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.

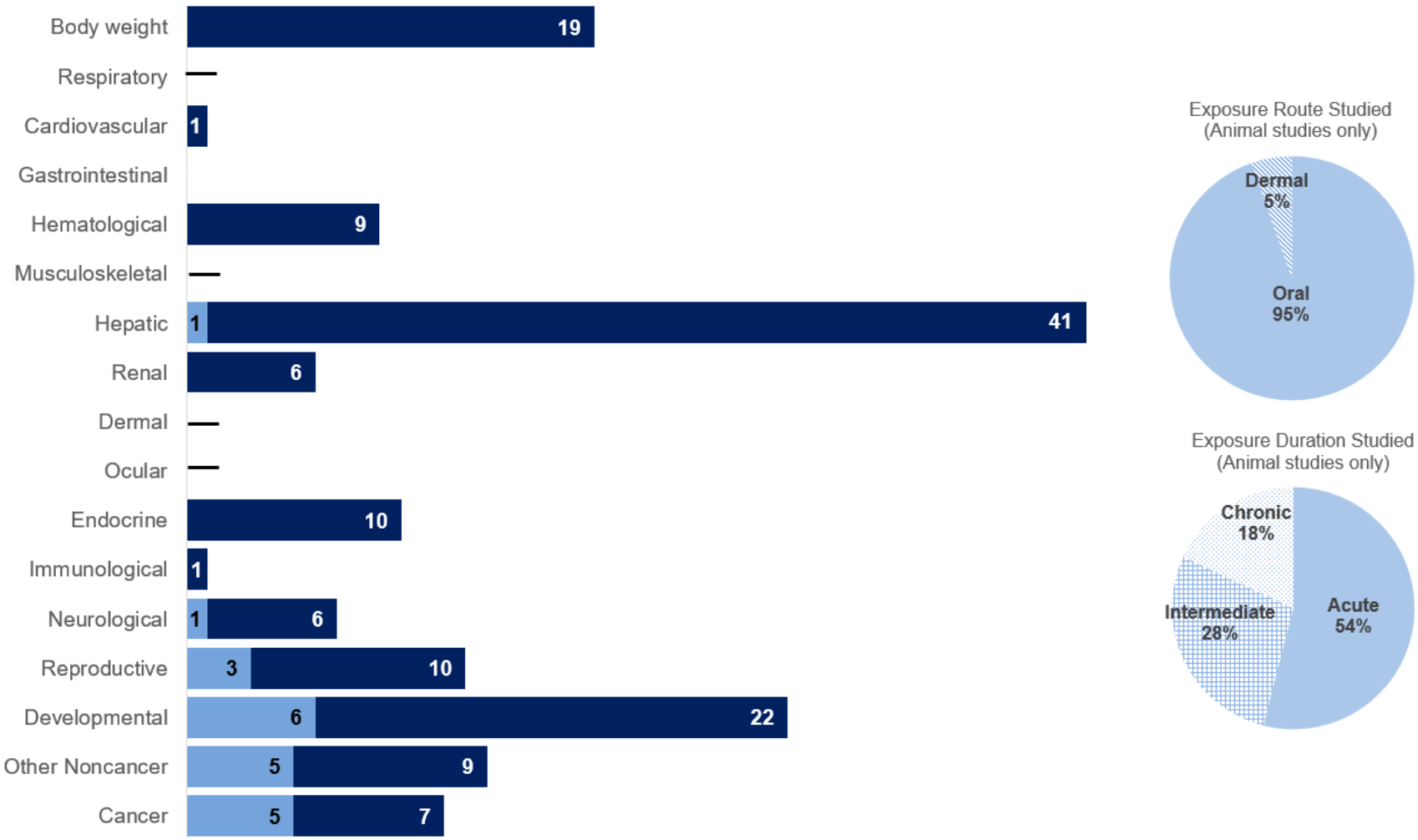
- Reproductive endpoint: Some men involved in the production of chlordecone exhibited decreases in sperm count and motility. Adverse effects on the reproductive system have been demonstrated in male and female animals exposed to chlordecone.

- 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

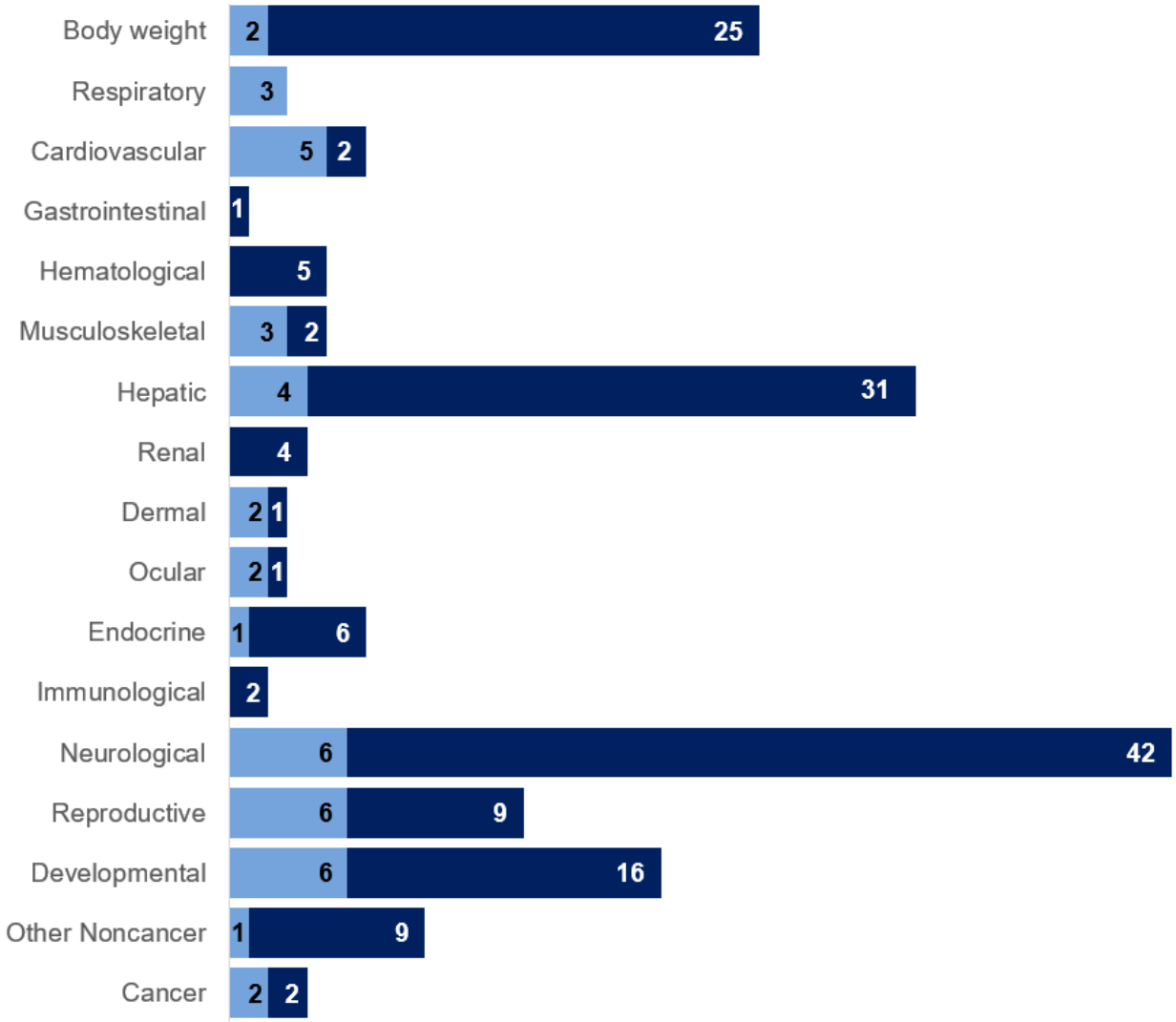
More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)

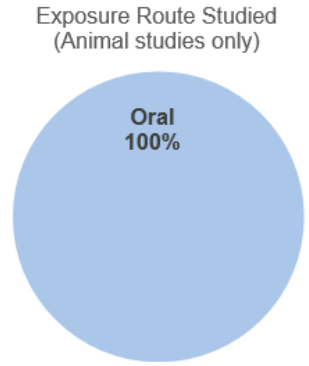


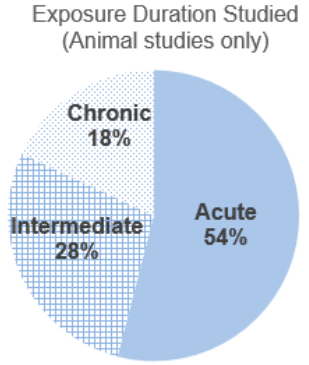
*Includes studies discussed in Chapter 2. A total of 161 studies include those finding no effect. Most studies examined multiple endpoints.

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)

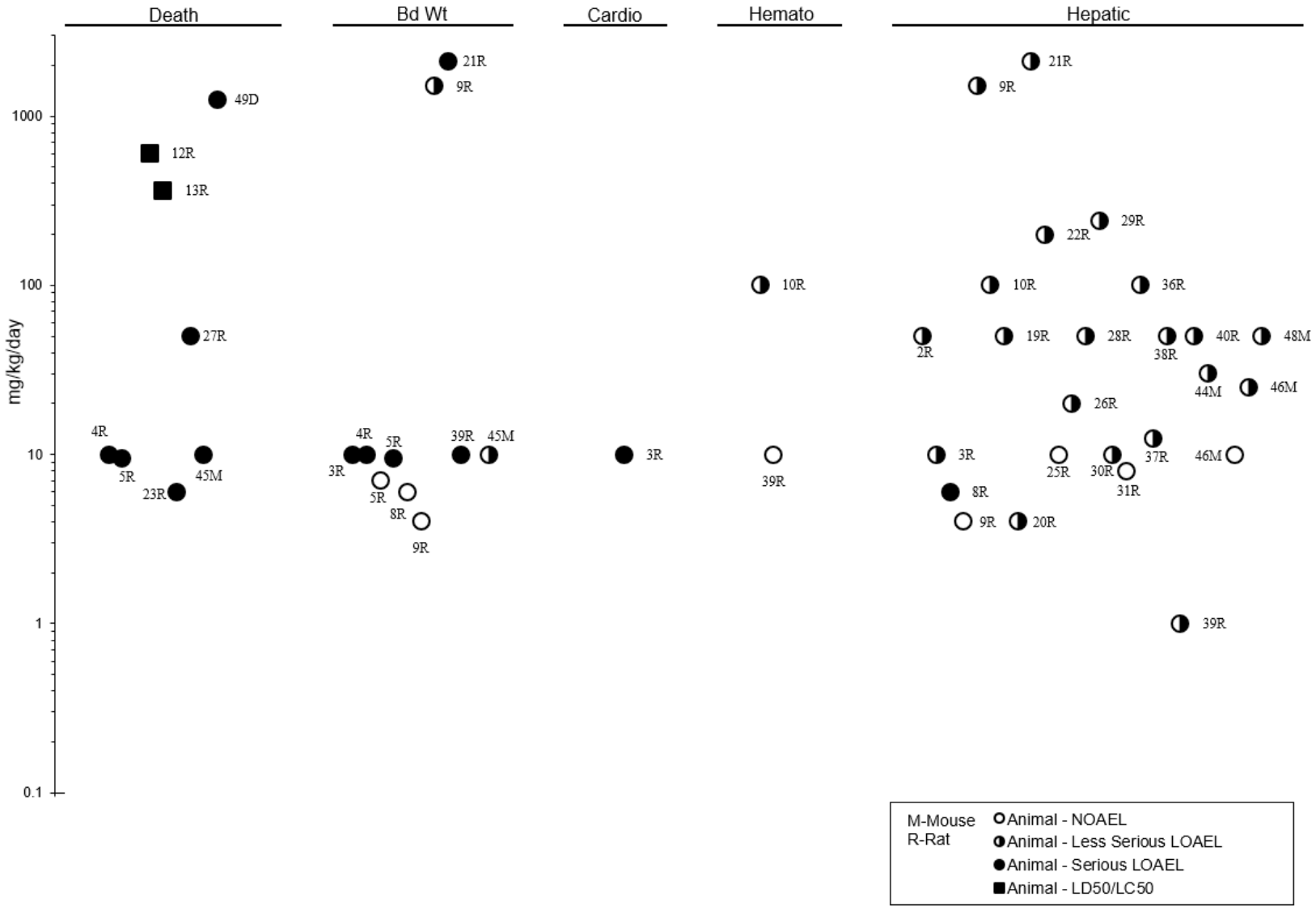


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Acute (≤14 days)

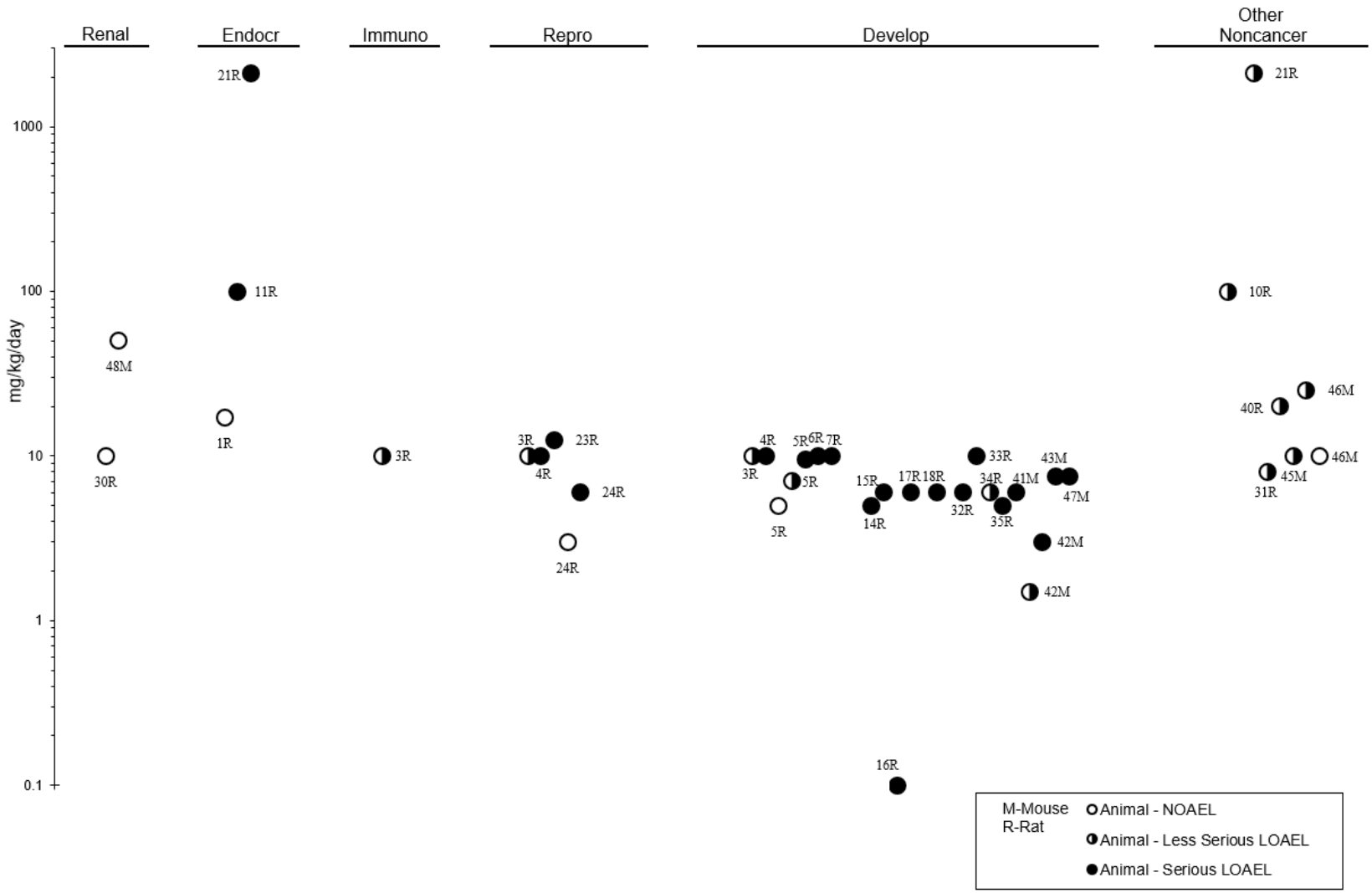


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Intermediate (15–364 days)

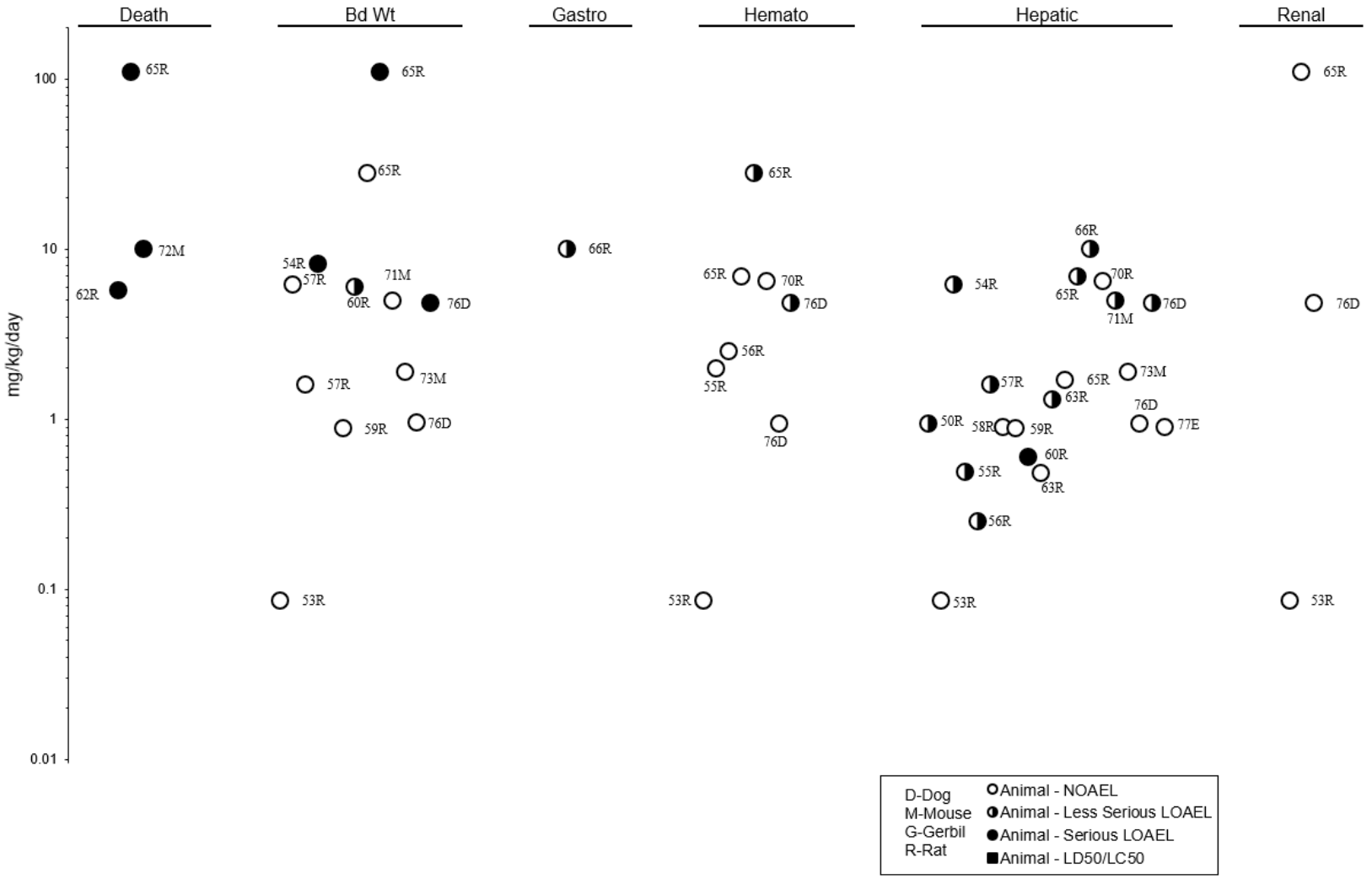


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Intermediate (15–364 days)

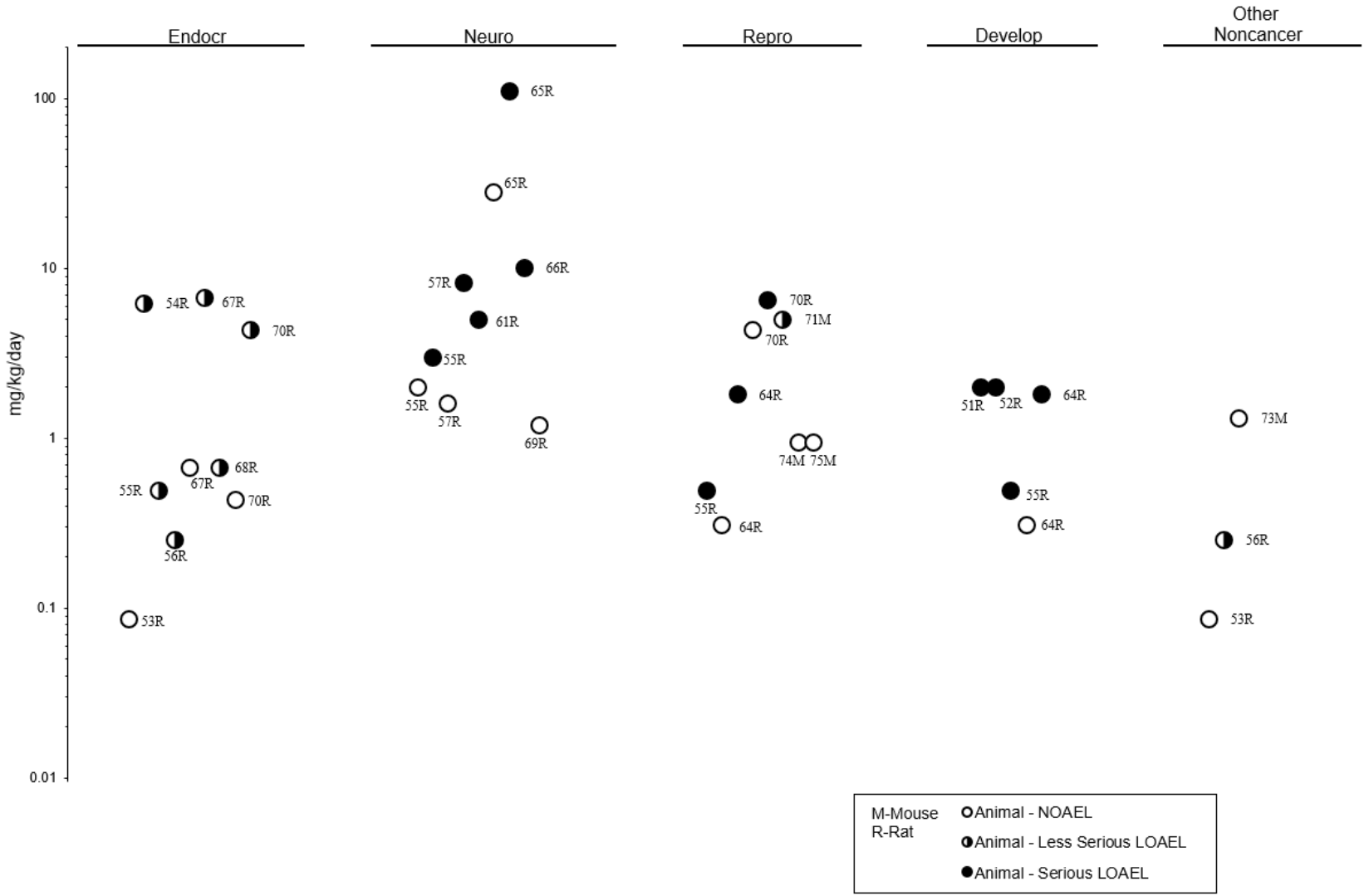


Figure 2-3. Levels of Significant Exposure to Mirex – Oral
Chronic (≥365 days)

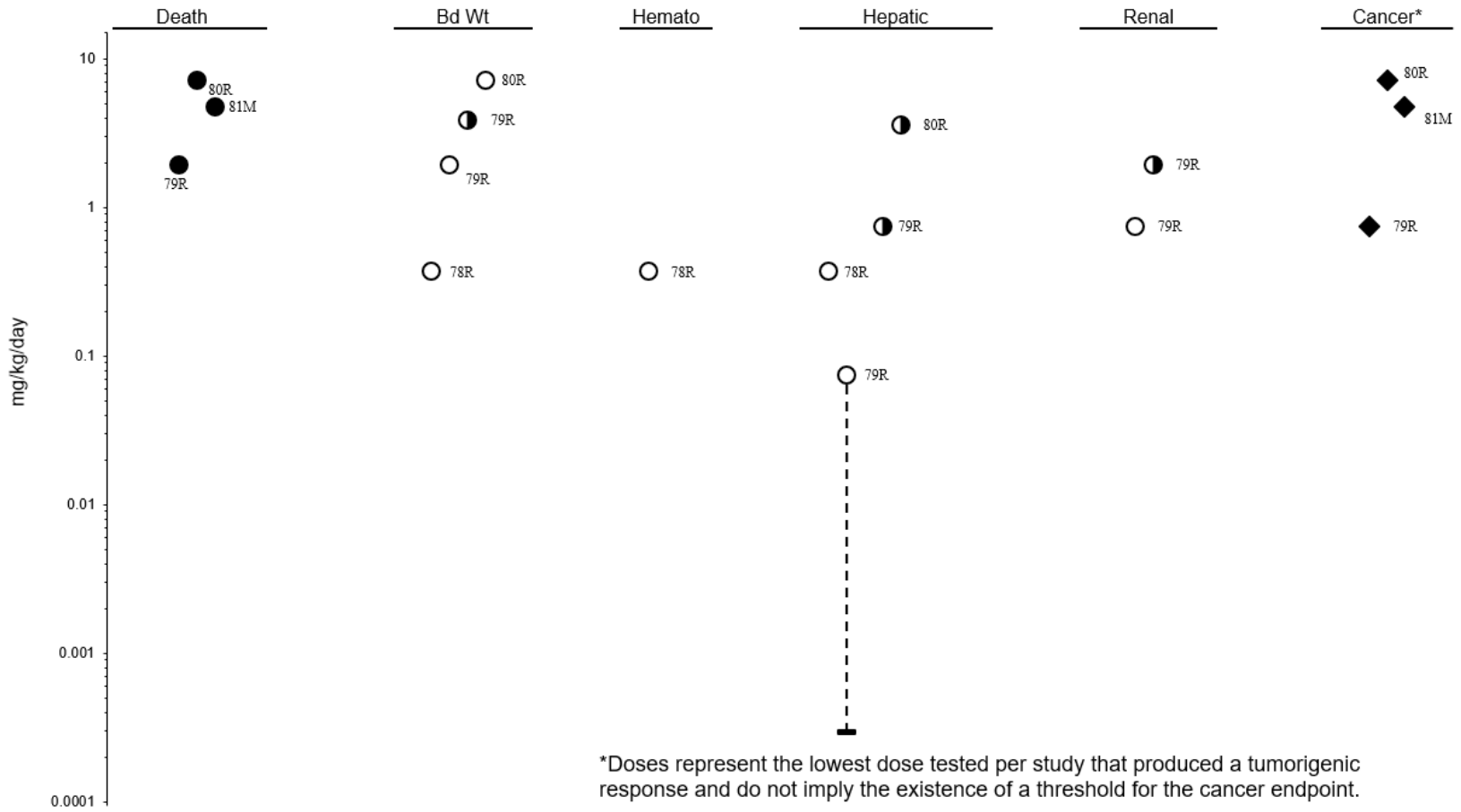


Table 2-4. Levels of Significant Exposure to Chlordecone – Oral

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)

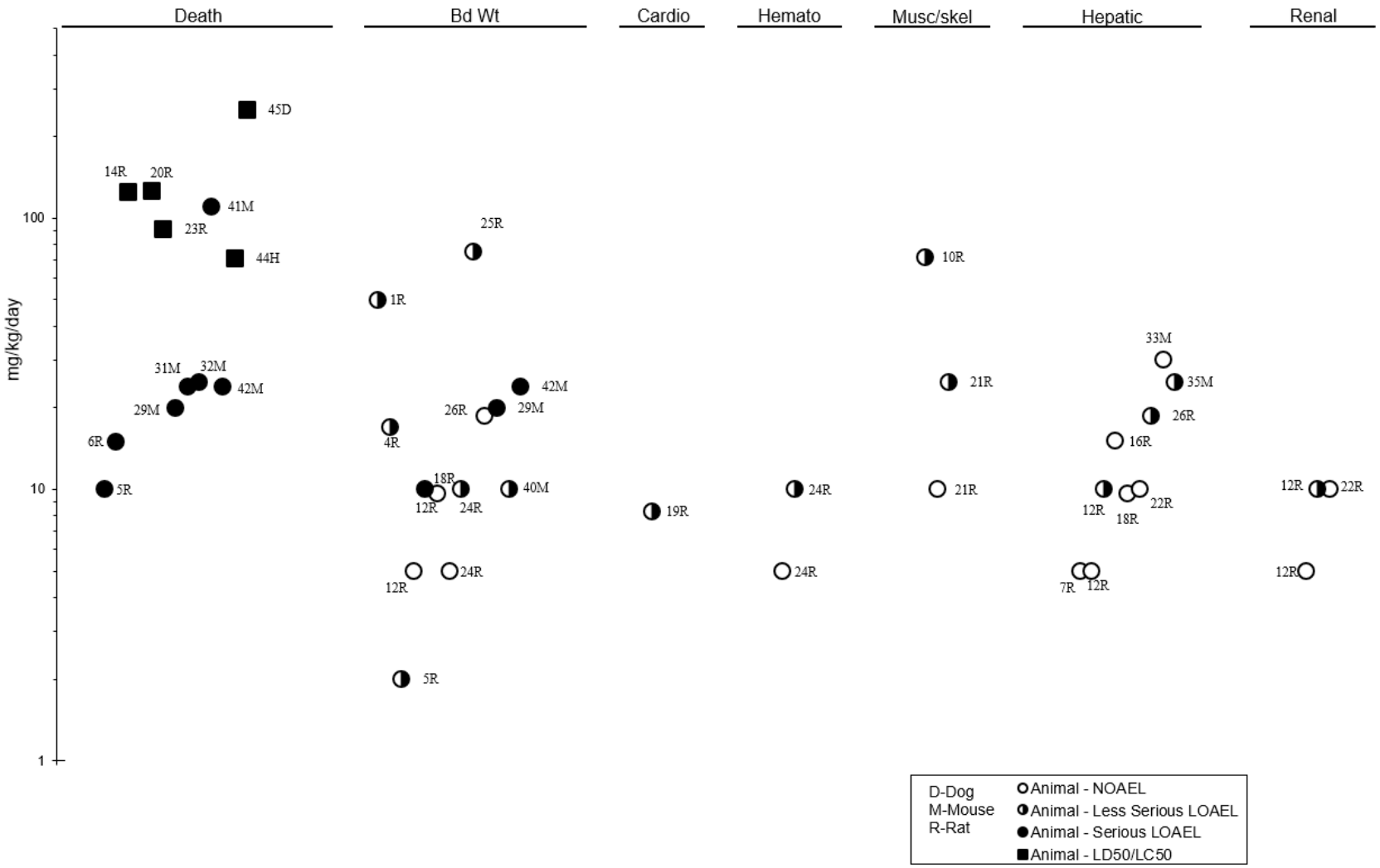


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral
Acute (≤14 days)

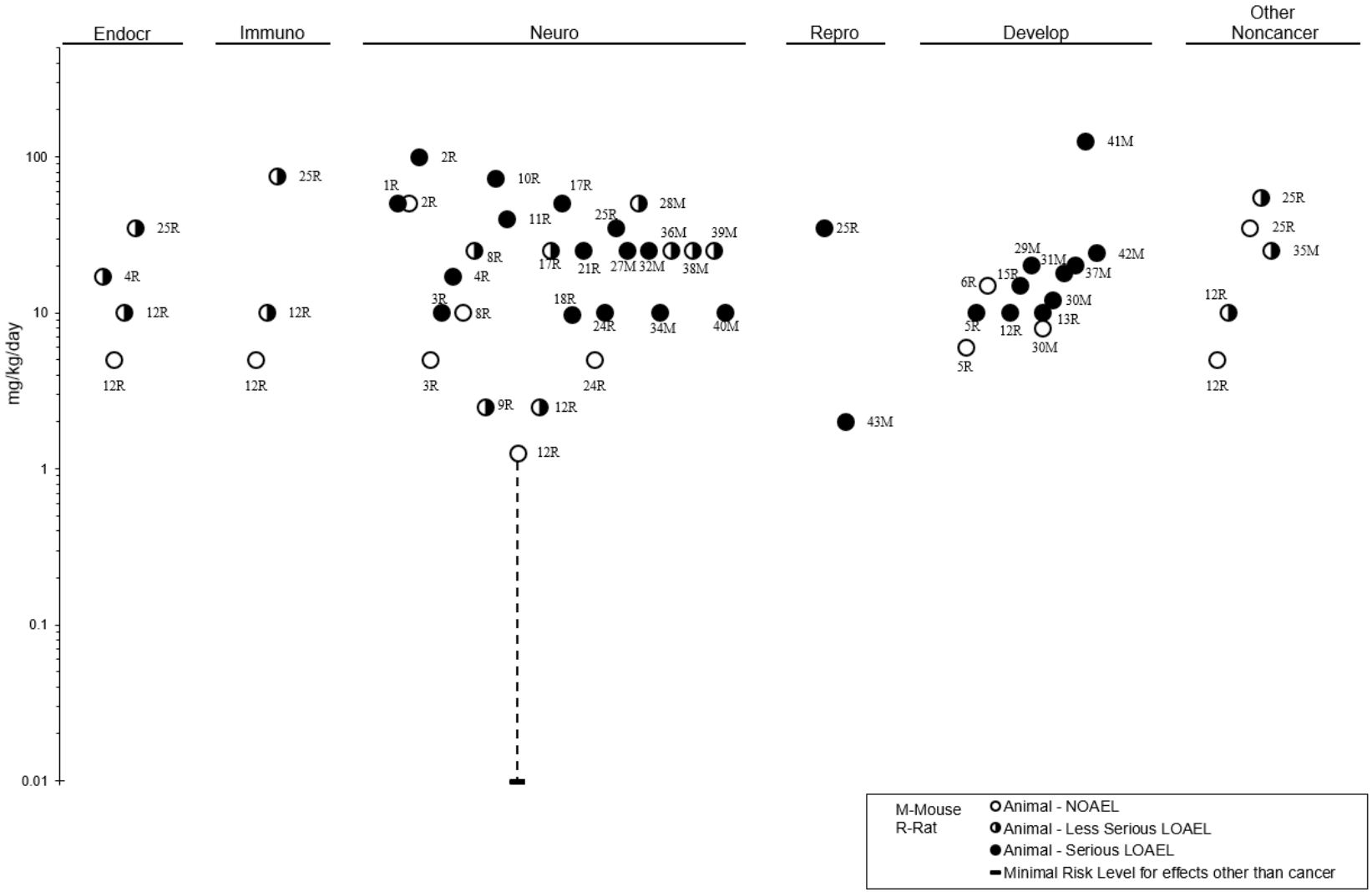


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral
Intermediate (15–364 days)

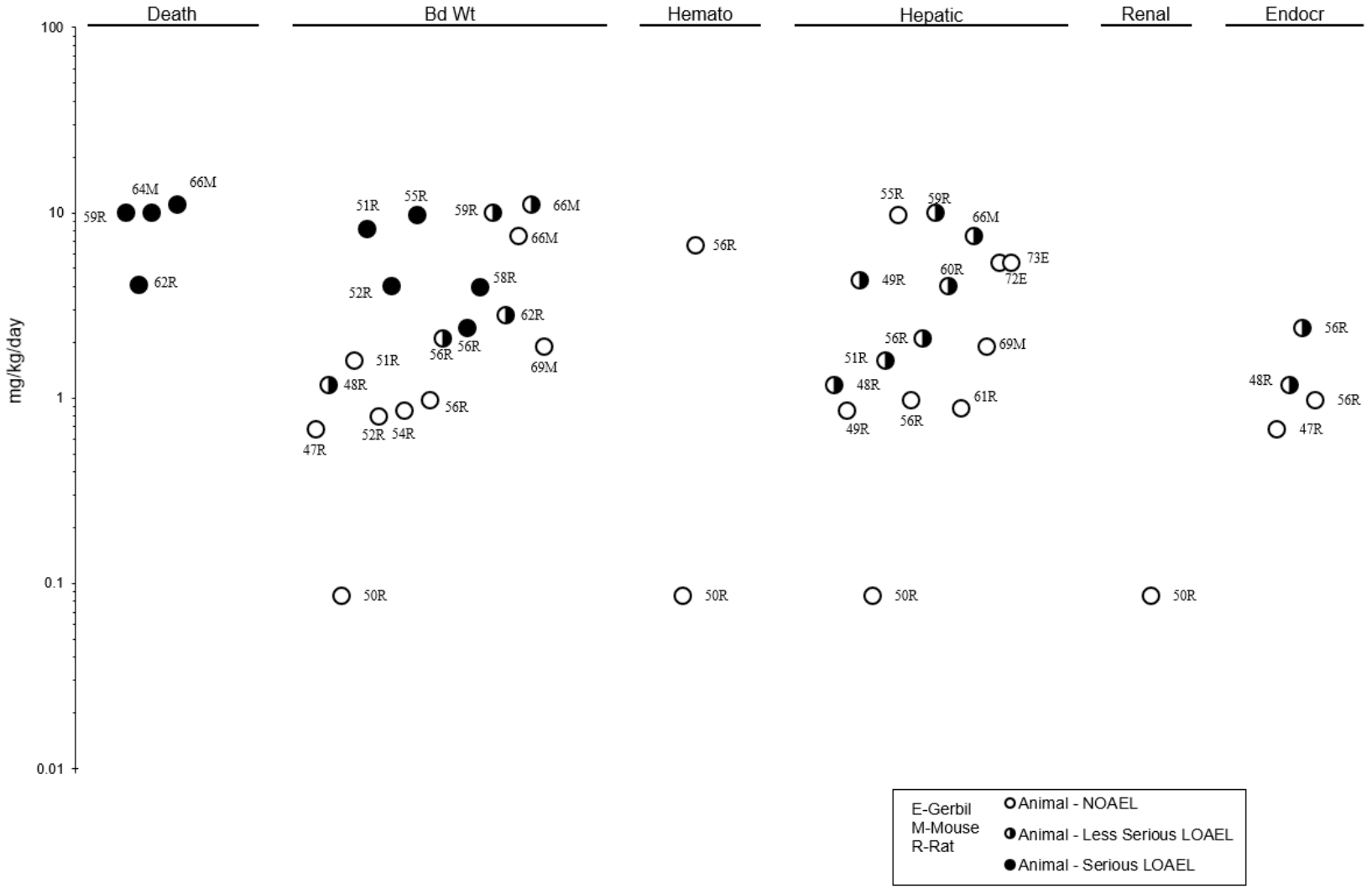


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral
Intermediate (15–364 days)

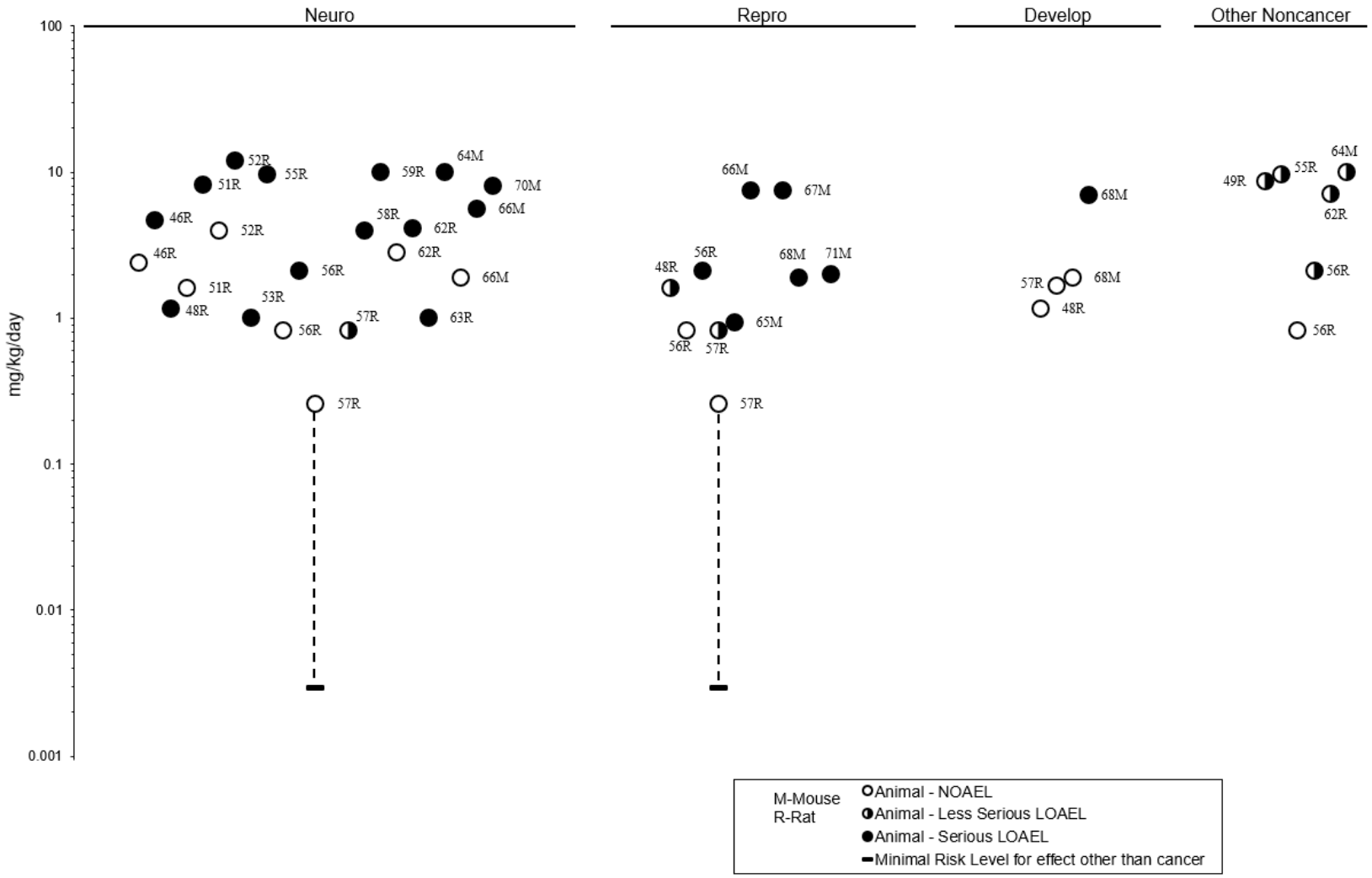


Figure 2-4. Levels of Significant Exposure to Chlordecone – Oral

Chronic (≥365 days)

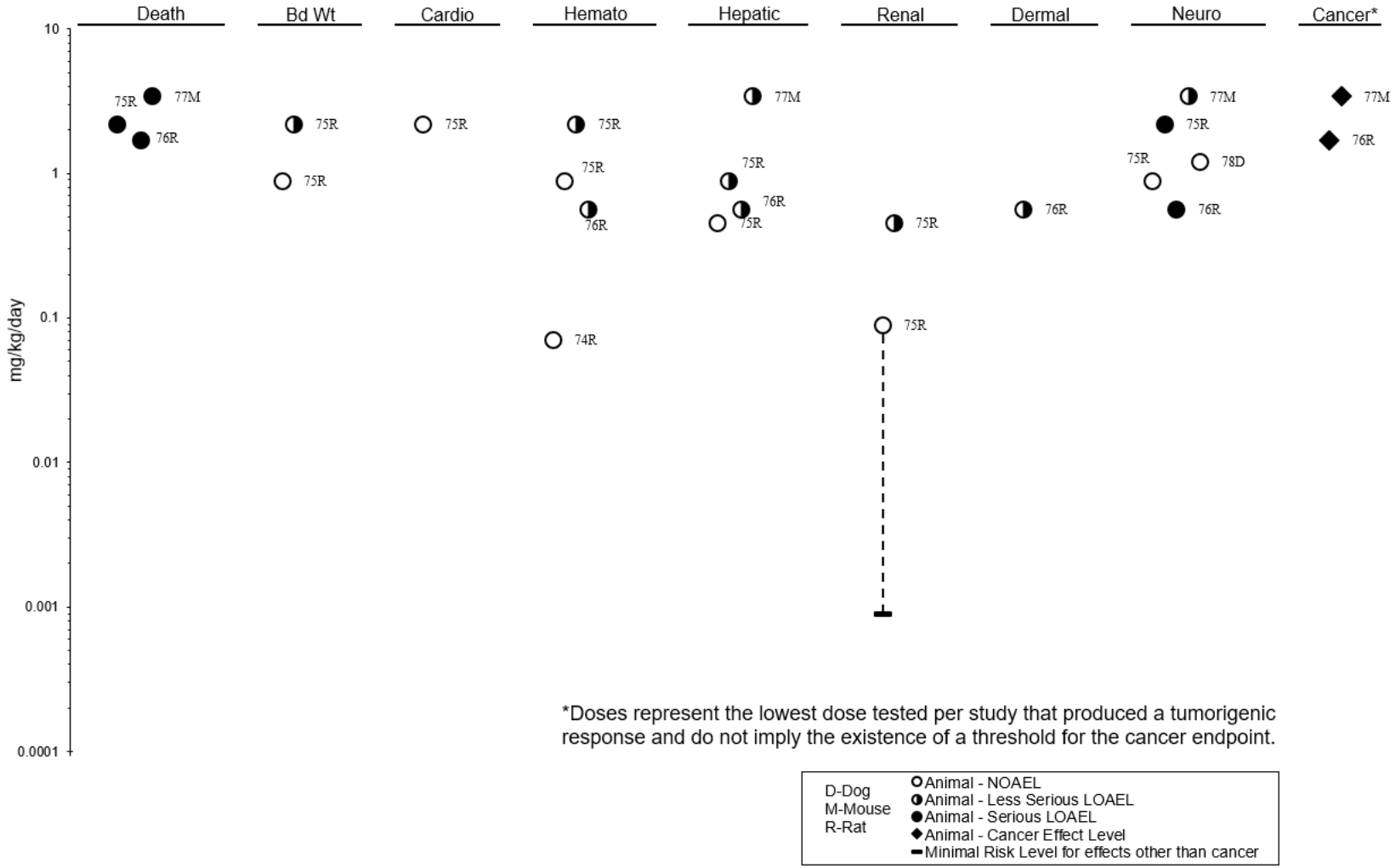


Table 2-5. Levels of Significant Exposure to Mirex – Dermal

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.