} atm m^3/mole[j]	m^3/mole[h]
Autoignition temperature	Nonflammable[b]	Nonflammable
Flashpoint	No data	No data
Flammability limits	Nonflammable[d] Supports combustion	Nonflammable
Conversion factors	1 ppm=0.041 mg/m^3	1 ppm=0.046 mg/m^3
Explosive limits	No data	No data

[a]All information obtained from Budavari et al. 1989, except where noted.
[b]IARC 1979.
[c]Verschueren 1983.
[d]NLM 2020.
[e]Kenaga 1980.
[f]IARC 1979.
[g]Niimi 1991.
[h]Howard 1991.
[i]Domine et al. 1992.
[j]Yin and Hassett 1986.

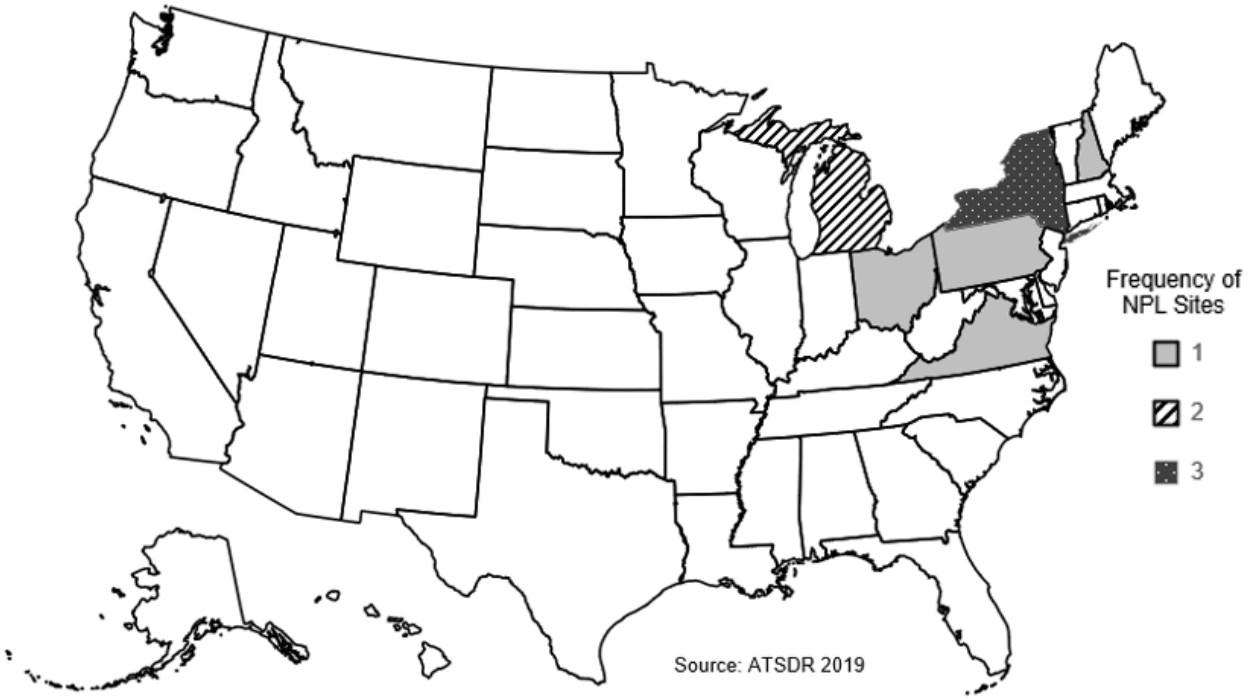
CCl_4 = carbon tetrachloride

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

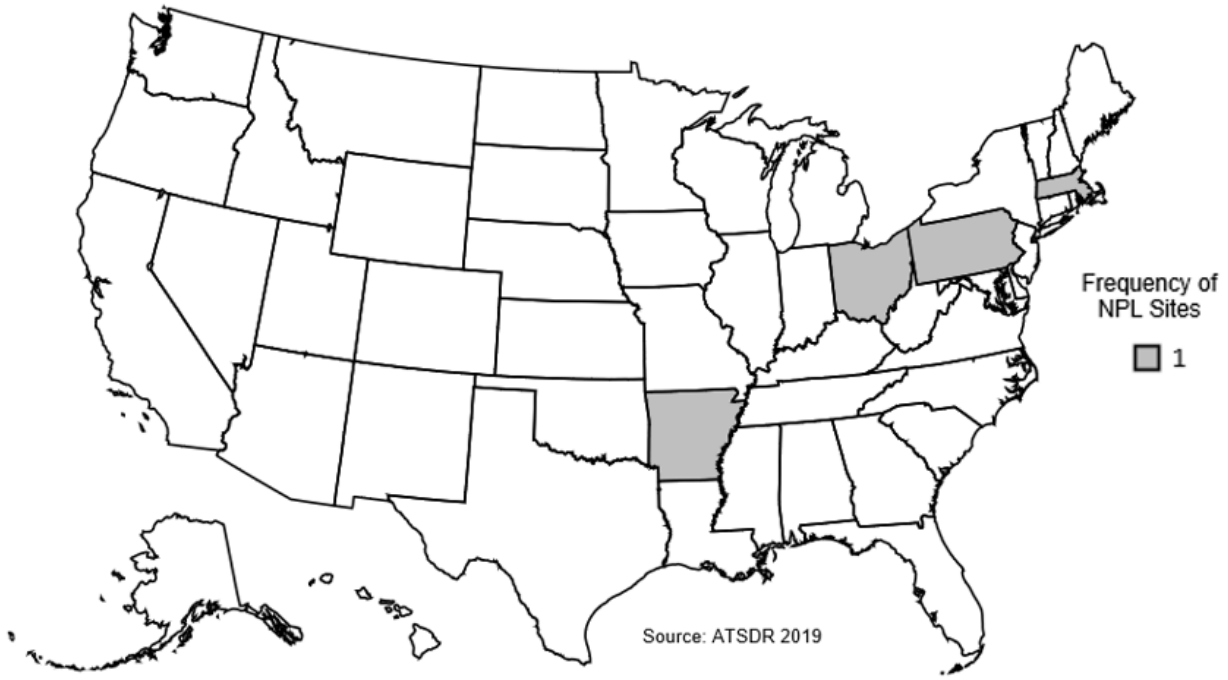
Mirex has been identified in at least 9 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which mirex has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

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



Chlordecone has been identified in at least 4 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which chlordecone has been evaluated is not known. The number of sites in each state is shown in Figure 5-2.

Figure 5-2. Number of NPL Sites with Chlordecone Contamination



- The most likely source of potential exposure of the general population to mirex or chlordecone is from consumption of contaminated food sources, particularly in the eastern portion of the United States where mirex and chlordecone were most frequently used.
- People who live or work near hazardous waste sites where mirex and/or chlordecone may be stored could most likely be exposed from contaminated sediment or soil.
- Both mirex and chlordecone bind strongly to organic matter in water, sediment, and soil where they may persist for long periods of time.
- Both mirex and chlordecone are lipophilic and bioaccumulate and biomagnify in aquatic and terrestrial food chains.

As a result of human health concerns, production of mirex ceased in 1976, at which time industrial releases of this chemical to surface waters were also curtailed. However, releases from waste disposal sites continue to add mirex to the environment. Virtually all industrial releases of mirex were to surface waters, principally Lake Ontario via contamination of the Niagara and Oswego Rivers. About 75% of the mirex produced was used as a fire retardant additive, while 25% was used as a pesticide. As a pesticide, mirex was widely dispersed throughout the southern United States where it was used in the fire ant eradication program for over 10 years.

Adsorption and volatilization are the more important environmental fate processes for mirex, which strongly binds to organic matter in water, sediment, and soil. When bound to organic-rich soil, mirex is highly immobile; however, when adsorbed to particulate matter in water, it can be transported great

distances before partitioning out to sediment. Atmospheric transport of mirex has been reported based on its detection in remote areas without anthropogenic sources, although this is not a major source of mirex in the environment. Given the lipophilic nature of this compound (high octanol-water partition coefficient), mirex is both bioaccumulated and biomagnified in aquatic and terrestrial food chains.

Mirex is a very persistent compound in the environment and is highly resistant to both chemical and biological degradation. The primary process for the degradation of mirex is photolysis in water or on soil surfaces; photomirex is the major transformation product of photolysis. In soil or sediments, anaerobic biodegradation is also a major removal mechanism whereby mirex is slowly dechlorinated to the 10-monohydro derivative. Aerobic biodegradation in soil is a very slow and minor degradation process. Twelve years after the application of mirex to soil, 50% of the mirex and mirex-related compounds remained on the soil. Between 65 and 73% of the residues recovered were mirex and 3–6% were chlordecone, a transformation product (Carlson et al. 1976).

Mirex has been detected at low concentrations in ambient air (mean 0.35 pg/m^3) and rainfall samples (<0.5 ng/L) from polluted areas of the Great Lakes region. In addition, the compound has been detected in drinking water samples from the Great Lakes area of Ontario, Canada. Mirex has also been detected in groundwater samples from agricultural areas of New Jersey and South Carolina.

Mirex has been monitored in surface waters, particularly during the period that it was still being produced. Concentrations of mirex in Lake Ontario, the Niagara River, and the St. Lawrence River were in the ng/L (ppt) range. The highest concentrations of mirex, 1,700 µg/kg (ppb), were found in sediments in Lake Ontario where they accumulated after the deposition of particulate matter to which the mirex was bound. A dynamic mass balance for mirex in Lake Ontario and the Gulf of St. Lawrence estimated that approximately 2,700 kg (6,000 pounds) of mirex have entered Lake Ontario over the past 40 years, of which 550 kg (1,200 pounds) have been removed (exclusive of sedimentation and burial) mainly by transport on sediment particles via outflowing water and migrating biota contaminated with mirex.

The high bioconcentration factor (BCF) values (up to 15,000 for rainbow trout) observed for mirex indicate that this compound will be found in high concentrations in aquatic organisms that inhabit areas where the water and sediments are contaminated with mirex. Fish taken from Lake Ontario, the St. Lawrence River, and the southeastern United States (areas where mirex was manufactured or used as a pesticide) had the highest mirex levels. There were fish consumption advisories in effect in three states (New York, Pennsylvania, and Ohio) that were triggered by mirex contamination in fish. Waterfowl and

game animals have also been found to accumulate mirex in their tissues. Data on mirex residues in foods do not show a consistent trend with regard to contaminant levels or frequency of detection. Mirex was irregularly detected in Food and Drug Administration (FDA) Pesticide Residue Monitoring Studies since 1978, but has not been detected in the most recent FDA survey. Little information on the specific foods in which residues were found or levels detected was located.

General population exposure to mirex has been determined as a result of several monitoring studies (CDC 2019; EPA 1986b; Kutz et al. 1979; Stehr-Green 1989). Levels of mirex in most tissues are very low (at or near the detection limit). Examination of the 1982 National Adipose Tissue Survey failed to detect mirex in the adipose tissues of children <14 years old, although mirex residues were detected in adults. People who live in areas where mirex was manufactured or used have higher levels in their tissues. Women who live in these areas were found to have detectable levels of mirex in their milk that could be passed on to their infants. Since mirex is no longer manufactured, occupational exposure currently is limited to workers at waste disposal sites or those involved in remediation activities involving the clean-up and removal of contaminated soils or sediments.

Production of chlordecone ceased in 1975 as a result of human health concerns; at that time industrial releases of this chemical to surface waters via a municipal sewage system were curtailed. However, releases from waste disposal sites may continue to add chlordecone to the environment. Major releases of chlordecone occurred to the air, surface waters, and soil surrounding a major manufacturing site in Hopewell, Virginia. Releases from this plant ultimately contaminated the water, sediment, and biota of the James River, a tributary to the Chesapeake Bay.

Atmospheric transport of chlordecone particles was reported during production years based on results from high volume air samplers installed at the site and up to 15.6 miles away. Chlordecone is not expected to be subject to direct photodegradation in the atmosphere. Chlordecone is very persistent in the environment. Chlordecone, like mirex, will strongly bind to organic matter in water, sediment, and soil. When bound to organic-rich soil, chlordecone is highly immobile; however, when adsorbed to particulate matter in surface water, chlordecone can be transported great distances before partitioning out to sediment. Sediment in extensive areas of the James River served as a sink or reservoir for this compound. The primary process for the degradation of chlordecone in soil or sediments is anaerobic biodegradation. Based on the lipophilic nature of this compound (high octanol-water partition coefficient), chlordecone has a tendency to both bioaccumulate and biomagnify in aquatic food chains. BCF values >60,000 have been measured in Atlantic silversides, an estuarine fish species.

No information was found on atmospheric concentrations of chlordecone other than historic monitoring data from samples collected in the vicinity of the manufacturing site. Chlordecone has been monitored in surface waters, particularly during the period shortly before and after production was terminated. In 1977, chlordecone was detected in surface water samples from the James River at low concentrations (<10 ng/L [ppt]), although it was not detected in more recent monitoring studies. The highest concentrations of this compound are found in sediments, principally in the James River where it had accumulated after the deposition of particulate matter to which the chlordecone was bound. In 1978, chlordecone was detected in sediments from the James River below its production site at concentrations in the mg/kg (ppm) range.

The high BCF values observed for chlordecone (>60,000) indicate that the compound will be found in high concentrations in aquatic organisms that dwell in waters or sediments contaminated with chlordecone. Chlordecone has been detected in fish and shellfish from the James River, which empties into the Chesapeake Bay, at levels in the μg/g (ppm) range. There was a fish consumption advisory in effect for the lower 113 miles of the James River. Chlordecone residues were detected in foods analyzed in 1978–1982 and 1982–1986 as part of the FDA Pesticide Residue Monitoring Studies. Chlordecone was detected in one of 27,065 food samples analyzed by 10 state laboratories, but was not detected in the FDA Pesticide Residue Monitoring Studies in 1986–1991 or in the most recent (2017) study. No information on the specific foods in which residues were found or levels detected was located.

General population exposure to chlordecone has not been determined because this compound has not been monitored in any national program (CDC 2019; EPA 1986b; Kutz et al. 1979; Phillips and Birchard 1991; Stehr-Green 1989). Levels of chlordecone were detected in 9 of 298 samples of human milk collected from women in the southern United States. Residues were detected only in residents of areas that had been extensively treated with the pesticide mirex for fire ant control. People who lived in the area where chlordecone was manufactured had higher levels in their blood during production years. Women who lived in these areas could pass chlordecone in their milk to their nursing infants. Workers who manufactured chlordecone developed an occupationally-related illness. However, chlordecone is no longer manufactured, so occupational exposure is limited to workers at waste disposal sites or those involved in remediation activities involving the clean-up and removal of contaminated soils or sediments.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

No information is available in the TRI database on facilities that manufacture or process mirex and chlordecone because these chemicals are not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

Mirex is not known to occur in the environment as a natural product (IARC 1979; Waters et al. 1977a). Although it was originally synthesized in 1946, mirex was not commercially introduced in the United States until 1959, when it was produced by the Allied Chemical Company under the name GC-1283 for use in pesticide formulations and as an industrial fire retardant under the trade name Dechlorane® (EPA 1978a; IARC 1979; Waters et al. 1977a). Mirex was produced as a result of the dimerization of hexachlorocyclopentadiene in the presence of an aluminum chloride catalyst (IARC 1979; Sittig 1980).

The technical grade of mirex consisted of a white crystalline solid in two particle size ranges, 5–10 and 40–70 microns (IARC 1979). Technical-grade preparations of mirex contained 95.18% mirex, with 2.58 mg/kg chlordecone as a contaminant (EPA 1978b; WHO 1984). Several formulations of mirex have been prepared in the past for various pesticide uses. Some of the more commonly used formulations of mirex used as baits were made from corn cob grit impregnated with vegetable oil and various concentrations of mirex. Insect bait formulations for aerial or ground applications contained 0.3–0.5% mirex, and fire ant formulations contained 0.075–0.3% mirex (IARC 1979).

Mirex is no longer produced commercially in the United States. Hooker Chemical Company (Niagara Falls, New York) manufactured and processed mirex from 1957 to 1976 (Lewis and Makarewicz 1988). An estimated 3.3 million pounds (1.5x106 kg) of mirex were produced by Hooker Chemical Company between 1959 and 1975, with peak production occurring between 1963 and 1968 (EPA 1978b). About 25% of the mirex produced was used as a pesticide and the remaining 75% was used as an industrial fire retardant additive (EPA 1978b). Hooker Chemical Company reported purchasing 1.5 million pounds of mirex (680,400 kg) from Nease Chemical Company during this period. The Nease Chemical Company of State College, Pennsylvania, manufactured mirex from 1966 to 1974 (EPA 1978b). Allied Chemical Company also manufactured technical-grade mirex and mirex bait in Aberdeen, Mississippi (EPA 1978b), but Allied Chemical formally transferred all registrations on mirex, along with the right to manufacture

and sell mirex bait, to the Mississippi Department of Agriculture on May 7, 1976 (IARC 1979; Waters et al. 1977a, 1977b).

Chlordecone is not known to occur in the environment as a natural product (IARC 1979). Chlordecone has been produced by reacting hexachlorocyclopentadiene and sulfur trioxide under heat and pressure in the presence of antimony pentachloride as a catalyst. The reaction product is hydrolyzed with aqueous alkali, neutralized with acid; chlordecone is recovered via centrifugation or filtration and hot air drying (Epstein 1978). Chlordecone was produced in 1951, patented in 1952, and introduced commercially in the United States by Allied Chemical in 1958 under the trade names Kepone® and GC-1189 (Epstein 1978; Huff and Gerstner 1978). The technical grade of chlordecone, which typically contained 94.5% chlordecone, was available in the United States until 1976 (IARC 1979). Chlordecone was also found to be present in technical-grade mirex at concentrations of up to 2.58 mg/kg and in mirex bait formulations at concentrations of up to 0.25 mg/kg (EPA 1978b; IARC 1979). Approximately 55 different commercial formulations of chlordecone have been prepared since its introduction in 1958 (Epstein 1978). The major form of chlordecone, which was used as a pesticide on food products, was a wettable powder (50% chlordecone) (Epstein 1978). Formulations of chlordecone commonly used for nonfood products were in the form of granules and dusts containing 5 or 10% active ingredient (Epstein 1978). Other formulations of chlordecone contained the following percentages of active ingredient: 0.125% (used in the United States in ant and roach traps), 5% (exported for banana and potato dusting), 25% (used in the United States in ant and roach bait), 50% (used to control mole crickets in Florida), and 90% (exported to Europe for conversion to kelevan for use on Colorado potato beetles in eastern European countries) (Epstein 1978).

Chlordecone is no longer produced commercially in the United States. Between 1951 and 1975, approximately 3.6 million pounds (1.6 million kg) of chlordecone were produced in the United States (Epstein 1978). During this period, Allied Chemical Company produced approximately 1.8 million pounds (816,500 kg) of chlordecone at plants in Claymont, Delaware; Marcus Hook, Pennsylvania; and Hopewell, Virginia. In 1974, because of increasing demand for chlordecone and a need to use their facility in Hopewell, Virginia, for other purposes, Allied Chemical transferred its chlordecone manufacturing to Life Sciences Products Company (EPA 1978b). Life Sciences Products produced an estimated 1.7 million pounds (771,000 kg) of chlordecone from November 1974 through July 1975 in Hopewell, Virginia (Epstein 1978). Hooker Chemical Company also produced approximately 49,680 (22,500 kg) pounds of chlordecone in the period from 1965 to 1967 at a plant at Niagara Falls,

New York. Nease Chemical Company produced approximately 65,780 pounds (30,000 kg) of chlordecone between 1959 and 1966 at a plant in State College, Pennsylvania (Epstein 1978).

5.2.2 Import/Export

No current data are available regarding import volumes of mirex. Mirex has reportedly been imported to the United States from Brazil, but data on the amounts of mirex imported are not available (DHHS 1991; IARC 1979).

No current data are available regarding import volumes of chlordecone.

Technical mirex and technical chlordecone are not exported since these substances are no longer produced in the United States.

Over 90% of the mirex produced from the 1950s until 1975 was exported to Latin America, Europe, and Africa (Sterret and Boss 1977). No other historic data regarding the export of mirex were located.

Diluted technical-grade chlordecone (80% active ingredient) was exported to Europe, particularly Germany, in great quantities from 1951 to 1975 by the Allied Chemical Company (Epstein 1978) where the diluted technical product was converted to an adduct, kelevan. Approximately 90–99% of the total volume of chlordecone produced during this time was exported to Europe, Asia, Latin America, and Africa (DHHS 1991; EPA 1978a).

5.2.3 Use

Because it is nonflammable, mirex was marketed primarily as a flame retardant additive in the United States from 1959 to 1972 under the trade name Dechlorane® for use in various coatings, plastics, rubber, paint, paper, and electrical goods (Budavari et al. 1989; EPA 1978b; IARC 1979; Kutz et al. 1985; Verschueren 1983). Mirex was most commonly used in the 1960s as an insecticide to control the imported fire ants (*Solenopsis invicta* and *S. richteri*) in Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Texas (Carlson et al. 1976; EPA 1978b; IARC 1979; Waters et al. 1977a, 1977b). From 1962 to 1976, approximately 132 million acres (53.4 million hectares) in nine states were treated with approximately 485,000 pounds (226,000 kg) of mirex at a rate of 4.2 g/hectare (later reduced to 1.16 g/hectare) (IARC 1979). Mirex was chosen for fire ant eradication

programs because of its effectiveness and selectiveness for ants (Carlson et al. 1976; Waters et al. 1977a, 1977b). It was originally applied aerially at concentrations of 0.3–0.5%.

However, aerial application of mirex was replaced by mound application because of suspected toxicity to estuarine species and because the goal of the fire ant program was changed from eradication to selective control. Mirex was also used successfully in controlling populations of leaf cutter ants in South America, harvester termites in South Africa, Western harvester ants in the United States, mealybugs in pineapples in Hawaii, and yellowjacket wasps in the United States (EPA 1978b; IARC 1979; Waters et al. 1977a). All registered products containing mirex were effectively canceled on December 1, 1977 (Sittig 1980). However, selected ground application was allowed until June 30 1978, at which time the product was banned in the United States with the exception of continued use in Hawaii on pineapples until stocks on hand were exhausted (EPA 1976; Holden 1976; Sittig 1980; Waters et al. 1977b).

Until August 1, 1976, chlordecone was registered in the United States for use on banana root borer (in the U.S. territory of Puerto Rico); this was its only registered food use. Additional registered formulations included nonfood use on nonfruit-bearing citrus trees to control rust mites; on tobacco to control tobacco and potato wireworms; and for control of the grass mole cricket, and various slugs, snails, and fire ants in buildings, lawns, and on ornamental shrubs (EPA 1978b; Epstein 1978; IARC 1979). The highest reported concentration of chlordecone in a commercial product was 50%, which was used to control the grass mole cricket in Florida (Epstein 1978). Chlordecone has also been used in household products such as ant and roach traps at concentrations of approximately 0.125% (IARC 1979). The concentration used in ant and roach bait was approximately 25% (Epstein 1978). All registered products containing chlordecone were effectively canceled as of May 1, 1978 (Sittig 1980).

5.2.4 Disposal

Since mirex and chlordecone are not flammable and are very stable in the environment, many disposal methods investigated for these chemicals have proven unsuccessful (Sullivan and Krieger 1992; Tabaei et al. 1991; Waters et al. 1977a).

Mirex is unaffected by hydrochloric, sulfuric, and nitric acids, and would be expected to be extremely resistant to oxidation except at the high temperatures of an efficient incinerator (EPA 1978b; Sittig 1980; WHO 1984). A recommended method of disposal for mirex is incineration or long-term storage (Holloman et al. 1975; IARC 1979). Polyethylene glycol or tetraethylene glycol and potassium

hydroxide when used in combination with sodium borohydride or alkoxyborohydrides, produce a powerful reducing media which quantitatively destroys mirex at 70°C. The reduction rate is further increased by using tetrahydrofuran and catalytic quantities of Bu_3SnH/AiBN, which produce 100% destruction of mirex to hexahydromirex within 1 hour at 58°C (Tabaei et al. 1991).

Chlordecone is considered an EPA hazardous waste and must be disposed of according to EPA regulations (EPA 1980). Degradation of chlordecone has been evaluated in the presence of molten sodium (Greer and Griwatz 1980). Addition of chlordecone to molten sodium at a temperature of 250°C resulted in significant degradation of chlordecone with small quantities of <12 ppm observed in the reaction products. Microwave plasma has also been investigated as a potential disposal mechanism for chlordecone (DeZearn and Oberacker 1980). An estimated 99% decomposition was observed in a 5-kw microwave plasma system for 80% chlordecone solution, slurry, or solid. Another recommended disposal method for chlordecone is destruction in an incinerator at approximately 850°C followed by off-gas scrubbing to absorb hydrogen chloride (IRPTC 1985).

Activated carbon adsorption has been investigated for the treatment of waste waters contaminated with chlordecone (EPA 1982). The discharge of chlordecone in sewage disposal systems is not recommended, as it may destroy the bacteriological system (IRPTC 1985). Chlordecone as a waste product in water may be dehalogenated by a process involving ultraviolet light and hydrogen as a reductant. The reaction is pH dependent, and degradation is best when the system contains 5% sodium hydroxide. Using this method, 95–99% of chlordecone is removed within 90 minutes. The degradation products are the mono-, di-, tri-, tetra-, and pentahydro derivatives of chlordecone. This degradation method is applicable to chlordecone in hazardous wastes at concentrations in the ppm (mg/L) range and lower (Reimers et al. 1989; Sittig 1980).

5.3 RELEASES TO THE ENVIRONMENT

Mirex has been detected in air, surface water, soil and sediment, aquatic organisms, and foodstuffs. Historically, mirex was released to the environment primarily during its production or formulation for use as a fire retardant and as a pesticide. There are no known natural sources of mirex and production of the compound was terminated in 1976. Hazardous waste disposal sites and contaminated sediment sinks in Lake Ontario were the major sources for mirex releases to the environment (Brower and Ramkrishnadas 1982; Comba et al. 1993).

Chlordecone has been detected in the air, surface water, soil and sediment, aquatic organisms and foodstuffs. Historically chlordecone was released to the environment primarily during its production at a manufacturing facility in Hopewell, Virginia. There are no known natural sources of chlordecone and production of the compound was terminated in 1975. Hazardous waste disposal sites and contaminated sediment sinks in the James River were the major sources for chlordecone release to the environment (EPA 1978a; Huggett and Bender 1980; Lunsford et al. 1987).

5.3.1 Air

There is no information on releases of mirex and chlordecone to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Little information on historic releases of mirex to the air was located. Some atmospheric contamination may have occurred due to releases from manufacturing facilities, which were primarily located near Niagara Falls, New York, and State College, Pennsylvania; however, no quantitative sampling data were located (EPA 1978a). Atmospheric releases of mirex could result from airborne dust from the production and processing of mirex or Dechlorane®, combustion of products containing Dechlorane®, or volatilization of mirex applied as a pesticide (WHO 1984). Because mirex was principally dispersed as a pesticide in a bait form associated with corn cob grit particles that settle rapidly, the amount of mirex remaining airborne should have been insignificant. Furthermore, volatilization of mirex after application should also have been insignificant because of the high melting point and low vapor pressure of the bait (EPA 1978a).

Although release of mirex to the atmosphere was probably small in comparison to amounts released to surface water, soil, and sediment, infrequent detections of minute concentrations of mirex in air (mean concentration 0.35 pg/m^3) and rainfall (<0.5 ng/L [ppt]) samples have been reported many years after production ceased (Hoff et al. 1992; Strachan 1990; Wania and MacKay 1993). Arimoto (1989) estimated that 5% of the total input of mirex to Lake Ontario was attributed to atmospheric deposition.

Large amounts of chlordecone were released into the air from a chemical manufacturing plant in Hopewell, Virginia, from April 1974 through June 1975. Throughout the manufacturing period, extensive areas of the environment were contaminated with chlordecone because of improper manufacturing and disposal processes (Lewis and Lee 1976). Concentrations of chlordecone in the air surrounding the plant ranged from 0.18 ng/m^3 to a maximum of 54.8 $\mu g/m^3$ which was found in a sample

collected 200 m from the plant (Epstein 1978). High-volume air samplers in operation 200 m from the plant were found to contain this chlordecone level, which constituted over 50% of the total particulate loading. Chlordecone concentrations at more distant sites (up to 15.6 miles away) ranged from 1.4 to 20.7 ng/m^3 (Epstein 1978). The long-range transport properties of chlordecone indicate that at least a small portion of the chlordecone emissions were of a fine particle size having a relatively long residence time in the atmosphere (Lewis and Lee 1976).

5.3.2 Water

There is no information on releases of mirex and chlordecone to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Mirex has been released to surface waters via waste waters discharged from manufacturing and formulation plants, in activities associated with the disposition of residual pesticides, and as a result of its direct use as a pesticide, particularly in the fire ant eradication program conducted in several southern states.

Releases of mirex in industrial wastes were greatest during the manufacture of this chemical between 1957 and 1976 by the Hooker Chemical and Plastics Corporation in Niagara Falls, New York. Releases to the Niagara River peaked between 1960 and 1962 at 200 kg/year (440 pounds/year), but subsequently declined to 13.3 kg/year (29 pounds/year) in 1979, and 8 kg/year (18 pounds/year) in 1981 (Durham and Oliver 1983; Lewis and Makarewicz 1988). Releases to the Oswego River occurred as a result of discharges from Armstrong World Industries Inc. in Volney, New York (Lum et al. 1987; Mudambi et al. 1992). Since production of mirex was discontinued in 1976 (Kaiser 1978), releases after 1976 were the result of leaching from dump sites adjacent to the Niagara and Oswego Rivers, both of which feed into Lake Ontario (Kaminsky et al. 1983) and releases of mirex from sediment sinks in Lake Ontario. Total loading of mirex to Lake Ontario has been estimated to be 688 kg (1,517 pounds), with half of this incorporated into the sediments (Van Hove Holdrinet et al. 1978; Lewis and Makarewicz 1988). A study by Comba et al. (1993), however, estimated total loading of mirex to Lake Ontario to be 2,700 kg (6,000 pounds) over 40 years, of which 550 kg (1,200 pounds) has been removed mainly by transport via outflowing water into the St. Lawrence River.

In addition to direct releases of mirex to surface waters that occurred at the manufacturing plant in Niagara Falls, New York, an estimated 226,000 kg (498,000 pounds) of mirex were used as a pesticide to

treat 132 million acres (53.4 million hectares) in nine southern states from 1962 to 1976 as part of the fire ant eradication program conducted by the Department of Agriculture (IARC 1979). Mirex insecticide baits were dispersed by aerial applications, and mirex could be released into surface water directly or could reach surface waters via runoff. Because mirex binds tightly to organic-rich soils, leaching is not generally expected to occur. However, mirex residues have been detected (concentration unspecified) in groundwater well samples collected in proximity to agricultural land in New Jersey (Greenburg et al. 1982). In a South Carolina study, mirex was also detected in potable water supplies in two rural counties. Mirex was detected in 12.5% of water samples at a mean concentration of 2 ng/L (ppt) (range from not detectable to 30 ng/L) in Chesterfield County and was detected in 72.7% of the water samples at a mean concentration of 83 ng/L (range of not detectable to 437 ng/L) in rural Hampton County. The authors attributed the higher mirex residues in the potable water of Hampton County to the extensive use of mirex in this county for fire ant control (Sandhu et al. 1978).

Chlordecone has been primarily released to surface waters in waste waters from a manufacturing plant in Hopewell, Virginia, and may be released in activities associated with the disposal of residual pesticide stocks, and as a result of the direct use of mirex. Chlordecone has been released directly as a contaminant of mirex and indirectly from the degradation of mirex.

Production of chlordecone at a manufacturing plant in Hopewell, Virginia, from 1966 to 1975, resulted in the release of the compound, primarily through industrial discharge of waste water into the Hopewell municipal sewage system, which discharged into Baileys Creek, and ultimately flowed into the James River. Leaching and erosion of contaminated soils from the plant site and direct discharge of solid wastes also contributed to the chlordecone content in the James River estuary (Colwell et al. 1981; Nichols 1990). Effluent from the manufacturing plant contained 0.1–1.0 mg/L (ppm) chlordecone, and water from the plant's holding ponds contained 2 to 3 mg/L (ppm) chlordecone (Epstein 1978). It has been estimated that 7,500–45,000 kg (16,500–100,000 pounds) of the 1,500,000 kg (3.3 million pounds) of chlordecone produced at the plant entered the estuary in industrial effluent or runoff (Colwell et al. 1981; Nichols 1990).

Another source of chlordecone release to water may result from the application of mirex containing chlordecone as a contaminant and by the degradation of mirex, which was used extensively in several southern states. Carlson et al. (1976) reported that dechlorinated products including chlordecone were formed when mirex bait, or mirex deposited on soil after leaching from the bait, was exposed to sunlight,

other forms of weathering, and microbial degradation over a period of 12 years. Chlordecone residues in the soil could find their way to surface waters via runoff.

5.3.3 Soil

There is no information on releases of mirex and chlordecone to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Mirex is not currently registered for use in the United States, so release of mirex to soil from pesticide applications is no longer of concern. However, use of mirex as a pesticide for fire ant control required the spraying of this chemical on soils of an estimated 132 million acres in the southern United States (IARC 1979). An estimated 226,000 kg (498,000 pounds) of mirex were used in nine states from 1962 to 1976 as part of the fire ant eradication program conducted by the Department of Agriculture (IARC 1979).

Releases of mirex to sediment as a result of industrial waste water discharges were noted in Lake Ontario near the mouth of the Niagara River. Lake Ontario sediment concentrations were correlated with the years of peak production and use, and were found to decrease in the upper sediments as use was restricted in the late 1970s (Durham and Oliver 1983). Total loading of mirex to Lake Ontario has been estimated to be 688 kg (1,517 pounds), with half of this amount incorporated into the sediments (Van Hove Holdrinet et al. 1978; Lewis and Makarewicz 1988). However, a study by Comba et al. (1993) involving development of a mass balance model for mirex in Lake Ontario and the Gulf of St. Lawrence estimated that over 40 years, approximately 2,700 kg (6,000 pounds) of mirex entered Lake Ontario, of which 550 kg (1,200 pounds) has been removed via transport to the St. Lawrence estuary. Removal of mirex from Lake Ontario has resulted primarily by outflowing water containing suspended sediment.

Chlordecone is not currently registered for use in the United States. However, use of chlordecone as a pesticide to control banana borers on bananas, tobacco wireworms on tobacco, mole crickets on turf, and various slugs, snails, and ants in buildings, lawns, and ornamental shrubs, required the application of this chemical to soils (Epstein 1978; IARC 1979). No estimate of the amount of chlordecone released from these uses was found. Chlordecone releases to soils may also occur as a result of the application of mirex containing chlordecone as a contaminant and by the degradation of mirex which was used extensively in a regional fire ant eradication program. As stated in Section 5.2.2, Carlson et al. (1976) reported that dechlorinated products, including chlordecone, were formed when mirex bait, or mirex deposited on soil after leaching from the bait, was exposed to sunlight, other forms of weathering, and microbial

degradation over a period of 12 years. No estimates of the amount of chlordecone released from the application and degradation of mirex are available.

Chlordecone releases to soil occurred at a production facility in Hopewell, Virginia. Soil samples adjacent to the site contained 1–2% chlordecone (l0,000–20,000 mg/kg [ppm]), and surface soils up to 3,000 feet from the site contained concentrations of 2–6 mg/kg (ppm) (Epstein 1978).

The major release of chlordecone to sediments, however, occurred indirectly as a result of waste water discharges, runoff of contaminated soil, and direct disposal of solid wastes at a production facility in Hopewell, Virginia. An estimated l0,000–30,000 kg (22,000–66,100 pounds) of chlordecone are associated with bottom sediment in the James River estuary (Huggett and Bender 1980; Nichols 1990). This sediment serves as a reservoir for future release of chlordecone via resuspension of sediments resulting from storms or dredging activities (Lunsford et al. 1987).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Mirex. Because mirex is a very hydrophobic compound with a low vapor pressure, atmospheric transport is unlikely (Hoff et al. 1992). These authors reported detecting mirex in only 5 of 143 samples at a maximum and mean concentration of 22 pg/m^3 and 0.35 pg/m^3, respectively. Based on a vapor pressure of <3x10^{-7} mm Hg at 25°C, mirex is expected to exist mainly in the particulate phase with a small proportion existing in the vapor phase in the ambient atmosphere (IARC 1979). A mass balance approach to the movement of mirex within Lake Ontario indicates that 5% of the total input of mirex to the lake can be attributed to atmospheric deposition compared with 72% of benzo(a)pyrene (Arimoto 1989).

Based on a calculated soil sorption coefficient (K_{oc}) of 1,200 (5,800 experimental) for mirex, this compound will tightly bind to organic matter in soil and, therefore, will be highly immobile. Thus, mirex is most likely to enter surface waters as a result of soil runoff (Kenaga 1980). In addition, most land applications of mirex to soils containing high organic content would result in very little leaching through soil to groundwater. However, leaching of mirex from some agricultural soils can occur as mirex has been detected in groundwater wells near agricultural areas (Greenburg et al. 1982; Sandhu et al. 1978).

When released to surface waters, mirex will bind primarily (80–90%) to the dissolved organic matter in the water with a small amount (10–20%) remaining in the dissolved fraction, because mirex is a highly

hydrophobic compound (Yin and Hassett 1989). Mean mirex concentrations in sediments, collected at four basins in Lake Ontario between 1982 and 1986, ranged from 30 to 38 µg/kg in three of the basins within the water circulation pattern of the lake. A fourth basin outside the pattern showed much lower concentrations (6.4 µg/kg), indicating that mirex was being transported with the lake water (Oliver et al. 1989). The residence time for mirex in Lake Ontario water was estimated to be 0.3 years. This indicated that mirex was either scavenged by particles or was chemically reactive and, therefore, was rapidly removed from the water column (Arimoto 1989).

Since the only sources of mirex in Lake Ontario are contaminated sediments, mirex in the water column is assumed to have come from resuspended sediments (Oliver et al. 1989). The source of the mirex in Lake Ontario surficial sediments was determined to be suspended sediments from the Niagara River, which were found to contain 8–15 and 55 µg/g (ppm) mirex in the upper and lower river sections, respectively. The surficial sediments contained 3 µg/g in the upper river (above the manufacturing and dump sites), 86 µg/g in the lower river (below the sites), and 10 µg/g in the western basin of Lake Ontario, indicating that mirex-containing sediments were being carried down the river with the current and deposited in Lake Ontario (Mudroch and Williams 1989). Kaminsky et al. (1983), reported a range of 8.2–62 ppb (µg/kg) in sediment from the eastern and central basins of Lake Ontario. Over 94% of the suspended particulate matter entering the lake is eventually deposited in lake sediments (Lum et al. 1987). Mirex concentrations in sediments of Lake Ontario show a strong correlation with peak production years (Durham and Oliver 1983; Eisenreich et al. 1989). Although there was evidence of sediment bioturbation by deposit-feeding worms and burrowing organisms, the sediment profiles for mirex and other chlorinated hydrocarbons were not destroyed (Eisenreich et al. 1989). Between the 1960s when mirex production began, and the early 1980s after production ceased, levels of mirex in bottom sediments increased in Lake Ontario, with the Niagara River being the major source of this compound (Allan and Ball 1990).

Mirex may be removed from Lake Ontario by several mechanisms, including the transport of contaminated suspended particulate material via water outflow into the St. Lawrence River, biomass removal through fishing and migration (e.g., migrating eels contaminated with mirex), volatilization, and photolysis (Comba et al. 1993; Lum et al. 1987). Transport of mirex accumulated in body tissues by eels has been estimated to be 2,270 grams annually or twice the amount of mirex removed by transport of suspended particulates (1,370 grams annually) (Lum et al. 1987).

The transport of mirex out of Lake Ontario, (a known reservoir), to its tributaries is also possible as a result of migrating fish, which move from the lake into the tributary streams to spawn. Fish, such as

Pacific salmon, become contaminated with mirex while in the lake. These fish then swim upstream in the tributaries to their spawning grounds, spawn, and die. A direct transfer of mirex may then occur when resident stream fish feed on the decomposing carcasses and/or eggs, both of which contain mirex residues. Indirect transfer can occur as a result of the release of mirex from the salmon into the water or sediments and subsequent movement up the food chain. Movement of mirex back into Lake Ontario is also possible when the contaminated eggs hatch and surviving juvenile salmon return to the lake (Lewis and Makarewicz 1988).

Algae are known to bioaccumulate mirex, with BCFs in the range of 3,200–7,300, while bacteria have a BCF of 40,000 with an octanol-water partition coefficient of 7.8 million (Baughman and Paris 1981). Based on a water solubility of 0.6 mg/L, a BCF of 820 was calculated for mirex (Kenaga 1980). Bioaccumulation of mirex also occurred in invertebrates exposed to 0.001–2.0 µg/g mirex in water; tissue residues ranged from 1.06 to 92.2 µg/g (de la Cruz and Naqvi 1973). After 28 days of exposure, the BCF values for the amphipod (*Hyallelu azteca*) and crayfish (*Orconectes mississippiensis*) were 2,530 and 1,060 respectively. Fathead minnows exposed to 33 µg/L (ppb) mirex for 56 days accumulated 122 µg/g (ppm) mirex tissue residues (BCF of 3,700), with no other evident metabolic products. Residues decreased to 88.6 µg/g 28 days after mirex was removed from the water (Huckins et al. 1982). The half-life of mirex in rainbow trout was >1,000 days in fish exposed for 96 days to a mean concentration of 4.1 ng/L, although equilibrium was not reached during the test period. A subsequent analysis comparing a laboratory BCF for mirex in rainbow trout (1,200) with an actual BCF found in rainbow trout in Lake Ontario (15,000), indicated that ingestion of contaminated food (as would occur in the lake), rather than absorption across the gills, is the primary exposure route for trout (Oliver and Niimi 1985).

Biomagnification of mirex is supported by a study of various aquatic organisms that comprise an aquatic food chain in Lake Ontario (Oliver and Niimi 1988) (see Table 5-1).

Table 5-1. Concentrations of Mirex in Aquatic Organisms

Sample	Mirex concentration (µg/kg wet weight unless otherwise noted)
Water	31±12 pg/L wet weight
Bottom sediment	3.9±1.9 µg/kg dry weight
Suspended sediment	15±4.4 µg/kg dry weight
Plankton	1.3±0.1
Mysids	8±2.8
Amphipods	12±6.7
Oligochaetes	6.9±2.9

Table 5-1. Concentrations of Mirex in Aquatic Organisms

Sample	Mirex concentration (µg/kg wet weight unless otherwise noted)
Sculpins	57
Alewives	45
Small smelts	26±3.6
Large smelts	53
Average fish	180±150

Source: Oliver and Niimi 1988

In these food chains, alewives feed primarily on mysids and to a lesser extent on amphipods; sculpins feed on amphipods, then mysids; smelt feed on mysids. Mysids feed on zooplankton, with amphipods and oligochaetes consuming detrital matter. The alewives and smelt are preyed upon by salmonids, such as trout (Oliver and Niimi 1988). A comparison of concentrations of mirex in lake trout, a predator species, with those in smelt, a prey species, gives a ratio of 1.26, indicating that biomagnification occurs up the food chain (Thomann 1989).

Mirex can also bioaccumulate in terrestrial plants. Azalea leaves, exposed to 0.023 µg/kg of mirex in greenhouse air, had significant uptake of the pesticide resulting in a BCF of 1.18×10^7 (log BCF=7.07) (Bacci et al. 1990). Mirex residues ranging from 10 to 1,710 µg/kg (ppb) were detected in soybeans, garden beans, sorghum, and wheat seedlings grown on substrates containing 0.3–3.5 mg/kg (ppm) mirex (de la Cruz and Rajanna 1975). Based on these data and known soil concentrations, it has been estimated that plants grown on contaminated soil could contain 0.0002–2 µg/kg (ppb) mirex (EPA 1978a). No information on the uptake of mirex by plants under field conditions was located.

In a 1972 residue study conducted in Mississippi during the time when mirex was being used extensively in fire ant control programs, Naqvi and de la Cruz (1973) reported mirex accumulation in grassland invertebrates (e.g., spiders and grasshoppers) ranging from 100 to 700 µg/kg (ppb) (mean 280 µg/kg). Hebert et al. (1994) studied organochlorine pesticides in a terrestrial food web on the Niagara Peninsula in Ontario, Canada, from 1987 to 1989. These authors reported mirex concentrations in the various food web compartments as follows: soil (not detectable), plants (not detectable), earthworms (not detectable to 0.4 µg/kg), mammals (not detectable to 0.5 µg/kg), starlings (0.9–1.6 µg/kg), robins (4.7–18.9 µg/kg), and kestrels (4.7–22.2 µg/kg), which suggests that biomagnification of mirex is occurring. The earthworm appeared to be a particularly important species for organochlorine transfer from the soil to organisms occupying higher trophic levels. Connell and Markwell (1990) reported transfer of lipophilic compounds

(such as mirex) through a three-phase system involving soil to soil water to earthworm partitioning. The transfer is a passive process and is principally dependent on the lipid content of the worms and the organic content of the soil.

Chlordecone. The fate and transport of chlordecone is very similar to mirex. Based on its low vapor pressure and high K_{oc}, chlordecone in the air may be expected to be associated primarily with particulate matter (Kenaga 1980). However, only small amounts of chlordecone may volatilize into the air. Chlordecone volatilizes more slowly from water (0.024% applied amount/mL of evaporated water) than from sand, loam, or humus soil (0.036, 0.035, and 0.032%, respectively) (Kilzer et al. 1979).

Atmospheric transport of chlordecone particles was reported as a result of emissions from a production facility in Virginia. Chlordecone concentrations at up to 15.6 miles away ranged from 1.4 to 20.7 ng/m^3 (Epstein 1978). The long-range transport properties of chlordecone indicate that at least a portion of the emissions were of a fine particle size having a relatively long residence time in the atmosphere (Lewis and Lee 1976).

The major industrial release of chlordecone occurred to surface waters of the James River. Chlordecone, because of its relatively low solubility in water and lipophilic nature, is readily absorbed to particulate matter in water and is ultimately deposited in sediments (EPA 1978a; Lunsford et al. 1987). Once adsorbed to sediments, chlordecone remains relatively immobile in the normal range of pH (7–8) and salinity (0.06–19.5 %) encountered in an estuary. While chlordecone is associated mainly with the organic portion of bottom sediments, sediment areas with high percentages of inorganic mineral grains are relatively free of contamination. The greatest mass of chlordecone (an estimated 6,260 pounds [2,840 kg]) was found in a sink where the sedimentation was relatively rapid. Transport is primarily through adsorption of chlordecone to fine organic particles in the water column. Its movement and deposition follow estuarine circulation, which is seaward from the freshwater reaches and upper estuarine water layer, and reflux downward for suspended materials (Nichols 1990).

While much of the chlordecone that was present in contaminated sediments in 1976 is still in the sediment, it is continuously being buried under several centimeters of new sediment each year (Huggett and Bender 1980). Storm activities and dredging are of concern because they would result in reenrichment of the surface sediments in areas with chlordecone contaminated sediment previously buried by natural ongoing sedimentation processes in the estuary (Huggett and Bender 1980; Lunsford et al. 1987).

Chlordecone has been found to have a very high bioaccumulation potential in fish and other aquatic organisms. Atlantic menhaden (*Brevoortia lyrunnus*) and Atlantic silver-sides (*Menidia menidiu*) had 28-day BCFs of 2,300–9,750 and 21,700–60,200, respectively (Roberts and Fisher 1985). Based on a water solubility of 3 mg/L, a BCF of 333 was estimated for chlordecone. However, the measured value was 8,400 (Kenaga 1980). Using a log octanol-water partition coefficient for chlordecone of 6.08, a BCF of 6,918 was estimated for the oyster (Hawker and Connell 1986). However, an oyster BCF of 10,000 has been reported with tissue concentrations at equilibrium within 8–17 days (Bahner et al. 1977). For estuarine organisms such as mysids, grass shrimp, sheepshead minnows, and spot, BCFs were measured to be 13,000, 11,000, 7,000, and 3,000, respectively (Bahner et al. 1977). Shad roe taken from the James River contained chlordecone levels that were 140% higher than muscle tissue residues, indicating a partitioning of the chemical into the lipid-rich eggs (Bender and Huggett 1984).

The accumulation of chlordecone was studied in a terrestrial/aquatic laboratory model ecosystem by Francis and Metcalf (1984). Radiolabeled chlordecone was applied to sorghum seedlings grown on the terrestrial portion of the aquarium. The treated seedlings were eaten by salt marsh caterpillars. In the aquatic portion, chlordecone was transferred through several species-an algae, snail, water flea mosquito larvae, and mosquito fish. After 33 days, the BCFs were 0.35 for the algae, 637.4 for the snails, 506.9 for the mosquito larvae, and 117.9 for the mosquito fish. A BCF for chlordecone of approximately 2.1 was determined for a water-algae-oyster food chain; however, a biomagnification factor >10.5 was measured for a water-brine shrimp-mysid-spot food chain with a water concentration of 0.1 mg/L (ppm) chlordecone (Bahner et al. 1977).

Plant uptake of chlordecone from the soil via the roots, and volatilization of chlordecone from soil with plant uptake via the leaves were found to be negligible in a closed laboratory system using barley seedlings. This indicates that bioaccumulation of chlordecone by plants (lowest on the terrestrial food chain) is very unlikely based on its log soil adsorption coefficient of almost 4.0 (Topp et al. 1986). No information on the uptake of chlordecone by plants under field conditions was located.

5.4.2 Transformation and Degradation

Air

Mirex. Little information was found on the degradation of mirex in the atmosphere. Mirex is expected to be stable against photogenerated hydroxyl radicals in the atmosphere (Eisenreich et al. 1981).

Chlordecone. Photolysis of chlordecone in the atmosphere does not appear to be an important degradation pathway for this compound. While nonvolatile products of photolysis were not monitored, only 1.8% of the chlordecone adsorbed on silica gel and exposed to ultraviolet light (wavelength >290 nm) was photolyzed to carbon dioxide or other volatile compounds (Freitag et al. 1985).

Water

Mirex. The degradation of mirex in water occurs primarily by photolysis. During the photo-decomposition of mirex, the chlorine atoms are replaced by hydrogen atoms. The primary photoreduction product of mirex in water is photomirex (Andrade et al. 1975); the rate of this reaction can be increased by the presence of dissolved organic matter (such as humic acids) and was greatest at 265 nm in Lake Ontario water (Mudambi and Hassett 1988). In Lake Ontario, Mudambi et al. (1992) reported that the ratio of photomirex to mirex (P/M) increased in the stratified surface layer of the lake from spring until autumn and in water from Oswego Harbor. P/M ratios in the mirex source sediments (the Niagara and Oswego Rivers) were very low (<0.07), whereas higher P/M ratios were seen in the lake bottom sediments (>0.10) and surface waters (>0.30). These findings suggest that photomirex in Lake Ontario is produced by photolysis of mirex present in the surface waters and it is then partitioned between water, sediment, and biota.

Chlordecone. Degradation of chlordecone to an unidentified compound was studied in water in a terrestrial/aquatic laboratory model ecosystem. Degradation occurred to some extent during the 33-day exposure period, and unidentified metabolites were detected in all organisms in the system-algae, snail, mosquito, and mosquito fish (Francis and Metcalf 1984). An earlier laboratory study in which fathead minnows were exposed to chlordecone in a flow-through diluter system for 56 days found that chlordecone was bioconcentrated 16,600 times by the minnows; however, only 1–5% of these residues were chlordecone (Huckins et al. 1982). Several observations suggested that some of the chlordecone residues present in the minnows were chemically bound to biogenic compounds.

Pseudomonas aeruginosa strain K03 and a mixed aerobic enrichment culture isolated from sewage sludge lagoon water were found to aerobically transform chlordecone to monohydrochlordecone in 8 weeks. Monohydrochlordecone constituted 14.2 and 14.5% of the chlordecone transformation products for the *P. aeruginosa* and mixed aerobic enrichment culture, respectively. The *P. aeruginosa* K03 strain and the mixed culture also produced 15.6 and 4.2% dihydrochlordecone, respectively (Orndorff and Colwell 1980). None of the bacterial strains were able to use chlordecone as a sole carbon source; therefore, co-metabolism appeared to be the only degradation process. Complete mineralization of chlordecone by bacteria is unlikely (Orndorff and Colwell 1980). Degradation of chlordecone can occur via microbial action, but the rate and extent of transformation are such that microbial action will not cause rapid removal of chlordecone from the environment except under highly enriched and selected conditions. Aerobic degradation of chlordecone by activated sludge from a municipal sewage plant showed that <0.1% of the applied chlordecone was degraded in 5 days, and the sludge showed a bioaccumulation factor of 9,900 compared with the concentration in the water (Freitag et al. 1985).

Sediment and Soil

Mirex. Degradation of mirex in soil may occur by photolysis or anaerobic biodegradation, both of which are very slow removal processes. Mirex is highly resistant to aerobic biodegradation and, as such, is extremely persistent in soils (estimated half-life of 10 years) (Carlson et al. 1976; Lal and Saxena 1982). Mirex appears to have no adverse effect on resident microbial communities (Jones and Hodges 1974). Upon exposure to ultraviolet light, mirex is known to degrade to chlordecone, photomirex, and/or dihydromirex (Francis and Metcalf 1984). Detectable levels of mirex photodegradation products (monohydro derivative and chlordecone hydrate) occur within 3 days after exposure of mirex to sunlight, although after 28 days of exposure, approximately 90% of the mirex was unchanged (Ivie et al. 1974b). Anaerobic degradation relies on iron(II) porphyrin as the reductant for the dehalogenation reaction (Kuhn and Suflita 1989).

Under anaerobic conditions, mirex was slowly dechlorinated to the 10-monohydro derivative by incubation with sewage sludge bacteria for 2 months (Andrade and Wheeler 1974; Andrade et al. 1975; Williams 1977). The primary removal mechanism for mirex was anaerobic degradation as demonstrated by the 6-month stability of the compound in nine aerobic soils and lake sediments (Jones and Hodges 1974).

Aerobic degradation of mirex is a very slow and minor degradation process. Twelve years after the application of mirex to soil at 1 pound/acre, 50% of the mirex and mirex-related organochlorine compounds remained in the soil; 65–73% of the residues consisted of mirex and 3–6% consisted of chlordecone. Although concentrations were slightly higher, similar ratios of mirex (76–81%) and chlordecone (1–6%) residues were seen 5 years after an accidental spill of mirex bait on soil. Mirex underwent photolysis to form four dechlorination products: two monohydro and two dihydro compounds (Carlson et al. 1976). Two soil microbes, *Bacillus sphaericus* and *Streptomyces albus*, isolated from a field previously treated with mirex, were able to utilize 1% mirex as a sole carbon source. However, the rate of degradation, as demonstrated by carbon dioxide evolution, was slow and only about 10–20% greater than the controls after 20 hours (Aslanzadeh and Hedrick 1985).

No evidence of microbial degradation was detected for mirex exposed to hydrosoils (soils formed under conditions of saturation, flooding, or ponding long enough during the growing season to develop anaerobic conditions in the upper part) from a reservoir (not previously contaminated with chlordecone) and from chlordecone-contaminated hydrosoils from the James River area of Virginia under either anaerobic or aerobic conditions for 56 days (Huckins et al. 1982). The concentrations of chlordecone in the anaerobic and aerobic hydrosoils averaged 0.38 and 0.54 µg/g, respectively. Some photodegradation of mirex to photomirex was seen in an artificial salt marsh ecosystem; the photomirex was subsequently photodegraded to the 2,8- or 3,8-dihydro derivative. Most mirex loss occurred during the first 7 days after application (from 2.65 to 2.13 mg/g) with a steady accumulation of photomirex (610 ppb/day [µg/kg/day]) through day 21, accumulation of 17 µg/kg/day of 2,8- or 3,8-dihydro derivative through day 35, and an accumulation rate of 206 µg/kg/day for the 10-monohydro photoproduct that is formed in the presence of amines. The 8-monohydro derivative (photomirex) was found to accumulate in the salt marsh organisms and sediment (Cripe and Livingston 1977).

Application of radiolabeled mirex to plants grown in a terrestrial/aquatic laboratory model ecosystem indicated that when the plant leaves were eaten by caterpillars, the aquatic system became contaminated. Mirex was detected in all segments of two aquatic food chains (alga > snail and plankton > daphnia > mosquito > fish) within 33 days. Undegraded mirex contributed to over 98.6, 99.4, 99.6, and 97.9% of the radiolabel in fish, snails, mosquitoes, and algae, respectively. No metabolites of mirex were found in any of the organisms (Francis and Metcalf 1984; Metcalf et al. 1973).

Chlordecone. Chlordecone is similar to mirex in structure and is also highly persistent in soils and sediments (half-life expected to be analogous to 10 years duration for mirex) because of its resistance to

biodegradation, although some microbial metabolism of chlordecone has been reported (Lal and Saxena 1982; Orndorff and Colwell 1980). No evidence of microbial degradation was detected for chlordecone exposed to hydrosoils from a reservoir (not previously contaminated with chlordecone) and from Bailey Creek (contaminated with chlordecone) under either anaerobic or aerobic conditions for 56 days (Huckins et al. 1982).

Three *Pseudomonas* species extracted from soil samples to which chlordecone was added (1 mg/mL) were found to utilize chlordecone, as a sole carbon source, with quantifiable degradation (67–84%) in 14 days. Among the degradation products of chlordecone, only hydrochlordecone and dihydrochlordecone were identified (George and Claxton 1988; George et al. 1986). Sewage sludge bacteria and sediment bacteria, primarily *P. aeruginosa* strain KO3, were able to aerobically degrade chlordecone by 10–14% to monohydrochlordecone and, to a lesser extent, dihydrochlordecone in 8 weeks. None of the bacterial strains was able to use chlordecone as a sole carbon source; therefore, co-metabolism appeared to be the only degradation process. Complete mineralization of chlordecone by bacteria is unlikely (Orndorff and Colwell 1980). Concentrations of chlordecone >0.2 mg/L are likely to inhibit microbial activity, whereas concentrations <0.01 mg/L had no effects on cell count or uptake of amino acids. Bacteria in James River sediment did not produce significant concentrations of chlordecone metabolites (Colwell et al. 1981).

Degradation of chlordecone in a terrestrial ecosystem was studied by applying the compound to soil, growing plants on the soil; and then determining the amount of chlordecone in each compartment after 1 week. During this time, only 0.1% of the applied chlordecone (2 mg/kg) was decomposed to carbon dioxide from the soil, and 0.3 mg/kg (approximately 15% of the applied concentration) was accumulated by the barley plants. Less than 10% of the applied chlordecone was degraded in the soil or converted by the barley plants, and there was no volatilization of the compound from the soil to the air (Kloskowski et al. 1981). A laboratory soil-plant system showed that degradation of chlordecone, as determined by soil residues remaining after volatilization and mineralization, was 1–3% after 1 week; this compared favorably with the residues remaining in soil in the field after one growing season (Scheunert et al. 1983). Analysis of soil contaminated with chlordecone collected in the vicinity of the chlordecone production facility showed some photolytic degradation of the compound with the production of small amounts of monohydro isomers of chlordecone (Borsetti and Roach 1978).

5.5 LEVELS IN THE ENVIRONMENT

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

The lowest limit of detections that are achieved by analytical analysis in environmental media are summarized in Table 5-2 for mirex and Table 5-3 for chlordecone.

Table 5-2. Lowest Limit of Detection for Mirex Based on Standards[a]

Media	Detection limit	Reference
Air	0.1 ng/m^3	Lewis et al. 1977
Drinking water	10 ng/L	Sandhu et al. 1978
Surface water and groundwater	10 ng/L	Sandhu et al. 1978
Soil	1 ppb	Seidel and Lindner 1993
Sediment	0.002 ppb	Sergeant et al. 1993
Whole blood	0.04 ng/g	Mes 1992

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

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

Media	Detection limit	Reference
Air	10 ng/sample	NIOSH 1984
Water	20 ng/L	Saleh and Lee 1978
Soil	10–20 ppb	Saleh and Lee 1978
Sediment	10–20 ppb	Saleh and Lee 1978
Whole blood	10 µg/L	Caplan et al. 1979

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

No data are available on levels of mirex or chlordecone in air, water, and soil at NPL sites (ATSDR 2019).

5.5.1 Air

Mirex. Mirex has been detected in wet precipitation over rural areas at concentrations <1 ng/L (ppt) (EPA 1981). Rain fall samples collected at several sites in 1985–1986 as part of the Great Lakes Organics Rain Sampling Network contained from >0.2 to <0.5 ng/L (ppt) of mirex. Mirex was not detected consistently at many stations throughout the sampling period; therefore, quantitative results for mirex were not presented (Strachan 1990). Air samples taken over southern Ontario in 1988 showed mirex in 5 of 143 samples, at an annual mean concentration of 0.35 pg/m^3 (range, 0.1–22 pg/m^3), with all of the positive samples detected in polluted environments (Hoff et al. 1992).

Chlordecone. Information on atmospheric concentrations of chlordecone is limited to air sampling results obtained at the Life Sciences Products Company production site in Hopewell, Virginia. High volume air filter samples collected 200 m from the plant in March 1974 prior to initiation of production at the site contained only 0.18 to 0.35 ng/m^3 of chlordecone. Subsequent air sampling after production was initiated ranged from 3 to 55 μg/m^3. During production years 1974 and 1975, air concentrations at more distant sites up to 15.6 miles from Hopewell, Virginia, ranged from 1.4 to 20.7 ng/m^3 (Epstein 1978).

5.5.2 Water

Mirex. Mirex was detected in rural drinking water samples at concentrations ranging from not detectable to 437 ng/L (ppt) (Sandhu et al. 1978). In a survey in 1987, mirex was detected in only 5 of 1,147 drinking water samples from Ontario, Canada (maximum concentration of 5 ng/L [ppt]) (Environment Canada 1992).

The pollution of the Niagara River from chemical manufacturing effluents and leachates from chemical manufacturing waste dumps has been well documented. Between 1975 and 1982, mirex was detected in the aqueous phase of 6 of 22 samples in the Niagara River at levels between 0.0005 and 0.0075 ng/L (ppt) (Allan and Ball 1990). Twelve percent of 104 whole water samples, collected from the Niagara River between 1981 and 1983, had mirex concentrations that ranged from below the detection limit (0.06 ng/L[ppt]) to 2.6 ng/L, with a median concentration of 0.06 ng/L (Oliver and Nicol 1984). Mirex was detected in the suspended particulate phase of 42 Niagara River water samples taken at the mouth of the river in 1986–1987; 17% of the samples had a mean mirex concentration of 0.022 ng/L (ppt) (Allan and Ball 1990).

In 1982, Mudambi et al. (1992) reported the mean mirex concentrations in the Lake Ontario system ranging from 1.85 to 30 pg/L. An intralake comparison of chemicals found in the Great Lakes during the 1986 spring turnover did not detect mirex in any of the lakes (Stevens and Neilson 1989), nor in the dissolved or particulate fractions of water from the St. Lawrence River between 1981 and 1987 (Germain and Langlois 1988). In 1986, low levels of mirex were found in 8 of 14 water samples taken at various locations along the St. Lawrence River (Kaiser et al. 1990). The highest concentration observed was 0.013 ng/L (ppt). Sergeant et al. (1993) reported mirex concentrations in Lake Ontario water samples declined from 0.0015 μg/L (1.5 ng/L) in 1986 to <0.0004 μg/L (0.4 ng/L) in 1988.

Mirex was detected in water samples taken in 1972 from areas in Mississippi that had been aerially treated with mirex to control the imported red fire ant (Spence and Markin 1974). Water samples taken from the bottom of a pond showed residue values that remained higher and more constant than those taken from the surface of the pond. Water showed the highest residues immediately after treatment (bottom, 0.53 μg/L [ppb]; surface, 0.02 μg/L [ppb]), and detectable levels were still present as long as 3 months after treatment (bottom, 0.005 μg/L [ppb]; surface, 0.003 μg/L [ppb]) (Spence and Markin 1974).

Chlordecone. The solubility of chlordecone in water is low (1–3 mg/L) and as with mirex, contamination is more likely to be associated with the particulate matter in the water rather than the water itself. Chlordecone was detected primarily in water samples collected in and around the production facility site in Hopewell, Virginia, and in adjacent waters of the James River estuary. Effluent from the Life Sciences Products Company facility contained 0.1–1.0 mg/L (ppm) chlordecone, while water in holding ponds at the site contained 2–3 mg/L (ppm) chlordecone (Epstein 1978). Levels of chlordecone in river water in August 1975 ranged from not detectable (<50 ng/L [ppt]) in the York River and Swift Creek areas, to levels of 1–4 μg/L (ppb) in Baileys Creek which received direct effluent discharges from the Hopewell Sewage Treatment Plant. Water concentrations of up to 0.3 μg/L (ppb) were detected in the James River at the mouth of Bailey Creek and in the Appomattox River (upstream from Hopewell) at 0.1 μg/L (ppb) (Epstein 1978). Hopewell drinking water drawn from the James River contained no detectable chlordecone levels (EPA 1978a; Epstein 1978). In 1977, 12 years after production of chlordecone began and 2 years after production ceased, average concentrations of chlordecone in estuarine water (dissolved) were <10 ng/L (ppt) (Nichols 1990). In October 1981, 6 years after production at the plant ceased, chlordecone water concentrations ranged from not detectable to 0.02 μg/L (ppb) (Lunsford et al. 1987).

5.5.3 Sediment and Soil

Mirex. Mirex was identified in sediment samples collected in 1979 from Bloody Run Creek, which is a drainage ditch for the Hyde Park landfill in Niagara Falls, New York. Mirex levels in the sediment ranged from 0.5 to 2 mg/kg (ppm) (detection limit, 0.5 mg/kg [ppm]) (Elder et al. 1981).

Between 1979 and 1981, mean mirex concentrations in suspended sediments of the Niagara River declined from 12 to 1 ng/L (ppt); concentrations in bottom sediments were generally low, ranging from <1 µg/kg (ppb) to a maximum value of 890 µg/kg (ppb), at a site believed to be the source of mirex to the river (Allan and Ball 1990). In 1981, mirex was detected in sediments of Lake Ontario near the mouth of the Niagara River at increasing concentrations to a maximum of 1,700 µg/kg (ppb) at a sediment depth of 9 cm. Concentrations decreased between 9 and 13 cm and were not detected in sediments below a depth of 13 cm. Concentrations were chronologically correlated with mirex production and peak sales periods and were reduced when its use was restricted (Durham and Oliver 1983). In 1982, mirex was detected in settling particulates from sediment traps in the Niagara River (average, 7 µg/kg [ppb]; range, 3.9–18 µg/kg [ppb]), resuspended bottom sediments from the Niagara Basin of Lake Ontario (average, 9.45 µg/kg [ppb], range 5.2−16 µg/kg [ppb]), and bottom sediments from Lake Ontario (average, 48 µg/kg [ppb]) (Oliver and Charlton 1984).

An analysis of urban runoff and sediment runoff collected between 1979 and 1983 from 12 urban areas in the Canadian Great Lakes Basin showed that mirex was not detected in any runoff waters, although it was found in 10% of 129 runoff sediment samples at a mean concentration of 1.3 µg/kg (ppb) (Marsalek and Schroeter 1988). Sediment samples collected from the St. Lawrence River between 1979 and 1981 contained low concentrations of mirex (median, <0.1 µg/kg; range, <0.1–3.3 µg/kg), indicating that Lake Ontario is the source of the contamination to the river (Sloterdijk 1991). Low levels of mirex were found in bottom sediment core samples taken from the riverine lakes in the St. Lawrence River in October 1985; the average concentration of mirex was 0.43 µg/kg (range, <0.01–0.95 µg/kg) (Kaiser et al. 1990). In 1987, mirex was detected in suspended sediments throughout the St. Lawrence River. At the St. Lawrence River stations near Kingston, the mirex concentration was approximately 5 µg/kg (ppb), but declined to about 1 µg/kg (ppb) near Quebec City (Kaiser et al. 1990).

In 1971 and 1972, mirex was detected in soil and sediment samples taken from areas in Louisiana and Mississippi that had been aerially treated with mirex to control the imported red fire ant (Spence and Markin 1974). In Louisiana, samples were collected throughout the first year after spraying. Soil and

sediment residues in the Louisiana study peaked after 1 month (soil, 2.5 µg/kg [ppb]; sediment, 0.7 µg/kg [ppb]) and gradually declined over the remainder of the year. In Mississippi, samples were collected for 4 months following spraying. Sediment residues in Mississippi also peaked about 1 month after spraying (1.1 µg/kg [ppb]) and gradually declined over the next couple of months. The residue levels found in soil in Mississippi were much more variable and showed no distinctive pattern (Spence and Markin 1974).

Less than 10% of the sediment samples taken from the San Joaquin River and its tributaries in California (an area of heavy organochloride pesticide use) in 1985 contained mirex residues; all samples contained <0.1 µg/kg (ppb) (Gilliom and Clifton 1990).

Studies of sediment from seven sampling stations in the Upper Rockaway River, New Jersey, showed that sediment quality corresponded to the land-use data for the area (Smith et al. 1987). The two upstream stations, which drain primarily forested areas of the Upper Rockaway Basin, had low mirex concentrations in the sediments (<0.1 µg/kg). The remaining stations, which drained an area consisting of residential, commercial, and industrial land including six EPA Superfund sites, had mirex concentrations ranging from 8.2 to 80 µg/kg (ppb) (Smith et al. 1987).

Sediment samples taken from 51 sampling locations in the Gulf of Mexico for the National Oceanic and Atmospheric Administration (NOAA) Status and Trends Mussel Watch Program were analyzed for mirex contamination (Sericano et al. 1990; Wade et al. 1988). Average mirex concentrations of 0.07 µg/kg (ppb) (range, <0.01–0.67) and 0.18 µg/kg (ppb) (range, <0.02–3.58) were found in sediments in 1986 and 1987, respectively. The sampling sites represent the contaminant loading for the Gulf of Mexico estuaries removed from known point-sources of contamination (Sericano et al. 1990; Wade et al. 1988).

Chlordecone. With the exception of the James River area of Virginia, very little information is available on chlordecone residues in soil and sediment. Chlordecone was detected in soil immediately surrounding the Life Sciences Products Company in Hopewell, Virginia, at levels of 1–2% (10,000–20,000 mg/kg) and contamination extended to 1,000 m at concentrations of 2–6 mg/kg (ppm) (Huggett and Bender 1980).

Assessment of sediment cores taken from the James River below Hopewell, Virginia, indicated that chlordecone concentrations were greatest nearest the release site. Sediment concentrations of chlordecone in Baileys Creek, the waterbody into which effluent from the Hopewell municipal sewage treatment facility was discharged, were 2.2 mg/kg (ppm) (Orndorff and Colwell 1980). Chlordecone

concentrations of 0.44–0.74 mg/kg were found at sediment depths of 55–58 cm in the main channel of the James River. This area had the highest sedimentation rate (>19 cm/year). Further downriver, (80 km from Hopewell) in the James River estuary, chlordecone concentrations decreased and maximum concentrations were found closer to the sediment surface. The highest chlordecone concentration of 0.18 mg/kg (ppm) was from a sediment depth of 46–48 cm in an area with a sedimentation rate of 10 cm/year (Cutshall et al. 1981).

5.5.4 Other Media

Mirex. In general, because releases of mirex from its production and use as a pesticide were terminated in the late 1970s, mirex residues in various biological organisms are much lower than those reported during or shortly after its peak years of production and use. This trend is supported by both regional and national studies.

In areas where mirex was historically used for fire ant control, it has been detected in fish and other aquatic biota from contaminated rivers. An analysis of mirex residues in primary, secondary, and tertiary consumers in oxbow lakes in Louisiana in 1980 indicated that although mirex was not detected in any water or sediment samples, or in the tissues of primary consumers (some fish), it was detected in the tissues of secondary consumers (fish and birds that consume invertebrates and insects), and in all tertiary consumers (fish-eating fish, birds, and snakes). The highest mean mirex concentrations were found in cottonmouth snakes (0.11 mg/kg [ppm]) (Niethammer et al. 1984). Fish taken from the lower Savannah River during 1985 had mirex residues in their tissues that ranged from nondetectable to 1 mg/kg (ppm) wet weight, although most residues were near 0.02 mg/kg (Winger et al. 1990).

Of all the Coho salmon collected from all of the Great Lakes in 1980, only fish taken from Lake Ontario contained detectable mirex residues at an average concentration of 0.14 µg/g (ppm) (Clark et al. 1984). The mean concentration of mirex residues in rainbow trout taken from Lake Ontario was 0.11 µg/g (ppm), while the mean water concentration in the lake was 0.008 ng/L (ppt) (Oliver and Niimi 1985). Borgmann and Whittle (1991) studied the contaminant concentration trends in Lake Ontario lake trout from 1977 to 1988. Mirex concentrations generally declined from 0.38 µg/g (ppm) in 1977 to 0.17 µg/g (ppm) in 1988, although there was considerable variability in the mirex residue data. The concentrations of mirex also showed a distinct east-west gradient across the lake. The highest mirex residues were detected in fish collected at the western side of the basin and were 70% above those detected in fish collected at the eastern portion of the basin. Suns et al. (1993) conducted a similar study of spatial and temporal trends of

organochlorine contaminants in spottail shiners from selected sites in the Great Lakes. These authors reported that mirex was only detected in fish from the Niagara River, the Credit River in western Lake Ontario, and in the St. Lawrence River at Cornwall. Mirex concentrations in spottail shiners collected during the late 1980s were generally lower than mirex residues found in spottail shiner samples collected during the 1970s. Considerable fluctuation in mirex residues in spottail shiners was observed, which precluded proper trend assessment. Based on the fish data, mirex inputs to Lake Ontario appeared to be continuing on an intermittent basis. Newsome and Andrews (1993) analyzed mirex in fillet samples of 11 commercial fish species from the Great Lakes. The highest mirex concentrations were found in carp from a closed fishery area (120 µg/kg [ppb]), eel (56.8 µg/kg), carp from an open fishery area (5.24 µg/kg), bullhead (3.63 µg/kg), and trout (2.38 µg/kg).

Burbot, a bottom-feeding fish, taken from remote lakes in Canada in 1985–1986, contained liver concentrations of mirex ranging between 3.7 and 17.4 µg/kg (ppb) lipid weight (detection limit, 0.5 µg/kg), while photomirex was not detected. The lowest mirex values were seen in fish from the most remote locations, suggesting that atmospheric transport of this compound was occurring (Muir et al. 1990).

Ninety percent of the mussels collected in 1985 at various points along the St. Lawrence River contained mirex at levels up to 1.6 µg/kg (ppb). The only source of mirex was contaminated particles entering the river from Lake Ontario; mussels collected from the Ottawa River, which does not receive its water from Lake Ontario, did not contain any mirex. The mirex concentrations in the mussels decreased with distance from the lake (Metcalfe and Charlton 1990).

Mirex concentrations were measured in 78 snapping turtles collected from 16 sites in southern Ontario, Canada, during 1988–1989 to evaluate the risk to human health (Hebert et al. 1993). Mean concentrations of mirex in the muscle tissue were below fish consumption guidelines for mirex (100 µg/kg [ppb]) and ranged from not detectable to 3.95 µg/kg (ppb). However, mirex concentrations in older turtles from some sites were as high as 9.3 µg/kg (ppb).

Freshwater fish sampled (as part of the U.S. Fish and Wildlife Service National Contaminant Biomonitoring Program) between 1980 and 1984 contained detectable concentrations of mirex. Mirex was detected in 18% of the 1980 samples (maximum concentration, 210 µg/kg [ppb]; mean concentration, 0.01 µg/g) and in 13% of the 1984 samples (maximum concentration, 440 µg/kg [ppb]; mean concentration, 10 µg/kg). The highest mirex concentrations were detected in whole fish taken from Lake

Ontario, the St. Lawrence River, and the southeastern United States, all areas where mirex had been manufactured or used (Schmitt et al. 1990). In the EPA National Study of Chemical Contaminants in Fish, mirex was detected at 38% of 362 sites sampled. The mean mirex concentration was 3.86 µg/kg (ppb) and the maximum concentration was 225 µg/kg (ppb). The highest concentrations of mirex were detected in fish collected in the Lake Ontario area of New York State (EPA 1992). In the EPA National Study of Chemical Contaminants in Lake Fish (EPA 2009a), mirex was detected in 2% of the 486 fish sampling locations for predator fish, with a maximum concentration of 9 ppb, and in 4.8% of the 395 sample locations for bottom dwelling fish, with a maximum concentration of 29 ppb.

Of oysters (*Crassostrea virginica*) sampled throughout the United States between 1965 and 1972 for the National Pesticide Monitoring Program, only those from South Carolina locations had detectable mirex residues (maximum concentration, 540 µg/kg [ppb]) with most residues being <38 µg/kg (ppb) (Butler 1973). Oysters taken from 49 sampling locations in the Gulf of Mexico for the NOAA Status and Trends Mussel Watch Program 1986–1987 were analyzed for mirex contamination (Sericano et al. 1990; Wade et al. 1988). Average mirex concentrations of 1.40 µg/kg (ppb) (range, <0.25–15.8 µg/kg) and 1.38 µg/kg (ppb) (range, <0.25–16.1) were found in oysters in 1986 and 1987, respectively (Sericano et al. 1990). The sampling sites represent the contaminant loading for the Gulf of Mexico estuaries removed from known point-sources of contamination (Wade et al. 1988).

Mirex was also detected in the muscle and liver tissues of seven species of aquatic and terrestrial mammals collected in areas of Alabama and Georgia that had been repeatedly treated with mirex to suppress fire ant populations from March 1973 through July 1976. At 6 months post-treatment, skunk and opossum muscle tissue contained the highest mean mirex concentrations of 3.50 and 1.5 1 µg/g (ppm), respectively (Hill and Dent 1985). Two years post-treatment, muscle residues declined in all species except the mink, which increased from 0.14 µg/g at 6 months post-treatment to a mean muscle residue of 0.28 µg/g at 1 year post-treatment and 0.53 µg/g at 2 years post-treatment.

Mirex was detected in the subcutaneous fat and breast muscle of 55 waterfowl collected in New York State during 1981 and 1982. Average mirex levels were 280 µg/kg (ppb) in fat and 2.0 µg/kg in breast muscle (Kim et al. 1985). Mirex was detected at a concentration of >500 µg/kg (ppb) in 24 of 164 samples of subcutaneous fat of six species of waterfowl (mallard, black duck, scaup, wood duck, bufflehead, and Canada goose) harvested by hunters in 1983–1984 (Foley 1992). Mirex was detected in fat samples from 5 of 26 goldeneyes shot by hunters in December 1988 in New York State; however, no quantitative information on mirex residues was provided (Swift et al. 1995). Gebauer and Weseloh

(1993) used farm-raised mallards as sentinels for accumulation of pollutants at three sites in southern Ontario, Canada. The sites included the Hamilton Harbor Confined Disposal Facility designated as an "Area of Concern" because of high pollutant concentrations of sediment; the Winona Sewage Lagoons, which contained high concentrations of metals; and Big Creek Marsh, which served as a reference area. The geometric mean concentrations of mirex detected in muscle tissue at each site were 7.1 μg/kg (ppb) at the Hamilton Harbor site after 115 days; 0.07 μg/kg at the sewage lagoon site after 112 days; and 0.14 μg/kg at the reference site after 30 days.

Mirex residues were detected in food samples analyzed as part of the FDA Pesticide Residue Monitoring Studies conducted from 1978 to 1982 of 49,877 food samples and from 1982 to 1986 of 49,055 food samples; however, the frequency of detection was unspecified but was <1 and 2% respectively (Yess 1988; Yess et al. 1991). Mirex was not detected in 27,065 samples of food collected in 10 state food laboratories from 1988 and 1989 (Minyard and Roberts 1991). Mirex was also not detected in domestically produced or imported foods sampled as part of the FDA Pesticide Residue Monitoring Study during 1989 (FDA 1990), was detected (at <1% occurrence) in foods sampled in 1990 (FDA 1991), and was not detected in foods sampled in 1991 (FDA 1992) and 1992 (FDA 1993) or in the most recent (2017) survey (FDA 2019).

Chlordecone. Because releases of chlordecone from its production and use ceased in the late 1970s, current chlordecone residues in various biological organisms are generally lower than those reported during its peak production years (1974–1975). Releases of chlordecone from the manufacturing plant in Hopewell, Virginia, severely contaminated the James River estuary in Virginia from 1966 through 1975. In 1977, 12 years after production of chlordecone began and 2 years after it ceased, average chlordecone concentrations in various biological organisms in the estuary were as follows (Nichols 1990): phytoplankton, 1.30 μg/g; zooplankton, 4.80 μg/g; freshwater fish, 2.50 μg/g; migratory fish, 0.40 μg/g; and benthic fauna (molluscs), 1.50 μg/g. Considerable variations in chlordecone concentrations detected in fish species in the James River were in part associated with different life histories and residence times of each species in the estuary (Huggett and Bender 1980). Freshwater species that were permanent residents in the upper estuary exhibited the highest range in tissue residues varying from <0.1 μg/g (ppm) for channel catfish to >2 μg/g for largemouth bass. Residues in marine fish increased with length of exposure time in the James River. American shad that inhabited the estuary only briefly showed average chlordecone residues of <0.1 μg/g. Longer-term residents that spent 6–9 months in the estuary, such as spot and croaker, contained 1 μg/g. Concentrations in resident estuarine species ranged from 0.7 μg/g for the bay anchovy to 2.7 μg/g for white perch.

Dredging of the James River in Virginia increased the chlordecone levels in resident clams (*Rangia cuneata*). The river has contaminated sediments containing up to 3.5 µg/g (ppm) chlordecone. Prior to the 2-week dredging period, chlordecone concentrations in the water column ranged from nondetectable to 0.02 µg/L (ppb); background concentrations in the clams ranged from 0.06 to 0.14 µg/g. During the dredging, body burdens of chlordecone in clams increased by 0.01–0.04 µg/g (ppm). Two weeks after the dredging was completed, residues in the clams had not returned to predredging levels (Lunsford et al. 1987).

In addition to the James River area, chlordecone residues of 0.025 and 0.23 mg/kg (ppm) were detected in trout and suckers, respectively, collected from Spring Creek 18 miles downstream of the Nease Chemical Plant in Pennsylvania (EPA 1978a). This plant produced small quantities of chlordecone from 1966 to 1974 (Epstein 1978).

Because chlordecone contamination of the James River in Virginia and Spring Creek in Pennsylvania represented relatively isolated incidents resulting from industrial negligence and because the compound was not used extensively on agricultural crops in the United States, monitoring for this compound has not been included as part of the U.S. Fish and Wildlife Service National Contaminant Biomonitoring Program (Schmitt et al. 1990), the EPA National Study of Chemical Residues in Fish (EPA 1992), EPA National Study of Chemical Contaminants in Lake Fish (EPA 2009a).

Chlordecone residues were detected in the FDA Pesticide Residue Monitoring Studies of 49,877 food samples from 1978 to 1982 and of 49,055 food samples from 1982 to 1986; however, the frequency of detection was unspecified but was less than 1 and 2%, respectively (Yess 1988; Yess et al. 1991). Chlordecone was also detected in 1 of 27,065 samples of food collected from 10 state laboratories during 1988 and 1989 (Minyard and Roberts 1991). Chlordecone was not detected in any domestically produced or imported foods analyzed as part of the FDA Pesticide Residue Monitoring Studies during 1988–1989, 1989–1990, 1990–1991, and 1991–1992 (FDA 1990, 1991, 1992, 1993) or in the most recent (2017) survey of imported foods (FDA 2019).

5.6 GENERAL POPULATION EXPOSURE

Mirex. Mirex has not been produced since 1976 and has not been used in the United States since 1977, when all registered uses of the product were canceled. The potential for exposure of the general

population, therefore, is relatively small and should continue to diminish over time. Members of the general population may be exposed to low concentrations of mirex primarily through consumption of contaminated food stuffs, in particular contaminated fish and shellfish from Lake Ontario, the St. Lawrence River, and Spring Creek in Pennsylvania, which were all contaminated by industrial discharges, and areas of the southern United States that were extensively treated with mirex for fire ant control. No dietary intake estimates are available (FDA 1990, 1991, 1992) since mirex has been so infrequently found in foodstuffs in recent years. Mirex exposure from drinking water has not been found to constitute significant human exposure since mirex is relatively insoluble in water and rapidly adsorbs to sediment (EPA 1978a).

Mirex has been detected in the general U.S. population. The National Human Monitoring Program for Pesticides detected mirex at low frequencies in human adipose tissue collected nationwide. In 1972, mirex was detected in 0.05% of all samples and in 1973, mirex was detected in 0.09% of all samples; however, by 1974, the percentage of positive samples had increased to 0.11% (Kutz et al. 1979). Mirex was detected in 13% of samples collected as part of the 1982 National Adipose Tissue Survey (EPA 1986b). Concentrations of mirex ranged from 0.008 to 0.39 µg/g (ppm) (mean concentration 0.025 µg/g). Further analysis of adipose tissue samples collected as part of the 1982 National Adipose Tissue Survey failed to detect mirex in any tissues from children (newborn infants to 14-year-olds); however, tissue samples from adults 15–44 and ≥45 years old were found to contain mirex residues. The greatest concentrations (values not provided) for 15–44-year-old adults were found in the Northeast and South Atlantic States, while the greatest concentrations for >45-year-old adults were found in the West South Central States and Northeast States (Phillips and Birchard 1991).

In a survey of human adipose tissue from residents of southwestern Ontario between 1976 and 1979, mirex was detected in 32.8% of the samples at mean concentrations of <0.01 mg/kg (ppm). In 1980–1981, it was detected in more samples (64.8%) at greater concentrations (mean concentration, 0.04 mg/kg); however, in 1983–1984, it was detected in only 6.2% of the samples at an average concentration of 0.06 mg/kg. Adipose tissue collected from 13 infants during this time contained <0.01 mg/kg mirex, except for one sample that contained 0.02 mg/kg. Mirex was not detected in any blood or human milk samples collected for this survey (Frank et al. 1988). A 1985 nationwide study of chlorinated hydrocarbons in the adipose tissue of Canadians found mirex to be present in all 108 samples collected nationwide at a mean concentration of 7 ng/g (ppb) (maximum concentration, 72 ng/g). The high rate of detection was a result of improved analytical procedures and lower limits of detection than those used in earlier studies. Residues were evenly distributed throughout the country and did not differ

significantly between the sexes or by age (Mes et al. 1990). In a 1990–1991 survey of human adipose tissue from residents of British Columbia, Canada, mirex was detected at a minimum, mean, and maximum concentration of 1.15, 6.10, and 33.3 ng/g (ppb) lipid, respectively (Teschke et al. 1993).

Mirex residues in human blood serum were measured as part of the National Report on Human Exposure to Environmental Chemicals. In the Second National Health and Nutrition Examination Survey (NHANES II), conducted between 1976 and 1980. Of the 4,038 samples analyzed, mirex concentrations ranged from not detectable to detected but below quantifiable levels (10 µg/L [ppb]) (Stehr-Green 1989). In the Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2019), mirex levels in serum (lipid adjusted) were reported according to various age groups, gender, and race/ethnicity. The results are presented in Tables 5-4, 5-5, 5-6, and 5-7.

Mirex was detected (mean detection limit 3 pg/g [ppt]) in 62% of 412 breast milk samples collected from women in all Canadian provinces (Mes et al. 1993). The mean, median, and maximum mirex concentrations were 0.14, 0.08, and 6.56 ng/g (ppb), respectively, in whole milk and 4.2, 2.3, and 124.5 ng/g, respectively, in milk fat. In previous studies, mirex residues were not detected. None of the 1,436 human milk samples collected in the United States in the late 1970s as part of the National Human Milk Study contained identifiable levels of mirex (Savage et al. 1981). A similar national study of nursing mothers in Canada (Mes et al. 1986) also failed to detect mirex in any human milk samples. The high rate of detection in the Mes et al. (1993) study was a result of improved analytical procedures and lower limits of detection.

An analysis of potential human exposure to contaminants in drinking water and foods was conducted in Ontario, Canada, in 1980. Mirex was detected only in edible fish taken from Toronto Harbor on Lake Ontario. The average mirex concentrations were 0.001 mg/kg (ppm) wet weight for white sucker, 0.01 mg/kg wet weight for rainbow trout, and 0.033 mg/kg wet weight for northern pike. Estimated human exposure levels, based on an average fish consumption of 0.53 kg/year for each fish species, were 0.0005 for white sucker, 0.005 for rainbow trout, and 0.017 mg/year for northern pike, respectively (Davies 1990).

Mirex is no longer manufactured, formulated, or used in the United States. Therefore, there is currently no occupational exposure to this chemical associated with its production or application as a pesticide. Current occupational exposure is most likely to occur for workers employed at waste disposal sites or those engaged in remediation activities including removal of soils and sediments contaminated with

Table 5-4. Geometric Mean and Selected Percentiles of Mirex (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	*[b]	<LOD	<LOD	<LOD	<LOD	1,853
	2001–2002	*	<LOD	<LOD	15.8 (<LOD–73.7)	57.1 (13.2–230)	2,257
	2003–2004	*	<LOD	<LOD	8.40 (<LOD–13.0)	13.2 (7.90–29.6)	1,951
Age group							
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	659
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	728
	2003–2004	*	<LOD	<LOD	<LOD	<LOD	592
≥20 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	1,194
	2001–2002	*	<LOD	<LOD	19.6 (<LOD–108)	71.0 (14.6–305)	1,529
	2003–2004	*	<LOD	<LOD	9.10 (<LOD–15.6)	15.4 (8.10–37.1)	1,359
Gender							
Males	1999–2000	*	<LOD	<LOD	<LOD	<LOD	887
	2001–2002	*	<LOD	<LOD	16.1 (<LOD–65.6)	50.8 (12.3–225)	1,052
	2003–2004	*	<LOD	<LOD	9.70 (<LOD–15.4)	15.5 (9.70–24.4)	949
Females	1999–2000	*	<LOD	<LOD	<LOD	<LOD	966
	2001–2002	*	<LOD	<LOD	15.0 (<LOD–108)	63.0 (12.0–374)	1,205
	2003–2004	*	<LOD	<LOD	<LOD	11.6 (<LOD–31.3)	1,002
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	<LOD	<LOD	<LOD	617
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	548
	2003–2004	*	<LOD	<LOD	<LOD	<LOD	459
Non-Hispanic blacks	1999–2000	*	<LOD	<LOD	15.5 (<LOD-42.2)	39.5 (<LOD–115)	398
	2001–2002	*	<LOD	13.7 (<LOD–47.3)	51.3 (15.4–230)	153 (30.5–425)	500
	2003–2004	*	<LOD	<LOD	18.1 (8.70–40.8)	40.3 (15.5–82.7)	484

Table 5-4. Geometric Mean and Selected Percentiles of Mirex (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	<LOD	<LOD	<LOD	688
	2001–2002	*	<LOD	<LOD	15.1 (<LOD–104)	66.7 (12.5–291)	1,049
	2003–2004	*	<LOD	<LOD	<LOD	11.6 (<LOD–23.4)	884

[a]The limit of detection for survey years 1999–2000, 2001–2002, and 2003–2004 were 14.6, 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.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-5. Weighted Arithmetic Mean and Unadjusted Standard Error of Mirex (Lipid Adjusted) Pooled 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) 2005–2010

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	*[e]	*	9
		2007–2008	*	*	6
		2009–2010	*	*	10
	20–39	2005–2006	3.88[f]	2.18	12
		2007–2008	*	*	15
		2009–2010	*	*	17
	40–59	2005–2006	6.39[f]	2.15	12
		2007–2008	4.25	0.31	16
		2009–2010	5.25	1.32	17
	≥60	2005–2006	5.32	0.61	15
		2007–2008	6.36	1.34	23
		2009–2010	4.89	0.44	21
Non-Hispanic white female	12–19	2005–2006	*	*	10
		2007–2008	*	*	7
		2009–2010	*	*	8
	20–39	2005–2006	*	*	16
		2007–2008	*	*	13
		2009–2010	*	*	19
	40–59	2005–2006	2.42	0.14	13
		2007–2008	2.05	0.28	17
		2009–2010	3.32	0.33	17
	≥60	2005–2006	3.51	0.24	17
		2007–2008	3.90	0.39	21
		2009–2010	4.42	0.4	22
Non-Hispanic black male	12–19	2005–2006	*	*	13
		2007–2008	*	*	6
		2009–2010	*	*	6
	20–39	2005–2006	2.68	0.59	6
		2007–2008	*	*	6
		2009–2010	*	*	7
	40–59	2005–2006	5.90	0.49	5
		2007–2008	16.8[f]	6.1	6
		2009–2010	6.44	1.04	7
	≥60	2005–2006	27.2[f]	10.1	5
		2007–2008	13.9	2.1	8
		2009–2010	14.2	4.1	9

Table 5-5. Weighted Arithmetic Mean and Unadjusted Standard Error of Mirex (Lipid Adjusted) Pooled 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) 2005–2010

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Non-Hispanic black female	12–19	2005–2006	*	*	14
		2007–2008	*	*	5
		2009–2010	*	*	6
	20–39	2005–2006	1.62	0.32	7
		2007–2008	*	*	8
		2009–2010	*	*	7
	40–59	2005–2006	5.92	0.65	7
		2007–2008	5.42	1.21	8
		2009–2010	5.03	0.84	7
	≥60	2005–2006	10.3	2.7	5
		2007–2008	24.0[f]	9.3	7
		2009–2010	7.49	1.68	7
Mexican American male	12–19	2005–2006	*	*	11
		2007–2008	*	*	6
		2009–2010	*	*	8
	20–39	2005–2006	*	*	9
		2007–2008	*	*	9
		2009–2010	*	*	8
	40–59	2005–2006	2.66	0.74	4
		2007–2008	4.37[f]	1.38	6
		2009–2010	3.08	0.83	8
	≥60	2005–2006	2.89	0.78	4
		2007–2008	11.0[f]	8.0	5
		2009–2010	5.1	1.27	5

Table 5-5. Weighted Arithmetic Mean and Unadjusted Standard Error of Mirex (Lipid Adjusted) Pooled 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) 2005–2010

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Mexican American female	12–19	2005–2006	*	*	16
		2007–2008	*	*	5
		2009–2010	*	*	7
	20–39	2005–2006	*	*	9
		2007–2008	*	*	8
		2009–2010	*	*	10
	40–59	2005–2006	1.84	0.34	6
		2007–2008	3.76[f]	1.3	6
		2009–2010	*	*	9
	≥60	2005–2006	2.84	0.37	3
		2007–2008	2.59	0.49	5
		2009–2010	4.04	0.97	6
All Hispanic male	12–19	2009–2010	*	*	11
	20–39	2009–2010	*	*	13
	40–59	2009–2010	4.58	1.27	13
	≥60	2009–2010	5.18	0.82	8
All Hispanic female	12–19	2009–2010	*	*	10
	20–39	2009–2010	*	*	14
	40–59	2009–2010	*	*	14
	≥60	2009–2010	4.13	0.55	11

[a]The limits of detection for survey years 2005–2006, 2007–2008, and 2009–2010 were 1.46, 1.4, and 2.19 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 eight persons.
[e]Not calculated: proportion of results below limit of detection was too high to provide a valid result.
[f]Standard error of the mean estimate is >30%.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-6. Geometric Mean and Selected Percentiles of Mirex (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	<LOD	<LOD	<LOD	1,853
	2001–2002	*	<LOD	<LOD	0.100 (<LOD–0.470)	0.410 (0.080–1.73)	2,257
	2003–2004	*	<LOD	<LOD	0.54 (<LOD–0.084)	0.093 (0.052–0.170)	1,951
Age group							
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	659
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	728
	2003–2004	*	<LOD	<LOD	<LOD	<LOD	592
≥20 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	1,194
	2001–2002	*	<LOD	<LOD	0.140 (<LOD–0.690)	0.470 (0.090–1.92)	1,529
	2003–2004	*	<LOD	<LOD	0.059 (<LOD–0.102)	0.106 (0.053–0.215)	1,359
Gender							
Males	1999–2000	*	<LOD	<LOD	<LOD	<LOD	887
	2001–2002	*	<LOD	<LOD	0.110 (<LOD–0.470)	0.370 (0.090–1.37)	1,052
	2003–2004	*	<LOD	<LOD	0.064 (<LOD–0.106)	0.108 (0.062–0.170)	949
Females	1999–2000	*	<LOD	<LOD	<LOD	<LOD	966
	2001–2002	*	<LOD	<LOD	0.090 (<LOD–0.510)	0.430 (0.070–1.79)	1,205
	2003–2004	*	<LOD	<LOD	<LOD	0.077 (<LOD–0.170)	1,002
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	<LOD	<LOD	<LOD	617
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	548
	2003–2004	*	<LOD	<LOD	<LOD	<LOD	459
Non-Hispanic blacks	1999–2000	*	<LOD	<LOD	0.090 (<LOD–0.220)	0.220 (<LOD–0.450)	398
	2001–2002	*	<LOD	0.090 (<LOD–0.240)	0.310 (0.090–1.41)	1.08 (0.170–3.02)	500
	2003–2004	*	<LOD	<LOD	0.112 (0.055–0.268)	0.256 (0.089–0.635)	484

Table 5-6. Geometric Mean and Selected Percentiles of Mirex (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	
Non-Hispanic whites	1999–2000	*	<LOD	<LOD	<LOD	<LOD	688
	2001–2002	*	<LOD	<LOD	0.100 (<LOD–0.610)	0.450 (0.080–1.79)	1,049
	2003–2004	*	<LOD	<LOD	<LOD	0.079 (<LOD–0.174)	884

[a]The limit of detection for survey years 1999–2000, 2001–2002, and 2003–2004 were 14.6, 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.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-7. Weighted Arithmetic Mean and Unadjusted Standard Error of Mirex (Whole Weight) Pooled 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) 2005–2010

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	*[e]	*	9
		2007–2008	*	*	6
		2009–2010	*	*	10
	20–39	2005–2006	0.027[f]	0.014	12
		2007–2008	*	*	15
		2009–2010	*	*	17
	40–59	2005–2006	0.048[f]	0.016	12
		2007–2008	0.031	0.003	16
		2009–2010	0.034	0.008	17
	≥60	2005–2006	0.036	0.004	15
		2007–2008	0.040	0.008	23
		2009–2010	0.030	0.003	21
Non-Hispanic white female	12–19	2005–2006	*	*	10
		2007–2008	*	*	7
		2009–2010	*	*	8
	20–39	2005–2006	*	*	16
		2007–2008	*	*	13
		2009–2010	*	*	19
	40–59	2005–2006	0.018	0.002	13
		2007–2008	0.014	0.002	17
		2009–2010	0.021	0.002	17
	≥60	2005–2006	0.026	0.002	17
		2007–2008	0.026	0.003	21
		2009–2010	0.027	0.002	22
Non-Hispanic black male	12–19	2005–2006	*	*	13
		2007–2008	*	*	6
		2009–2010	*	*	6
	20–39	2005–2006	0.016	0.004	6
		2007–2008	*	*	6
		2009–2010	*	*	7
	40–59	2005–2006	0.038	0.003	5
		2007–2008	0.109[f]	0.04	6
		2009–2010	0.041	0.008	7
	≥60	2005–2006	0.168[f]	0.062	5
		2007–2008	0.084	0.012	8
		2009–2010	0.076	0.023	9

Table 5-7. Weighted Arithmetic Mean and Unadjusted Standard Error of Mirex (Whole Weight) Pooled 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) 2005–2010

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
Non-Hispanic black female	12–19	2005–2006	*	*	14
		2007–2008	*	*	5
		2009–2010	*	*	6
	20–39	2005–2006	0.009	0.002	7
		2007–2008	*	*	8
		2009–2010	*	*	7
	40–59	2005–2006	0.038	0.004	7
		2007–2008	0.032	0.008	8
		2009–2010	0.028	0.005	7
	≥60	2005–2006	0.067	0.016	5
		2007–2008	0.146[f]	0.057	7
		2009–2010	0.043	0.01	7
Mexican American male	12–19	2005–2006	*	*	11
		2007–2008	*	*	6
		2009–2010	*	*	8
	20–39	2005–2006	*	*	9
		2007–2008	*	*	9
		2009–2010	*	*	8
	40–59	2005–2006	0.022[f]	0.007	4
		2007–2008	0.031[f]	0.01	6
		2009–2010	0.020	0.005	8
	≥60	2005–2006	0.022[f]	0.008	4
		2007–2008	0.074[f]	0.052	5
		2009–2010	0.031	0.008	5
Mexican American female	12–19	2005–2006	*	*	16
		2007–2008	*	*	5
		2009–2010	*	*	7
	20–39	2005–2006	*	*	9
		2007–2008	*	*	8
		2009–2010	*	*	10
	40–59	2005–2006	0.014	0.003	6
		2007–2008	0.024[f]	0.008	6
		2009–2010	*	*	9
	≥60	2005–2006	0.022	0.005	3
		2007–2008	0.018	0.003	5
		2009–2010	0.023	0.005	6
All Hispanic male	12–19	2009–2010	*	*	11
	20–39	2009–2010	*	*	13
	40–59	2009–2010	0.031	0.008	13
	≥60	2009–2010	0.032	0.005	8

Table 5-7. Weighted Arithmetic Mean and Unadjusted Standard Error of Mirex (Whole Weight) Pooled 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) 2005–2010

Category	Age (years)	Survey years[a]	Weighted arithmetic mean[b]	Unadjusted standard error[c]	Number of pools[d]
All	12–19	2009–2010	*	*	10
Hispanic	20–39	2009–2010	*	*	14
female	40–59	2009–2010	*	*	14
	≥60	2009–2010	0.027	0.003	11

[a]The limits 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 eight persons.
[e]Not calculated: proportion of results below limit of detection was too high to provide a valid result.
[f]Standard error of the mean estimate is >30%.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

mirex. There is a slight possibility of exposure for workers involved in dredging activities (e.g., sediment remediation work performed by the Corps of Engineers).

Chlordecone. Chlordecone has not been produced since 1975 or used in the United States since 1978 when all registered uses of the product were canceled. The potential for exposure of the general population, therefore, is relatively small and should continue to diminish over time. Members of the general population may be exposed to low concentrations of chlordecone primarily through consumption of contaminated foodstuffs, in particular contaminated fish and shellfish from the James River in Virginia. No dietary intake estimates are available (FDA 1990, 1991, 1992) since chlordecone has been so infrequently found in foodstuffs in recent years. Chlordecone exposure from drinking water has not been found to constitute significant human exposure since chlordecone is relatively insoluble in water and rapidly adsorbs to sediment (EPA 1978a).

No information was located for the general population on chlordecone concentrations in human adipose tissue or blood as this compound was not included in any major national study (e.g., National Human Adipose Study). Chlordecone was detected in 9 of 298 samples of human milk collected in the southern United States; however, the detection limit was relatively high (1 μg/kg) (EPA 1978a).

With regard to occupational exposures, chlordecone was detected in blood samples from workers at the Life Sciences Products Company in Hopewell, Virginia. Chlordecone levels in the blood of 32 workers at the manufacturing plant ranged from 0.165 to 26.0 µg/mL (ppm) (Epstein 1978). The mean blood level of workers exhibiting symptoms of nervousness and tremors was 8.48 µg/mL, compared to a mean of 1.57 µg/mL in workers exhibiting no symptoms (Epstein 1978). In another occupational study, Cannon et al. (1978) reported maximum chlordecone blood levels in workers at the Hopewell facility of 11.8 µg/mL. Chlordecone blood levels of workers who reported illness averaged 2.53 µg/mL, while blood levels for workers reporting no illness averaged 0.6 µg/mL.

In 1975, when chlordecone was still being produced, over half of the workers at a manufacturing plant developed clinical illness characterized by nervousness, tremor, weight loss, opsoclonus, pleuritic and joint pain, and oligospermia (Cannon et al. 1978). During the years of production, chlordecone was also detected in family members of the plant workers at the Life Sciences Products Company in Hopewell, Virginia. Although half of the workers at the plant had clinical signs of chlordecone poisoning, such signs were detected in only two family members who washed contaminated clothes (Cannon et al. 1978). Another study also found higher chlordecone levels in members of chlordecone workers' families compared with families of workers at other local industries or other community residents (Taylor et al. 1978). Such illness could have been mitigated by appropriate occupational health measures that would prevent the transport of contaminated materials from the workplace, such as not bringing work clothes home (Knishkowy and Baker 1986).

Current occupational exposure is most likely to occur for workers employed at waste disposal sites or those engaged in remediation activities associated with the clean-up or removal of soils or sediments that are contaminated with chlordecone.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

A susceptible population will exhibit a different or enhanced response to mirex and chlordecone than will most persons exposed to the same level of mirex or chlordecone in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting endproduct metabolites). For these

reasons, the elderly with declining organ function and the youngest of the population with immature and developing organs are generally expected be more vulnerable to toxic substances than healthy adults.

Review of the literature regarding toxic effects of mirex and chlordecone did not reveal any human populations that are known to be unusually sensitive to mirex or chlordecone. However, based on knowledge of the toxicities of mirex and chlordecone, some populations can be identified that may demonstrate unusual sensitivity to these chemicals. Those with potentially high sensitivity to mirex include the very young. Those with potentially high sensitivity to chlordecone include juvenile and elderly person and persons being treated with some classes of antidepressants that affect serotonin or the anticonvulsant, diphenylhydantoin.

In experimental animals, mirex administered within the week after birth causes a high incidence of cataracts and other lesions of the lens (Chernoff et al. 1979a; Gaines and Kimbrough 1970; Rogers and Grabowski 1984; Scotti et al. 1981). These effects were observed whether the neonatal animals received mirex through the milk of lactating dams or directly by gavage. Although it is unclear whether the lens of humans also undergoes a similar period of susceptibility, the possibility exists that newborn children may also develop cataracts if exposed to mirex shortly after birth.

Studies in rats have demonstrated that certain treatments exacerbate the tremors associated with chlordecone exposure. These include pretreatment with the anticonvulsant, diphenylhydantoin (Hong et al. 1986; Tilson et al. 1985, 1986), and treatment with the nonselective serotonergic receptor agonist, quipazine (Gerhart et al. 1983). Therefore, persons being treated with diphenylhydantoin for epilepsy or quipazine for depression may be likely to experience more severe tremors upon exposure to high levels of chlordecone. Extrapolating from the effects seen in animals with quipazine, it might be likely that persons taking the prescription drug Prozac®, a SSRI used to treat depression, will also experience more severe tremors. Furthermore, the elderly may be a susceptible population because serotonin metabolism is increased during aging (Walker and Fishman 1991).

Studies in animals have also shown that juvenile animals experience a higher death rate than adults following exposure to chlordecone at equivalent mg/kg doses (Huber 1965). No explanation was given for these findings, but similar sensitivities may exist in children. Furthermore, although inhibition of Na+-K+ATPase, Mg2+ATPase, and Ca2+ATPase activities have not been definitively shown to be the mechanism underlying chlordecone toxicity, sufficient evidence exists to suggest that their inhibition may be involved in a number of adverse effects. Neonatal rats have shown a greater inhibition of these

enzymes than adult rats (Jinna et al. 1989). This provides additional support for the suggestion that infants and young children may represent a susceptible population to the toxic effects of chlordecone.

In contrast, a study of developing postnatal rats has shown that the young may be less susceptible to at least one of the toxic effects of chlordecone. Young and adolescent rats show less potentiation of carbon tetrachloride toxicity than adult rats (Cai and Mehendale 1993). This may be due to a combination of incomplete development of the microsomal enzyme systems and a higher level of hepatic regenerating activity in the very young rats. In adolescent rats (35 and 45 days old), the microsomal enzyme activity is comparable to adult levels, but the level of damage is still less than in adult rats (60 days old). This may be due to that fact that hepatic regenerating activity remained higher in the adolescents than in the adults.

In studies performed by Sobel and coworkers (Sobel et al. 2005, 2006; Wang et al. 2008), chronic exposure of systemic lupus erythematosus-prone female (NZB x NZW) F1 mice to chlordecone via subcutaneously-implanted pellets significantly shortened the time to onset of elevated autoantibody titers and renal disease in a dose-related manner. These effects were not seen in nonlupus-prone BALB/c mice. These results indicate that humans with lupus may be particularly sensitive to chlordecone toxicity.

Members of the general population who currently have potentially high exposures to mirex include recreational and subsistence fishers who may consume large quantities of fish and shellfish from waterbodies with mirex contamination, hunters who consume game species that may be contaminated with mirex, populations living near sites where mirex was manufactured or waste disposal sites contaminated with mirex, or populations living in areas where mirex was used extensively for fire ant control.

Mirex contamination has triggered the issuance of several human health advisories nationwide. In 1993, mirex was identified as the causative pollutant in eight fish consumption advisories in three different states (Ohio, New York, and Pennsylvania) (EPA 1993). In 2019, New York still had mirex fish advisories in six waterbodies (Lake Ontario, Niagara River downstream of Niagara Falls, Irondequoit Bay, Oswego River, Salmon River, and St. Lawrence River) (NYS 2019).

Persons living in areas where mirex has been used for fire ant control or near where it was manufactured may be at increased risk of exposure. Human tissue samples (unspecified) taken from 186 people at sites treated with mirex over the previous 10 years had mirex residues in the range of <1–1.32 μg/g (ppm) (mean concentration, 0.38 μg/g) (EPA 1980). A 1975–1976 survey of 624 human adipose tissue samples

from subjects living in eight southern states where mirex had been used for fire ant control indicated that 10.2% of the population in the area had detectable levels of mirex at a geometric mean concentration of 0.286 µg/g (ppm). Populations living in two states, Texas and North Carolina, had no detectable mirex residues in their tissues, whereas 51.1% of the samples from populations in Mississippi had detectable levels (mean concentration, 0.290 µg/g) (Kutz et al. 1985). Mirex was detected in human adipose tissue samples from residents of northeast Louisiana during the late 1970s (Greer et al. 1980). Concentrations of mirex in adipose tissue collected during surgery and during postmortem examinations ranged from 0.01 to 0.60 µg/g (ppm) with a mean mirex concentration of 0.14 µg/g. Human adipose tissue samples from northeastern Louisiana, an agricultural area, contained detectable amounts of mirex in 20 of 22 samples in 1977 at a mean concentration of approximately 0.15 µg/g (ppm), 10 of 10 samples in 1980 at a mean concentration of 0.25 µg/g, and only 2 of 10 samples in 1984 at a mean concentration of 0.15 µg/g (Holt et al. 1986).

A comparison of mirex residues in adipose tissue samples collected between 1979 and 1981 from residents of Kingston, Ontario (a city located on Lake Ontario), and residents of Ottawa, Ontario, indicated that persons living in Kingston had significantly higher mirex and photomirex residues than those in Ottawa (27 and 9 ng/g [ppb], respectively, in Kingston versus 11 and 6 ng/g, respectively, in Ottawa). Males from Kingston had significantly higher levels of mirex (38 ng/g) than females from the area (12 ng/g); this gender difference was not explained or seen in the Ottawa samples (Williams et al. 1984). A subsequent 1984 study examined mirex levels in six additional cities on the Canadian portion of Lake Ontario. The overall mean mirex residue in human adipose tissue was 11±13 ng/g (ppb) (males, 12±15 ng/g; females, 9.6±10 ng/g) (Williams et al. 1988).

Mirex levels in the blood of pregnant women in Jackson, Mississippi, and the Mississippi Delta area where mirex was extensively used were correlated with the health of the infants they bore. The mean mirex level in maternal blood was 0.54 µg/L (ppb) for 106 samples; however, mirex levels in the blood of the infants were not correlated with differences in gestation times, Apgar score, or other problems at birth. Only three children with neurological problems had mothers with pesticide levels, including mirex, above the mean levels (Lloyd et al. 1974).

In 1977, mirex was detected in human milk and colostrum samples of women living in upstate New York. Milk from women in Oswego and Rochester, areas adjacent to Lake Ontario (known to be contaminated with mirex), was compared with milk from women in Albany (considered to be free from mirex contamination). Mean mirex concentrations from women in each area were as follows: 0.057 ng/g in

colostrum (n=24) and 0.07 ng/g in milk (n=6), Albany; 0.51 ng/g in colostrum (n=18) and 0.120 ng/g in milk (n=16), Oswego; and 0.035 ng/g in colostrum (n=4) and 0.162 ng/g in milk (n=6), Rochester. Only 2 of the 28 milk samples (both from Oswego) were below the detection limit of 0.01 ng/g (ppb), while 16 of 24 colostrum samples in Albany, 10 of 18 colostrum samples from Oswego, and 2 of 4 colostrum samples from Rochester were below the detection limit. None of the women reported eating freshwater fish, a possible source of the mirex contamination (Bush et al. 1983).

Members of the general population currently having potentially higher exposure to chlordecone include recreational and subsistence fishers who may consume large quantities of fish and shellfish from waterbodies with chlordecone contamination, populations living near sites where chlordecone was manufactured, or waste disposal sites contaminated with chlordecone.

Chlordecone contamination has triggered the issuance of one human health advisory. As of September 1993, chlordecone was identified as the causative pollutant in an advisory issued by the State of Virginia for the 113 miles of the James River Estuary. The advisory extends from Richmond, Virginia, downstream to the Hampton-Norfolk Bridge Tunnel including all tributaries to the James River (EPA 1993).

The only data on chlordecone residues in populations living near a production site are historic and were collected several decades ago. The EPA initiated a community survey in August 1975 shortly after production of chlordecone was halted to determine chlordecone levels in blood of persons living in the vicinity of the Hopewell manufacturing plant. Two hundred nine community residents, none of whom had ever been employed at the Allied Chemical plant or Life Sciences Products Company (LSPC) were surveyed. Chlordecone blood levels were <5 ppb in 39% of residents living 0.25 miles south of the LSPC plant, in 7.7% of residents living 0.25 miles north of the LSPC plant, in 5.9% of residents living 0.5 miles from the site, in 2.6% of residents living 0.75 miles from the site, and in 3.3% of residents living 1 mile from the site. Chlordecone blood levels were approximately linear as a function of proximity to the LSPC site (Epstein 1978). No additional information was located on current chlordecone levels in residents of the Hopewell, Virginia, area.

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 mirex and chlordecone 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 mirex and chlordecone.

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.

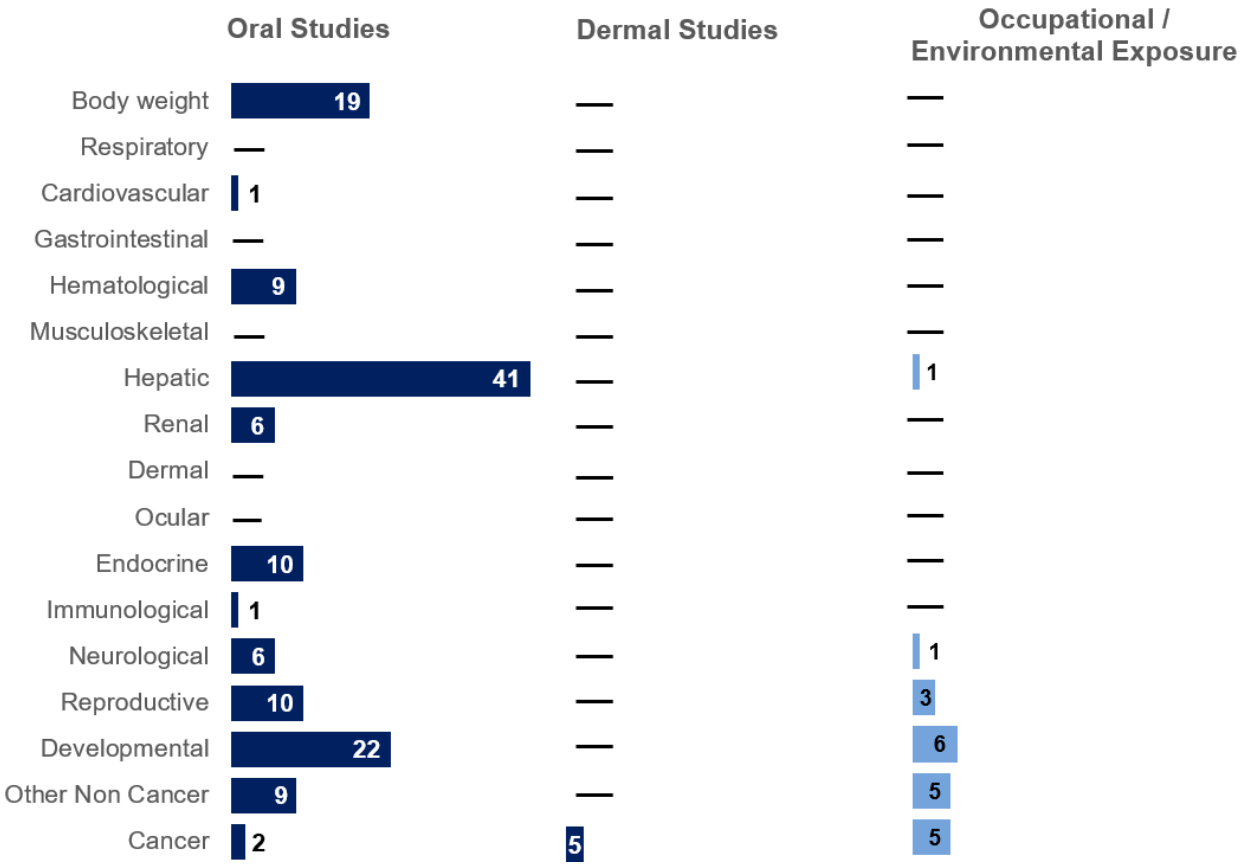
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to mirex and chlordecone that are discussed in Chapter 2 are summarized in Figures 6-1 and 6-2, respectively. The purpose of these figures is to illustrate the information concerning the health effects of mirex and chlordecone. 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.

Epidemiological data regarding potential health effects in humans exposed to mirex are essentially limited to investigations using mirex levels in blood samples (one study included placental mirex) as the basis for exposure data. Human data for chlordecone come from reports of an occupational cohort of workers exposed during the manufacture of chlordecone and from investigations using chlordecone levels in blood samples or cord blood as the basis for exposure data. In the occupational cohort, exposure was classified as intermediate-to-chronic; no precise duration or level of exposure to chlordecone could be quantified from these reports. A single route of exposure could not be established for this worker population; poor hygiene in the plant made inhalation, oral, and dermal exposure routes likely to occur. The information on human exposure in this study is extremely limited because of the possible contamination with the precursor used to manufacture chlordecone, hexachloropentadiene.

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

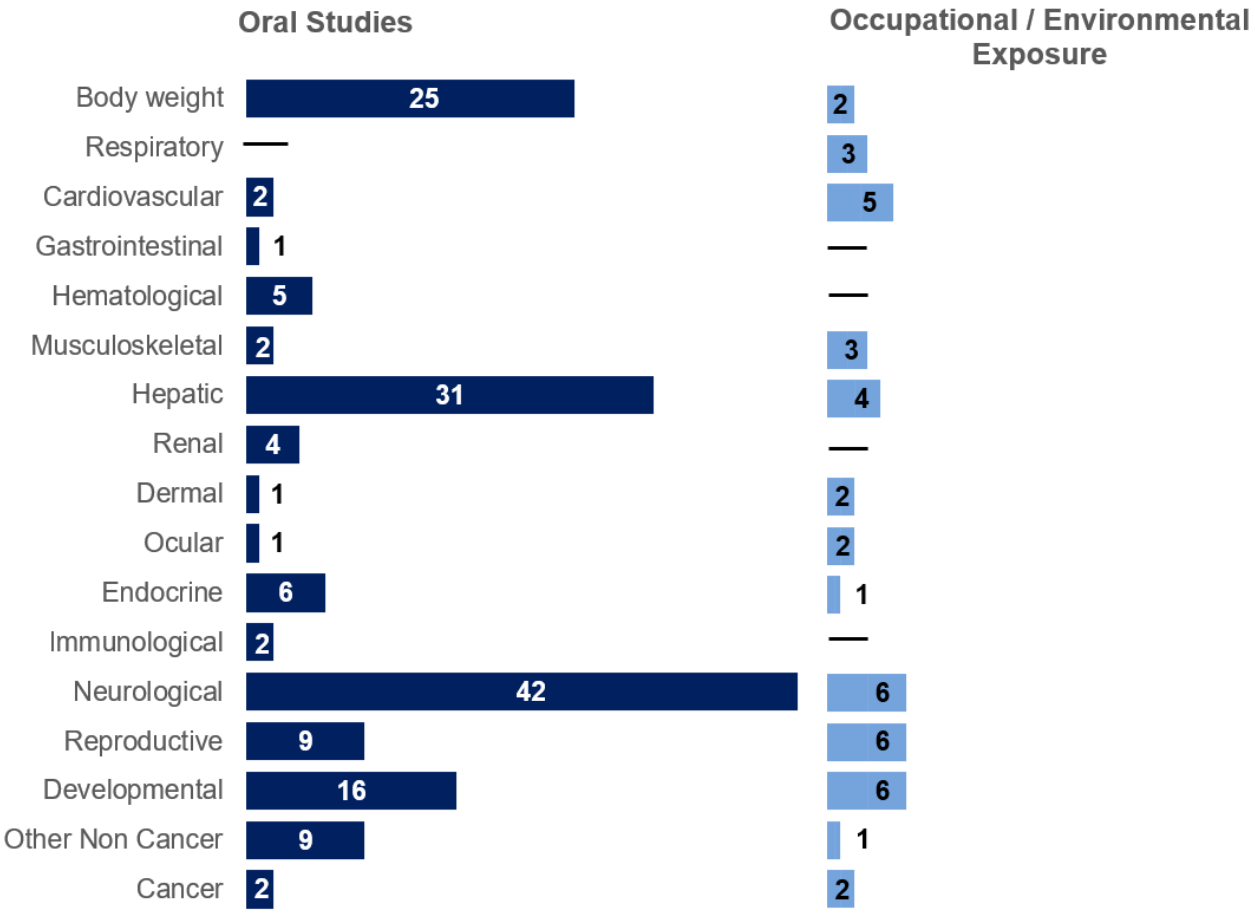
Potential body weight, liver, and developmental effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect and those examining multiple endpoints. No inhalation studies were located.

Figure 6-2. Summary of Existing Health Effects Studies on Chlordecone By Route and Endpoint*

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



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect and those examining multiple endpoints. No inhalation or dermal studies in humans or animals were located.

The database for the health effects of mirex and chlordecone following oral administration in experimental animals is more substantial. However, no information is available on the health effects of inhalation exposure to mirex or chlordecone in animals.

People living near hazardous waste sites may be exposed to mirex or chlordecone primarily via dermal contact with or ingestion of contaminated soils since mirex and chlordecone are bound to soil particles. Another possible mechanism for oral exposure to mirex and chlordecone is the ingestion of pesticide-laden dust carried by the wind from a waste site or treated field and deposited on garden crops. Ingestion of contaminated water is not likely to be a significant route of exposure since mirex and chlordecone have very limited water solubility and are generally not found in groundwater. Likewise, inhalation exposure to mirex and chlordecone via volatilization from contaminated media is not a likely major route of exposure since mirex and chlordecone are essentially nonvolatile. For the general population, the primary route of exposure to mirex and chlordecone is via ingestion of residues on contaminated foods. Therefore, information on the toxicity following ingestion and dermal exposure is most relevant for individuals living in the vicinity of hazardous waste sites.

6.2 Identification of Data Needs

Missing information in Figures 6-1 and 6-2 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. No acute-duration inhalation MRLs were derived for mirex or chlordecone because no exposure-response inhalation data were located. No acute-duration oral MRL was derived for mirex because the lowest LOAEL from available acute-duration oral studies was for serious effects (heart block and arrhythmias in fetuses from dams exposed during gestation) and the effects were observed at the lowest dose tested (Grabowski 1983). An acute-duration oral MRL was derived for chlordecone based on neurological effects in an animal study. Human data for mirex are essentially limited to evaluations of health outcomes associated with mirex blood levels for which exposure-response data and information regarding duration of exposure are not available. Human data for chlordecone are limited as well. Data are available from one cohort of workers involved in the production of chlordecone (Cannon et al. 1978; Guzelian et al. 1980; Martinez et al. 1978; Sanborn et al. 1979; Taylor 1982, 1985; Taylor et

al. 1978). No particular exposure route or exposure duration could be established and the workers were likely exposed to other toxic substances as well. Other available human studies consist of evaluations of health outcomes associated with chlordecone blood levels for which exposure-response data are not available. Oral exposure to mirex or chlordecone from food sources grown in mirex- or chlordecone-contaminated soil is the most likely source of mirex or chlordecone blood levels at present because mirex and chlordecone have not been used as pesticides for decades, although they persist in soil. Additional animal studies could be designed to determine an appropriate basis for deriving acute-duration inhalation MRLs for mirex and chlordecone and an acute-duration oral MRL for mirex. Inhalation data do not appear to be particularly necessary because significant inhalation exposure is not likely since neither mirex nor chlordecone readily enter the air from other media where they may be present.

Intermediate-Duration MRLs. Limited human data are not suitable for MRL derivation. No intermediate-duration inhalation MRLs were derived for mirex or chlordecone because no exposure-response inhalation data were located. No intermediate-duration oral MRL was derived for mirex because the most suitable point of departure based on available data is a LOAEL for endocrine effects in weanling rats in the absence of a NOAEL. Application of a total uncertainty factor of 1,000 (10 for extrapolation from a LOAEL to a NOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) would result in an intermediate-duration oral MRL that is lower than the chronic-duration oral MRL derived for mirex. An intermediate-duration oral MRL was derived for chlordecone based on neurological effects reported in a rat study (Linder et al. 1983). Additional animal studies could be designed to determine an appropriate basis for deriving intermediate-duration inhalation MRLs for mirex and chlordecone and an intermediate-duration oral MRL for mirex. Inhalation data do not appear to be particularly necessary because significant inhalation exposure is not likely since neither mirex nor chlordecone readily enter the air from other media where they may be present.

Chronic-Duration MRLs. Limited human data are not suitable for MRL derivation. No chronic-duration inhalation MRLs were derived for mirex or chlordecone because no exposure-response inhalation data were located. A chronic-duration oral MRL was derived for mirex based on histopathologic liver effects in a 2-year rat study (NTP 1990). A chronic-duration oral MRL was derived for chlordecone based on renal effects in a 2-year rat study (Larson et al. 1979b). Additional animal studies could be designed to determine an appropriate basis for deriving chronic-duration inhalation MRLs for mirex and chlordecone. However, inhalation data do not appear to be particularly necessary because significant inhalation exposure is not likely since neither mirex nor chlordecone readily enter the air from other media where they may be present.

Health Effects.

Hepatic Effects. There is some evidence of hepatic effects associated with occupational exposure to chlordecone when it was being produced (Guzelian 1982a, 1982b; Taylor 1982, 1985; Taylor et al. 1978). There is limited evidence of mirex-related effects on CYP-induced metabolism (Lambert et al. 1992). A variety of oral studies in animals identify the liver as a target of mirex and chlordecone toxicity. Additional animal data do not appear necessary. However, human populations with potential for exposure to mirex or chlordecone should be monitored for possible exposure-related hepatic effects.

Neurological Effects. Examinations of workers occupationally exposed to chlordecone during its production revealed some signs of neurotoxicity (e.g., tremors, anxiety, visual difficulties, irritability, poor recent memory, blurred vision, headaches) (Cannon et al. 1978; Taylor 1982, 1985; Taylor et al. 1978). Sural nerve biopsies from workers with the most notable signs of neurotoxicity revealed decreased numbers of small myelinated and unmyelinated axons (Martinez et al. 1978). Neurological effects have been widely reported in animal studies that employed oral exposure to mirex or chlordecone. Additional animal studies to not appear necessary. However, human populations with potential for exposure to mirex or chlordecone should be monitored for possible exposure-related neurological effects.

Renal Effects. No information was located regarding mirex- or chlordecone-induced renal effects in humans. However, the kidney was identified as a target of mirex and chlordecone toxicity in 2-year rat studies (Larson et al. 1979b; NTP 1990). Additional animal studies do not appear necessary. However, human populations with potential for exposure to mirex or chlordecone should be monitored for possible exposure-related renal effects.

Reproductive Effects. There is some evidence of adverse effects on the male reproductive system associated with occupational exposure to chlordecone when it was being produced (Guzelian 1982a, 1982b; Taylor 1982, 1985; Taylor et al. 1978). Results from two human studies provide evidence that mirex in the blood may be associated with female reproductive effects (Grindler et al. 2015; Upson et al. 2013). A variety of oral studies in animals identify the reproductive system as a target of mirex and chlordecone toxicity. Additional animal data do not appear necessary. However, human populations with potential for exposure to mirex or chlordecone should be monitored for possible exposure-related reproductive effects.

Developmental Effects. Limited results from human studies provide suggestive evidence that blood levels of mirex (Araki et al. 2018; Puertas et al. 2010) or chlordecone (Boucher et al. 2013; Cordier et al. 2015; Dallaire et al. 2012; Kadhel et al. 2014) may be associated with developmental effects. A variety of oral studies in animals identify developmental endpoints as targets of mirex and chlordecone toxicity. Additional animal data do not appear necessary. However, human populations with potential for exposure to mirex or chlordecone should be monitored for possible exposure-related developmental effects.

Cancer. Limited human data provide little evidence for mirex- or chlordecone-induced carcinogenicity. In population-based, case-control studies, lipid-adjusted serum mirex was associated with risk of non-Hodgkin's lymphoma (Spinelli et al. 2007) and plasma chlordecone was associated with risk of prostate cancer (Multigner et al. 2010). Other human studies that evaluated potential associations between blood mirex and selected cancer endpoints found no evidence for an association (Itoh et al. 2009; Koutros et al. 2015a, 2015b; Moysich et al. 1998; Sawada et al. 2010). The carcinogenicity of mirex and chlordecone has been demonstrated in rats and mice (NCI 1976; NTP 1990). Additional animal carcinogenicity studies do not appear necessary. However, human populations with potential for exposure to mirex or chlordecone should be monitored for possible exposure-related carcinogenic effects.

Epidemiology and Human Dosimetry Studies. A single epidemiological cohort was located for occupational exposure to chlordecone (Cannon et al. 1978; Guzelian et al. 1980; Sanborn et al. 1979; Taylor 1982, 1985). The routes of exposure in this study were probably mixed because of the poor hygiene in the chlordecone manufacturing plant (Taylor 1982, 1985). The most likely identifiable subpopulations exposed to mirex or chlordecone would be individuals who live in areas where these pesticides may persist in environmental media or have become bioconcentrated in food sources. Well-designed epidemiological studies of these subpopulations specifically examining a wide range of health endpoints would be useful to evaluate possible human health outcomes similar to those observed in animal studies.

Biomarkers of Exposure and Effect. The biomarkers of exposure to mirex and chlordecone are well established and specific to each compound. The known biomarkers of exposure to mirex are its concentrations in blood, fat, feces, and milk. The known biomarkers of exposure for chlordecone include its concentrations in blood, saliva, and tissues, and concentrations of chlordecone or its metabolite in

feces or bile. Of the biomarkers of exposure listed for chlordecone, the blood is the most useful biological material to monitor in order to determine exposure to chlordecone.

Several potential biomarkers for the effects of mirex and chlordecone have been identified. These include levels of urinary D-glucaric acid to measure hepatic enzyme induction, elevated urinary protein and renal histopathology to assess renal damage, electromyography and tremorograms to assess tremor, oculography to measure visual disturbances, and sperm counts and tests of motility to assess toxic effects on sperm (Guzelian 1985; Larson et al. 1979b; Taylor et al. 1978). However, these biomarkers are not specific for either mirex or chlordecone. Measurement of serum bile acids may be helpful in assessing hepatobiliary function after exposure to chlordecone. Examination of this possibility and further investigation of other serum biomarkers of effect in populations exposed to mirex or chlordecone would be helpful.

Absorption, Distribution, Metabolism, and Excretion. No data were located regarding absorption of mirex in humans following inhalation, oral, or dermal exposure. Limited epidemiological data were located regarding the distribution and excretion of mirex following inhalation, oral, and dermal exposure. Mirex is not metabolized by humans or animals. There are a number of animal studies describing absorption, distribution, metabolism, and excretion of mirex following oral exposure. Information is available to assess the relative rates and extent of these toxicokinetic parameters by the oral route. Most of the toxicokinetic data, however, involve acute exposures to mirex; only very limited data deal with intermediate or chronic exposures. Additional intermediate and chronic data would be useful to adequately assess the rates and extent of the toxicokinetic parameters for these durations. Limited animal data were located regarding the absorption, distribution, and excretion of mirex following inhalation exposure. Additional acute-, intermediate-, and chronic-duration data would be useful to adequately assess the relative rates and extent of the toxicokinetic parameters by this route. No animal data were located for the toxicokinetic parameters by the dermal exposure route.

Limited occupational data exist regarding absorption, distribution, metabolism, and/or excretion of chlordecone by humans. There are a number of animal studies describing the absorption, distribution, metabolism, and excretion of chlordecone following oral exposure. Most of these data concern acute exposures. However, the available data are sufficient to assess the relative rates and extent of the pharmacokinetics following oral exposure. Dermal absorption occurs only to a limited extent. No studies were located regarding distribution, metabolism, or excretion following dermal exposure. No animal data were located regarding absorption, distribution, metabolism, or excretion of chlordecone following

inhalation exposure. Additional acute-, intermediate-, and chronic-duration data would be useful to adequately compare the toxicokinetic parameters across all routes of exposure.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of mirex and chlordecone have been studied in animals. However, information on the toxicokinetics of mirex and chlordecone in humans is very limited. Furthermore, little information is available regarding interspecies differences in the kinetics of mirex. Toxicokinetic studies have been performed for chlordecone using multiple animal species. Based on the available data, rats, guinea pigs, and hamsters are not good animal models for studying chlordecone metabolism in humans because they do not convert chlordecone to chlordecone alcohol (Fariss et al. 1980; Guzelian et al. 1981; Houston et al. 1981). Gerbils and pigs were found to be the most practical animal models of chlordecone metabolism in humans because they converted chlordecone to chlordecone alcohol (Houston et al. 1981; Soine et al. 1983). Additional studies of various animal species would be useful to determine the most appropriate animal model(s) to predict the toxicokinetics of mirex and chlordecone in humans.

Children's Susceptibility. Results from animal studies suggest that the fetus and newborn may be more sensitive than adults to mirex or chlordecone toxicity. Mirex administered within 1 week after birth caused a high incidence of cataracts and other lesions of the lens in experimental animals. Infants and young children should be monitored for potential mirex- or chlordecone-related effects, particularly in areas with potential for significant exposure to these persistent pesticides.

Physical and Chemical Properties. The physical and chemical properties of mirex and chlordecone are sufficiently documented to permit estimation of their environmental fate. No further information is necessary.

Production, Import/Export, Use, Release, and Disposal. Mirex and chlordecone are no longer being produced or used in the United States. Mirex was most commonly used from 1962 to 1976 as an insecticide to control fire ants. Mirex was also used as a flame retardant from 1959 to 1972 in various coatings, plastics, rubber, paint, paper, and electrical goods. Until 1976, chlordecone was used as an insecticide on bananas, non-bearing citrus trees, tobacco, and ornamental shrubs. It was also used in household products such as ant and roach traps. However, all registered products containing mirex and chlordecone were canceled in 1977 and 1978, respectively. Since mirex and chlordecone are not flammable and are very stable in the environment, many disposal methods have proven unsuccessful. Since mirex is not identified by EPA as a hazardous waste under SARA Title III, no regulatory

information is available for the disposal of mirex. However, the recommended method of disposal for mirex is incineration. Efficient disposal methods exist for chlordecone. Chlordecone is considered an EPA hazardous waste and must be disposed of according to EPA regulations.

Environmental Fate. Mirex and chlordecone released to the environment partition to soil and sediment. Small amounts may remain dissolved in water. Mirex and chlordecone released to the atmosphere are eventually deposited on soil or surface waters. On the surface of soil or water, mirex undergoes photolysis with the subsequent loss of a chlorine atom. Both compounds are resistant to aerobic degradation, although some anaerobic biodegradation does occur. When not exposed to sunlight or anaerobic conditions, mirex and chlordecone persist in soil, particularly sediments, for many years. Additional information on the persistence of mirex and chlordecone in water and soil would be useful.

Bioavailability from Environmental Media. Both mirex and chlordecone can be absorbed following oral exposure, although chlordecone is more readily absorbed than mirex. No data were located regarding absorption of mirex following dermal exposure. Limited animal data indicate that dermal absorption of chlordecone is low. Information regarding the bioavailability of mirex and chlordecone from oral exposure via contaminated food sources and dermal contact with contaminated soils would be helpful, particularly for populations living near areas where mirex and/or chlordecone were used in the past.

Food Chain Bioaccumulation. Both mirex and chlordecone are highly lipophilic and, therefore, have high bioconcentration potentials. They are bioaccumulated in aquatic food chains with virtually no degradation of the compounds by exposed organisms. Uptake and bioaccumulation of mirex in terrestrial food chains have also been shown to occur. No further information is necessary. Only limited information is available on uptake and bioaccumulation of chlordecone in terrestrial food chains, and little uptake of chlordecone by plants was observed. Additional information on uptake of chlordecone in plants under field conditions would be helpful.

Exposure Levels in Environmental Media. Environmental monitoring data are available for mirex levels in air, water, soil, and sediment. Limited information on mirex concentrations in groundwater is available; however, because mirex binds tightly to organic matter in soil, additional leaching data are not necessary. Data on atmospheric releases and levels of chlordecone are available only for 2 years (1974–1975) of its production at the Hopewell, Virginia facility; however, since chlordecone production in the United States ceased in 1975 and because most of the chlordecone produced was exported or was used in

insect bait traps so that it was not widely dispersed in the environment, no additional current information on chlordecone in the atmosphere is required. Historic chlordecone levels in surface waters, soils, and sediments in the vicinity of the Hopewell, Virginia facility have been well characterized. Because chlordecone binds tightly to organic matter in soil, leaching into groundwater is not anticipated to occur extensively. Minimal information was found on the uptake of mirex and chlordecone by plants grown under field conditions. Adequate information on mirex and chlordecone levels in fish and shellfish are available. Further information on foods other than fish and shellfish, particularly in foods grown in areas where mirex was used as a pesticide, would be helpful in estimating current human and animal intake.

Exposure Levels in Humans. Mirex has been detected in human adipose tissue, blood, and milk. Because of the lipophilic nature of mirex, most determinations of exposure are based on residues found in adipose tissue. Higher levels in tissue have been correlated with areas of mirex usage, manufacture, or disposal at waste sites. Chlordecone has not been detected in human adipose tissue or in blood samples from the general population, although it has been detected in human milk samples. Adequate information is available regarding chlordecone levels in blood of occupationally exposed workers and their families during 1974–1975 employed at the Hopewell, Virginia site. Additional information for mirex and chlordecone would be helpful in determining areas with greatest potential for human exposure.

Exposures of Children. Fetuses and nursing infants may be exposed to mirex or chlordecone via their mothers. Available animal data indicate that early stages of life may be relatively sensitive timepoints for mirex or chlordecone toxicity. Areas where mirex or chlordecone may persist in soil or food sources should be monitored for potential pre- and postnatal exposure.

Analytical Methods. Improvements in detection sensitivity for mirex and chlordecone in environmental media would be useful for monitoring these pesticides in areas with potential for significant exposure.

6.3 Ongoing Studies

No ongoing studies were identified for mirex or chlordecone.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding mirex and chlordecone 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 mirex and chlordecone.

Table 7-1. Regulations and Guidelines Applicable to Mirex and Chlordecone

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 1992, 2009
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	No data	EPA 2012
	National primary drinking water regulations	No data	
	RfD		
	Mirex	0.0002 mg/kg/day	IRIS 1992
	Chlordecone	0.0003 mg/kg/day	IRIS 2009
WHO	Drinking water quality guidelines	Mirex excluded from guideline value derivation because unlikely to occur in drinking water	WHO 2017
FDA	EAFUS	No data[a]	FDA 2013
	Cancer		
ACGIH	Carcinogenicity classification	No data	ACGIH 2016
HHS	Carcinogenicity classification		
	Mirex	Reasonably anticipated to be a human carcinogen[b]	NTP 2016b
	Chlordecone	Reasonably anticipated to be a human carcinogen[b]	NTP 2016a
EPA	Carcinogenicity classification		
	Mirex	No data	IRIS 1992

Table 7-1. Regulations and Guidelines Applicable to Mirex and Chlordecone

Agency	Description	Information	Reference
	Chlordecone	Likely to be carcinogenic to humans	IRIS 2009
IARC	Carcinogenicity classification		
	Mirex	Group 2B[c]	IARC 1979
	Chlordecone	Group 2B[c]	IARC 1979
	Occupational		
ACGIH	TLV	No data	ACGIH 2016
OSHA	PEL (8-hour TWA) for general industry, construction, and shipyards	No data	OSHA 2016a, 2016b, 2017
NIOSH	REL (up to 10-hour TWA)		
	Chlordecone	0.001 mg/m^3[d]	NIOSH 2016
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
DOE	PACs-air		DOE 2016a
	Mirex		
	PAC-1[e]	6.3 mg/m^3	
	PAC-2[e]	69 mg/m^3	
	PAC-3[e]	410 mg/m^3	
	Chlordecone		
	PAC-1[e]	1.6 mg/m^3	
	PAC-2[e]	17 mg/m^3	
	PAC-3[e]	100 mg/m^3	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]Based on sufficient evidence of carcinogenicity from studies in experimental animals.
[c]Group 2B: Possibly carcinogenic to humans.
[d]Potential occupational carcinogen.
[e]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2016b).

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

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies were identified for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: No acute-duration oral MRL was derived for mirex because serious effects (arrhythmias in neonatal pups from maternal exposure during gestation) were observed at the lowest dose tested (0.1 mg/kg/day) (Grabowski 1983). ATSDR does not derive MRLs based on serious effects in the absence of identified NOAEL values.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: Intermediate-duration oral studies in humans are lacking for mirex. The most suitable animal study provides a LOAEL of 0.67 mg/kg/day for endocrine effects (dilation of rough endoplasmic reticulum cisternae of the thyroid) in weanling Sprague-Dawley rats (Singh et al. 1985). Application of a total uncertainty factor of 1,000 (10 for extrapolation from a NOAEL to a LOAEL, 10 for animal to human extrapolation, and 10 for human variability)and a modifying factor of 3 to be protective of mirex-induced developmental toxicity, including arrhythmias in neonatal pups following maternal exposure during gestation at a dose level as low as 0.1 mg/kg/day in the absence of an identified NOAEL (Grabowski 1983) would yield an intermediate-duration oral MRL of 0.0001 mg/kg/day. This potential MRL is lower than the chronic-duration oral MRL of 0.0003 mg/kg/day derived from an NTP (1990) study in rats (see chronic-duration oral MRL). Another candidate study for derivation of an intermediate-duration oral MRL for mirex identifies a LOAEL of 0.49 mg/kg/day for cataracts in female rat pups (4/10 versus 0/14 controls) (Chu et al. 1981b). The parental rats had been administered mirex in the diet for 91 days prior to mating and during mating (males and females) and throughout gestation and lactation (females). This LOAEL of 0.49 mg/kg/day is considered a serious LOAEL and the study did not identify a NOAEL. Therefore, no intermediate-duration oral MRL was developed for mirex.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mirex
CAS Numbers: 2385-85-5
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL 0.0003 mg/kg/day
Critical Effect: Histopathologic liver lesions
Reference: NTP 1990
Point of Departure: NOAEL of 0.075 mg/kg/day
Uncertainty Factor: 100
Modifying Factor: 3
LSE Graph Key: 79
Species: Rat

MRL Summary: An MRL of 0.0003 mg/kg/day has been derived for chronic-duration oral exposure to mirex based on dose-related hepatic changes from a 2-year oral study of male and female F344/N rats (NTP 1990). The NOAEL of 0.075 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) and a modifying factor of 3 (to protect for developmental toxicity).

Selection of the Critical Effect: Available animal data identify the liver and kidney as critical targets of mirex toxicity following chronic-duration oral exposure. Potential candidate studies for deriving a chronic-duration oral MRL for mirex are summarized in Table A-1; the lowest LOAEL is 0.75 mg/kg/day for hepatic effects and the corresponding NOAEL is 0.075 mg/kg/day.

Table A-1. NOAELs and LOAELs Identified in Chronic-Duration Oral Studies of Mirex

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	11% lower mean body weight in female rats treated for 2 years	1.95	3.85	NTP 1990
Body weight	No effect in rats treated for 21 months	0.37		Chu et al. 1981c
Hepatic	No effect in rats treated for 21 months	0.37		Chu et al. 1981c
Hepatic	Focal and centrilobular necrosis; fatty metamorphosis; dilation of sinusoids in rats treated for 2 years	0.075	0.75	NTP 1990
Hepatic	Megalocytosis in rats treated for 18 months followed by 6 months of recovery		3.6	Ulland et al. 1977
Renal	Increased severity of nephrotoxicity in rats treated for 2 years	0.75	1.95	NTP 1990

Table A-1. NOAELs and LOAELs Identified in Chronic-Duration Oral Studies of Mirex

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Renal	Increased incidence of epithelial hyperplasia of the renal pelvis in rats treated for 2 years	0.075	0.75	NTP 1990

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

Selection of the Principal Study: NTP (1990) was selected as the principal study for deriving a chronic-duration oral MRL for mirex because it identified the lowest reliable LOAEL for liver effects, a clearly sensitive effect of mirex toxicity.

Summary of the Principal Study:

NTP. 1990. Toxicology and carcinogenesis studies of mirex (CAS No. 2385-85-5) in F344/N rats (feed studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTP TR 313.

Groups of male and female F344/N rats (52/sex/group; approximately 7–8 weeks of age) were administered mirex (95% purity) in the diet at 0, 0.1, 1.0, 10, 25, or 50 ppm for 104 weeks (first study). During the first 6 months of the study, additional groups of groups of female rats were started on 0, 50, or 100 ppm mirex in the diet (second study), based on the lack of observable toxic effects in the initial groups of female rats. Based on body weight and food consumption data, the study authors estimated average mirex doses to 0.1, 1, 10, 25, and 50 ppm groups from the first study at 0.007, 0.07, 0.7, 1.8, and 3.8 mg/kg/day, respectively, for the males and 0.007, 0.08, 0.7, 2.0, and 3.9 mg/kg/day, respectively, for the females (for the combined sexes, the author estimated doses at 0.007, 0.075, 0.75, 1.95, and 3.85 mg/kg/day, respectively). Estimated doses to the 50 and 100 ppm groups of females from the second study were 3.9 and 7.7 mg/kg/day, respectively. Animals were monitored for survival, clinical signs, body weight, and food intake. All rats were subjected to gross pathologic examination and all major organs and tissues were processed for histopathologic examination.

Survival of 1.95 and 3.85 mg/kg/day male rats was significantly less than that of controls (19/52 and 15/52, respectively, compared to 44/52 controls), most deaths occurred after treatment weeks 86–87. Survival was not affected in mirex-dosed females. By week 100, mean body weights of 1.95 and 3.85 mg/kg/day surviving males were 11–18% less than that of controls and mean body weights of 3.9 and 7.7 mg/kg/day females were 12–18% less than that of controls. The most notable compound-related histopathologic lesions were observed in the liver of male and female rats and included dose-related increased incidence of fatty metamorphosis, cytomegaly, angiectasis (males only), and necrosis. The NOAEL for liver effects was 0.075 mg/kg/day and the LOAEL was 0.75 mg/kg/day for focal and centrilobular necrosis, fatty metamorphosis, and dilation of sinusoids. Incidences of nephropathy occurred at similar frequency in controls and mirex-dosed groups; however, the severity was judged to be greater in the 1.95, 3.9, and 7.7 mg/kg/day groups. Hyperplasia of the renal pelvis epithelium occurred at significantly increased incidence in male rats of the 10, 25, and 50 ppm groups (5/52, 14/51, and 9/52, respectively, versus 0/51 among controls). Incidences of neoplastic nodules in the liver were significantly greater in 0.75, 1.95, and 3.85 mg/kg/day groups of males than controls (14/52, 15/52, and 26/52, respectively, versus 3/52 in control males). Incidences of neoplastic liver nodules in the female rats of the first study were not significantly different from that of controls. However, the incidence among control

females (10/52 or 19%) was significantly greater than the historical control incidence (2.8%). In the second study that included 0, 3.9, and 7.7 mg/kg/day groups of female rats, incidences of neoplastic liver nodules (usually consisting of enlarged hepatocytes with eosinophilic or clear cytoplasm arranged in irregular distorted cords one or two cell layers thick, but some consisting of cells with basophilic cytoplasm) were 23/52 (44%), and 30/52 (58%), respectively, versus 2/52 (4%) within a concurrent control group. Incidences of transitional cell papillomas of the renal pelvis of male rats occurred with a positive trend ($p<0.02$). The incidence in the 3.85 mg/kg/day males was 3/52 (6%) compared to 0/51 (0%) among controls and was noted to be higher than the highest incidence previously observed in controls (1/48 or 2%). Incidences of pheochromocytomas of the adrenal gland occurred with a positive trend and the incidences in 1.95 and 3.85 mg/kg/day male rats were significantly greater than that of controls. Incidences of mononuclear cell leukemia in analysis of all female rats in the first and second studies (combined) were significantly increased in the 0.75, 1.95, 3.9, and 7.7 mg/kg/day groups (14/52 or 27%, 18/52 or 35%, 27/104 or 26%, and 14/52 or 27%) versus 14/104 (13%) among controls.

Selection of the Point of Departure: The treatment-related increased incidence of renal pelvis hyperplasia identified in the 2-year dietary study of rats (NTP 1990) was not considered an appropriate basis for deriving a chronic-duration oral MRL for mirex because the hyperplasia was observed in areas of the kidney that also exhibited tumors. Therefore, the hyperplasia may represent a preneoplastic lesion. However, the liver lesions (focal and centrilobular necrosis, fatty metamorphosis, dilation of sinusoids) identified in the same study (NTP 1990) are nonneoplastic effects that were selected as the critical effects for deriving a chronic-duration oral MRL. The NOAEL of 0.075 mg/kg/day for liver effects was selected as the point of departure for deriving a chronic-duration oral MRL for mirex.

Uncertainty Factor: The NOAEL of 0.075 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Modifying Factor: A modifying factor of 3 was applied to be protective of mirex-induced developmental toxicity (see Section 2.17), including arrhythmias in neonatal pups following maternal exposure during gestation at a dose level as low as 0.1 mg/kg/day in the absence of an identified NOAEL (Grabowski 1983).

Other Additional Studies or Pertinent Information that Lend Support: Adverse hepatic effects were reported in a number of intermediate- or chronic-duration animal studies that employed oral exposure to mirex (Bell and Mehendale 1985; Chu et al. 1980c, 1981a, 1981b; Curtis and Hoyt 1984; Dai et al. 2001; Davison et al. 1976; Gaines and Kimbrough 1970; Larson et al. 1979a; Mehendale 1981; Ulland et al. 1977).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

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

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified for chlordecone.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies were identified for chlordecone.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified for chlordecone.

Agency Contact (Chemical Manager): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Chlordecone
CAS Numbers:	143-50-0
Date:	October 2020
Profile Status:	Final
Route:	Oral
Duration:	Acute
MRL	0.01 mg/kg/day
Critical Effect:	Neurological effects
Reference:	EPA 1986a
Point of Departure:	NOAEL of 1.25 mg/kg/day
Uncertainty Factor:	100
LSE Graph Key:	12
Species:	Rat

MRL Summary: An acute-duration oral MRL of 0.01 mg/kg/day was derived for chlordecone based on neurological effects (increased startle response) observed in young adult male Fischer 344 rats in a 10-day gavage study conducted by EPA (1986a). The MRL is based on a NOAEL of 1.25 mg/kg/day and a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Numerous studies have evaluated the toxicity of chlordecone following acute-duration oral exposure. Many studies reported treatment-related neurological effects or developmental effects. Other studies collectively identified the following targets: body weight, cardiovascular system, hematological system, musculoskeletal system, liver, renal system, endocrine system, immunological system, and female reproductive system.

Recent reports evaluated development of the reproductive system following gavage treatment of pregnant mice with chlordecone at 0.1 mg/kg/day during gestation days 6.5–15.5. Gely-Pernot et al. (2018) reported significantly decreased numbers of spermatozoa in adult F1 and F3 mice (note only the parental [F0] dams were administered chlordecone). Legoff et al. (2019) reported delayed vaginal opening and adverse ovarian follicular effects in F1 mice. Both studies only tested a single dose; thus, dose-response relationships cannot be evaluated. The lack of dose-response data along with weaknesses in the reporting of the study design and results preclude using either study as the basis of an MRL. Study weaknesses include the lack of examination for potential maternal toxicity, although the study authors stated that the selected dose level (0.1 mg/kg/day) "has no effect on murine health;" lack of information regarding numbers of pregnant mice/group, numbers of litters produced, numbers of litters contributing to the quantitative data reported; and use of only four progeny/group in some of the analyses.

A summary of the lowest reliable LOAELs for each endpoint is presented in Table A-2. A comparison of the LOAEL values across endpoints supports the identification of the nervous system as the most sensitive target of toxicity.

Table A-2. Lowest LOAELs Identified in Acute-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	15% depressed maternal body weight gain in rats gavaged daily on gestation days 7–16		2	Chernoff and Rogers 1976
Hematological	Decreased neutrophils in rats exposed for 10 days	5	10	Smialowicz et al. 1985
Hepatic	Increased serum alkaline phosphatase, ALT, gamma-glutamyl transferase in rats gavaged daily for 10 days	5	10	EPA 1986a
Renal	Increased blood urea nitrogen in rats gavaged daily for 10 days	5	10	EPA 1986a
Endocrine	Depletion of epinephrine in adrenal medulla of rats treated for 8 days in diet		17	Baggett et al. 1980
Immunological	Decreases in spleen and thymus weights, leukocyte counts, natural killer cell activity, Concanavalin A responsiveness in rats gavaged daily for 10 days	5	10	EPA 1986a
Neurological	Increased startle response in young adult male rats gavaged daily for 10 days	1.25	2.5	EPA 1986a
Reproductive	Persistent estrus in rats gavaged once		35	Swanson and Woolley 1982
	Induction of persistent vaginal estrus in mice repeatedly gavaged for 4 or 6 weeks		2	Swartz et al. 1988
Developmental	86% decreased postnatal day 3 pup survival following daily gavage treatment of maternal rats during gestation days 7–16		10	EPA 1986a

ALT = alanine aminotransferase; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The lowest reliable LOAEL values were identified for body weight, neurological effects, and effects on the female reproductive system. Chernoff and Rogers (1976) reported decreases in maternal body weight gain in rat dams administered 2 mg/kg/day chlordecone on gestation days 7–16. Swartz et al. (1988) reported the induction of persistent vaginal estrus in sexually mature mice administered chlordecone by gavage at 2 mg/kg/day, 5 days/week for 2 weeks. EPA (1986a) reported increased startle response in young adult male rats administered 2.5 mg/kg/day chlordecone for 10 days. These comparable LOAELs are at least 4 times lower than the LOAELs for hematological, hepatic, renal, immunological, and developmental effects. The EPA (1986a) study was selected as the principal study for deriving an acute-duration oral MRL for chlordecone because it identified a NOAEL (1.25 mg/kg/day).

Summary of the Principal Study:

EPA. 1986a. Final report on the evaluation of four toxic chemicals in an '*in vivo/in vitro'* toxicological screen: Acrylamide, chlordecone, cyclophosphamide, and diethylstilbestrol. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory. EPA600186002.

Groups of young adult male Fischer 344 rats (10/group) were administered chlordecone (in corn oil vehicle) by gavage for 10 days at 0, 0.625, 1.25, 2.5, 5.0, or 10.0 mg/kg/day. Animals were monitored for survival and body weight. Motor activity (performance in a figure 8 maze) and acoustic startle response were evaluated at 1 day following the final dose treatment. Urine was collected for urinalysis and blood was drawn for serum chemistry. At sacrifice, selected organ weights were determined. At ≥2.5 mg/kg/day, the amplitude of the acoustic startle response was significantly increased. At the other two doses, the amplitude was increased with all decibel stimuli. Motor activity in a figure-8 maze was decreased at the highest dose tested. Terminal body weight was depressed by 12% at 10 mg/kg/day. Relative liver weight was significantly increased at 5 and 10 mg/kg/day (15–16% higher than controls). Selected serum chemistry parameters were statistically significantly different from controls only in the high-dose group.

Selection of the Point of Departure: The NOAEL of 1.25 mg/kg/day was selected as the point of departure for deriving an acute-duration oral MRL for chlordecone.

Uncertainty Factor: The NOAEL of 1.25 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support: As stated above, numerous animal studies reported neurological effects associated with acute-duration oral exposure to chlordecone (Albertson et al. 1985; Aldous et al. 1984; Baggett et al. 1980; Chang-Tsui and Ho 1979; Desaiah et al. 1980a; Egle et al. 1979; End et al. 1981; Fujimori et al. 1982a; Hoskins and Ho 1982; Huang et al. 1980; Jordan et al. 1981; Klingensmith and Mehendale 1982a; Mactutus et al. 1984; Mishra et al. 1980; Smialowicz et al. 1985; Swanson and Wooley 1982; Tilson et al. 1985).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL 0.003 mg/kg/day
Critical Effect: Neurological and male reproductive effects
Reference: Linder et al. 1983
Point of Departure: NOAEL of 0.26 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 57
Species: Rat

MRL Summary: An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure to chlordecone based on neurological and male reproductive effects from a 90-day oral study of male Sprague-Dawley rats (Linder et al. 1983). The NOAEL of 0.26 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Studies that evaluated chlordecone toxicity in humans did not include dose-response data; therefore, human data were not considered for MRL derivation. Treatment-related effects on the liver, nervous system, body weight, cardiovascular system, endocrine system, reproductive system, and development have been consistently associated with intermediate-duration oral exposure of laboratory animals to chlordecone. A summary of the lowest LOAELs for each endpoint is presented in Table A-3.

Table A-3. Lowest LOAELs Identified in Intermediate-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	13% decreased body weight gain in rats treated for 3 months in diet		1.17	Cannon and Kimbrough 1979
Hepatic	Focal necrosis in rats treated for 3 months in diet		1.17	Cannon and Kimbrough 1979
Endocrine	Reversible hyperplasia of adrenal cortex in rats treated for 3 months in diet		1.17	Cannon and Kimbrough 1979
Neurological	Hyperexcitability, mild tremors in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983
Reproductive	46–48% decreased sperm motility and viability; 19% decreased epididymal sperm concentration in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983

Table A-3. Lowest LOAELs Identified in Intermediate-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Developmental	Decreased postnatal survival in pups from parental mice treated for up to 130 days in diet	1.9	7	Huber 1965

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

A comparison of the LOAEL values across endpoints supports the identification of the nervous system and male reproductive system as the most sensitive targets of toxicity. The identification of the neurotoxicity and reproductive toxicity as sensitive endpoints for chlordecone is supported by several other intermediate-duration studies, which are summarized in Tables A-4 and A-5, respectively.

Table A-4. Selected LOAELs for Neurological Effects Identified in Intermediate-Duration Oral Studies of Chlordecone

Species (strain)	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat (Sprague-Dawley)	Tremors in rats treated for 15 days in diet		4.7	Agarwal and Mehendale 1984a
Rat (Sherman)	Tremors, hyperexcitability, exaggerated startle response in rats treated for 3 months in diet		1.17 M 1.62 F	Cannon and Kimbrough 1979
Rat (Zivac-Miller)	Tremors, decreased operant behavior in rats repeatedly gavaged for 90 days		1	Dietz and McMillan 1979
Rat (Wistar)	Tremors (dose-related earlier onset and increased severity) in rats treated for up to 6 months in diet		2.1 M 2.4 F	Larson et all 1979b
Rat (Sprague-Dawley)	Hyperexcitability, mild tremors in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983
Rat (Sprague-Dawley)	Tremors, hypersensitivity to noise and stress in rats treated for 16 days in diet		3.95	Mehendale et al. 1978
Rat (Fischer 344)	Increased startle response in rats repeatedly gavaged for 15 weeks	2.8	4.1	Pryor et al. 1983
Rat (Fischer 344)	Exaggerated startle response in rats treated for 90 days in diet		1.0	Squibb and Tilson 1982a
Mouse (BALB/c)	Tremor in mice treated for 2–12 months in diet	1.9	5.6	Huber 1965

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

Table A-5. Lowest LOAELs for Reproductive Effects Identified in Intermediate-Duration Oral Studies of Chlordecone

Species (strain)	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat (Sherman)	Decreased number of litters born to control males mated to females treated for 3 months in diet		1.62	Cannon and Kimbrough 1979
Rat (Wistar)	Testicular atrophy in 4/5 males treated for 3 months in diet		2.1	Larson et al. 1979b
Rat (Sprague-Dawley)	46–48% decreased sperm motility and viability; 19% decreased epididymal sperm concentration in rats treated for 90 days in diet	0.26	0.83	Linder et al. 1983
Mouse (BALB/c)	36% decrease in second litters in mice treated for 5 months (including 1 month premating) in diet		0.94	Good et al. 1965
Mouse (BALB/c)	8% decrease in litter size and 19% increase in pair-days to litter among mice treated for 130 days (1 month premating) in diet		1.9	Huber 1965
Mouse (CD-1)	Increased ovulation, persistent vaginal estrus in mice gavaged for 4 or 6 weeks (5 days/week)		2	Swartz et al. 1988

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

Selection of the Principal Study: The study of Linder et al. (1983) identified the lowest LOAEL (0.83 mg/kg/day) for both tremors and impaired sperm parameters; the NOAEL was 0.26 mg/kg/day. This multiple dose study was selected as the principal study for derivation of an intermediate-duration oral MRL for chlordecone.

Summary of the Principal Study:

Linder RE, Scotti TM, McElroy WK, et al. 1983. Spermotoxicity and tissue accumulation of chlordecone (Kepone) in male rats. J Toxicol Environ Health 12:183-192.

Groups of 20 adult male Sprague-Dawley rats were administered technical grade chlordecone (purity not specified) in the diet at 0, 5, 15, or 30 ppm for 90 days. Rats were monitored for clinical signs, body weight, and food intake. The study authors estimated chlordecone doses to the 5, 15, and 30 ppm groups to have been 0.26, 0.83, and 1.67 mg/kg/day, respectively. After the 90-day treatment period, 10 rats/group were sacrificed; testes, epididymides, prostate, and seminal vesicles were weighed; epididymal fluid was extracted for evaluation of spermatozoal motility and viability. Reproductive tissues were then processed for histologic examination. The other 10 rats/group were returned to normal diet and each bred to two untreated virgin females during a 14-day posttreatment period. Mated females were sacrificed on gestation day 20 and fetal weights, fetal viability, and total implants were determined. Male rats used for breeding were sacrificed at 4.5 months after cessation of treatment for evaluation of recovery from chlordecone treatment.

One 0.83 mg/kg/day rat died on treatment day 84; one rat each in the 0.26 and 1.67 mg/kg/day groups died during the recovery period (recovery days 64 and 30, respectively). Clinical signs of neurotoxicity, including hyperexcitability and mild tremors, were observed in rats of the 0.83 and 1.67 mg/kg/day groups (incidences not included in the study report). The 1.67 mg/kg/day group sacrificed at 90 days exhibited approximately 7% lower mean final body weight than controls (not considered an adverse effect because the decrease was <10%). The 1.67 mg/kg/day group of rats exhibited significantly lower absolute weights of seminal vesicles and prostate (12 and 24%, respectively, less than controls). Sperm concentration (sperm count) and incidences and type of morphologically abnormal spermatozoa were similar between controls and all chlordecone-treated groups. However, within the 0.83 and 1.67 mg/kg/day groups, decreases in sperm motility (48 and 39%, respectively, less than controls), sperm viability (46 and 33%, respectively, less than controls), and epididymal concentration (19% less than controls for both 0.83 and 1.67 mg/kg/day groups) were observed. There were no chlordecone treatment-related effects on reproductive performance (number of males siring litters, live litters, average litter size, average number of implants, percent resorptions, or fetal weight). At the end of the recovery period, sperm parameters and reproductive organ weights were similar to those of controls. The study identified a NOAEL of 0.26 mg/kg/day and a LOAEL of 0.83 mg/kg/day for clinical signs of neurotoxicity (tremors) and effects on sperm parameters. The LOAEL for effects on sperm parameters is not considered a serious LOAEL due to the lack of effects on reproductive performance.

Selection of the Point of Departure: The NOAEL of 0.26 mg/kg/day was selected as the point of departure for deriving an intermediate-duration oral MRL for chlordecone.

Benchmark dose (BMD) analysis of the neurological effects in the principal study (Linder et al. 1983) was precluded by lack of incidence data for the treatment-related tremors. BMD analysis was conducted on the datasets for sperm motility and sperm viability (Table A-6) to identify potential points of departure for deriving an intermediate-duration oral MRL for chlordecone.

Table A-6. Sperm Motility and Viability Data for Sprague-Dawley rats Administered Chlordecone in the Diet for 90 Days

Dose (mg/kg/day)	0	0.26	0.83	1.67
Number of rats	10	10	10	10
Percent motile sperm[a]	37.0±3.9	33.2±3.8	19.2±4.4[b]	22.6±5.5[b]
Percent live sperm[a]	46.0±4.7	36.2±3.3	25.0±3.3[b]	30.9±4.8[b]

[a]Mean ± standard error of the mean (SEM).
[b]Significantly different from control ($p<0.05$).

Source: Linder et al. 1983

The data for sperm motility and for sperm viability were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2). The following procedure for fitting continuous data was used: the simplest model (linear) was first applied to the data while assuming constant variance; if the data were consistent with the assumption of constant variance ($p\geq0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by four criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR), and BMDL that was not 10 times lower than the lowest non-zero dose. Among all models providing adequate fit to the data, the lowest BMDL (the lower limit of a one-sided 95% confidence interval [CI] on the BMD) was selected as a reasonably conservative

point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was chosen. For both datasets, a BMR of 1 standard deviation (SD) change from the control was used.

Table A-7 presents the results of the BMD modeling with constant variance of the sperm motility data. Although most models provided adequate statistical fit, visual inspection of the plotted data indicated a poor fit of the estimated mean values to the measured mean values for the two dose levels closest to the BMD and BMDL.

Table A-7. Results of BMD Analysis (with Constant Variance) of Percent Motile Sperm in Rats Exposed to Chlordecone in the Diet for 90 Days (Linder et al. 1983)

Model	BMD_{1SD}[a] (mg/kg)	$BMDL_{1SD}$[a] (mg/kg)	Test 4 p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Exponential 2[d]	1.27	0.63	0.185	330.23	0.95	0.34
Exponential 3[d]	1.27	0.63	0.185	330.23	0.94	0.34
Exponential 4[d]	0.65	0.20	0.209	330.44	-0.90	-0.25
Exponential 5			NA	331.19	0.00	0.00
Hill[d,e]			0.564	329.19	0.00	0.01
Polynomial Degree 3[d]	1.55	0.93	0.124	331.03	0.80	0.61
Polynomial Degree 2[d]	1.55	0.93	0.124	331.03	0.80	0.61
Power[d]	1.55	0.93	0.124	331.03	0.80	0.61
Linear	1.55	0.93	0.124	331.03	0.80	0.61

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]The Hill model was not considered adequate since less than five dose groups were used.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 10% relative deviation from control)

The results of BMD analysis of sperm viability are presented in Table A-8. For the sperm viability data, the Exponential Model 4 was the only model to provide adequate statistical fit to the mean data. However, visual inspection of the plotted data from Exponential Model 4 indicated a poor fit of the estimated mean values to the measured mean values for sperm viability. Therefore, the BMDL estimated from this model was not considered suitable as the basis of the MRL.

Table A-8. Results of BMD Analysis (with Constant Variance) of Percent Sperm Viability in Rats Exposed to Chlordecone in the Diet for 90 Days (Linder et al. 1983)

Model	BMD_{1SD}[a] (mg/kg)	$BMDL_{1SD}$[a] (mg/kg)	Test 4 p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Exponential 2[d]			0.0331	326.91	1.25	1.11
Exponential 3[d]			0.0331	326.91	1.25	1.11
Exponential 4[d]			0.2064	323.68	0.33	-0.08
Exponential 5	0.32	0.10	NA	325.23	0.00	0.05
Hill[d]			0.2857	323.23	0.00	0.00
Polynomial Degree 3[d]			0.0218	327.73	1.04	1.36
Polynomial Degree 2[d]			0.0218	327.73	1.04	1.36
Power[d]			0.0218	327.73	1.04	1.36
Linear			0.0218	327.73	1.04	1.36

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 10% relative deviation from control)

A NOAEL/LOAEL approach to deriving an intermediate-duration oral MRL for chlordecone was applied because a BMD approach was precluded by lack of adequate modeling results.

Uncertainty Factor: The NOAEL of 0.26 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support: Squibb and Tilson (1982a) reported chlordecone-induced exaggerated startle response in male rats administered chlordecone in the diet for 90 days at 1.0 mg/kg/day). Cannon and Kimbrough (1979) reported tremors, hyperactivity, and exaggerated startle response among male and female rats receiving chlordecone from the diet for 3 months at 1.17 and 1.62 mg/kg/day, respectively (lowest exposure level tested). Good et al. (1965) reported decreased numbers of second litters produced by mice at a chlordecone dose level as low as 0.94 mg/kg/day. Cannon and Kimbrough (1979) reported decreased number of litters born to control males mated to chlordecone-treated females dosed at 1.62 mg/kg/day. Larson et al. (1979b) reported testicular atrophy in male rats administered chlordecone for 3 months at 2.1 mg/kg/day.

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlordecone
CAS Numbers: 143-50-0
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL 0.0009 mg/kg/day
Critical Effect: Renal effects
Reference: Larson et al. 1979b
Point of Departure: NOAEL of 0.089 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 75
Species: Rat

MRL Summary: An MRL of 0.0009 mg/kg/day was derived for chronic-duration oral exposure to chlordecone based on renal effects in rats administered chlordecone in the diet for up to 2 years (Larson et al. 1979b). The NOAEL of 0.089 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Treatment-related effects on body weight, hematological system, liver, renal system, and nervous system, and dermal irritation have been associated with chronic-duration oral exposure of laboratory animals to chlordecone. A summary of the lowest LOAELs for each endpoint is presented in Table A-9. A comparison of the LOAEL values across endpoints supports the identification of the renal system as the most sensitive target of toxicity.

Table A-9. Lowest LOAELs Identified in Chronic-Duration Oral Studies of Chlordecone

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	>10% depressed body weight in rats treated for 1 or 2 years in diet	0.89	2.2	Larson et al. 1979b
Hematological	Anemia in male rats treated for 80 weeks in diet		0.56	NCI 1976
Hepatic	Fatty infiltration and degeneration in male rats treated for 80 weeks in diet		0.56	NCI 1976
Renal	Proteinuria and increased severity of glomerulosclerosis in rats treated for up to 2 years in diet	0.089	0.45	Larson et al. 1979b
Dermal	Dermatitis in rats treated for 80 weeks in diet		0.56	NCI 1976
Neurological	Tremors in rats treated for 80 weeks in diet		0.56	NCI 1976

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

Results from several studies were considered in the selection of the critical effect for derivation of a chronic-duration oral MRL for chlordecone. Larson et al. (1979b) administered chlordecone in the diet to rats for up to 2 years and reported depressed body weight gain, decreased hematocrit levels, and tremors at 2.2 mg/kg/day; fatty changes in the liver at 0.89 mg/kg/day; and proteinuria and increased severity of glomerulosclerosis in the kidney at 0.45 mg/kg/day. In an 80-week study of rats administered chlordecone in the diet (NCI 1976), adverse dermal, hepatic, hematological, and neurological effects were observed at the lowest dose tested (0.56 and 1.4 mg/kg/day for males and females, respectively). Similarly-treated mice exhibited adverse hepatic and neurological effects at the lowest dose tested (3.4 and 3.5 mg/kg/day for males and females, respectively). Larson et al. (1979b) also treated dogs for up to 128 weeks at doses up to 1.2 mg/kg/day and observed no neurological effects. Chu et al. (1981c) reported histopathological thyroid lesions in male Sprague-Dawley rats treated with chlordecone in the diet for 21 months at 0.07 mg/kg/day. However, the study report indicated that 4/10 control rats exhibited thyroid lesions (mild degenerative and proliferative changes in follicular epithelium without alteration in colloid density) and that 4/6 chlordecone-treated rats exhibited mild histological changes that may have included decreased colloid density. Thus, it is not clear whether a significant difference existed between controls and chlordecone-treated rats regarding thyroid lesions. Therefore, the thyroid lesion data were not considered for MRL derivation.

Selection of the Principal Study: Larson et al. (1979b) was selected as the principal study for deriving a chronic-duration oral MRL for chlordecone because it identified a NOAEL (0.089 mg/kg/day) associated with the lowest LOAEL (0.45 mg/kg/day for renal effects). The kidney effect observed in rats treated for up to 2 years represents the lowest reliable LOAEL (0.45 mg/kg/day) among the candidate treatment-related adverse effects from chronic-duration oral exposure to chlordecone, and was therefore selected as the critical effect for deriving a chronic-duration oral MRL for chlordecone.

Summary of the Principal Study:

Larson PS, Egle JL Jr, Hennigar CR, et al. 1979b. Acute, subchronic, and chronic toxicity of chlordecone. Toxicol Appl Pharmacol 48:29-41.

Groups of Wistar rats (40/sex/group) were administered chlordecone in the diet for up to 2 years at 0, 5, 10, 25, 50, or 80 ppm. Other groups of male and female Wistar rats (40/sex/group) were administered chlordecone in the diet for up to 2 years at 0 or 1 ppm (estimated chlordecone doses of 0 and 0.089 mg/kg/day, respectively) and similarly evaluated. Estimated chlordecone doses of 0, 0.089, 0.45, 0.89, 2.2, 4.5, and 7.1 mg/kg/day were calculated for the 1, 5, 10, 25, 50, and 80 ppm dietary concentrations, respectively, using a time-weighted average (TWA) of reported body weights (0.254 kg) and a food consumption rate (0.0226 kg/day) calculated using EPA's (1988) allometric equation. After 1 year, five rats/sex/dose group were sacrificed. All rats in the 4.5 and 7.1 mg/kg/day groups died by week 25. Proteinuria was noted in all 0.45, 0.89, and 2.2 mg/kg/day groups at all intervals after 3 months except in males at 21 and 24 months when control levels were elevated, and in females at 24 months when the levels in only the 0.89 and 2.2 mg/kg/day were elevated. There was no indication of proteinuria in the 0.089 mg/kg/day of male or female rats. The severity of observed glomerulosclerosis was increased in both males and females at ≥0.45 mg/kg/day. Non-statistically significantly increased kidney weight relative to body weight was reported. The NOAEL for kidney effects was 0.089 mg/kg/day. At 1- and 2-year sacrifice, NOAELs of 0.45 and 0.89 mg/kg/day and their respective LOAELs (0.89 mg/kg/day for fatty changes in the liver and 2.2 mg/kg/day for depressed hematocrit levels) were identified.

Selection of the Point of Departure for the MRL: The NOAEL of 0.089 mg/kg/day was selected as the point of departure for deriving a chronic-duration oral MRL for chlordecone. The proteinuria and

glomerulosclerosis severity data were not amenable to BMD modeling because standard deviations were not reported.

Uncertainty Factor: The NOAEL of 0.089 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Although other available chronic-duration oral studies did not identify renal effects in chlordecone-treated animals, adverse dermal, hepatic, hematological, and/or neurological effects were observed at doses in the range of 0.4–2.6 mg/kg/day.

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MIREX AND CHLORDECONE

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 mirex and chlordecone.

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 mirex and chlordecone. 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 mirex and chlordecone 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 mirex and chlordecone are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for mirex and chlordecone released for public comment in May 2019. The following main databases were searched in October 2019:

- 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 mirex and chlordecone. 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 mirex and chlordecone 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	
10/2019	("Mirex"[mh] OR 2385-85-5[rn] OR "Chlordecone"[mh] OR 143-50-0[rn] OR "1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene"[tw] OR "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene dimer"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, 1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-"[tw] OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, dodecachlorooctahydro-"[tw] OR "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-, dimer"[tw] OR "Bichlorendo"[tw] OR "CG-1283"[tw] OR "Cyclopentadiene, hexachloro-, dimer"[tw] OR "Dechlorane"[tw] OR "Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene"[tw] OR "Dodecachloropentacyclo(3.2.2.0(sup 2,6),0(sup 3,9),0(sup 5,10))decane"[tw] OR "Dodecachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane"[tw] OR "Dodecachloropentacyclo(5.2.1.02,6.03,9.05,8)decane"[tw] OR "Dodecachloropentacyclodecane"[tw] OR "Dodecaclor"[tw] OR "Ferriamicide"[tw] OR "Fire Ant Bait"[tw] OR "GC 1283"[tw] OR "Hexachlorocyclopentadiene dimer"[tw] OR "HRS 1276"[tw] OR "HRS l276"[tw] OR "Mirex"[tw] OR "Paramex"[tw] OR "Pentacyclodecane, dodecachloro-"[tw] OR "Perchlordecone"[tw] OR "Perchlorodihomocubane"[tw] OR "Perchloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane"[tw] OR "Perchloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decane"[tw] OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decane"[tw] OR "Perchloropentacyclodecane"[tw] OR "1,1a,3,3a,4,5,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "1,2,3,4,5,5,6,7,8,9,10,10-Dodecachlorooctahydro-1,3,4-metheno-2-cyclobuta(c,d)pentalone"[tw] OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-"[tw] OR "2,3,3a,4,5,6,7,7a,8,8a-Decachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one"[tw] OR "Chlordecone"[tw] OR "Ciba 8514"[tw] OR "Clordecone"[tw] OR "Compound 1189"[tw] OR "Decachloro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "Decachloroketone"[tw] OR "Decachlorooctahydro-1,3,4-methano-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "Decachlorotetracyclodecanone"[tw] OR "Decachlorotetrahydro-4,7-methanoindeneone"[tw] OR "GC 1189"[tw] OR "General chemicals 1189"[tw] OR "Kepone"[tw] OR "Kepone-2-one, decachlorooctahydro-"[tw] OR "Merex"[tw] OR "1,2,3,5,6,7,8,9,10,10-Decachloro(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decano-4-one"[tw] OR "Decachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5),(8))decan-4-one"[tw] OR "Decachloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decan-4-one"[tw] OR "Decachloropentacyclo(5.3.0.0(sup 2,6).0(sup 4,10).0(sup 5,9))decan-3-one"[tw] OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decan-5-one"[tw]) AND (2017/04/01:3000[mhda] OR 2017/04/01:3000[crdt] OR 2017/04/01:3000[edat] OR 2016/04/01:3000[dp])
	("1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachloroactahydro-1,3,4-metheno-1H-cyclobuta[cd]pentalene"[tw] OR "Dodecachlor"[tw] OR "Dodecachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalene"[tw] OR "Dodecachloropentacyclo[5.3.0.0(2.6).0(3.9).0(4.8)]decane"[tw] OR "Perchloropentacyclo[5.2.1.02,6.03,9.05,8]decane"[tw] OR "Perchloropentacyclo[5.3.0.02,6.03,9.04,8]decane"[tw] OR "1,1a,3,3a,4,5,5,5a,5b,6-Decachloro-octahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR "1,1a,3,3a,4,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta [cd]pentalen-2-one"[tw] OR "1,3,4-Metheno-2H-cyclobuta[cd]pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobuta[cd]pentalen-2-one, 1,1a,3,3a,4,5,5a,5b,6-decachlorooctahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobuta[cd]pentalen-2-one, decachlorooctahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobutal [cd]pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloro-octahydro-"[tw] OR "1,3,4-Metheno-2H-cyclobutal[cd]pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloroctahydro-"[tw] OR "Decachloroctalhydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Decachloropentacyclo[5.2.1.02,6.03,9.05,8]decan-4-one"[tw]) AND (1993:3000[dp] OR 1993:3000[mhda] OR 1993:3000[edat] OR 1993:3000[crdat]))
Toxline	
10/2019	"Mirex" OR 2385-85-5[rn] OR "Chlordecone" OR 143-50-0[rn] Year of Publication 2016 through 2019
	"1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene" OR "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene dimer" OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, 1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-" OR "1,3,4-Metheno-1H-cyclobuta(cd)pentalene, dodecachlorooctahydro-" OR "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-, dimer" OR "Bichlorendo" OR "CG-1283" OR "Cyclopentadiene, hexachloro-, dimer" OR "Dechlorane" OR "Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene" Year of Publication 2016 through 2019
	"Dodecachloropentacyclo(3.2.2.0(sup 2,6),0(sup 3,9),0(sup 5,10))decane" OR "Dodecachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane" OR "Dodecachloropentacyclo(5.2.1.02,6.03,9.05,8)decane" OR "Dodecachloropentacyclodecane" OR "Dodecaclor" OR "Ferriamicide" OR "Fire Ant Bait" OR "GC 1283" OR "Hexachlorocyclopentadiene dimer" OR "HRS 1276" OR "HRS l276" OR "Mirex" OR "Paramex" OR "Pentacyclodecane, dodecachloro-" Year of Publication 2016 through 2019
	"Perchlordecone" OR "Perchlorodihomocubane" OR "Perchloropentacyclo(5.2.1.0(2,6).0(3,9).0(5,8))decane" OR "Perchloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decane" OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decane" OR "Perchloropentacyclodecane" OR "1,1a,3,3a,4,5,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "1,2,3,4,5,5,6,7,8,9,10,10-Dodecachlorooctahydro-1,3,4-metheno-2-cyclobuta(c,d)pentalone" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-" Year of Publication 2016 through 2019
	"2,3,3a,4,5,6,7,7a,8,8a-Decachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one" OR "Chlordecone" OR "Ciba 8514" OR "Clordecone" OR "Compound 1189" OR "Decachloro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "Decachloroketone" OR "Decachlorooctahydro-1,3,4-methano-2H-cyclobuta(cd)pentalen-2-one" OR "Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "Decachlorotetracyclodecanone" OR "Decachlorotetrahydro-4,7-methanoindeneone" OR "GC 1189" OR "General chemicals 1189" Year of Publication 2016 through 2019
	"Kepone" OR "Kepone-2-one, decachlorooctahydro-" OR "Merex" OR "1,2,3,5,6,7,8,9,10,10-Decachloro(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decano-4-one" OR "Decachloropentacyclo(5.2.1.0(2,6).0(3,9).0(5),(8))decan-4-one" OR "Decachloropentacyclo(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))decan-4-one" OR "Decachloropentacyclo(5.3.0.0(sup 2,6).0(sup 4,10).0(sup 5,9))decan-3-one" OR "Perchloropentacyclo(5.3.0.0(2,6).0(3,9).0(4,8))decan-5-one" Year of Publication 2016 through 2019
	"1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachloroactahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene" OR "Dodecachlor" OR "Dodecachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalene" OR "Dodecachloropentacyclo(5.3.0.0(2.6).0(3.9).0(4.8))decane" OR

Table B-2. Database Query Strings

Database search date	Query string
	"Perchloropentacyclo(5.2.1.02,6.03,9.05,8)decane" OR "Perchloropentacyclo(5.3.0.02,6.03,9.04,8)decane" Year of Publication 1993 through 2019
	"1,1a,3,3a,4,5,5,5a,5b,6-Decachloro-octahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "1,1a,3,3a,4,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta (cd)pentalen-2-one" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, 1,1a,3,3a,4,5,5a,5b,6-decachlorooctahydro-" OR "1,3,4-Metheno-2H-cyclobuta(cd)pentalen-2-one, decachlorooctahydro-" Year of Publication 1993 through 2019
	"1,3,4-Metheno-2H-cyclobutal(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloro-octahydro-" OR "1,3,4-Metheno-2H-cyclobutal(cd)pentalen-2-one, 1,1a,3,3a,4,5,5,5a,5b,6-decachloroctahydro-" OR "Decachloroctalhydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" OR "Decachloropentacyclo(5.2.1.02,6.03,9.05,8)decan-4-one" Year of Publication 1993 through 2019
Toxcenter	
10/2019	FILE 'TOXCENTER' ENTERED AT 11:37:01 ON 08 OCT 2019 CHARGED TO COST=EH038.06.01.LB.02 L1 6689 SEA FILE=TOXCENTER 2385-85-5 OR 143-50-0 L2 6678 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 6545 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 206 SEA FILE=TOXCENTER L3 AND ED>=20170401 L48 36 SEA FILE=TOXCENTER L4 AND MEDLINE/FS L49 170 SEA FILE=TOXCENTER L4 NOT MEDLINE/FS L50 179 DUP REM L48 L49 (27 DUPLICATES REMOVED) ANSWERS '1-179' FROM FILE TOXCENTER L*** DEL 36 S L4 AND MEDLINE/FS L*** DEL 36 S L4 AND MEDLINE/FS L51 36 SEA FILE=TOXCENTER L50 L*** DEL 170 S L4 NOT MEDLINE/FS L*** DEL 170 S L4 NOT MEDLINE/FS L52 143 SEA FILE=TOXCENTER L50 L53 143 SEA FILE=TOXCENTER (L51 OR L52) NOT MEDLINE/FS D SCAN L53

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2019	Compounds searched: 2385-85-5, 143-50-0
NTP	
10/2019	"2385-85-5" "143-50-0" "Mirex" "Chlordecone" "Dechlorane" "Dodecachloropentacyclodecane" "Dodecaclor" "Kepone" "Fire Ant Bait" "Paramex" "Perchloropentacyclodecane" "Decachloroketone" "Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one" "Perchlordecone" "Clordecone" "Ferriamicide" "Dodecachlor"
Regulations.gov	
10/2019	Compounds searched: 2385-85-5, 143-50-0
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 331
- Number of records identified from other strategies: 10
- Total number of records to undergo literature screening: 431

B.1.2 Literature Screening

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

- 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.

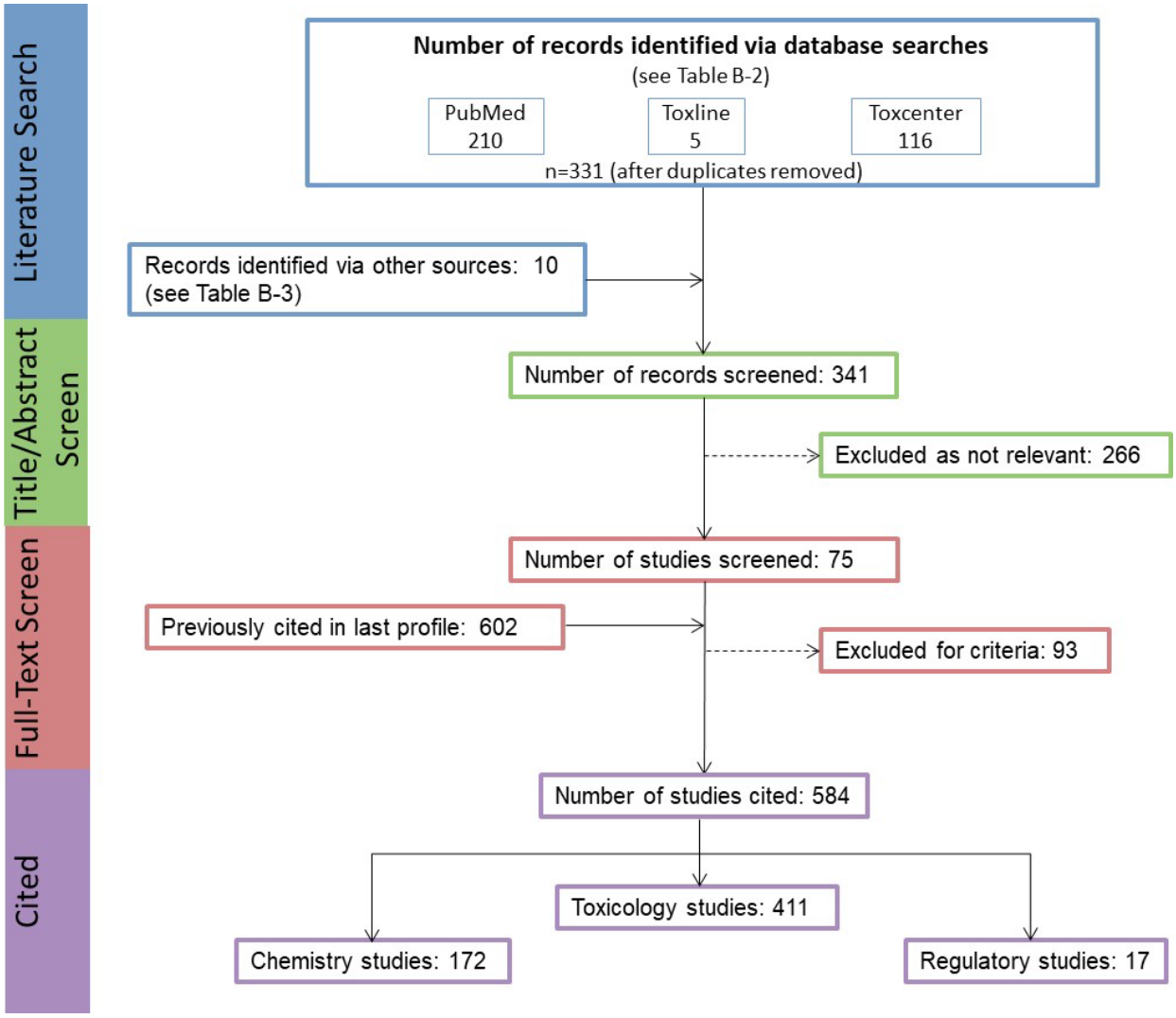
- Number of titles and abstracts screened: 431
- Number of studies considered relevant and moved to the next step: 75

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: 75
- Number of studies cited in the pre-public draft of the toxicological profile: 602
- Total number of studies cited in the profile: 584

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

Figure B-1. October 2019 Literature Search Results and Screen for Mirex and Chlordecone



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.

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									

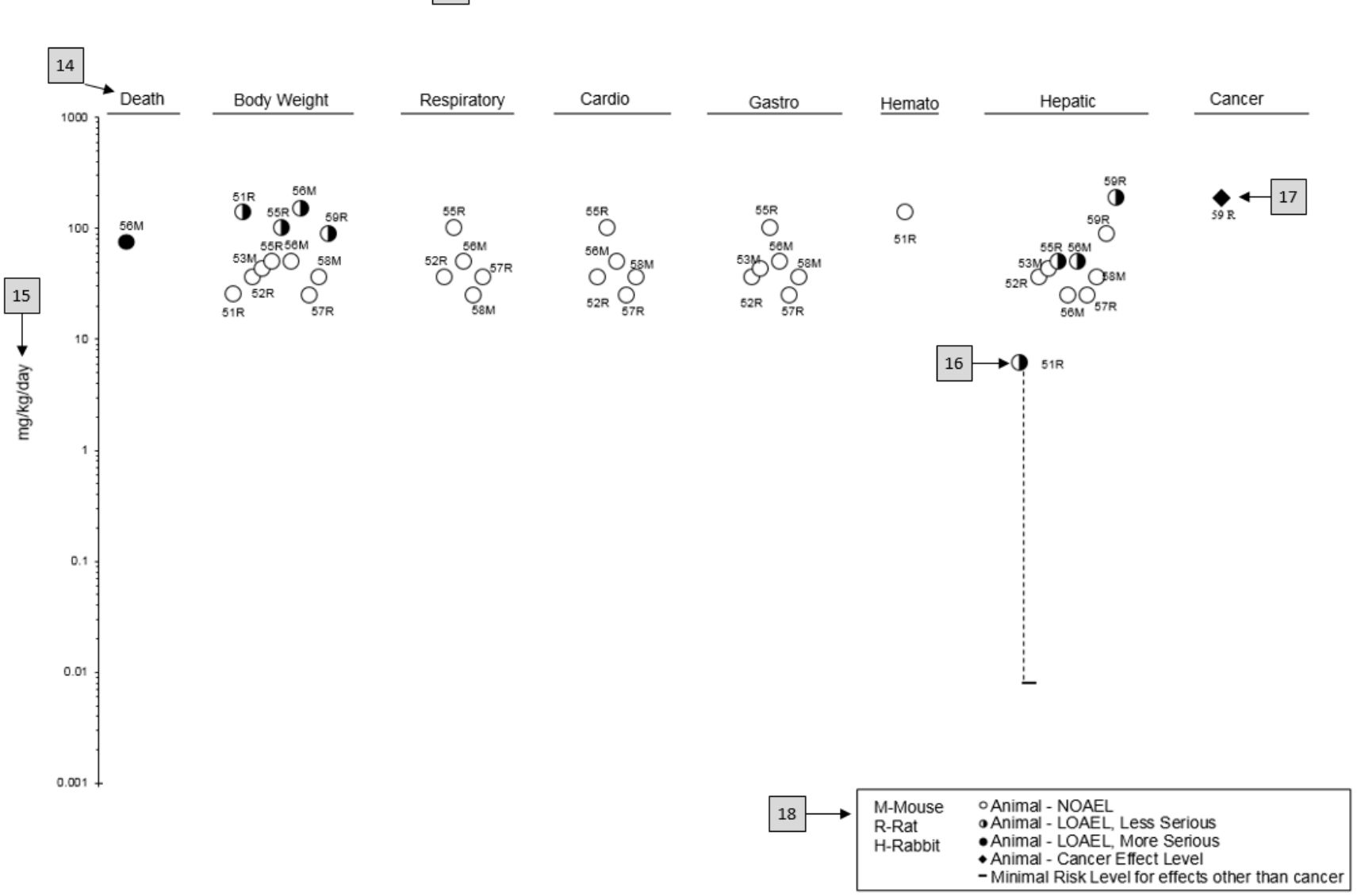
[a]The number corresponds to entries in Figure 2-x.

(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).

APPENDIX C

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

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
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