# 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 of 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. 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 produce similar toxicities in a number of organs. However, several aspects of the toxicity of mirex are distinctly different from those of chlordecone, and vice versa. Because the toxicity profiles of mirex and chlordecone differ significantly, each chemical will be discussed separately below.

## 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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 first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure 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 end point 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 end points. 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 user of this profile 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.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of mirex and chlordecone are indicated in Tables 2-l and 2-2 and Figures 2-l and 2-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for mirex and chlordecone. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

### 2.2.1 Inhalation Exposure

Information regarding health effects following inhalation exposure to mirex or chlordecone is limited. No data on health effects resulting from inhalation exposure to mirex were located. Health effects data on chlordecone resulting from inhalation exposure are limited to information on a single group of 133 men exposed to chlordecone at a facility in Hopewell, Virginia, where chlordecone was manufactured over a period of 21-22 months (Cannon et al. 1978; Guzelian 1982a; Guzelian et al. 1980; Martinez et al. 1978; Sanbom et al. 1979; Taylor 1982, 1985; Taylor et al. 1978). Hygiene conditions at the plant were extremely poor, and substantial inhalation, dermal, and even oral exposures could have occurred. Because of uncertainties regarding exposure levels at the facility, possible contribution of exposure by the various routes, and concomitant exposure to the precursor used to manufacture chlordecone (hexachlorocyclopentadiene), no NOAELS or LOAELs could be established following inhalation exposure for the effects described below.

#### 2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to mirex. No deaths were reported to result from exposure to chlordecone (Cannon et al. 1978; Taylor et al. 1978).
No studies were located regarding death in animals following inhalation exposure to mirex or chlordecone.

### 2.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, renal or endocrine effects in humans or animals following inhalation exposure to mirex or chlordecone. The systemic effects observed after inhalation exposure are discussed below.

**Respiratory Effects.** No studies were located regarding respiratory effects in humans following inhalation exposure to mirex. Thirty-two of 133 workers examined for toxicity following intermediateor chronic-duration inhalation exposures (exact duration periods unknown) at a chlordecone-manufacturing facility reported experiencing pleuritic chest pains (Cannon et al. 1978); among 23 workers with blood levels in excess of 2 μg/L, 18 reported pleuritic chest pains. Further examination of these workers did not reveal any dyspnea, and chest x-rays revealed no lung pathology (Taylor 1982, 1985). Therefore, the significance of the chest pains is unknown. No studies were located regarding respiratory effects in animals following inhalation exposure to mirex or chlordecone.

**Cardiovascular Effects.** No studies were located regarding cardiovascular effects in humans following inhalation exposure to mirex. Electrocardiography of 23 workers with active symptoms of chlordecone intoxication resulting from intermediate- or chronic-duration inhalation exposures to high blood concentrations (in excess of 2 μg/L) of chlordecone revealed no adverse effects on the heart (Taylor 1982, 1985).

No studies were located regarding cardiovascular effects in animals following inhalation exposure to mirex or chlordecone.

**Musculoskeletal Effects.** No studies were located regarding musculoskeletal effects in humans following inhalation exposure to mirex. 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 inhalation exposures 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 the lipochrome 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. In addition, 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.

No studies were located regarding musculoskeletal effects in animals following inhalation exposure to mirex or chlordecone.

**Hepatic Effects.** No studies were located regarding hepatic effects in humans following inhalation exposure to mirex. Mild hepatomegaly (occasionally with splenomegaly) was noted in 9 of 23 workers with 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 in 32 men exposed to high concentrations of chlordecone while employed for l-22 months (5.6 months average) in the production of chlordecone were compared to those of healthy men of the same age, hepatomegaly had occurred in 20 of the 32 exposed workers, with minimal splenomegaly in 10 of these 20 workers (Guzelian et al. 1980). In the exposed workers, urinary excretion of glucaric acid was significantly increased and the half-life of 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. 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 was normal; serum levels of bilirubin, albumin, globulin, alanine and aspartate aminotransferase activity, and γ-glutamyl transferase activity were also normal. No studies were located regarding hepatic toxicity in animals following inhalation exposure to mirex or chlordecone.

**Dermal Effects.** No studies were located regarding dermal effects in humans following inhalation exposure to mirex. Eighty-nine of the 133 workers interviewed as a result of intermediate- or chronic-duration inhalation exposures to high concentrations of chlordecone during its manufacture experienced skin rashes of an erythematous, macropapular nature at some time during their exposure (Cannon et al.

1978). Among 23 workers with blood chlordecone levels in excess of 2 μg/L, 6 men had 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 exposure.

No studies were located regarding dermal effects in animals following inhalation exposure to mirex or chlordecone.

**Ocular Effects.** Vision was blurred in 15 of the 23 workers examined as a result of intermediateor chronic-duration inhalation exposures to high blood concentrations (in excess of 2 μg/L) of chlordecone during its production. The effects on vision were characterized by a disruption of ocular motility following a horizontal saccade by rapid random multidirectional eye movements. Visual acuity and smooth eye movements were unaffected (Taylor 1982, 1985). The rapid eye movements were probably due to disturbance of the brain stem.

No studies were located regarding ocular effects in animals following inhalation exposure to mirex or chlordecone.

**Body Weight Effects.** No studies were located regarding body weight effects in humans following inhalation exposure to mirex. Twenty-seven of 133 workers examined as a result of intermediate- or chronic-duration exposures to chlordecone experienced weight loss (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).

#### 2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to mirex or chlordecone.

#### 2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to mirex. Sixty-one of 133 workers examined as a result of intermediate- or chronic-duration inhalation

exposures to high concentrations of chlordecone during its production experienced tremors; 58 experienced nervousness or unfounded anxiety; and 42 experienced 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). The effects on vision were characterized as a disruption of ocular motility following a horizontal saccade by rapid random multidirectional eye movements (Taylor 1982, 1985). Visual acuity and smooth eye movements were unaffected. Headaches of mild-to-moderate severity were reported by 9 of the 23 workers. Three of these 9 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 5 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 the chlordecone had 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).

No studies were located regarding neurological effects in animals following inhalation exposure to mirex or chlordecone.

### 2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to mirex. 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; Taylor 1982, 1985; Taylor et al. 1978). The threshold for abnormally low sperm counts was =l ug 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, effects on sperm morphology were not examined, and possible chlordecone exposure via oral and dermal routes may have occurred.

No studies were located regarding reproductive effects in animals after inhalation exposure to mirex or chlordecone.

### 2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to mirex or chlordecone. Although impaired spermatogenesis among male workers exposed to chlordecone via inhalation did not affect their fertility (Guzelian 1982a; Taylor 1982, 1985; Taylor et al. 1978), it is unclear whether abnormalities in their sperm may have resulted in developmental effects in offspring. No increase in birth defects among offspring conceived after termination of exposure was mentioned (Taylor 1982, 1985).

No studies were located regarding developmental effects in animals after inhalation exposure to mirex or chlordecone.

### 2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following inhalation exposure to mirex or chlordecone.

Genotoxicity studies are discussed in Section 2.4.

### 2.2.1.8 Cancer

No studies were located regarding cancer in humans following inhalation exposure to mirex. Extremely limited information was located regarding cancer in humans following inhalation exposure to chlordecone. Liver biopsy samples taken from 12 workers with hepatomegaly resulting from intermediate- or chronic-duration exposures to high concentrations 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.

No studies were located regarding cancer in animals after inhalation exposure to mirex or chlordecone.

## 2.2.2 Oral Exposure

### 2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to mirex. No deaths were reported to have occurred from exposure to chlordecone (Cannon et al. 1978; Taylor et al. 1978).

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 females and males were 600 and 740 mg/kg, respectively, after administration in corn oil but in excess of 3,000 mg/kg after administration in peanut oil (Gaines 1969). No explanation for the vehicle effect was given. In male dogs, a single oral dose of 1,250 mg/kg was lethal in 3 of 5 treated animals (Larson et al. 1979a). No deaths were observed in the dogs following a single oral dose of 1,000 mg/kg. When dosing occurs over several days, mortality is observed at substantially lower daily doses. Increased mortality in multiple-dose, acute-

duration studies has been observed in female rats at doses as low as 50 mg/kg/day (Mehendale et al. 1973). Pregnant rats appear to be somewhat more sensitive to the lethal effect of mirex. Although a single oral dose of 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. 1979b; Khera et al. 1976). Similarly, a 32-36% mortality was observed in rat and mouse pups exposed through the milk during the first 4 days of lactation at these doses (Chernoff et al. 1979b). Male rats showed approximately 5% mortality at 6 mg/kg/day for 10 days (Khera et al. 1976). Male mice had slightly higher mortality with 80% mortality following 14 daily doses with 10 mg/kg/day (Fujimori et al. 1983).

In intermediate-duration studies, mortality occurred at only slightly lower doses of mirex than in the multiple-dose, acute-duration studies in rats, but mice and dogs appeared more sensitive. In rats, mortality was increased in adult males at doses as low as 5 mg/kg/day for 30 days (Mehendale 1981b); in adult females at doses as low as 6.2 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 O-25% mortality occurred at 0.65 mg/kg/day for 120 days (Ware and Good 1967). In dogs, 50% mortality occurred at 2.5 mg/kg/day for 13 weeks (Larson et al. 1979a), but this value may not be reliable because only 2 dogs/sex/group were tested. In a 2-year study in rats, males exhibited increased mortality at 1.8 mg/kg/day (63% mortality versus 15% mortality in controls), but females exhibited no decrease in survivol at as much as 7.7 mg/kg/day (NTP 1990). All mice ingesting 3.6 mg/kg/day for 18 months died prior to termination of the study (mortality in controls was 11%) (Innes et al. 1969), and 20% and 92% mortality occurred in mice ingesting 0.24 and 2.4 mg/kg/day, respectively, for 15 months. Mortality among controls was less than 10% (Wolfe et al. 1979).

Single-dose oral $LD_{50}$ values in rats for chlordecone were reported to be 126 mg/kg in females (Larson et al. 1979b) and between 91.3 (Pryor et al. 1983) and 132 mg/kg (Larson et al. 1979b) in males. The combined 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 25% mortality in pregnant mice (Kavlock et al. 1985). No mortality was observed in male rats at approximately 10 mg/kg/day for 10 days (Simmons et al. 1987), but mortality in pregnant rats was 19% at 10 mg/kg/day during gestation (Chernoff and Rogers 1976). Ingestion of 24 mg/kg/day for 5 days during gestation resulted in 19% mortality in pregnant mice

(Seidenberg et al. 1986). Ingestion of milk from dams given 18 mg/kg/day during the first 4 days of lactation resulted in 64% mortality in mouse pups (Chernoff et al. 1979b). Ingestion of 25 mg/kg/day for 12 days resulted in 100% mortality in male mice (Desaiah et al. 1980a).

In intermediate-duration studies in male rats, 40% mortality occurred at 5 mg/kg/day for 5 weeks (Mehendale 1981b), and 60% mortality occurred at 4.1 mg/kg/day for 15 weeks (Pryor et al. 1983). In mice of both sexes, at a dose of 7.8 mg/kg/day for up to 12 months, only 1 of 8 adult mice died whereas 4 of 4 juvenile mice died, indicating a greater sensitivity in immature mice (Huber 1965). All male mice at 10 mg/kg/day died by day 33 of dosing (Fujimori et al. 1983). Survivol was decreased in female rats at 1.25 mg/kg/day in a 2-year feeding study (Larson et al. 1979b) and in both male and female rats at 1.2-l .3 mg/kg/day in an 80-week feeding study (NCI 1976). Male mice showed decreased survivol at 2.6 mg/kg/day and above in an 80-week feeding study (NCI 1976).

All $LD_{50}$ and LOAEL values from each reliable study for death in rats and mice following acute-, intermediate-, and chronic-duration exposure are recorded for mirex in Table 2-l and for chlordecone in Table 2-2, and plotted for mirex in Figure 2-l and for chlordecone in Figure 2-2.

#### 2.2.2.2 Systemic Effects

The systemic effects observed after oral exposure to mirex and chlordecone are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded for mirex in Table 2-l and for chlordecone in Table 2-2, and plotted for mirex in Figure 2-l and for chlordecone in Figure 2-2.

**Respiratory Effects.** No studies were located regarding respiratory effects in humans following oral exposure to mirex. Pleuritic chest pain was reported by 32 of 133 workers employed at a facility that manufactured chlordecone (Cannon et al. 1978). Among 23 workers with blood chlordecone levels in excess of 2 μg/L, 18 reported pleuritic chest pains. Further examination of these 18 workers revealed no dyspnea and chest x-rays were normal (Taylor 1982, 1985; Taylor et al. 1978); thus, the cause of the chest pains is unknown. Although oral exposures are not normally encountered in occupational situations, hygiene was particularly poor at this plant and oral exposures were likely. Therefore, intermediate- and chronic-duration oral exposure to chlordecone cannot be ruled out as a possible cause for the chest pains.

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| | **ACUTE EXPOSURE** | | | | | | |
| | **Death** | | | | | | |
| 1 | Rat (CD) | Gd7-16 10 d 1x/d (GO) | | | | 9.5 F (16% mortality in dams) | Chemoff et al. 1979a |
| 2 | Rat (Sherman) | Once (GO) | | | | 365 (LD50) | Gaines and Kimbrough 1970 |
| 3 | Rat (Wistar) | Gd6-15 10 d 1x/d (GO) | | | | 6 F (20% mortality in dams) | Khera et al. 1976 |
| 4 | Rat (CD-1) | 5 d 1x/d (GO) | | | | 50 (25% mortality in females) | Mehendale et al. 1973 |
| 5 | Mouse (ICR) | 14 d 1x/d (GO) | | | | 10 M (80% mortality) | Fujimori et al. 1983 |
| 6 | Dog (Mongrel) | Once (GO) | | | | 1,250 (60% mortality) | Larson et al. 1979a |
| | **Systemic** | | | | | | |
| 7 | Rat (Sprague-Dawley) | 8 d ad lib (F) | Endocr | 17 | | | Baggett et al. 1980 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 8 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Hepatic | | 50 (impaired biliary excretion of glucuronide conjugates; increased bile flow) | | Berman et al. 1986 |
| 9 | Rat (CD) | Gd5, Gd5-9, Gd5-14 1, 5, or 10d 1x/d (GO) | Cardio | | | 10 F (significant decrease of heart weight; decreased maternal cardiac output) | Buelke-Sam et al. 1983 |
| | | | Hepatic | | 10 F (significant increase in liver weight) | | |
| | | | Bd Wt | | | 10 F (35-52% decrease in maternal weight gain) | |
| 10 | Rat (CD) | Gd7-16 10 d 1x/d (GO) | Bd Wt | 7 | | 9.5 (36% decrease in maternal weight gain) | Chernoff et al. 1979a |
| 11 | Rat (Sprague-Dawley) | 14 d ad lib (F) | Hepatic | | 5 (disruption of liver cord cells; focal stasis) | 5 (central or midzonal hepatocellular necrosis) | Davison et al. 1976 |
| 12 | Rat (Wistar) | 3-7 d ad lib (F) | Hepatic | | 750 (decreased hepatic glycogen; increased lipid accumulation) | | Elgin et al. 1990 |
| | | | Bd Wt | | 750 (16-17% decrease in body weight gain) | | |
| 13 | Rat (Sprague-Dawley) | Once (GO) | Hemato | | 100 (12% increased hematocrit) | | Ervin and Yarbrough 1983 |
| | | | Hepatic | | 100 (significantly decreased hepatic glycogen) | | |
| | | | Other | | 100 (decreased blood glucose) | | |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Less Serious (mg/kg/day) | | Serious (mg/kg/day) | | |
| 14 | Rat (Sprague-Dawley) | Once (GO) | Endocr | | | | 100 | (88% increase in serum adrenocorticotropic hormone) | Ervin and Yarbrough 1985 |
| 15 | Rat (Sprague-Dawley) | Once (GO) | Hepatic | | 50 | (increased bile flow rate) | | | Hewitt et al. 1986a |
| 16 | Rat (Wistar) | 7 d ad lib (F) | Hepatic | | 2 | (two-fold increase in liver weight; increased cholesterol and triglycerides) | | | Jovanovich et al. 1987 |
| 17 | Rat (Wistar) | 4 d (F) | Hepatic | | 1000 F | (two-fold increase in liver weight and serum triglycerides; 25% decrease in liver glycogen and glucose) | | | Jovanovich et al. 1987 |
| | | | Endocr | | 1000 F | (two-fold increase in adrenal weight) | | | |
| | | | Bd Wt | | 1000 F | (30% reduction in body weight; 77% reduction in body fat) | | | |
| | | | Other | | 1000 F | (reduced food intake; 88% reduction in serum glucose) | | | |
| 18 | Rat (Mai-Wistar) | Once (GO) | Hepatic | | 200 | (hepatic glycogen depletion; periportal liposis; degeneration of endoplasmic reticulum) | | | Kendall 1979 |
| 19 | Rat (Sprague-Dawley) | Once (GO) | Hepatic | 10 | | | | | Klingensmith and Mehendale 1983b |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 20 | Rat (Sprague-Dawley) | 72 h Once (GO) | Hepatic | | 20 (induction of P450b and P450e mRNAs in liver) | | Kocarek et al. 1991 |
| 21 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Hepatic | | 50 (suppressed biliary excretion; increased bile flow) | | Mehendale 1977c |
| 22 | Rat (Sprague-Dawley) | 1 d 1x/d or 2x/d (GO) | Hepatic | | 240 (increased serum alanine aminotransferase) | | Mitra et al. 1990 |
| 23 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Hepatic | | 10 (swollen hepatocytes) | | Plaa et al. 1987 |
| | | | Renal | 0.5 | | | |
| 24 | Rat (Sprague-Dawley) | Once (GO) | Hepatic | 5 | | | Robinson and Yarbrough 1978a |
| | | | Other | | 5 (decreased blood glucose) | | |
| 25 | Rat (Sprague-Dawley) | Once (GO) | Hepatic | | 100 (decreased hepatic glutathione) | | Sunahara and Chiesa 1992 |
| 26 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Hepatic | | 12.5 F (decreased hepatic ion transport) | | Teo and Vore 1990 |
| 27 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Hepatic | | 50 (decreased biliary function, decrease bile flow, decreased concentration and secretion of bile acid) | | Teo and Vore 1991 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 28 | Rat (Sprague-Dawley) | 14 d 1x/d (GO) | Hemato | 10 | | | | | Villeneuve et al. 1977 |
| | | | Hepatic | | 1 | (significantly increased relative liver weight; significantly increased serum lactic dehydrogenases) | | | |
| | | | Hepatic | | 10 | (significant increases in serum sorbitol dehydrogenase) | | | |
| | | | Bd Wt | | | | 10 | (55% decrease in body weight gains) | |
| 29 | Rat (Sprague-Dawley) | Once (GO) | Hepatic | | 50 | (two-fold increase in liver mass) | | | Williams and Yarbrough 1983 |
| | | | Other | | 20 | (increased serum corticosterone) | | | |
| 30 | Mouse (C57BL/6) | 2 d 1x/d (GO) | Hepatic | | 30 | (elevated serum alanine and aspartate aminotransferases) | | | Fouse and Hodgson 1987 |
| 31 | Mouse (ICR) | 4 d ppd54 and 58 (GO) | Hepatic | 10 | 25 | (decreased hepatic glycogen) | | | Fujimori et al. 1983 |
| | | | Other | 10 | 25 | (decreased serum glucose and lactate; decrease free fatty acids) | | | |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 32 | Mouse (ICR) | 14 d 1x/d (GO) | Bd Wt | | 10 (>10% decrease in body weight) | | Fujimori et al. 1983 |
| | | | Other | | 10 (20% decreased plasma glucose; decrease food and water consumption) | | |
| 33 | Mouse (Swiss-Webster) | Once (GO) | Hepatic | | 50 (slight hepatocyte vacuolization and loss of basophilic staining) | | Hewitt et al. 1979 |
| | | | Renal | 50 | | | |
| | **Immuno./Lymphor** | | | | | | |
| 34 | Rat (CD) | Gd5, Gd5-9, Gd5-14 1, 5, or 10 d 1x/d (GO) | | | 10 F (32% decrease in spleen weight) | | Buelke-Sam et al. 1983 |
| | **Reproductive** | | | | | | |
| 35 | Rat (CD) | Gd 5, Gd5-9, Gd5-14 1, 5 or 10 d 1x/d (GO) | | | 10 (decreased blood flow to ovaries, uterus, and fetuses; decreased ovarian and uterine weight) | | Buelke-Sam et al. 1983 |
| 36 | Rat [CRL-COBS; CD(SD)] | Gd5-14 Gd6-15 10 d 1x/d (GO) | | | | 10 F (24-25% mortality in dams) | Byrd et al. 1981 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|
| 37 | Rat (CRL-COBS CD(SD)) | Gd5-14 Gd6-15 10 d 1x/d (GO) | | | | 10 | (>30% decreased dam body weight; >20% decreased gravid uterine weight) | Byrd et al. 1981 |
| 38 | Rat (Long-Evans) | Gd8.5- 15.5 Gd6.5- 15.5 8 d or 10 d 1x/d (GO) | | 7 | | 10 | (decreased number of litters) | Grabowski and Payne 1980 |
| 39 | Rat (Wistar) | Gd6-15 10 d 1x/d (GO) | | | | 12.5 | (pregnancy failure in 45%) | Khera et al. 1976 |
| 40 | Rat (Wistar) | 10 d 1x/d (GO) | | 3 | | 6 | (significantly decreased fertility) | Khera et al. 1976 |
| | **Developmental** | | | | | | | |
| 41 | Rat (CD) | Gd5, Gd5-9, Gd5-14 1,5 or 10 d 1x/d (GO) | | | | 10 | (decreased pup viability and pup weight; increased resorptions, fetal edema) | Buelke-Sam et al. 1983 |
| 42 | Rat (CrL-COBS CD(SD)) | Gd5-14 Gd6-15 10 d 1x/d (GO) | | | | 10 | (>59% fetuses with edema and increased prenatal mortality) | Byrd et al. 1981 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 43 | Rat (CRL-COBS CD(SD)) | Gd5-14 Gd6-15 10 d 1x/d (GO) | | | | 10 (>20% decreased pup body weight) | Byrd et al. 1981 |
| 44 | Rat (Long-Evans) | ppd1-4 4 d 1x/d (GO) | | | | 10 F (35-36% mortality in pups) | Chernoff et al. 1979a |
| 45 | Rat (Long-Evans) | Once (GO) | | | | 10 (cataracts) | Chernoff et al. 1979a |
| 46 | Rat (CD) | Gd7-16 10 d 1x/d (GO) | | 5 | | 7 (delayed ossification; edematous live fetuses)<br>9.5 (enlarged cerebral ventricles; undescended testes) | Chernoff et al. 1979a |
| 47 | Rat (Long-Evans) | Gd8.5- 15.5 8 d 1x/d (GO) | | | | 6 (36% edematous fetuses) | Grabowski 1981 |
| 48 | Rat (Long-Evans) | Gd8.5- 15.5 or Gd15.5-21.5 6 or 7 d 1x/d (GO) | | | | 0.1 F (cardiac arrhythmia) | Grabowski 1983a |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 49 | Rat (Long-Evans) | Gd8.5- 15.5 Gd6.5- 15.5 8 d or 10 d 1x/d (GO) | | | | 5 (first degree heartblock in fetuses) | Grabowski and Payne 1980 |
| 50 | Rat (Long-Evans) | Gd8.5- 15.5 8 d 1x/d (GO) | | | | 6 (23% stillborn pups; dyspnea; cardiac rhythm blockade) | Grabowski and Payne 1983a |
| 51 | Rat (Long-Evans) | Gd8.5- 15.5 8 d 1x/d (GO) | | | | 6 (first degree heart block in fetuses; 14% increased fetal mortality) | Grabowski and Payne 1983b |
| 52 | Rat (Long-Evans) | Gd8-15 8 d 1x/d (GO) | | | | 6 (cataracts in 49.6% of fetuses; 14% fetal mortality on Gd 21) | Rogers and Grabowski 1983 |
| 53 | Rat (Long-Evans) | ppd1-4 4 d 1x/d (GO) | | | | 10 (cataracts) | Rogers and Grabowski 1984 |
| | | | | | 10 (10-20% decrease in pup weight) | | |
| 54 | Rat (Long-Evans) | Gd8-15 8 d 1x/d (GO) | | | 6 (decrease in fetal hematocrit and plasma glucose) | | Rogers et al. 1984 |
| 55 | Rat (Sherman) | ppd1-4 5 d 1x/d (GO) | | | | 5 (neonatal cortical degeneration and necrosis in lens of eye) | Scotti et al. 1981 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 56 | Mouse (CD-1) | Gd8-12 5 d 1x/d (GO) | | | | 7.5 (increased mortality, decreased pup weight on Ld 1 and 3) | Chernoff and Kavlock 1982 |
| 57 | Mouse (CD-1) | ppd1-4 4 d 1x/d (GO) | | | | 6 (32% pup mortality) | Chernoff et al. 1979a |
| 58 | Mouse (CD-1) | ppd1-4 4 d 1x/d (GO) | | 1.5 | 1.5 (11-14% decrease in pup weight) | 3 (cataracts) | Chernoff et al. 1979a |
| 59 | Mouse (CD-1) | Gd8-12 5 d 1x/d (G) | | | | 7.5 (56% increased mortality in pups) | Gray et al. 1983 |
| | **INTERMEDIATE EXPOSURE** | | | | | | |
| | **Death** | | | | | | |
| 60 | Rat (Sherman) | 90 d ad lib (F) | | | | 6.2 M (LDLO) | Gaines and Kimbrough 1970 |
| 61 | Rat (Charles River) | 13 wk ad lib (F) | | | | 64 (50% mortality in males; 100% mortality in females) | Larson et al. 1979a |
| 62 | Mouse (ICR) | 15 d 1x/d (GO) | | | | 10 (100% mortality) | Fujimori et al. 1983 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| | **Systemic** | | | | | | |
| 63 | Rat (Sprague-Dawley) | 15 d ad lib (F) | Hepatic | | 0.5 M (decreased hepatobiliary function) | | Bell and Mehendale 1985 |
| 64 | Rat (Sprague-Dawley) | 28 d ad lib (F) | Hemato | 0.05 | | | Chu et al. 1980a |
| | | | Hepatic | | 0.05 (fatty degeneration of liver) | | |
| | | | Renal | 0.05 | | | |
| | | | Endocr | 0.05 | | | |
| | | | Bd Wt | 0.05 | | | |
| | | | Other | 0.05 | | | |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | Less Serious (mg/kg/day) | | Serious (mg/kg/day) | |
| 65 | Rat (Sprague-Dawley) | 28 days (GO) | Hepatic | | 6.2 | (>34% increase in liver weight) | | Chu et al. 1980b |
| | | | | | 6.2 M | (panlobular ballooning of hepatocytes, anisokaryosis and fatty vacuolation) | | |
| | | | | | 6.2 F | (moderate lobular pattern with perinuclear clear zone and perivenous cytoplasmic balooning with anisokaryosis) | | |
| | | | Endocr | | 6.2 M | (reduced colloid density with collapse of follicles, increased epithelial height increased in thyroid gland) | | |
| | | | | | 6.2 F | (mild to moderate increase in epithelial height and follicular collapse in thyroid gland) | | |
| 66 | Rat (Sprague-Dawley) | 148 d ad lib (F) | Hemato | 2 | | | | Chu et al. 1981a |
| | | | Endocr | | 0.25 | (colloid density reduction and thickening of follicular epithelia in thyroid) | | |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 67 | Rat (Sprague-Dawley) | 28 d ad lib (F) | Hemato | 2.5 | | | Chu et al. 1981b |
| | | | Hepatic | | 0.25 (cytoplasmic vacuolation, decreased aggregated basophilia, anisokaryosis, and hyperchromicity) | | |
| | | | Endocr | | 0.25 (reduction of colloid in thyroid) | | |
| | | | Other | | 0.25 (decreased serum glucose) | | |
| 68 | Rat (Sprague-Dawley) | 15 d ad lib (F) | Hepatic | | 1 M (impaired biliary excretion) | | Curtis and Hoyt 1984 |
| | | | Bd Wt | 1 | | 5 M (39% decrease in body weight gain) | |
| 69 | Rat (Sprague-Dawley) | 15 d ad lib (F) | Hepatic | 0.5 | | | Curtis et al. 1981 |
| 70 | Rat (Sprague-Dawley) | 28 d ad lib (F) | Hepatic | | | 0.5 (disruption of liver cord cells; focal bile stasis; central or midzonal hepatocellular necrosis) | Davison et al. 1976 |
| | | | Bd Wt | | 5 (17% decrease in body weight) | | |
| 71 | Rat (Sherman) | 166 d ad lib (F) | Hepatic | 0.48 | 3.1 (bile stasis; decreased hepatic glycogen, multinucleation) | | Gaines and Kimbrough 1970 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 72 | Rat (Charles River) | 13 wk ad lib (F) | Hemato | 4 | 16 (decreased hemoglobin) | | Larson et al. 1979a |
| | | | Hepatic | 1 | 4 (hepatocellular vacuolation) | | |
| | | | Renal | 64 | | | |
| | | | Bd Wt | 16 | | 64 (33-34% decrease in body weight) | |
| 73 | Rat (Sprague-Dawley) | <30 d ad lib (F) | Gastro | | 5 (diarrhea) | | Mehendale 1981b |
| | | | Hepatic | | 5 (impaired biliary excretion) | | |
| 74 | Rat (Sprague-Dawley) | 15 d ad lib (F) | Hepatic | 0.5 | | | Mehendale et al. 1991 |
| 75 | Rat (Sprague-Dawley) | 28 d ad lib (F) | Endocr | 0.25 | 2.5 (increased large irregularly shape lysosomes in the thyroid) | | Singh et al. 1982 |
| 76 | Rat (Sprague-Dawley) | 28 d ad lib (F) | Endocr | | 0.25 M (dilation of rough endoplasmic reticulum cisternae of thyroid of weanling rats) | | Singh et al. 1985 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 77 | Rat (Sprague-Dawley) | 28 d ad lib (F) | Hemato | 3.75 | | | Yarbrough et al. 1981 |
| | | | Hepatic | 3.75 | | | |
| | | | Endocr | 0.25 | 2.5 M (significantly decreased serum thyroid $T_3$ factor ) | | |
| | | | | 2.5 | 3.75 M (significantly decreased serum thyroid $T_4$ factor ) | | |
| 78 | Mouse (Swiss-Webster) | 15 d ad lib (F) | Hepatic | 1.3 | | | Mehendale et al. 1989 |
| | | | Bd Wt | 1.3 | | | |
| | | | Other | 1.3 | | | |
| 79 | Dog (Beagle) | 13 wk ad lib (F) | Hemato | 0.5 | 2.5 (increased hematocrit and leukocyte count) | | Larson et al. 1979a |
| | | | Hepatic | 0.5 | 2.5 (increased serum alkaline phosphatase) | | |
| | | | Renal | 2.5 | | | |
| | | | Bd Wt | 0.5 | | 2.5 (58-74% decrease in body weight gain) | |
| 80 | Gerbil (Mongolian) | 15 d ad lib (F) | Hepatic | 5.4 | | | Cai and Mehendale 1990 |
| | **Neurological** | | | | | | |
| 81 | Rat (Sprague-Dawley) | 148 d ad lib (F) | | | | 2 (hypoactivity, irritability, and tremors) | Chu et al. 1981a |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | | |
| 82 | Rat (Sprague-Dawley) | 15 d ad lib (F) | | 1 | | 5 M | (lethargy) | Curtis and Hoyt 1984 |
| 83 | Rat (Zivac-Miller) | NS 5-6d/wk 1x/d (GO) | | | | 5 | (decrease in operant behavior) | Dietz and McMillan 1979 |
| 84 | Rat (Charles River) | 13 wk ad lib (F) | | 16 | | 64 | (hyperexcitability, tremors, convulsions) | Larson et al. 1979a |
| 85 | Rat (Sprague-Dawley) | <30 d ad lib (F) | | | | 5 M | (lethargy) | Mehendale 1981b |
| 86 | Rat (Long-Evans) | 61-113 d ad lib (F) | | 0.9 | | | | Thorne et al. 1978 |
| | **Reproductive** | | | | | | | |
| 87 | Rat (Sprague-Dawley) | 148 d ad lib (F) | | | | 0.25 | (decreased litter size; decreased mating) | Chu et al. 1981a |
| 88 | Rat (Sherman) | 2 gen repro ad lib (F) | | 0.31 | | 1.8 | (decreased number of litters) | Gaines and Kimbrough 1970 |
| 89 | Rat (Sprague-Dawley) | 28 d ad lib (F) | | | | 3.75 | (hypocellularity of the seminiferous tubules; testicular degeneration) | Yarbrough et al. 1981 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 90 | Mouse (BALB/c) (CFW) | 120 d ad lib (F) | | 0.65 | | | | | Ware and Good 1967 |
| 91 | Mouse (BALB/c) | 120 d ad lib (F) | | 0.65 | | | | | Ware and Good 1967 |
| | **Developmental** | | | | | | | | |
| 92 | Rat (CD) | ppd1-46 46 d ad lib (F) | | | 1.25 | (10-19% decrease in postnatal growth) | 1.25 | (cataracts, outlined lenses) (increased still births; decreased postnatal viability) | Chernoff et al. 1979b |
| 93 | Rat (CD) | Gd4- ppd46 68 d ad lib (F) | | | | | 1.25 | (decreased postnatal viability; increased stillbirths, cataracts, and outlined lenses) | Chernoff et al. 1979b |
| 94 | Rat (Sprague-Dawley) | 148 d ad lib (F) | | | | | 0.25 | (cataracts in pups) | Chu et al. 1981a |
| 95 | Rat (Sherman) | Ld1-21 21 d ad lib (F) | | | | | 1.8 | (increased mortality in pups, cataracts in pups) | Gaines and Kimbrough 1970 |
| 96 | Rat (Sherman) | 2 gen repro ad lib (F) | | 0.31 | | | 1.8 | (cataracts, decreased live births, increased mortality through weaning) | Gaines and Kimbrough 1970 |

TABLE 2-1. Levels of Significant Exposure to Mirex - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | **Cancer** | | | | | | | | |
| 97 | Rat (Sprague-Dawley) | 148 d ad lib (F) | | | | | 0.25 | (liver and thyroid lesions in adults and pups) | Chu et al. 1981a |
| | **CHRONIC EXPOSURE** | | | | | | | | |
| | **Death** | | | | | | | | |
| 98 | Rat (F344/N) | 2 yr ad lib (F) | | | | | 1.8 | (63% mortality in males) | NTP 1990 |
| 99 | Mouse (C57BL/6 x C3H/ANF) (C57BL/6 x AKR) | 18 mo (GF) | | | | | 3.8 | (100% mortality; 11% in controls) | Innes et al. 1969 |
| | **Systemic** | | | | | | | | |
| 100 | Rat (Sprague-Dawley) | 21 mo | Hepatic | | 0.07 | (significant increases in microsomal aniline hydroxylase and aminopyrine-*N*-demethylase;hepatic focal biliary hyperplasia; pericentral cytoplasmic vacuolization; lobular pattern with mild anisokaryosis) | | | Chu et al 1981c |
| | | | Endocr | | 0.07 | (degenerative and proloferative changes in the follicular epithelium of thyroid) | | | |

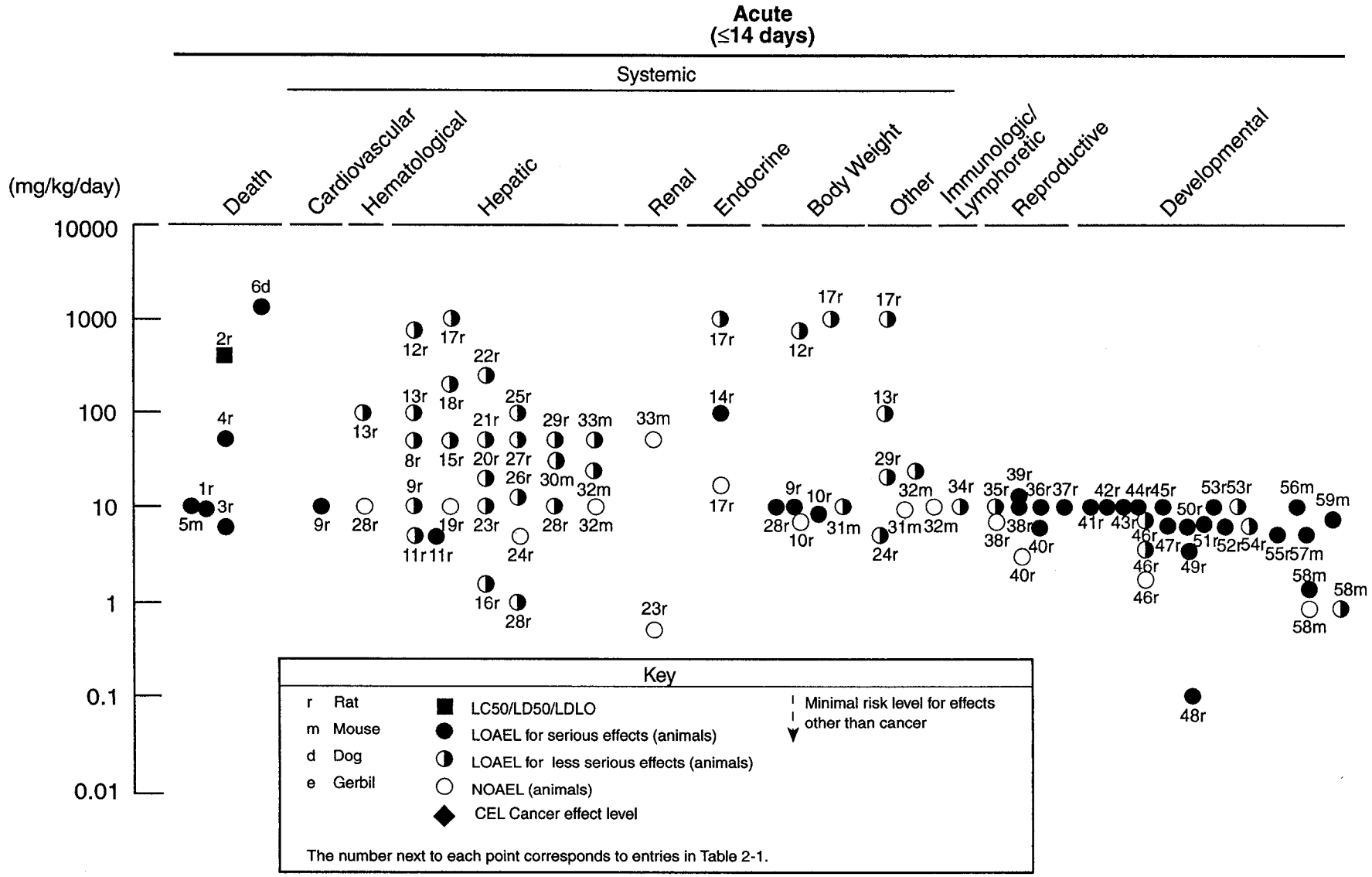
TABLE 2-1. Levels of Significant Exposure to Mirex Oral (continued)

| Key to [a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 101 | Rat (F344/N) | 2 yr ad lib (F) | Hepatic | 0.075 [b] | 0.7 (focal and centrilobular necrosis; fatty metamorphosis; dilation of sinusoids) | | NTP 1990 |
| | | | Renal | 0.075 | 0.7 (increased severity of nephropathy) | | |
| | | | Endocr | 0.075 | 0.7 (cystic follicles in thyroid) | | |
| 102 | Rat (F344/N) | 2 yr ad lib (F) | Hepatic | 3.9 | 7.7 (focal and centrilobular necrosis) | | NTP 1990 |
| | | | Renal | | 3.9 (increased severity of nephropathy) | | |
| | | | Bd Wt | 3.9 | (12-18% decrease in body weight) | | |
| **Cancer** | | | | | | | |
| 103 | Rat (F344/N) | 2 yr ad lib (F) | | | | 0.7 (CEL - neoplastic nodules in liver) | NTP 1990 |
| 104 | Rat (CD) | 18 mo ad lib (F) | | | | 4.9 (CEL - neoplastic nodules in liver) | Ulland 1977a |

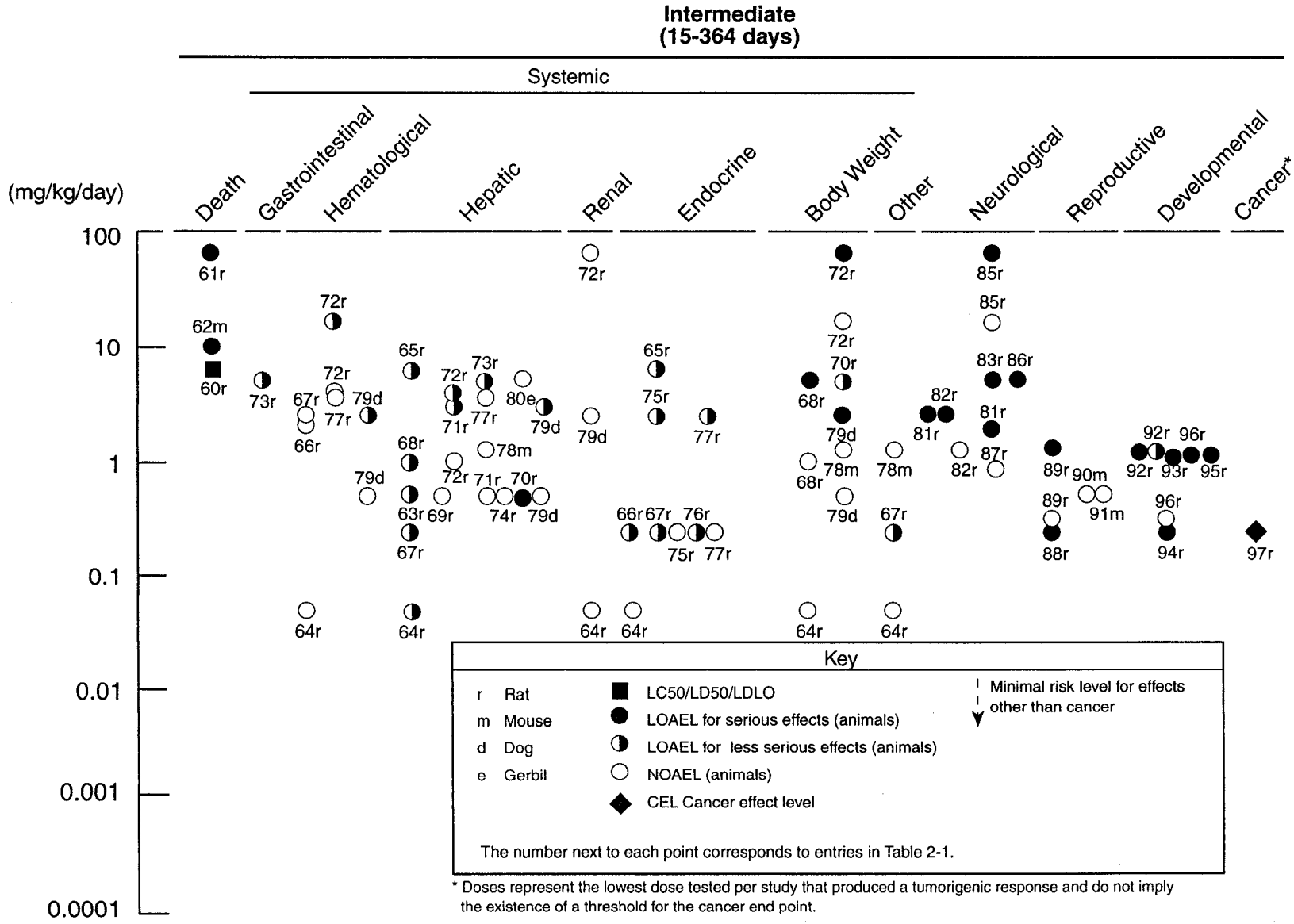
[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive a chronic oral minimal risk level (MRL) of 0.0008 mg/kg/day for mirex; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiological; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; gen = generation(s); (GF) = gavage or diet; (GO) = gavage (oil); h = hour(s); Hemato = hematological; Ld = lactation day(s); $LD_{50}$ = lethal dose, 50% kill; LDLO = lowest lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; ppd = postpartum day(s); repro = reproductive; T3 = triiodothyronine; wk = week(s); x = time(s); yr = year(s)

## Figure 2-1. Levels of Significant Exposure to Mirex – Oral

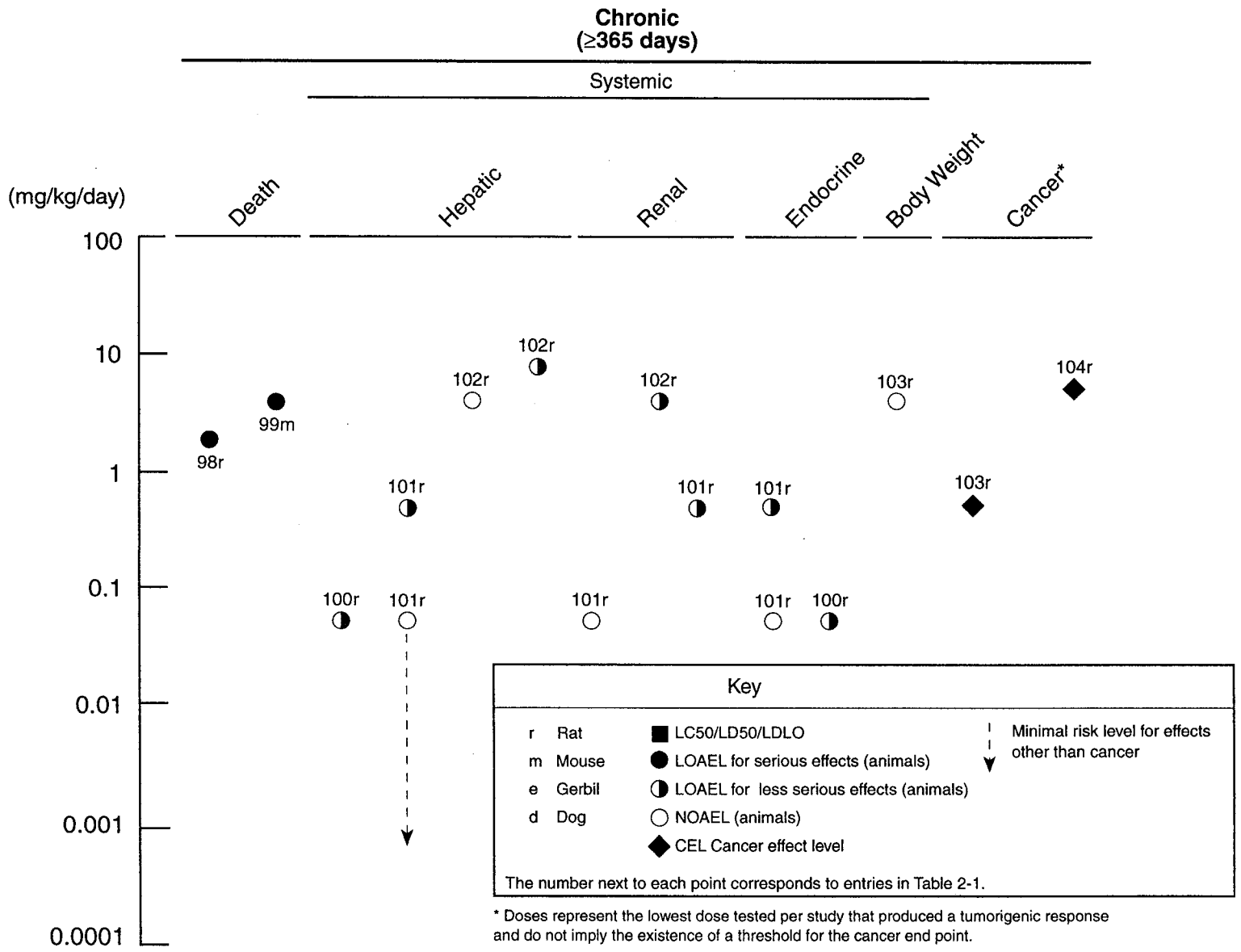


## Figure 2-1. Levels of Significant Exposure to Mirex – Oral (continued)




* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

## Figure 2-1. Levels of Significant Exposure to Mirex – Oral (continued)




* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|
| | **ACUTE EXPOSURE** | | | | | | | |
| | **Death** | | | | | | | |
| 1 | Rat (CD) | 10 d Gd7-16 1x/d (GO) | | | | 10 | (19% mortality) | Chernoff and Rogers 1976 |
| 2 | Rat (Long-Evans) | 4 d 1x/d (GO) | | | | 15 | (40% mortality) | Chernoff et al. 1979a |
| 3 | Rat (Wistar) | Once (GO) | | | | 132 | (LD50 - male) | Larson et al. 1979b |
| | | | | | | 126 | (LD50 - female) | |
| 4 | Rat (Fischer-344) | Once (GO) | | | | 91.3 | (LD50 - male) | Pryor et al. 1983 |
| 5 | Mouse (CD-1) | 5 d 1x/d Gd8-12 (GO) | | | | 20 | (16% mortality) | Chernoff and Kavlock 1982 |
| 6 | Mouse (ICR) | 12 d 1x/d (GO) | | | | 25 | (100% mortality) | Desaiah et al. 1980b |
| 7 | Mouse (CD-1) | Gd8 Once (GO) | | | | 110 | (25% mortality) | Kavlock et al. 1985 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 8 | Mouse (ICR/SIM) | 5 d 1x/d Gd8-12 (GO) | | | | 24 (18% mortality) | Seidenberg et al. 1986 |
| 9 | Dog (NS) | Once (GO) | | | | 250 (LD50) | Larson et al. 1979b |
| 10 | Rabbit (Wistar) | Once (GO) | | | | 71 (LD50 - male) | Larson et al. 1979b |
| | **Systemic** | | | | | | |
| 11 | Rat (Sprague-Dawley) | Once (GO) | Bd Wt | | 50 (11% weight loss) | | Albertson et al. 1985 |
| 12 | Rat (Sprague-Dawley) | 8 d (F) | Endocr | | 17 (depletion of epinephrine in adrenal medulla) | | Baggett et al. 1980 |
| | | | Bd Wt | | 17 (depletion of body fat) | | |
| 13 | Rat (CD) | 10 d Gd7-16 1x/d (GO) | Bd Wt | | 2 (15% decrease in body weight gain) | | Chernoff and Rogers 1976 |
| 14 | Rat (Sprague-Dawley) | Once (GO) | Hepatic | 5 | | | Davis and Mehendale 1980 |
| 15 | Rat (Sprague-Dawley) | Once (GO) | Musc/skel | | 72-98 (muscle weakness) | | Egle et al. 1979 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 16 | Rat (Fischer-344) | 10 d 1x/d (GO) | Hepatic | 5 | 10 | (increased serum alkaline phosphatase, glutamate-pyruvate transaminase, and gamma-glutamyl transferase) | | | EPA 1986 |
| | | | Renal | 5 | 10 | (increased blood urea nitrogen) | | | |
| | | | Other | 5 | 10 | (decreased serum cholesterol and glucose) | 10 | (65% decrease in body weight gain) | |
| 17 | Rat (Sprague-Dawley) | Once (GO) | Hepatic | 15.2 | | | | | Glende and Lee 1985 |
| 18 | Rat (Sprague-Dawley) | 5 d (F) | Hepatic | 5 | | | | | Klingensmith and Mehendale 1982a |
| | | | Bd Wt | 5 | | | | | |
| 19 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Cardio | | 8.3 | (decreased $^{45}Ca$-uptake and $Ca^{2+}$ ATPase activity) | | | Kodavanti et al. 1990a |
| 20 | Rat (Sprague-Dawley) | 8 d (F) | Hepatic | | 10 | (decreased biliary excretion of imipramine; increased bile flow) | | | Mehendale 1977b |
| 21 | Rat (Sprague-Dawley) | 2-3 d 1x/d (GO) | Musc/skel | 10 | 25 | (increased $Mg^{2+}$- ATPase activity in muscle sarcoplasmic reticulum) | | | Mishra et al. 1980 |
| 22 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Hepatic | 10 | | | | | Plaa et al. 1987 |
| | | | Renal | 10 | | | | | |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 23 | Rat (Fischer-344) | 10 d 1x/d (GO) | Hemato | 5 | 10 (decreased neutrophils) | | Smialowicz et al. 1985 |
| | | | Bd Wt | 5 | 10 (19% decrease in body weight) | | |
| 24 | Rat (Sprague-Dawley) | Once (GO) | Endocr | | 35 (increased relative adrenal weight) | | Swanson and Woolley 1982 |
| | | | Bd Wt | | 75 (12% decrease in body weight) | | |
| | | | Other | 35 | 55 (decrease in colonic temperature) | | |
| 25 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | Hepatic | | 18.75 (increased bile flow; decreased bile acid concentration and secretory rate) | | Teo and Vore 1991 |
| | | | Bd Wt | 18.75 | | | |
| 26 | Mouse (CD-1) | 5 d 1x/d Gd8-12 (GO) | Bd Wt | | | 20 (61% decrease in maternal bodyweight gain) | Chernoff and Kavlock 1982 |
| 27 | Mouse (C57BL/6) | 2 d 1x/d (GO) | Hepatic | 30 | | | Fouse and Hodgson 1987 |
| 28 | Mouse (ICR) | 4 d 1x/d (GO) | Hepatic | | 25 (decreased hepatic glycogen) | | Fujimori et al. 1983 |
| | | | Other | | 25 (decreased serum glucose and lactate) | | |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 29 | Mouse (ICR) | 2-14d 1x/d (GO) | Bd Wt | | 10 (10-15% weight loss) | | Huang et al. 1980 |
| 30 | Mouse (ICR) | 5 d 1x/d Gd8-12 (GO) | Bd Wt | | | 24 (85% decrease in maternal weight gain) | Seidenberg et al. 1986 |
| | **Immuno./Lymphor** | | | | | | |
| 31 | Rat (Fischer-344) | 10 d 1x/d (GO) | | 5 | 10 (decreased spleen and thymus weights, leukocyte counts, natural killer cell activity, and Concanavlin A responsiveness) | | EPA 1986c |
| 32 | Rat (Fischer-344) | 10 d 1x/d (GO) | | 5 | 10 (decreased relative spleen and thymus weight; decreased mitogenic responsiveness; decreased natural killer cell activity) | | Smialowicz et al. 1985 |
| 33 | Rat (Sprague-Dawley) | Once (GO) | | | 75 (decreased thymus weight) | | Swanson and Woolley 1982 |
| | **Neurological** | | | | | | |
| 34 | Rat (Sprague-Dawley) | Once (GO) | | | | 50 (tremors; splaying of legs) | Albertson et al. 1985 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 35 | Rat (Sprague-Dawley) | Once (GO) | | | | 100 (mild tremors) | Aldous et al. 1984 |
| 36 | Rat (Sprague-Dawley) | 10 d 1x/d (GO) | | 5 | | 10 (mild tremors) | Aldous et al. 1984 |
| 37 | Rat (Sprague-Dawley) | 8 d (F) | | | | 17 (tremor, hyperexcitability) | Baggett et al. 1980 |
| 38 | Rat (Sprague-Dawley) | 2-3 d 1x/d (GO) | | 10 | 25 (decreased dopamine binding and uptake; decreased norepinephrine uptake) | | Desaiah 1985 |
| 39 | Rat (Sprague-Dawley) | 10 d 1x/d (GO) | | | 2.5 (>20% decreased total brain calmodulin) | | Desaiah et al. 1985 |
| 40 | Rat (Sprague-Dawley) | Once (GO) | | | | 72-98 (tremors; hyperexcitability; abnormal gait) | Egle et al. 1979 |
| 41 | Rat (NS) | Once (G) | | | | 40 (tremors) | End et al. 1981 |
| 42 | Rat (Fischer-344) | 10 d 1x/d (GO) | | 1.25[b] | 2.5 (increased startle response) | | EPA 1986c |
| 43 | Rat (Sprague-Dawley) | 3 d 1x/d (GO) | | | 25M (decreased $Na^+$-$K^+$ATPase; decreased oligomycin sensitive $Mg^{2+}$ATPase) | 50 M (increased activity; tremor; exaggerated startle response; abnormal gait) | Jordan et al. 1981 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Less Serious (mg/kg/day) | | Serious (mg/kg/day) | | |
| 44 | Rat (Sprague-Dawley) | 5 d (F) | | | | | 5 | (tremors; exaggerated startle response) | Klingensmith and Mehendale 1982a |
| 45 | Rat (Sprague-Dawley) | 2-3 d 1x/d (GO) | | | | | 25 | (tremors) | Mishra et al. 1980 |
| 46 | Rat (Fischer-344) | 10 d 1x/d (GO) | | 5 | | | 10 | (tremors) | Smialowicz et al. 1985 |
| 47 | Rat (Sprague-Dawley) | Once (GO) | | | | | 35 | (tremor; exaggerated startle response) | Swanson and Woolley 1982 |
| 48 | Mouse (ICR) | 2-4 d 1x/d (GO) | | | | | 25 | (severe tremors; motor incoordination) | Chang-Tsui and Ho 1979 |
| 49 | Mouse (ICR) | 2-3 d 1x/d (GO) | | | 50 | (decreased dopamine and norepinephrine uptake; decreased dopamine binding) | | | Chang-Tsui and Ho 1980 |
| 50 | Mouse (ICR) | 12 d 1x/d (GO) | | | | | 25 | (mild tremors) | Desaiah et al. 1980b |
| 51 | Mouse (ICR) | 1-11 d 1x/d (GO) | | | | | 10 | (motor incoordination) | Fujimori et al. 1982b |
| 52 | Mouse (ICR) | 5 d or 8 d 1x/d (GO) | | | 25 | (decreased striatal dopamine synthesis uptake and release) | | | Fujimori et al. 1986 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 53 | Mouse (ICR) | Once (GO) | | | 25 | (increased brain calcium in 6-8 week-olds; decreased brain calcium in adults) | | | Hoskins and Ho 1982 |
| 54 | Mouse (ICR) | 8 d 1x/d (GO) | | | 25 | (decreased brain calcium) | 25 | (tremors) | Hoskins and Ho 1982 |
| 55 | Mouse (ICR) | 4-12 d 1x/d (GO) | | | | | 10 | (decreased motor coordination; tremors) | Huang et al. 1980 |
| | **Reproductive** | | | | | | | | |
| 56 | Rat (Sprague-Dawley) | Once (GO) | | | 55 | (decreased ovarian weight) | 35 | (persistent estrus) | Swanson and Woolley 1982 |
| 57 | Mouse (CD-1) | 2 wk 5d/wk 1x/d (GO) | | | | | 2 | (induction of persistent vaginal estrus, PVE) | Swartz et al. 1988 |
| | **Developmental** | | | | | | | | |
| 58 | Rat (CD) | 10 d Gd7-16 1x/d (GO) | | 2 | 6 | (5% decrease in fetal weight; skeletal ossification in 5% of fetuses) | 10 | (increased number of fetuses with enlarged renal pelvis, edema, undescended testes, or enlarged cerebral ventricles) | Chernoff and Rogers 1976 |
| 59 | Rat (Long-Evans) | 4 d 1x/d ppd1-4 (GO) | | 10 | | | | | Chernoff et al. 1979a |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 60 | Rat (Fischer-344) | Gd 7-16 1x/d (GO) | | | | 10 (decreased pup survival and weight) | EPA 1986c |
| 61 | Rat (Sprague-Dawley) | 7 d 1x/d Gd14-20 (GO) | | | | 15 (anovulation and persistent vaginal estrus in offspring) | Gellert and Wilson 1979 |
| 62 | Mouse (CD-1) | 5 d 1x/d Gd8-12 (GO) | | | | 20 (decreased survival and body weight of pups on ppd1 and 3) | Chernoff and Kavlock 1982 |
| 63 | Mouse (CD-1) | 10 d 1x/d Gd7-16 (GO) | | 8 | | 12 (increased fetal deaths; increased club foot) | Chernoff and Rogers 1976 |
| 64 | Mouse (CD-1) | 4 d ppd1-4 1x/d (GO) | | | | 18 (64% pup mortality) | Chernoff et al. 1979a |
| 65 | Mouse (CD-1) | 5 d 1x/d Gd8-12 (G) | | | | 20 (decreased postnatal viability) | Gray et al. 1983 |
| 66 | Mouse (CD-1) | Once Gd8 (GO) | | | | 125 (increased resorptions and malformations; decreased viable litters) | Kavlock et al. 1985 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 67 | Mouse (ICR) | 5 d 1x/d Gd8-12 (GO) | | | | 24 (decreased fetal survival and neonatal weight gain; increased still births) | Seidenberg et al. 1986 |
| | **INTERMEDIATE EXPOSURE** | | | | | | |
| | **Death** | | | | | | |
| 68 | Rat (Sprague-Dawley) | 30-35 d (F) | | | | 5 (40% mortality) | Mehendale 1981b |
| 69 | Rat (Fischer-344) | 15 wks 5d/wk 1x/d (GO) | | | | 4.1 (60% mortality died) | Pryor et al. 1983 |
| 70 | Mouse (ICR) | 33 d 1x/d (GO) | | | | 10 (100% mortality) | Fujimori et al. 1983 |
| 71 | Mouse (BALB/c) | 2-12 mo (F) | | | | 7.8 (12% mortality in adults; 100% mortality in juveniles) | Huber 1965 |
| | **Systemic** | | | | | | |
| 72 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 0.5 (increased bile flow) | | Agarwal and Mehendale 1984b |
| 73 | Rat (Fischer-344) | 105 d (F) | Endocr | 0.3 | | | Ali et al. 1982 |
| | | | Bd Wt | 0.3 | | | |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 74 | Rat (Sherman) | 3 mo (F) | Hepatic | | 1.17 (focal necrosis) | | Cannon and Kimbrough 1979 |
| | | | Endocr | | 1.17 (reversible hyperplasia of adrenal cortex;) | | |
| | | | Bd Wt | | 1.17 (13% decrease in body weight gain) | | |
| 75 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | 0.5 | 2.5 (significantly increased serum nonprotein nitrogen compounds and enzymes) | | Chetty et al. 1993a |
| | | | Other | | 5 (decreased serum triglycerides, LDL and cholesterol) | | |
| 76 | Rat (Sprague-Dawley) | 28 d (F) | Hemato | 0.05 | | | Chu et al. 1980a |
| | | | Hepatic | | 0.05 (focal lymphoid aggregates; cytoplasmic ballooning) | | |
| | | | Renal | | 0.05 (eosinophilic inclusions in proximal tubules) | | |
| | | | Bd Wt | 0.05 | | | |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 77 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 1 M (impaired biliary excretion) | | Curtis and Hoyt 1984 |
| | | | | | 5 M (significant increase in liver weight) | | |
| | | | Bd Wt | | 5 M (significantly increased serum glutamate-pyruvate transaminase and glutamate-oxaloacetate transaminase) | | |
| | | | | 1 | | 5 M (99% decrease in body weight gain) | |
| 78 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 0.5 M (decreased hepatobiliary function) | | Curtis and Mehendale 1979 |
| | | | Bd Wt | 0.5 M | | 2.5 M (63% decrease in body weight gain) | |
| | | | Metabolic | | 2.5 M (Inhibition of $Mg^{2+}$-ATPase activity) | | |
| 79 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 0.5 (decreased biliary excretion, depletion of hepatic glycogen) | | Curtis et al. 1979 |
| 80 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 0.5 (deformed bile canalculi; fragmented rough endoplasmic reticulum) | | Curtis et al. 1981 |
| 81 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 0.5 M (minute vacuolation in hepatocyte cytoplasm) | | Faroon and Mehendale 1990 |
| | | | Bd Wt | 0.5 | | | |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| 82 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 0.5 (moderately fragmented rough endoplasmic reticulum; cup-shaped mitochondria) | | Faroon et al. 1991 |
| 83 | Rat (Sprague-Dawley) | 15 d or 20d (F) | Hepatic | 5 | | | Klingensmith and Mehendale 1982a |
| | | | Bd Wt | | | 5 (48-49% decrease in body weight gain) | |
| | | | Other | | 5 (36% decrease in epididymal fat; 7% decrease in food consumption) | | |
| 84 | Rat (Wistar) | 3 mo (F) | Cardio | 1.25 | 2.5 (vasodilation) | | Larson et al. 1979b |
| | | | Hemato | 4.0 | | | |
| | | | Hepatic | 0.5 | 1.25 M (swollen hepatocytes) | | |
| | | | Renal | 4.0 | | | |
| | | | Endocr | 0.5 | 1.25 (loss of adrenal lipid) | | |
| | | | Bd Wt | 0.5 | 1.25 (decreased body weight gain) | | |
| 85 | Rat (Wistar) | 1 yr (F) | Cardio | 1.25 | | | Larson et al. 1979b |
| | | | Hemato | 0.5 | 1.25 (depressed hematocrit levels) | | |
| | | | Hepatic | 0.25 | 0.5 (fatty changes in liver) | | |
| | | | Renal | 0.05 [c] | 0.25 (proteinuria and increased severity of glomerulosclerosis) | | |
| | | | Bd Wt | 0.5 | 1.25 (decrease in body weight gain) | | |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 86 | Rat (Sprague-Dawley) | ≤35 d (F) | Hepatic | | 5M (impaired biliary function) | | Mehendale 1981b |
| | | | Bd Wt | | 5M (significantly decreased body weight gain) | | |
| 87 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | | 2.5 (decreased hepatobiliary function) | | Mehendale 1990a |
| 88 | Rat (Sprague-Dawley) | 15 d (F) | Hepatic | 0.5 | | | Mehendale et al. 1991 |
| 89 | Rat (Fischer-344) | 15 wks 5d/wk 1x/d (GO) | Bd Wt | | 2.8 (>10% decrease in body weight gain) | | Pryor et al. 1983 |
| | | | Other | | 7.1 (increased body temperature) | | |
| 90 | Mouse (ICR) | 33 d 1x/d (GO) | Gastro | | NS (mild diarrhea) | | Fujimori et al. 1983 |
| | | | Other | | 10 (decreased adipose tissue; decreased plasma glucose) | | |
| 91 | Mouse (BALB/c) | 2-12 mo (F) | Hepatic | | 5.2 (focal necrosis, cellular hypertrophy, hyperplasia, congestion; liposphere formation and decreased numbers of mitochondria) | | Huber 1965 |
| | | | Bd Wt | 5.2 | 7.8 (decreased body weight in juveniles and adults) | | |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|
| 92 | Mouse (Swiss-Webster) | 15 d (F) | Hepatic | 1.3 | | | | Mehendale et al. 1989 |
| | | | Bd Wt | 1.3 | | | | |
| 93 | Gerbil (Mongolian) | 15 d (F) | Hepatic | 5.4 | | | | Cai and Mehendale 1990 |
| 94 | Gerbil (Mongolian) | 15 d (F) | Hepatic | 5.4 | | | | Cai and Mehendale 1991b |
| | **Neurological** | | | | | | | |
| 95 | Rat (Sprague-Dawley) | 15 d (F) | | 1.25 | | 2.5 | (tremors) | Agarwal and Mehendale 1984c |
| 96 | Rat (Sherman) | 3 mo (F) | | | | 1.17 | (tremor; hyperactivity; exaggerated startle response) | Cannon and Kimbrough 1979 |
| 97 | Rat (Sprague-Dawley) | 15 d (F) | | 1 | | 5 | (tremors and hypersensitivity to sound and touch) | Curtis and Hoyt 1984 |
| 98 | Rat (Sprague-Dawley) | 15 d (F) | | 2.5 | | 7.5 M | (tremors; hyperexcitability) | Curtis and Mehendale 1979 |
| 99 | Rat (Zivac-Miller) | 90 d 5-6d/wk 1x/d (GO) | | | | 1 | (decrease in operant behavior; tremors) | Dietz and McMillan 1979 |
| 100 | Rat (Sprague-Dawley) | 15d or 20d (F) | | | | 5 M | (progressively increased constant tremors) | Klingensmith and Mehendale 1982a |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | | |
| 101 | Rat (Wistar) | 3 mo (F) | | 0.5 | | 1.25 | (tremor) | Larson et al. 1979b |
| 102 | Rat (Sprague-Dawley) | 90 d (F) | | 0.26 | | 0.83 | (hyperexcitability; mild tremors) | Linder et al. 1983 |
| 103 | Rat (Sprague-Dawley) | 35 d (F) | | | | 5 | (tremors, hyperactivity, exaggerated startle response) | Mehendale 1981b |
| 104 | Rat (Sprague-Dawley) | 16 d (F) | | | | 2.5 | (tremors; hypersensitivity to noise and stress) | Mehendale et al. 1978b |
| 105 | Rat (Fischer-344) | 15 wks 5d/wk 1x/d (GO) | | 2.8 | | 4.1 | (increased startle response) | Pryor et al. 1983 |
| 106 | Rat (Fischer-344) | 90 d (F) | | | | 0.5 M | (exaggerated startle response) | Squibb and Tilson 1982b |
| 107 | Mouse (ICR) | 33 d 1x/d (GO) | | | | 10 | (tremors; decreased motor coordination) | Fujimori et al. 1983 |
| 108 | Mouse (BALB/c) | 2-12 mo (F) | | 1.3 | | 3.9 | (tremor) | Huber 1965 |
| 109 | Mouse (CD-1) | 4 wks 5d/wk 1x/d (GO) | | | | 8 | (slight tremors; increased reactivity to noise) | Swartz and Schutzmann 1986 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | | LOAEL Serious (mg/kg/day) | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| **Reproductive** | | | | | | | | | |
| 110 | Rat (Sherman) | 4.5 mo (F) | | | 1.62 | (partially reversible decrease in the number of litters) | | | Cannon and Kimbrough 1979 |
| 111 | Rat (Wistar) | 3 mo (F) | | 0.25 | | | 0.5 | (testicular atrophy) | Larson et al. 1979b |
| 112 | Rat (Sprague-Dawley) | 90 d (F) | | 0.26 | 0.83 | (reversible decrease in sperm motility and viability; decreased sperm reserves) | | | Linder et al. 1983a |
| 113 | Mouse (BALB/c) | 5 mo (F) | | | | | 0.65 | (36% decrease in second litters) | Good et al. 1965 |
| 114 | Mouse (BALB/c) | 2-12 mo (F) | | | | | 5.2 | (increased estrus) | Huber 1965 |
| 115 | Mouse (BALB/c) | 130 d (F) | | | 1.3 | | 1.3<br>3.9 | (8% decrease in litter size and 19% increase in pair-days to litter)<br>(constant estrus) | Huber 1965 |
| 116 | Mouse (BALB/c) | 160 d (F) | | | | | 5.2 | (persistent vaginal estrus; reversible reproductive failure) | Huber 1965 |
| 117 | Mouse (CD-1) | 4 or 6 wk 5d/wk 1x/d (GO) | | | | | 2 | (increased ovulation; persistent vaginal estrus) | Swartz et al. 1988 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| | **Developmental** | | | | | | |
| 118 | Rat (Sherman) | 3 mo (F) | | 1.17 | | | Cannon and Kimbrough 1979 |
| 119 | Rat (Sprague-Dawley) | 90 d (F) | | 1.67 | | | Linder et al. 1983 |
| 120 | Rat (Fischer-344) | 60 d plus Gd and Ld0-12 (F) | | | 0.3 (altered serotonin turnover and dopamine levels and response to stress in offspring) | | Rosencrans et al. 1982 |
| 121 | Rat (Fischer-344) | approx 93 d (F) | | | 0.05 F (decreased body weight at postpartum day 100 in females; increased reactivity to apomorphine administration in males)<br>0.3 F (increased negative geotaxis latencies) | | Squibb and Tilson 1982a |
| 122 | Mouse (BALB/c) | 130 d (F) | | 1.3 | | 3.9 (decreased postnatal survival) | Huber 1965 |
| | **CHRONIC EXPOSURE** | | | | | | |
| | **Death** | | | | | | |
| 123 | Rat (Wistar) | 2 yrs (F) | | | | 1.25 F (decreased survival) | Larson et al. 1979b |
| 124 | Mouse (B6C3F1) | 80 wk (F) | | | | 2.6 M (42% mortality; 8% mortality in control males) | NCI 1976 |

TABLE 2-2. Levels of Significant Exposure to Chlordecone - Oral (continued)

| Key to figure[a] | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|
| **Systemic** | | | | | | | |
| 125 | Rat (Sprague-Dawley) | 21 mo (GO) | Hepatic | | 0.07 M (decrease in the hepatic microsomal aniline hydroxylase)<br>M (panlobular cytoplasmic vacuolation with loss of basophilia, fatty infiltration, anisokaryosis in liver) | | Chu et al. 1981c |
| | | | Endocr | | 0.07 M (reduction in follicular size and colloid density and increase in epithelial height in thyroid) | | |
| | | | Hemato | 0.07 | | | |
| 126 | Rat (Wistar) | 2 yr (F) | Cardio | 1.25 | | | Larson et al. 1979b |
| | | | Hemato | 0.5 | 1.25 (depressed hematocrit levels) | | |
| | | | Hepatic | 0.25 | 0.5 (fatty changes in liver) | | |
| | | | Renal | 0.05 [d] | 0.25 (proteinuria and increased severity of glomerulosclerosis) | | |
| | | | Bd Wt | 0.5 | 1.25 (decrease in body weight gain) | | |
| 127 | Rat (Osborne-Mendel) | 80 wk (F) | Hemato | | 0.4 M (anemia)<br>0.9 F | | NCI 1976 |
| | | | Hepatic | | 0.4 M (fatty infiltration and liver<br>0.9 F degeneration) | | |
| | | | Derm | | 0.4 M (dermatitis)<br>0.9 F | | |

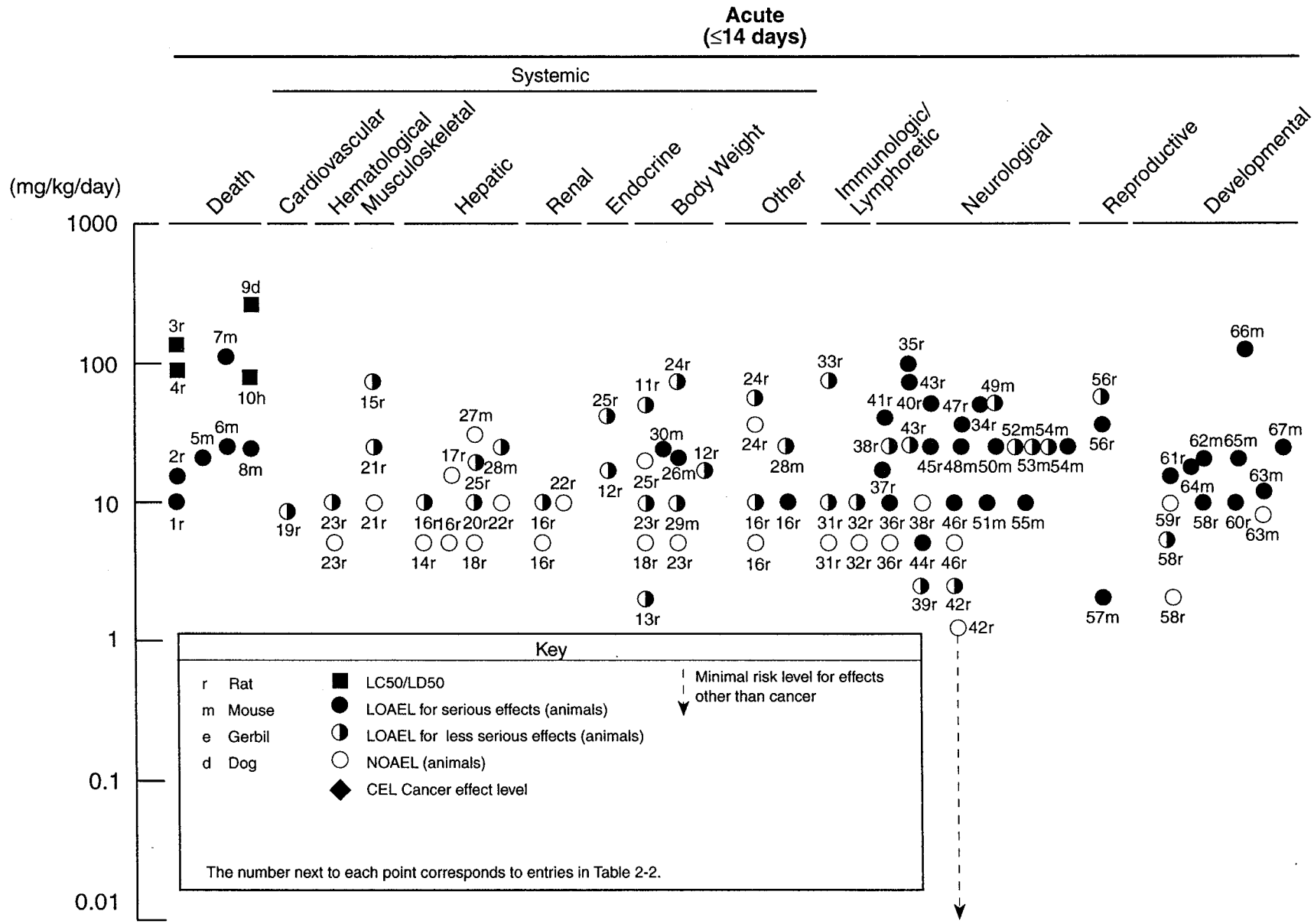
**TABLE 2-2. Levels of Significant Exposure to Chlordecone Oral (continued)**

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Less Serious (mg/kg/day) | | Serious (mg/kg/day) | | |
| 128 | Mouse (B6C3F1) | 80 wk (F) | Hepatic | | 2.6 | (hepatocellular hyperplasia) | | | NCI 1976 |
| | **Neurological** | | | | | | | | |
| 129 | Rat (Wistar) | 2 yrs (F) | | 0.5 | | | 1.25 | (tremor) | Larson et al. 1979b |
| 130 | Rat (Osborne-Mendel) | 80 wk (F) | | | | | 0.4 | (tremors) | NCI 1976 |
| 131 | Dog (beagle) | 124-128 wks (F) | | 0.625 | | | | | Larson et al. 1979b |
| | **Cancer** | | | | | | | | |
| 132 | Rat (Osborne-Mendel) | 80 wk (F) | | | | | 1.2 | (CEL -hepatocellular carcinoma) | NCI 1976 |
| 133 | Mouse (B3C6F1) | 80 wk (F) | | | | | 2.6 | (CEL - hepatocellular carcinoma) | NCI 1976 |

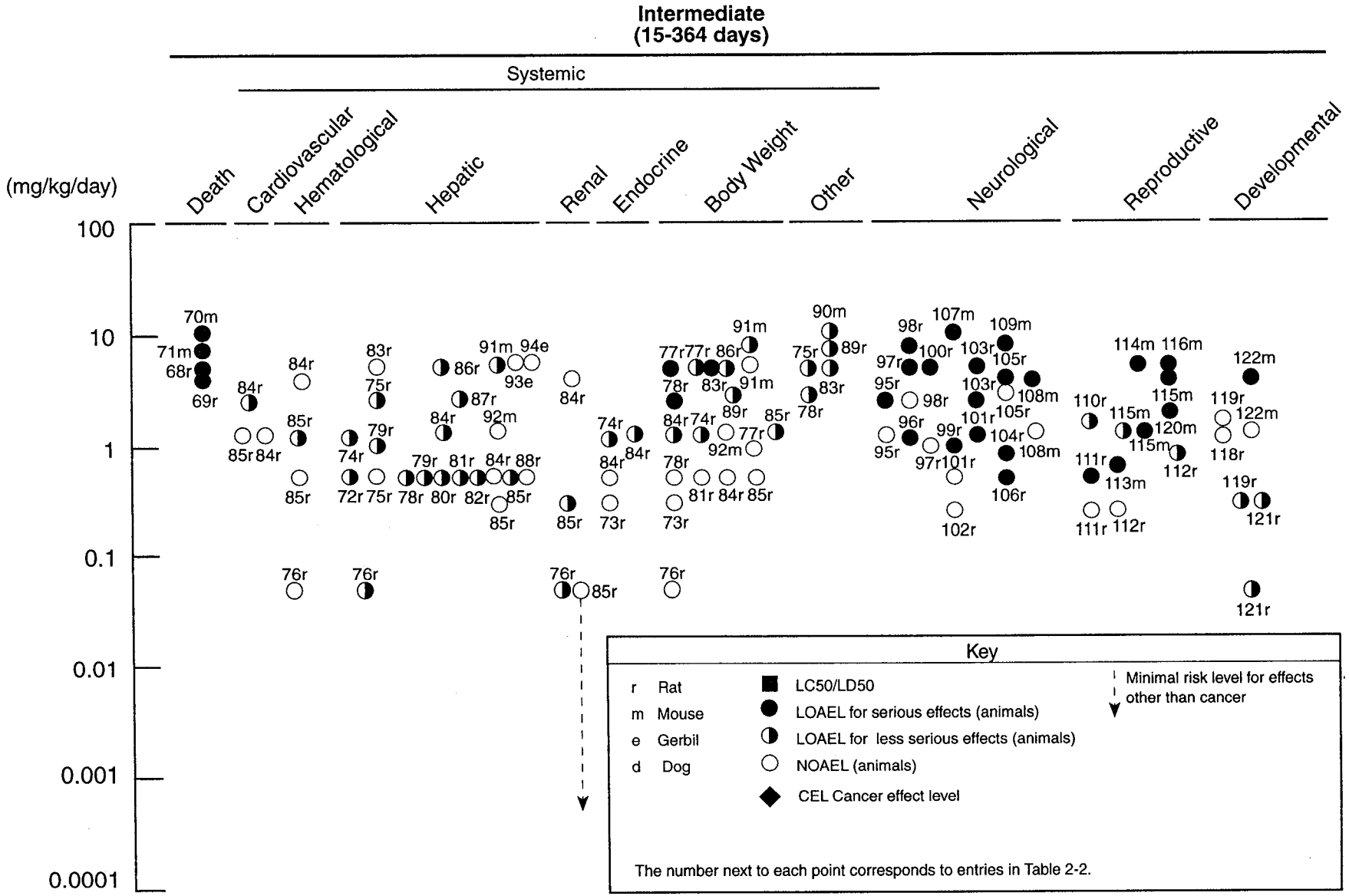
[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute oral Minimal Risk Level (MRL) of 0.01 mg/kg/day for chlordecone; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans 10 for human variability).
[c]Used to derive an intermediate oral MRL of 0.0005 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).
[d]Used to derive a chronic oral MRL of 0.0005 mg/kg/day chlordecone; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATPase = adenosinetriphosphatase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; con A = concanavalin A; d = day(s); Derm = dermal; Endocr = endocrine; F = female; (F) = feed; (G) = gavage, not specified; Gastro = gastrointestinal; Gd = gestation day(s); (GO) = gavage (oil; Hemato = hematological; Ld = lactation day(s); $LD_{50}$ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; oc = ocular; ppd = post partum day(s); wk = week(s); x = time(s); yr = year(s)

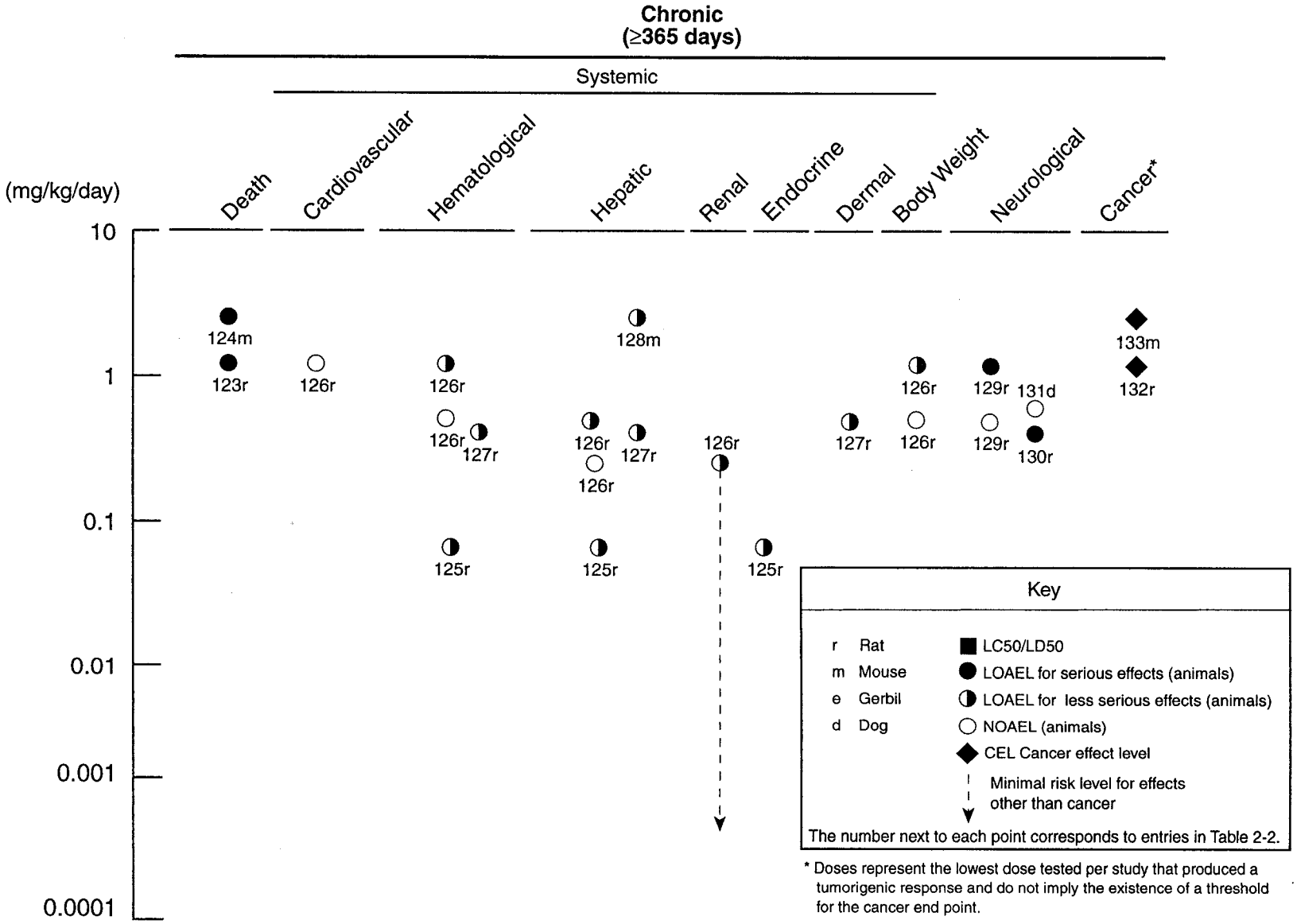
## Figure 2-2. Levels of Significant Exposure to Chlordecone – Oral



## Figure 2-2. Levels of Significant Exposure to Chlordecone – Oral (continued)



## Figure 2-2. Levels of Significant Exposure to Chlordecone – Oral (continued)




* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

No studies were located regarding respiratory effects in animals following oral exposure to mirex. Extremely lirnited 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). These studies are limited in that it is unclear how many lung tissue samples were actually examined, and the dog study is also limited in that the number of animals used (two/sex/dose) was low. These studies provide no possible explanation for the pleuritic chest pains experienced by workers exposed to chlordecone.

**Cardiovascular Effects.** No studies were located regarding cardiovascular effects in humans following oral exposure to mirex. 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 of .electrocardiography of 23 workers with active symptoms of chlordecone intoxication were normal. Although oral exposures are not normally encountered in occupational situations, hygiene was particularly poor at this plant and oral exposures were likely.

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 10 mg/kg/day mirex for varying periods during pregnancy. 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 (Buelke-Sam et al. 1983). 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. Routine gross and histopathological analyses of heart tissues obtained from rats at doses as high as 64 mg/kg/day for 13 weeks showed no adverse compound-related effects on the heart (Larson et al. 1979a), but this study is limited in that the number of heart samples examined was not reported. An increase in chronic myocarditis at 2.5 and 5 mg/kg/day was reported by Reuber (1977) following a review of tissue slides from an 18-month rat cancer bioassay, but no control data were presented to support this conclusion. The conclusions of this independent review are disputed by the onginal authors; the

conclusions are considered a misrepresentation of the data by the onginal study author (Ulland et al. 1977b).

Available information regarding the cardiovascular effects of chlordecone in animals is also limited. Acute-duration studies have primarily examined biochemical parameters. For example, gavage doses of chlordecone (10 mg/kg/day and greater for 3 days) resulted in inhibition of myocardial $Na^{+}K^{+}$ATPase in rats (Desaiah 1980). At 25 mg/kg/day and above, inhibition of mitochondrial $mg^{2+}$ATPase occurred, and at 50 mg/kg/day decreased norepinephrine and dopamine binding to myocardial membranes was observed. Similarly, inhibition of calcium uptake, $Ca^{2+}$ATPase activity, and protein phosphorylation was observed in rat cardiac sarcoplasmic reticulum following gavage doses of 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 could indicate a decrease in cardiac effectiveness.

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

Routine histopathological analyses of rat heart samples have not shown significant changes following exposure to 1.25 mg/kg/day chlordecone for 2 years or following exposure of dogs to 0.625 mg/kg/day for 124-128 weeks (Larson et al. 1979b). However, these studies are limited in that it is unclear how many heart samples were actually examined. Also, the dog study is limited in that too few dogs were used (two/sex/dose). Following an independent review of data from a rat cancer bioassay conducted by the NCI (1976), Reuber (1978a, 1979c) reported polyarteritis in male rats orally treated with chlordecone for 80 weeks. However, arteries were not routinely sectioned in this study so the ongin of data used by this reviewer to reach this conclusion is unclear.

**Gastrointestinal Effects.** No studies were located regarding gastrointestinal effects in humans after oral exposure to mirex or chlordecone.

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 derive a LOAEL for this effect. Diarrhea was identified as a predominant sign in female rats that died during a lo-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 a dietary study in which rats were fed a total of 365 mg/kg over 12 days, but the daily dose was not specified (Kendall 1974a). Mild diarrhea was observed in treated rats (5 mg/kg/day) starting on the 8th day of exposure and continuing over the duration of a 30-day dietary study (Mehendale 1981b). Diarrhea was also observed in a 90-day gavage study in 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. Necropsy showed hemorrhagic intestines, indicating a gastrointestinal ongin for the diarrhea rather than a neurally mediated response (Fujimori et al. 1983).

Mild diarrhea has also been observed in a 33-day gavage study in mice exposed to 10 mg/kg/day chlordecone. However, no effects on stomach or intestines at necropsy (Fujimori et al. 1983). Likewise, routine histopathological analyses of gastrointestinal tissues (described simply as “gut”) also showed no compound-related effects in rats after 2 years of exposure 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 the number of dogs used was too low (two/sex/dose).

**Hematological Effects.** No studies were located regarding hematological effects in humans after oral exposure to mirex or chlordecone.

Adverse hematological effects have not been reported to be a prominent feature of mirex toxicity in animals. However, a few studies in which high doses of mirex were used have shown mild hematological effects. No effects on standard hematological parameters were observed after 14 days exposure of male rats to 10 mg/kg/day of mirex (Villeneuve et al. 1977). However, a single oral dose of 100 mg/kg mirex resulted in a 12% increase in hematocrit in treated rats (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 at doses as high as 3.75 mg/kg/day for 28 days (Chu et al. 1980a; Yarbrough et al. 1981). In addition, no effect on rats was seen in a 148-day feeding study at 2 mg/kg/day (Chu et al. 1981a). In contrast, hemoglobin of rats decreased at 16 mg/kg/day and leukocytes increased at 64 mg/kg/day exposure during a 13-week study (Larson et al. 1979a). Hematocrit increased at 2.5 mg/kg/day in a male dog that died during a 13-week dietary study (Larson et al. 1979a).

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 0.05 mg/kg/day (Chu et al. 1980a) or 90 days of dietary exposure to 4 mg/kg/day (Larson et al. 1979b). Similarly, in chronic-duration studies, no effects were seen during routine hematology in rats exposed for 2 years at up to 1.25 mg/kg/day or in dogs exposed for 124-128 weeks up to 0.625 mg/kg/day (Larson et al. 1979b). Although anemia was reported in rats during an 80-week dietary study (Reuber 1978a, 1979c) based on a review of the study conducted by NCI (1976), the onginal pathology review of the study did not include any incidence of anemia among the treated rats. Thus, the interpretation of data used by this reviewer for drawing a conclusion is unclear.

**Musculoskeletal Effects.** No studies were located regarding musculoskeletal effects in humans following oral exposure to mirex. Skeletal muscle biopsies obtained from six workers who experienced tremors, muscle weakness, gait ataxia, and incoordination resulting from intermediate- or chronic-duration exposure to high levels 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 the lipochrome is unknown. In addition, arthralgia in the proximal joints was experienced by 4 of 23 workers with active symptoms of chlordecone intoxication (Taylor 1982, 1985). No cause for the joint pain could be determined. Although oral exposure is not generally considered to be significant in occupational exposure situations, hygiene at the plant at which these men were employed was extremely poor and oral exposures were considered to be likely.

No studies were located regarding musculoskeletal effects in animals after oral exposure to mirex. Studies examining the effects of acute-duration oral exposure to large amounts of chlordecone suggest

that direct toxic effects of chlordecone on muscle occur. However, chronic exposure of rats and dogs to chlordecone revealed no adverse effects on the skeletal muscles. A single gavage dose of between 72 and 98 mg/kg of chlordecone resulted in increasing muscle weakness in treated rats (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 (25 and 50 mg/kg/day), inhibition of $mg^{2+}$ATPase was observed in sarcoplasmic reticulum of treated rats (Mishra et al. 1980). It is unclear whether this inhibition contributed to the muscle weakness observed by Egle et al. (1979). In longer duration, lower-dose studies, no effect was observed during routine histopathological analyses of skeletal muscle. For example, no compound-related effects were reported following routine histopathological analysis of skeletal muscle from rats exposed to doses of chlordecone as high as 4 mg/kg/day for 90 days or 1.25 mg/kg/day for 2 years, or from dogs after 124-128 weeks of exposure to doses as high as 0.625 mg/kg/day (Larson et al. 1979b).

**Hepatic Effects.** Hepatic changes were observed in one chronic human exposure to mirex, as well as in a number of workers exposed to chlordecone for intermediate or chronic durations. In the mirex study, human subjects (sex and number not specified) from a chronically exposed cohort from southeast Ohio (route of exposure not specified, assumed to be oral) were assessed for cytochrome P-4501A2 induction using a breath test that measures caffeine metabolism. The subjects exposed to mirex had elevated caffeine metabolism as compared to negative control individuals (subjects with no known exposure to polyhalogenated biphenyls or other related chemicals) in which the metabolism did not increase (Lambert et al. 1992). In the chlordecone study, liver function and structure in 32 men exposed to high levels of chlordecone while employed for l-22 months (5.6 months average) in the production of chlordecone were compared to those of healthy men of the same age. Although oral exposures are generally not considered to be significant in occupational situations, hygiene conditions at this plant were extremely poor and accidental ingestion of the chlordecone was considered to have been likely. Hepatomegaly occurred in 20 of the 32 exposed workers, with minimal splenomegaly in 10 of these. Urinary excretion of glucaric acid was significantly increased, and the half-life of antipyrine in the blood was significantly decreased in exposed workers, indicating increased microsomal enzyme activity. Needle biopsies of hepatic tissues from 12 of the 32 workers showed marked proliferation of smooth endoplasmic reticulum in several samples. 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. 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. Retention of sulfobromophthalein was normal; serum levels of bilirubin, albumin, globulin, alanine and aspartate aminotransferase activity, and γ-glutamyl transferase activity were also normal (Guzelian et al. 1980).

The hepatic effects of mirex 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; these include increase in liver weight or size (Abston and Yarbrough 1976; Byard et al. 1975; Chadwick et al. 1977; Chambers and Trevethan 1983; Chu et al. 1980b, 1981a, 1981b; Curtis and Hoyt 1984; 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 1981b; 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, 1978c; 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). Other effects observed include hepatocellular hypertrophy (Davison et al. 1976; Fulfs et al. 1977; Gaines and Kimbrough 1970; Ulland et al. 1977a; Yarbrough et al. 1981), cytoplasmic eosinophilia with migration of basophilic granules (Chu et al. 1981a; NTP 1990; Yarbrough et al. 198 l), an increase in the smooth endoplasmic reticulum (Baker et al. 1972; Curtis et al. 1981; Davison et al. 1976; Fulfs et al. 1977; Gaines and Kimbrough 1970; Mehendale et al. 1989), an increase in microsomal protein (Chambers and Trevethan 1983; Davison et al. 1976; Elgin et al. 1990; Karl and Yarbrough 1984; Klingensmith and Mehendale 1983b; Pittz et al. 1979; Villeneuve et al. 1977; Yarbrough et al. 1981, 1986a), an increase in cytochrome P-450 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 1983b; Kocarek et al. 1991; Peppriell 1981; Robacker et al. 1981; Robinson and Yarbrough 1978a; Yarbrough et al. 1981, 1986a), and an increase in $NADPH_2$-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).

In addition to the adaptive effects described above, marked hepatic toxicity has been observed after acute-duration oral exposure of animals to mirex. The primary form of hepatotoxicity observed in rats after acute-duration oral exposures is hepatobiliary toxicity (Berman et al. 1986; Davison et al. 1976; Hewitt et al. 1986a; Mehendale 1976, 1977c, 1979; Teo and Vore 1991). Administration of mirex by gavage at 50 mg/kg/day for 3-5 days resulted in inhibition of the excretion of morphine glucuronide (Berman et al. 1986), production of polar imipramine metabolites (Berman et al. 1986; Mehendale 1977c), chlorinated biphenyl metabolites (Mehendale 1976). It also caused a decrease in taurocholate extraction from the blood and excretion in the bile (Teo and Vore 1991), and decreased sulfobromophthalein clearance (Mehendale 1977c). These decreases in hepatobiliary excretion generally occurred in the presence of increased bile flow (Berman et al. 1986; Curtis and Mehendale 1979; Dahlstrbm-King et al. 1992; Hewitt et al. 1986a; Mehendale 1977c, 1979, 1981b; Teo and Vore 1991), but the decrease in taurocholate transfer to the bile was observed in the presence of decreased bile flow (Teo and Vore 1991). Decreased uptake of substances into rat hepatocytes was observed after gavage dosing with 12.5 mg/kg/day and above for 3 days, suggesting that transport of substances into hepatocytes may contribute to the decrease in their biliary excretion (Teo and Vore 1990). If mirex was given to rats in the diet for 14 days, focal bile stasis was observed at 5 mg/kg/day (Davison et al. 1976). Other hepatic effects observed after 14 days of dietary exposure at 5 mg/kg/day included hepatocyte swelling, liver cord cell disruption, and necrosis of central or midzonal hepatocytes (Davison et al. 1976). Other evidence of generalized hepatic toxicity includes: (1) increases in serum alanine and/or aspartate aminotransferase in mice following gavage doses of 30 mg/kg/day for 2 days (Fouse and Hodgson 1987), and in rats after 2 doses of 120 mg/kg on a single day (Mitra et al. 1990); (2) periportal liposis and degeneration of the endoplasmic reticulum after a single oral dose of 200 mg/kg in rats (Kendall 1979); (3) increased hepatic lipids or decreased hepatic glutathione or glucocorticoid receptors after single oral doses of 100 mg/kg in rats (Ervin and Yarbrough 1983; Sunahara and Chiesa 1992; Thottassery and Yarbrough 1991); (4) swollen hepatocytes after 3 days of exposure of rats to 10 mg/kg/day (Plaa et al. 1987); (5) increased hepatic lipid in rats after 7 days of exposure at 2 mg/kg/day; (6) increased serum tnglycerides after 4 days of exposure of rats to 1,000 mg/kg/day (Jovanovich et al. 1987); and (7) increased vacuolization with a loss of basophilic staining in mice after a single oral dose of 50 mg/kg/day (Hewitt et al. 1979).

Several investigators have observed hepatic glycogen depletion in rats (Ervin and Yarbrough 1983; Elgin et al. 1990; Jovanovich et al. 1987; Kendall 1974a, 1979) and in mice (Fujimori et al. 1983). In rats, glycogen depletion occurred after a single gavage dose as low as 100 mg/kg (Ervin and

Yarbrough 1983). In mice, glycogen depletion occurred following gavage doses of 25 mg/kg/day for 4 days (Fujimori et al. 1983).

Similar toxic effects were observed in laboratory animals after intermediate-duration oral exposure to mirex, but the doses at which these effects were observed were lower. Impaired biliary excretion was observed in rats following mirex or chlordecone doses as low as 0.5 mg/kg/day for 1.5 days or 19 mg/kg/day for 3 days (Bell and Mehendale 1985; Curtis and Hoyt 1984; Curtis and Mehendale 1979; Mehendale 1981b; Teo and Vore 1991). In dogs, impaired biliary excretion was observed at a dose of 2.5 mg/kg/day administered for 13 weeks (Larson et al. 1979a). The dog study is limited in that too few animals (two/sex/dose) were used, and it is unclear whether dogs at all doses were tested for hepatobiliary function. In a dietary study, histopathological analyses showed focal bile stasis, disruption of liver cord cells, and central or midzonal necrosis in rats at 0.5 mg/kg/day for 28 days (Davison et al. 1976). Decreased hepatic glycogen and bile canalicular degeneration were observed in this study at 5 mg/kg/day. Twenty-eight-day exposure of rats to mirex also resulted in cytoplasmic vacuolation, hepatocellular necrosis, and anisokaryosis at 0.25 mg/kg/day; pericentral fatty vacuolation at 2.5 mg/kg/day (Chu et al. 1981b); and panlobular ballooning of hepatocytes, anisokaryosis, and fatty vacuolation in males and moderate lobular pattern with perinuclear clear zone and perivenous cytoplasmic ballooning with anisokaryosis in females at 6.2 mg/kg/day (Chu et al. 1980b). Cytoplasmic vacuolation, moderately decreased aggregated basophilia, nuclear anisokaryosis, and hyperchromicity were found in the liver of both sexes of rats dosed at 0.25 mg/kg/day for 28 days (Chu et al. 1981b). A similar study found comparable effects after 21 months in both sexes of rats dosed at 0.07 mg/kg/day (Chu et al. 1981c). Hepatocellular vacuolation was also observed in rats following exposure to 4 mg/kg/day for 13 weeks (Larson et al. 1979a). Lipid accumulation was observed in livers of rats exposed to 0.65 mg/kg/day for up to 10 months (Fulfs et al. 1977). Bile stasis, decreased hepatic glycogen, and hepatocellular vacuolation were observed in rats after dietary exposure to 1.3-3.1 mg/kg/day for 166 days (Gaines and Kimbrough 1970). These effects were not observed at doses ranging from 0.21 to 0.48 mg/kg/day (Gaines and Kimbrough 1970).

No data were located regarding the effects of mirex on hepatobiliary function following chronicduration oral exposure. However, other adverse liver effects have been reported in animals following chronic oral exposures. In an 18-month dietary study in rats, increased fatty degeneration, cystic degeneration, necrosis, biliary hyperplasia, and periportal fibrosis were observed at the lowest dose tested (2.4 mg/kg/day) (Ulland et al. 1977a). F344/N male and female rats fed mirex doses (males =

0.007, 0.07, 0.7, 1.8, 3.8 mg/kg/day; females = 0.007, 0.08, 0.7, 2.0, 3.9 mg/kg/day) for 2 years developed histopathological changes, which included hepatocytomegaly with eosinophilic cytoplasm were observed in males and females at ≥0.7 mg/kg/day. Fatty metamorphosis (cytoplasmic vacuoles consistent with intracellular fat accumulation) and necrosis of hepatocytes (focal and centrilobular) were increased in males and females at ≥0.7 mg/kg/day. Dilation of the sinusoids (by blood or proteinaceous material) was observed in males at ≥0.7 mg/kg/day and in females only at the highest dose tested (NTP 1990). An MRL of 0.0008 mg/kg/day, based on a LOAEL of 0.075 mg/kg/day for histopathological evidence of hepatic damage from this study, was derived for chronic-duration oral exposure to mirex.

Like mirex, 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: (1) increases in liver size or weight (Cannon and Kimbrough 1979; Chernoff and Rogers 1976; Curtis and Mehendale 1979; EPA 1986c; Fabacher and Hodgson 1976; Fujimori et al. 1983; Huber 1965; Larson et al. 1979b; Mehendale 1981b; Mehendale et al. 1977b, 1978b; Purushotham et al. 1988; Simmons et al. 1987; Swartz and Schutzmann 1986, 1987); (2) increased hepatocellular hypertrophy (Cannon and Kimbrough 1979); (3) increased smooth endoplasmic reticulum (Curtis et al. 1981; Lockard et al. 1983a, 1983b; Mehendale et al. 1989); (4) increased microsomal protein (Chambers and Trevethan 1983; Klingensmith and Mehendale 1982b, 1983b; Mehendale et al. 1977b, 1978b); (5) increased cytochrome P-450 content (Agarwal and Mehendale 1984a; 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. 1977b, 1978b); (6) increased $NADPH_2$-cytochrome c reductase (Chambers and Trevethan 1983; Fujimori et al. 1983; Mehendale et al. 1977b, 1978b); (7) and/or increased 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. 1977b, 1978b).

Impaired biliary excretion in the presence of increased bile flow has been observed in three acuteduration studies conducted with mirex or chlordecone in rats (Curtis and Mehendale 1979; Mehendale 1977b; Teo and Vore 1991) as well as in two intermediate duration studies (Mehendale 1981b; Curtis and Mehendale 1979). Administration of 10 mg/kg/day of chlordecone to rats by gavage for 8 days resulted in decreased biliary excretion of imipramine metabolites and increased bile flow (Mehendale

1977b). Similarly, administration of 18.75 mg/kg/day to rats for 3 days resulted in decreased bile acid concentration, decreased bile acid secretion, and increased bile flow (Teo and Vore 1991). In the intermediate-duration studies, results of the analysis of hepatobiliary function and overt toxicity in Sprague-Dawley rats dosed with mirex or chlordecone doses of 5 mg/kg/day for 30 or 35 days, respectively, provided evidence of a correlation between hepatobiliary function (as indicated by increased bile flow) and overt toxicity (as measured by tremors and diarrhea). Starting on the 8th day of treatment, rats began showing overt toxicity (diarrhea, tremors, hyperactivity, and exaggerated startle response to touch and noise) as well as increased biliary flow. Biliary excretion of intravenously administered phenolphthalein glucuronide was significantly depressed at 10 days and continued to decrease until exposure was terminated at 30 days (approximately l/4 of normal at 25 days). Biliary excretion returned to normal by 20 days post-exposure. Total bile flow was increased throughout the exposure and recovery period (Mehendale 1981b). A similar result was reported for chlordecone alone at a dose of 0.5 mg/kg/day for 15 days (Curtis and Mehendale 1979). No effects on hepatocyte uptake of 17β-estradiol glucuronide, taurocholate, or L-alanine were observed at this dose. Other indicators of hepatic toxicity observed after acute-duration oral exposure included: (1) increased serum alkaline phosphatase and alanine aminotransferase after exposure of rats to 10 mg/kg/day for 10 days (EPA 1986c); (2) increased mannitol recovery (indicates decreased permeability of the canalicular membrane) (Hewitt et al. 1986a) or increased lysosomal fragility (Hewitt et al. 1990) after a single oral exposure of rats to 50 mg/kg; (3) increased cytoplasmic vacuolation and decreased basophilic staining of hepatocytes in mice after a single oral dose of 50 mg/kg (Hewitt et al. 1979); and (4) decreased hepatic glycogen in mice after gavage dosing with 25 mg/kg/day for 4 days (Fujimori et al. 1983). Single oral doses of 5 mg/kg in rats were without effect on hepatobiliary excretion (Davis and Mehendale 1980). Single oral doses of up to 50 mg/kg were without other adverse effects as determined by histopathological analyses and/or determination of serum alanine and aspartate aminotransferases (Glende and Lee 1985; Iijima et al. 1983; Klingensmith and Mehendale 1983b; Plaa et al. 1987).

Significantly increased serum nonprotein nitrogen compounds and enzymes, and decreased serum tnglycerides and LDL cholesterol were observed in Sprague-Dawley rats following 15 days dietary exposure to 5 mg/kg/day chlordecone (Chetty et al. 1993a, 1993b). In another study, impaired biliary function was also observed in intermediate-duration studies with chlordecone in experimental animals, although conflicting results were obtained regarding LOAELs and NOAELs for this effect. Although no effect on biliary excretion or flow was observed in several dietary studies in rats at 0.5 mg/kg/day

for 15 days (Agarwal and Mehendale 1982, 1983c; Agarwal et al. 1983; Bell and Mehendale 1985; Curtis and Mehendale 1980), inhibition of biliary excretion of phenolphthalein glucuronide was shown in a dietary study in rats at 0.5 mg/kg/day for 15 days (Curtis and Mehendale 1979; Curtis et al. 1979b; Mehendale 1981b). In addition, inhibition of exogenous taurocholate excretion was shown in a dietary study in rats at 1 mg/kg/day for 1.5 days (Curtis and Hoyt 1984). Also, ultrastructural analysis showed that bile canaliculi from rats exposed at 0.5 mg/kg/day for 15 days appeared tortuous and contained deformed and swollen microvilli (Curtis et al. 1981). Inhibition of phenolphthalein glucuronide was observed in rats following ingestion of 2.5 mg/kg/day for 15 days (Mehendale 1990a), 5 mg/kg/day for up to 35 days (Mehendale 1981b), and 7.5 mg/kg/day for 15 days (Curtis and Mehendale 1979). Increased bile flow was also observed by Mehendale (1981b) and Curtis and Mehendale (1979). Other evidence of hepatotoxicity seen in intermediate-duration studies in rats included increased incidences of swollen hepatocytes following ingestion of 1.25 mg/kg/day for 90 days (Larson et al. 1979b); areas of focal necrosis at 1.17 mg/kg/day for 90 days (Cannon and Kimbrough 1979); depletion of hepatic glycogen (Curtis et al. 1979b); and fragmentation of and/or a decrease in rough endoplasmic reticulum (Curtis et al. 1981; Faroon et al. 1991), or minute vacuolation of the cytoplasm (Faroon and Mehendale 1990) in rats at 0.5 mg/kg/day for 15 days. However, similar ultrastructural effects have not been observed in the same strain of rats after 15 days exposure to 0.5 mg/kg/day chlordecone (Lockard et al. 1983a, 1983b). In mice, ingestion of 5.2 mg/kg/day for up to 12 months resulted in increased incidences of areas of focal necrosis (Huber 1965). Gerbils had no increase in serum alanine or aspartate aminotransferase and no increase in adverse histopathological findings following ingestion of 1 mg/kg/day for 15 days (Cai and Mehendale 1991b). In another intermediate-duration rat study, 10 male weanling Sprague-Dawley rats were fed diets containing either corn oil or chlordecone dissolved in corn oil for 28 days, and then sacrificed. There were mild histological changes in the liver, consisting of multiple focal lymphoid aggregates, perivenous cytoplasmic ballooning, and perinuclear halos in the portal area in the treated rats. The livers from 5 rats contained average chlordecone levels of 6.1 ppm (Chu et al. 1980a).

Limited information is available regarding hepatotoxicity of chlordecone following chronic-duration oral exposures. A 21-month study in Sprague-Dawley rats reported a decrease in hepatic microsomal aniline hydroxylase activity at a dose of 0.07 mg/kg/day. Histopathological findings in this study included panlobular cytoplasmic vacuolation with loss of basophilia, fatty infiltration, and anisokaryosis in liver (Chu et al. 1981c). A National Cancer Institute (NCI) cancer bioassay showed fatty infiltration and hepatocellular degeneration in rats at doses as low as 0.4 mg/kg/day for 80 weeks

(NCI 1976). In $B6C3F_1$ mice, an 80-week exposure to 2.6 mg/kg/day of chlordecone resulted in hepatocellular hyperplasia (NCI 1976). Routine histopathological analyses of livers from rats exposed up to 1.25 mg/kg/day for 2 years or dogs exposed at up to 0.625 mg/kg/day for 2 years showed no increase in adverse compound-related effects (Larson et al. 1979b). Both of these studies are limited in that it is unclear whether all tissues were examined; in addition, the study in dogs is limited in that too few animals were tested (two/sex/dose).

**Renal Effects.** No studies were located regarding renal effects in humans after oral exposure to mirex or chlordecone.

Animal studies indicate that acute- and intermediate-duration exposures to mirex are without significant renal toxicity but that chronic-duration exposure to low levels of mirex may result in toxic effects on the kidneys. No effect on rat kidney weight or blood urea nitrogen and no adverse histopathological findings were reported following a single oral dose of 50 mg/kg or 3 daily doses of 10 mg/kg/day (Plaa et al. 1987). Similarly, no effect on kidney weight, blood urea nitrogen, or ion exchange in the kidneys and no adverse histopathological findings were reported following a single oral dose of 50 mg/kg in mice (Hewitt et al. 1979). Thirteen-week exposures of rats to doses as high as 64 mg/kg/day and of dogs to doses as high as 2.5 mg/kg/day caused no increase in adverse histopathological findings or effects on urinalysis parameters (Larson et al. 1979a). At 0.05 mg/kg/day, 2 of 10 rats were reported to have moderate focal lymphoid aggregates and multiple focal interstitial mononuclear infiltrates in the kidneys following 28 days of dietary exposure (Chu et al. 1980a). 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. As indicated above, chronic-duration studies have shown increased nephrotoxicity following exposure to mirex. Nephropathy was observed to increase in severity in both male and female rats following exposure in a 2-year dietary study (NTP 1990). In males, this effect was observed at 20.7 mg/kg/day. In females, this effect was observed at 2 mg/kg/day and above. Similarly, in an independent evaluation of an l&month rat carcinogenicity bioassay, Reuber (1977) reported an increased incidence of nephritis in both males and females at 2.5 mg/kg/day and an increased incidence of renal necrosis in females at $\geq$2.5 mg/kg/day. However, the onginal study author (Ulland et al. 1977b) disputed this interpretation and considers this conclusion a misrepresentation of the data since the conclusion is not supported by data produced in this study (Ulland et al. 1977b).

Like mirex, chlordecone produced observable renal effects following oral exposure primarily in chronic-duration studies. However, no adverse renal effects were observed after acute exposure. Although increases in blood urea nitrogen and kidney weight were observed following a lo-day exposure of rats to 10 mg/kg/day of chlordecone (EPA 1986c), no effect on rat kidney weight or blood urea nitrogen, and no adverse histopathological findings were reported following a single oral dose of 50 mg/kg or 3 doses of 10 mg/kg/day (Plaa et al. 1987). Similarly, no effect on kidney weight, blood urea nitrogen, or ion exchange in the kidneys and no adverse histopathological findings were reported following a single oral dose of 50 mg/kg in mice (Hewitt et al. 1979). Exposure of rats to up to 4 mg/kg/day for 90 days also resulted in no adverse histopathological findings in the kidneys or in urinalysis parameters (Agarwal et al. 1983; Larson et al. 1979b). An increase in eosinophilic inclusions in the proximal tubules was observed in 2 of 10 rats examined following exposure at 0.05 mg/kg/day for 28 days (Chu et al. 1980a). 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. In contrast to the negative findings observed in acute-duration studies, renal pathology was observed in rats following intermediate- and chronic-duration exposures to small doses of chlordecone (Larson et al. 1979b). In a 2-year feeding study with rats, groups of Wistar rats of both sexes were administered 0, 0.05, 0.25, 0.5, 1.25, 2.5, or 4.0 mg/kg/day for a period of 1 year. After 1 year, 5 rats/sex/dose group were sacrificed. Additionally, 3 to 5 rats of each sex receiving 0.25 or 0.5 mg/kg/day and 3 males receiving 1.25 mg/kg/day were returned to the control diet for 4 weeks and then sacrificed. Proteinuria was noted in all treatment groups at all intervals after 3 months except in males at 21 and 24 months when control levels were elevated and in females at 24 months when the levels in only the 0.5 and 1.25 mg/kg/day groups were elevated. The severity of observed glomerulosclerosis was increased in both males and females at ≥0.25 mg/kg/day as compared to undosed controls (Larson et al. 1979b). Intermediate- and chronic-duration MRLs of 0.0005 mg/kg/day were derived for oral exposure to chlordecone based on the NOAEL of 0.05 mg/kg/day for histopathological evidence of renal damage from this study. An independent review of an NTP (1990) mirex bioassay in rats, which reported nephrotoxicity in the treated animals, concluded that fibrosis of the kidney was more frequent in chlordecone-treated rats (Reuber 1978a, 1979c) but the doses at which this effect was observed were not reported. However, the onginal pathology review of the study did not include any significant incidence of renal fibrosis among the treated rats. Thus, the ongin of data used by this reviewer to reach this conclusion is unclear. Dogs appeared to be less sensitive to chlordecone than rats; no

increases in urinary protein or adverse histopathological changes were seen in the kidneys of dogs ingesting 0.625 mg/kg/day for 124-128 weeks (Larson et al. 1979b).

### Endocrine Effects.

*Thyroid*. No studies were located regarding thyroid effects in humans after oral exposure to mirex or chlordecone.

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 0.25 mg/kg/day 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 $T_3$ or $T_4$ (Chu et al. 1980b, 1981a, 1981b). Ultrastmctural analyses of thyroids from rats treated for 28 days showed dilation of the rough endoplasmic reticulum at 0.25 mg/kg/day and increased columnar cells with irregularly shaped lysosomal bodies, dilation of cisternae, and increased vacuolization at 2.5 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). A similar study found comparable effects after 21 months in both sexes of rats dosed at 0.07 mg/kg/day (Chu et al. 1981c). 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). No studies were located regarding thyroid effects in animals following oral exposure to chlordecone.

*Adrenal*. No studies were located regarding adrenal effects in humans after oral exposure to mirex or chlordecone.

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 increased adrenal weight, increased cholesterol, lipid, and protein content (Williams and Yarbrough 1983), and increased serum adrenocorticotropic hormone (Ervin and Yarbrough 1985). Seven days of exposure to 1,000 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 to 17 mg/kg/day mirex in rats (Baggett et al. 1980).

Less information is available regarding the effects of chlordecone on the adrenal glands of animals. Increased relative adrenal weight was observed following a single oral dose of 35 mg/kg in rats (Swanson and Wooley 1982). An enlarged adrenal with hyperplasia and hypertrophy of the cortical cells was observed in a 30-day dietary study in rats at 1.17 mg/kg/day (Cannon and Kimbrough 1979). Also, decreased adrenal lipid was observed at 1.25 mg/kg/day in a 90-day dietary study in rats (Larson et al. 1979b). Consistent with a corticosterone-induced increase in lipid utilization, decreased body fat was observed following a 16-day dietary exposure at 2.5 or 5 mg/kg/day in rats (Mehendale et al. 1977b, 1978b), 15 or 20 days of dietary exposure at 5 mg/kg/day in rats (Klingensmith and Mehendale 1982a), or 33 days of dietary exposure to 10 mg/kg/day in mice (Fujimori et al. 1983). In contrast to the absence of effects of mirex on the adrenal medulla, chlordecone at 17 mg/kg/day for 8 days resulted in a decrease in the medullary content of epinephrine in rats (Baggett et al. 1980).

**Dermal Effects.** No studies were located regarding dermal effects in humans after oral exposure to mirex. Eighty-nine of 133 workers interviewed as a result of intermediate- or chronic-duration exposures to high levels of chlordecone during its manufacture reported skin rashes of an erythematous, macropapular nature that occurred at some time during their exposure (Cannon et al. 1978). Among 23 workers with blood chlordecone levels above 2 μg/L, 16 reported exposure-related rashes (Taylor et al. 1978). While it is likely that these rashes were the direct result of dermal exposure, insufficient information was given to eliminate a systemic effect resulting from oral exposure.

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 over a 12-day period (Kendall 1974a), 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, 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.

No effects on the skin were observed during routine histopathological analyses of the skin of rats exposed to chlordecone for 90 days at doses as high as 4 mg/kg/day or for 2 years at doses as high as

1.25 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 in rats at doses as low as 0.4 mg/kg/day (NCI 1976).

**Ocular Effects.** No studies were located regarding ocular effects in humans after oral exposure to mirex or chlordecone.

Production of cataracts in the very young was observed in animals as a result of oral exposure to mirex in an acute-duration exposure study in which rats were given a total of 365 mg/kg over a 12-day period (Kendall 1974a), but 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 exposure (Chernoff et al. 197913; Rogers and Grabowski 1984; Scotti et al. 1981). Cataracts were characterized as diffuse anterior cornea1 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 doses of 5 mg/kg/day mirex by gavage directly (Scotti et al. 1981) and in those that received the mirex indirectly through the mother's milk (Chernoff et al. 1979b; 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 doses as low as 1.25 mg/kg/day during postpartum days l-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 the production of 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. 1979b). Thus, the very young represent a population especially susceptible to this effect (see also Section 2.7). Eye irritation was also reported in a 90-day gavage study in rats (5, 12.5, 25 mg/kg/day), but the specific dose associated with this effect was not specified, thus, precluding determination of LOAELs (Dietz and McMillan 1979).

In contrast to the results obtained with mirex, chlordecone was not found to be cataractogenic in the very young (Chernoff et al. 1979b). Exposure of maternal rats to doses as high as 10 mg/kg/day or

maternal mice to doses as high as 24 mg/kg/day during the first 4 days of lactation, and the resulting exposure of the young through the mother's milk, resulted in no incidences of cataracts among the offspring of treated dams.

**Body Weight Effects.** No studies were located regarding effects on body weight in humans after oral exposure to mirex. Twenty-seven of 133 workers examined as a result of intermediate or chronic-duration exposures to chlordecone experienced weight loss (Cannon et al. 1978). Weight loss (up to 60 pounds in 4 months) was reported in 10 of these workers (Taylor et al. 1978).

Decreases greater than 10% in body weight or body weight gain have been observed in a number of acute-duration studies (Buelke-Sam et al. 1983; Byrd et al. 1981; Chadwick et al. 1977; Chernoff et al. 1979a, 1979b; Elgin et al. 1990; Fujimori et al. 1983; Jovanovich et al. 1987; Khera et al. 1976; Mehendale et al. 1973; Ritchie and Ho 1982; Rogers and Grabowski 1984; Villeneuve et al. 1977), intermediate-duration studies (Chernoff et al. 1979b; Chu et al. 1981b; Curtis and Hoyt 1984; Davison et al. 1976; Fujimori et al. 1983; Larson et al. 1979a; NTP 1990), and chronic-duration studies (NTP 1990) with mirex.

Decreases greater than 10% in body weight or body weight gain have also been observed in several chlordecone acute-duration studies (Albertson et al. 1985; Chernoff and Kavlock 1982; Chernoff and Rogers 1976; EPA 1986c; Huang et al. 1980; Kavlock et al. 1987b; Seidenberg et al. 1986; Simmons et al. 1987; Smialowicz et al. 1985; Swanson and Wooley 1985), intermediate-duration studies (Cannon and Kimbrough 1979; Curtis and Hoyt 1984; Curtis and Mehendale 1979; Fabacher and Hodgson 1976; Klingensmith and Mehendale 1982a; Larson et al. 1979b; Mehendale et al. 1977b, 1978b; Pryor et al. 1983), and chronic-duration studies (Larson et al. 1979b). 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.

### Other Systemic Effects

*Serum Glucose*. No studies were located regarding effects on serum glucose in humans after oral exposure to mirex or chlordecone.

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 5 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). Reports of chlordecone-induced effects on serum glucose 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.* No studies were located regarding effects on thermoregulation in humans after oral exposure to mirex or chlordecone.

Also, no studies were located regarding effects on thermoregulation in animals following oral exposure to mirex. 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).

### 2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to mirex or chlordecone.

The only information about the immunological effects of mirex exposure in animals was provided by one acute oral study in rats in which decreased spleen weight was reported (Buelke-Sam et al. 1983). Two reports were located regarding effects of chlordecone on immunological end points in rats following acute exposure. 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 1986c; Smialowicz et al. 1985). Similarly, 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-l mouse lymphoma) tumor cell lines (EPA 1986c; Smialowicz et al. 1985), were observed only at a dose (10 mg/kg/day) producing generalized toxicity. Also, a slight decrease in total leukocyte count (EPA 1986c) and a 49% decrease in neutrophils (Smialowicz et al. 198.5) 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 in male Sprague-Dawley rats on the effects of calcium deficiency on the toxicity of chlordecone, an increase in plaque-forming cells was observed at the lowest dose tested (0.5 mg/kg/day) (Chetty et al. 1993c).

A significant reduction of thymus weight was also observed in Sprague-Dawley rats 3 weeks after a single oral dose of 75 mg/kg of chlordecone (Swanson and Wooley 1982). It is likely that this effect may also have been associated with generalized toxicity in the experimental animals.

#### 2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to mirex. Sixty-one of 133 workers examined as a result of intermediate- or chronic-duration exposures to high levels of chlordecone during its production experienced tremors; 58 experienced nervousness or unfounded anxiety; and 42 experienced visual difficulties during exposure (Cannon et al. 1978). While oral exposures are generally not thought to contribute significantly in occupational exposure situations, hygiene at the facility was very poor and oral exposures (from food and water) were considered to have been likely. Tremors were observed in all 23 workers with blood levels >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). The effects on vision were characterized as a

disruption of ocular motility following a horizontal saccade by rapid random multidirectional eye movements (Taylor 1982, 1985). Visual acuity and smooth eye movements were unaffected. Headaches of mild-to-moderate severity were reported by 9 of the 23 workers. Three of these 9 had increased cerebrospinal fluid pressure and papilledema (Sanbom 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 5 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 had 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 reported emotional problems (Taylor 1982, 1985).

Clinical signs indicative of neurotoxicity were not 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 to >365 mg/kg) of mirex, lethargy, weakness, hyperexcitability, and/or tremors have been observed (Gaines and Kimbrough 1970; Kendall 1974a). Although the precise doses associated with specific neurotoxic effects were not specified in these studies, single oral doses of 100 mg/kg or greater were necessary. Juvenile rats showed a high sensitivity to acute exposure to mirex immediately after birth. Ingestion of the milk of dams treated with 2.5 mg/kg/day on lactation days l-4 caused no behavioral abnormalities at the time of exposure but resulted in increased activity in the animals when they 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 5 mg/kg/day during both 15- and 30-day dietary studies in rats (Curtis and Hoyt 1984; Mehendale 1981b). Decreased operant responding was also observed in a 90-day gavage study in rats at 5 mg/kg/day (Dietz and McMillan 1979). At 10 mg/kg/day, mirex had no effect on motor coordination of mice, but some mice were observed to become too weak to balance on a glass rod during a 15-day gavage study

(Fujimori et al. 1983). Dietary exposure to 16 mg/kg/day was observed to have no effect on the behavior of rats over 13 weeks of exposure, but at 64 mg/kg/day for 13 weeks, rats were observed to become hyperexcitable and develop tremors and convulsions (Larson et al. 1979a). Similarly, longer-duration exposures also resulted in increased excitability. Dietary exposure to 2 mg/kg/day for 148 days resulted in hypoactivity, irritability, and tremors in treated rats (Chu et al. 1981a).

In contrast to the limited information regarding the neurotoxicity of mirex, the neurotoxicity of chlordecone, which included tremoring and/or a time-dependent exaggerated startle response, was readily apparent in studies with 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 following dosing (Swanson and Wooley 1982). In mice, tremors, decreased motor coordination, and hyperexcitability were observed following a single oral dose of 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. 1980a; Fujimori et al. 1982b; 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 doses as low as 5 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 1986c). This study was part of a toxicity screen performed at EPA in which male Fischer-344 rats received gavage doses of 1.25 or 2.5 mg/kg/day chlordecone for 10 consecutive days. At 2.5 mg/kg/day and above, the amplitude of the acoustic startle response was significantly increased with all decibel stimuli used. Motor activity in a figure-8 maze was also decreased at the highest dose tested. At the other 2 doses, the amplitude was increased with all decibel stimuli. Motor activity in a figure-8 maze was decreased at the highest dose tested (EPA 1986c). An acute oral MRL of 0.01 has been developed for chlordecone based on the NOAEL of 1.25 mg/kg from this study.

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. 1980a; 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. Although 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 tremongenic doses, no effect was observed on norepinephrine or on dopamine content (Aldous et al. 1984; End et al. 1981) or synthesis (End et al. 1981) at equally tremongenic 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).

Tremoring, accompanied or unaccompanied by increased responsiveness to touch and noise, have also been observed in a number of intermediate-duration studies (Agarwal and Mehendale 1984c; 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 1981b; Mehendale et al. 1978; Pryor et al. 1983; Squibb and Tilson 1982b; Swartz and Schutzmann 1986, 1987). Mild tremors were observed in rats at doses as low as 0.83 mg/kg/day for 90 days (Linder et al. 1983). At 0.5 mg/kg/day for 90 days, an increase in the startle response of rats was observed, 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 function (Squibb and Tilson 1982b). Chronic-duration studies in rats have also demonstrated increased tremoring. Tremoring was observed at 1.25 mg/kg/day but not at 0.5 mg/kg/day in a 2-year rat dietary study (Larson et al. 1979b). NCI (1976) bioassays in mice and rats reported tremoring at 3.0 and 0.4 mg/kg/day, respectively. No tremors or other behavioral abnormalities were observed in dogs ingesting 0.625 mg/kg/day in a companion 2-year dietary study (Larson et al. 1979b).

The highest NOAEL and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded for mirex in Table 2-l and for chlordecone in Table 2-2 and plotted for mirex in Figure 2-l and for chlordecone in Figure 2-2.

### 2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to mirex. Occupational exposure to chlordecone for up to 1.5 years caused oligospermia and decreased sperm motility in male workers. However, no loss of fertility was reported by the workers (Guzelian 1982a; Taylor 1982, 1985; Taylor et al. 1978). Refer to Section 2.2.1.5 for further details.

Studies in animals suggest that both male and female reproductive systems are adversely affected by mirex. Acute exposure 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 of the 6 mg/kg/day dose-group males, 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 exposure 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.

In a 28-day dietary study, decreased sperm count was noted in male rats at dosages as low as 0.025 mg/kg/day; testicular degeneration was observed at dosage levels of 2.5 and 3.7 mg/kg/day (Yarbrough et al. 1981). However, mirex fed to male rats at 1.3-3.1 mg/kg/day for 2 generations resulted in no decrease in fertility (Gaines and Kimbrough 1970). In contrast, females given 1.8-2.8 mg/kg/day for 2 generations produced a decreased number of litters (Gaines and Kimbrough 1970). Administration of 0.25 mg/kg/day to male and female rats for 91 days prior to mating and then through lactation resulted in a decreased mating and litter size (Chu et al. 1981a). Male and female

mice at 0.65 mg/kg/day for 30 days prior to mating, and then for an additional 90 days, experienced reduced fecundity and had 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 also produced reproductive toxicity in both male and female animals. Exposure of male rats to doses of chlordecone as low as 0.625 mg/kg/day for 10 days resulted in a decreased sperm count, although at the highest dose tested (10 mg/kg/day) decreased testes weight and an increase in sperm count was observed (EPA 1986c). A dominant lethal study, designed to test the effect of oral mirex doses on male fertility in Sprague-Dawley rats, showed no effect on the fertility of the male rats. The male rats were mated with naive, nulliparous females each week for 14 consecutive weeks two days after oral gavage dosing at 11.4 mg/kg/day for 5 days (Simon et al. 1986). Persistent vaginal estrus was reported in female mice receiving 2 mg/kg chlordecone daily for 2 weeks (Swartz et al. 1988).

Effects observed after intermediate-duration exposure of male and female mice to chlordecone included decreased numbers of litters, litter size, and frequency of litter production (Good et al. 1965; Huber 1965). These effects were observed at doses as low as 1.3 mg/kg/day for 130 days (Huber 1965) or 0.65 mg/kg/day for 6 months (Good et al. 1965).

Intermediate- and chronic-duration studies in rodents indicate that decreases in sperm count and testicular atrophy may result from exposure to chlordecone. Dietary exposure of male rats to 0.83 mg/kg/day and above of chlordecone for 90 days decreased sperm motility and viability; at 1.67 mg/kg/day and above, there was a decrease in the weight of seminal vesicles and prostate (Linder et al. 1983). Despite these effects, the fertility, litter size, sperm morphology, sperm count, and histopathology of male gonads were unaffected. Exposure of male rats to 1.17-1.58 mg/kg/day for 4.5 months prior to mating also had no effect on fertility (Cannon and Kimbrough 1979). In mice 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). In contrast to the absence of adverse histopathological changes reported by Linder et al. (1983), testicular atrophy has been reported following dietary exposure of rats to 0.5 mg/kg/day of chlordecone for 90 days (Larson et al. 1979b). It was suggested that the difference in the two studies was due to

the use of younger males in the study by Larson et al. (1979b), suggesting that adolescent males may be more susceptible to adverse effects on the gonads.

Intermediate-duration studies with treated females show that exposure to chlordecone may result in persistent vaginal estrus, decreased ovulation, and reproductive failure. Persistent vaginal estrus was observed in female mice at doses as low as 2 mg/kg/day for 3-6 weeks (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) have been observed after 4 weeks of exposure to 8 mg/kg/day of chlordecone. Similarly, decreased corpora lutea have been observed following administration of 3.9 mg/kg/day for 130 days (Huber 1965). Decreased numbers of litters or complete reproductive failure have been observed after exposure of female rats to 1.62-l .7 1 mg/kg/day for 4.5 months or female mice to 5.2 mg/kg/day for 160 days (Huber 1965).

The highest NOAEL and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded for mirex in Table 2-l and for chlordecone in Table 2-2 and plotted for mirex in Figure 2-l and for chlordecone in Figure 2-2.

#### 2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to mirex or chlordecone.

Exposure of maternal rats and mice to mirex during gestation resulted in increases in resorptions and stillbirths and decreases in postnatal viability (Buelke-Sam et al. 1983; Byrd et al. 1981; Chernoff and Kavlock 1982; Chernoff et al. 1979a; Grabowski 1983a; Grabowski and Payne 1980, 1983a, 1983b; Gray and Kavlock 1984; Gray et al. 1983; Khera et al. 1976; Rogers and Grabowski 1983) at doses as low as 1.25 mg/kg/day when administered from gestation days 4 through 22. 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. 1979a; Grabowski 1981, 1983a; Grabowski and Payne 1980, 1983a, 1983b; Kavlock et al. 1982; Khera et al. 1976; Rogers and Grabowski 1983). 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 1983a). 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. 1979a; Kavlock et al. 1982; Khera et al. 1976). Additional effects observed in fetuses included decreased skeletal ossification (Chernoff et al. 1979a), 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), serum glucose and hematocrit (Rogers et al. 1984), serum plasma proteins (Grabowski 1981), fetal liver weight and glycogen content (Kavlock et al. 1982), renal protein and alkaline phosphatase (Kavlock et al. 1982), and kidney weights at postpartum day 250 (Gray and Kavlock 1984; Gray et al. 1983), and increased dyspnea (Grabowski and Payne 1983a) and liver and thyroid lesions (Chu et al. 1981a). Cataracts were also observed in offspring in several studies (Chernoff et al. 1979a; 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. 1979b; Rogers and Grabowski 1984; Scotti et al. 1981) (see Section 2.2.2.2) indicating that in utero exposure was not critical for their development.

Gestational exposure of rats and mice to chlordecone also resulted in increased stillbirths and decreased postnatal viability (Chernoff and Kavlock 1982; Chernoff and Rogers 1976; EPA 1986c; Gray and Kavlock 1984; Gray et al. 1983; 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 1986c) 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 1986c; 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 pelves, 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 given 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 1982a). 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) and increased striatal dopamine binding (Seth et al. 1981). Furthermore, offspring of mice exposed to 0.05 mg/kg/day in this exposure paradigm showed an increased reactivity to apomorphine (a dopamine agonist) (Squibb and Tilson 1982a). These studies suggest that perinatal exposure to low doses of chlordecone may affect dopaminergic function in adult offspring.

The highest NOAEL values and all reliable LOAEL values from each reliable study for developmental effects in each species and duration category are recorded for mirex in Table 2-l and for chlordecone in Table 2-2 and plotted for mirex in Figure 2-l and for chlordecone in Figure 2-2.

### 2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to mirex or chlordecone.

There were also no studies regarding potential adverse morphological changes in chromosomes in somatic cells of whole animals after oral exposure to mirex or chlordecone. However, a dominant lethal assay was conducted in male rats (20 males/group; strain not specified) receiving oral doses of 1.5, 3.0, or 6.0 mg/kg mirex by gavage daily for 10 consecutive days (Khera et al. 1976). At the end of treatment, individual males were mated with two untreated virgin females for 5 days; the mating sequence was continued until 14 sequential matings were completed. Females were sacrificed 13-15 days following separation from the males, and the uterine contents were examined for deciduomas, corpora lutea, and viable embryos. Although there was a significant decrease in the incidence of pregnancies in the 6.0-mg/kg group following the first mating, parameters indicative of dominant lethality were unaffected by treatment. Mirex was also detected in the testes; therefore, the failure to induce a dominant lethal effect was not associated with an inability of the test material to reach the target organ.

Chlordecone was evaluated in a dominant lethal mutation assay in which groups of 10 male Sprague-Dawley rats were administered 3.6 or 11.4 mg chlordecone/kg/day for 5 consecutive days by oral

gavage (Simon et al. 1986). Two days after administration of the final dose, individual males were mated with two naive, nulliparous females for 1 week; the mating sequence was continued for 14 weeks. Females were sacrificed on gestation day 14, and uteri and ovaries were examined for deciduomata, corpora lutea, implantation sites, and live and dead implants. Reduced fertility indices (i.e., number inseminated/number mated) were seen in the high-dose group following the first two matings; however, no adverse effects on male fertility were seen at any week in either treatment group. Similarly, there was no consistent pattern of dose- or time-related dominant lethal action. In an additional phase of the study, chlordecone was shown to be distributed throughout the reproductive tract with the highest concentration initially observed in the vas deferens, and in decreasing order in seminal vesicular fluid, unwashed sperm, prostate, seminal vesicles, and washed sperm. This distribution persisted as levels declined over the 21-day observation period. Therefore, the absence of a dominant lethal effect was not due to a failure to expose spermatozoa.

Administration of single oral doses of 90 or 120 mg/kg mirex by gavage to female Sprague-Dawley rats resulted in induction of hepatic ornithine decarboxylase activity; there was, however, no evidence of significant damage to deoxyribonucleic acid (DNA) as measured by alkaline elution (Mitra et al. 1990).

Marked disturbances in the distribution of ploidy (diploid and tetraploid nuclei) have been observed in the livers of male Sprague-Dawley rats fed a dietary concentration of 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). Similarly, 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).

In agreement with hepatic functional activity studies conducted with mirex, chlordecone administered orally to female Sprague-Dawley rats at l/5 and 3/5 of the $LD_{50}$ (19 and 57 mg/kg, respectively) caused a significant increase in omithine decarboxylase activity, but there was no evidence of DNA damage at either level (Kitchin and Brown 1989).

The only data from an *in vivo* assay suggesting possible genotoxicity for chlordecone were reported by Ikegwuonu and Mehendale (1991). In this study, chlordecone was administered orally in corn oil at a dose of 10 mg/kg to groups of male Sprague-Dawley rats. Following treatment, animals were subdivided into groups that received either hydroxyurea (a DNA repair stimulator) or dimethyl sulfoxide (solvent for hydroxyurea). Animals were sacrificed at an unspecified time, and hepatocytes recovered from the various groups were subjected to a battery of biochemical assays to measure effects on DNA. Chlordecone alone induced a low level of unscheduled DNA synthesis in recovered hepatocytes; 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, as would be expected when DNA strand breaks occur.
Other genotoxicity studies are discussed in Section 2.4.

### 2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to mirex. Extremely limited information was located regarding cancer in humans following oral exposure to chlordecone. Liver biopsy samples taken from 12 workers with hepatomegaly resulting from intermediate or chronic-duration exposures to 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 were examined immediately after exposure.

Mirex was found to be carcinogenic by the oral route in mice and rats in several studies. The predominant carcinogenic lesions observed in these studies were hepatomas and neoplastic nodules of the liver, and mononuclear cell leukemia and transitional cell papillomas of the kidney. A positive trend in pheochromocytomas was also observed in one of the studies. Both male and female mice (18/sex/dose) of the (C57BL/6 x C3H/ANF)$F_1$ or (C57BL/6 x AKR)$F_1$ 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 and then in the diet until 18 months of age (time-weighted-average dose = 3.6 mg/kg/day) (Innes et al. 1969).

In rats, an increase in the incidence of neoplastic nodules was also observed in male CD rats administered mirex (4.9 mg/kg/day) in the diet for 18 months. However, the number of rats (20-26 males and females) tested was rather low and the duration of dosing should have been longer to have maximum sensitivity of testing (Ulland et al. 1977a). In 2-year feeding studies, F344/N rats (52/sex) were administered mirex in the diet for 104 weeks in two separate bioassays (NTP 1990). In one of the bioassays both sexes of F344/N rats were used, while only females were used in the second. It was concluded that under the conditions of the 2-year feeding studies of mirex, there is clear evidence of carcinogenic activity for male and female F344/N rats, as indicated by marked increased incidences of neoplastic nodules of the liver (at ≥0.7 mg/kg/day in males and ≥3.8 mg/kg/day in females) and by dose-related increase in the incidences of mononuclear cell leukemias in females (1.8 mg/kg/day in males, ≥1.8 mg/kg/day in females in the first study, and 7.7 mg/kg/day in females in the second study; $p < 0.05$), as well as by a positive trend in the incidence of transitional cell papillomas of the renal pelvis in males (at 3.8 mg/kg/day; $p = 0.018$ by Life Table Tests). The 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 (CE) for mirex in F344/N rats under the conditions of the bioassay (NTP 1990).

Chlordecone was also 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 a time-weighted average of 1.2 mg/kg/day in males and 1.3 mg/kg/day in females (NCI 1976). In the NCI (1976) bioassay in rats, the incidence of hepatocellular carcinomas was significantly increased ($p<0.05$) in both 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 of exceedence of the Maximum Tolerated Dose (MTD) 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 also, and only pooled controls were used in this bioassay.

Administration of chlordecone to B6C3$F_1$ mice for 80 weeks also resulted in significantly increased incidences of hepatocellular carcinomas in both males and females at doses as low as 2.6 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 with a dose-related trend. The incidence of hepatocellular carcinomas was 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 exceedence of the Maximum Tolerated Dose (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 controls animals as well.

In its evaluations, the 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 1994). However, neither mirex nor chlordecone has been classified by the EPA with regard to cancer inducing potential (EPA 1994).

The cancer effect levels (CELs) for mirex and chlordecone in chronic-duration studies in rats and mice are recorded for mirex in Table 2-l and for chlordecone in Table 2-2 and plotted for mirex in Figure 2-l and for chlordecone in Figure 2-2.

### 2.2.3 Dermal Exposure

No data on health effects resulting from dermal exposure to mirex in humans were located. Data on health effects resulting from dermal exposure to chlordecone are limited to information on a single

group of men exposed to chlordecone at a facility in Hopewell, Virginia, where chlordecone was manufactured over a 21-22-month period. Hygiene conditions at the plant were extremely poor and substantial dermal exposure could have occurred. Inhalation and oral exposures were also thought to have occurred. Studies of this group of men are limited by the uncertainties regarding exposure levels and route and by exposure to the precursor used to manufacture chlordecone, hexachlorocyclopentadiene.

### 2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to mirex. No deaths were reported in humans after exposure to chlordecone (Cannon et al. 1978; Taylor et al. 1978).

The dermal $LD_{50}$ value for both mirex and 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). All reliable $LD_{50}$ values for death in rats and rabbits following acute-duration exposure for mirex and chlordecone are recorded in Tables 2-3 and 2-4, respectively.

### 2.2.3.2 Systemic Effects

Several studies were presented in Section 2.2.1.2 regarding the systemic effects experienced by workers occupationally exposed to chlordecone (Cannon et al. 1978; Guzelian et al. 1980; Martinez et al. 1978; Taylor 1982, 1985; Taylor et al. 1978). Dermal exposure was probably a major route of exposure in the occupational situation described in these studies; however, the results of these studies are not repeated in this section since Section 2.2.1.2 contains a complete description of the systemic effects associated with occupational exposure (route of exposure unspecified; either inhalation, oral, and/or dermal) to chlordecone. No additional studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, endocrine, ocular, or bodyweight effects in humans or animals after dermal exposure to mirex or chlordecone. The systemic effects believed to result directly from dermal exposure are discussed below. The LOAEL value for systemic effects in mice after intermediate-duration dermal exposure is recorded for mirex in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to Mirex - Dermal

| Species/ (Strain) | Exposure/ Duration/ Frequency/ (Specific Route) | System | NOAEL | LOAEL | | Reference |
|---|---|---|---|---|---|---|
| | | | | Less Serious | Serious | |
| **ACUTE EXPOSURE** | | | | | | |
| **Death** | | | | | | |
| Rat (Sherman) | NS | | | | >2000 mg/kg (LD50) | Gaines 1969 |
| **INTERMEDIATE EXPOSURE** | | | | | | |
| **Cancer** | | | | | | |
| Mouse (CD-1) | 4 wk 3x/wk (paint) | | | | 3.6 mg/kg/ day F (skin tumor promotion) | Meyer et al. 1993 |
| Mouse (CD-1) | 20 wk 2x/wk (paint) | | | | 3.6 mg/kg/ day F (skin tumor promotion) | Meyer et al. 1994 |
| Mouse (CD-1) | 4 wk 3x/wk (paint) | Dermal | | 3.6 mg/kg/ day F (mild epidermal hyperplasia) | | Moser et al. 1992 |
| Mouse (CD-1) | 20 or 34 wk 3x/wk (paint) | | | | 0.45 mg/kg/ day F (skin tumor promotion) | Moser et al. 1992 |
| Mouse (CD-1) | 20 wk 3x/wk (paint) | | | | 0.45 mg/kg/ day (skin tumor promotion) | Moser et al. 1993 |

F = female; $LD_{50}$ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s)

TABLE 2-4. Levels of Significant Exposure to Chlordecone - Dermal

| Species/ (Strain) | Exposure/ Duration/ Frequency/ (Specific Route) | System | NOAEL | LOAEL | | | Reference |
|---|---|---|---|---|---|---|---|
| | | | | Less Serious | Serious | | |
| **ACUTE EXPOSURE** | | | | | | | |
| **Death** | | | | | | | |
| Rat (Sherman) | NS | | | | >2000 mg/kg | (LD50) | Gaines 1969 |
| Rabbit (NS) | NS | | | | 410 mg/kg | (LD50 - Male) | Larson et al. 1979b |

$LD_{50}$ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-level; NS = not specified

**Hematological Effects.** No studies were located regarding hematological effects in humans after dermal exposure to mirex or chlordecone.

The only information located regarding hematological effects of mirex in animals was found in a study in which an unspecified amount of mirex was applied to the skin of rabbits for 9 weeks, 5 days/week, for 6-7 hours/day (Larson et al. 1979a). Hematological analyses from these rabbits revealed no compound-related effects.

No studies were located regarding hematological effects in animals after dermal exposure to chlordecone.

**Renal Effects.** No studies were located regarding renal effects in humans after dermal exposure to mirex or chlordecone.

The only information located regarding the renal effects of mirex in experimental animals was found in a study in which an unspecified amount of mirex was placed in contact with the skin of rabbits for 6-7 hours/day, 5 days/week, for 9 weeks (Larson et al. 1979a). Routine urinalyses revealed no compound-related effects on the kidneys.

No studies were located regarding renal effects in animals after dermal exposure to chlordecone.

**Dermal Effects.** No studies were located regarding dermal effects in humans after dermal exposure to mirex. Eighty-nine of the 133 workers interviewed as a result of intermediate- or chronic-duration exposures to high levels of chlordecone during its manufacture experienced skin rashes of an erythematous, macropapular nature at some time during their exposure (Cannon et al. 1978). Among 23 workers with blood chlordecone levels in excess of 2 μg/L, 6 men reported exposure-related rashes (Taylor et al. 1978). It is likely that these rashes were the direct result of dermal exposure. However, insufficient information was given to eliminate the possibility of a systemic effect resulting from derrnal exposure.

Dermal exposure of mice to 3.6 mg/kg of mirex, three times/week for 4 weeks, resulted in mild epidermal proliferation (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 reported to be reversible after 2 days without treatment. No signs of dermal irritation were observed in rabbits exposed to varying amounts of a 20% solution of chlordecone in corn oil (Larson et al. 1979b).

### 2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to mirex or chlordecone.

### 2.2.3.4 Neurological Effects

The neurological effects observed after occupational exposure to chlordecone were described in Section 2.2.1.4 (Cannon et al. 1978; Martinez et al. 1978; Sanbom et al. 1979; Taylor 1982, 1985; Taylor et al. 1978). Dermal exposure to chlordecone probably constituted a major route of such occupational exposures. Section 2.2.1.4 contains a complete description of the neurological effects associated with occupational exposure to chlordecone. No additional studies were located regarding neurological effects in humans or animals after dermal exposure to mirex or chlordecone.

### 2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to mirex. The available data in humans indicate that chlordecone causes male reproductive effects. Occupational exposure to chlordecone for up to 1.5 years caused oligospermia and decreased sperm motility in male workers. However, there were no reported infertility in these male subjects despite loss of sperm motility in some workers (refer to Section 2.2.1.5 for further details).

No studies were located regarding reproductive effects in animals after dermal exposure to mirex. 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 at dose levels of 5 or 10 mg/kg for 8 hours/day, 5 days/week, for 3 weeks induced testicular atrophy in two of six rabbits at 5 mg/kg and in one of six rabbits 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.

### 2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to mirex or chlordecone. Although impaired spermatogenesis among male workers exposed to chlordecone was not reported to have affected their fertility (Guzelian 1982a; Taylor 1982, 1985; Taylor et al. 1978), it is unclear whether sperm abnormalities resulted in developmental effects in offspring. A follow-up of workers with initially lowered sperm levels did not indicate an increase in birth defects among offspring (Taylor 1982, 1985).

No studies were located regarding developmental effects in animals after dermal exposure to mirex or chlordecone.

### 2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to mirex or chlordecone.

Genotoxicity studies are discussed in Section 2.4.

### 2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to mirex or chlordecone. In animals, mirex has been shown to be a nonmutagenic hepatocarcinogen (see Sect. 2.2.2.7, 2.2.2.8, 2.4). In animal studies, mirex, was tested at a dermal dose of 3.6 mg/kg 4 weeks in female CD-l mice for tumor promoter activity and evidence of epidermal hyperplasia after initiation with 200 nmol/day 7,12-dimethyl-benz[a]anthracene (DMBA) for 1 week. 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 were treated with both 3.6 mg/kg mirex and 2 nmol/day TPA for 4 week following initiation with DMBA. Multiple applications of mirex for 4 weeks to the DMBA-initiated mice resulted only in minimal increase 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 give 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 (Meyer et al. 1993, Moser et al. 1992, 1993). 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 also 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-l mice than in male CD-l mice or OVX mice (Meyer et al. 1994).

## 2.3 TOXICOKINETICS

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

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

The specific mechanisms by which mirex and chlordecone are transferred from the gut, lungs, or skin to the blood are not known. However, mirex is a highly stable, lipophilic compound that is resistant to metabolism. It has a high 1ipid:water partition coefficient, so it partitions readily into fat and demonstrates a very high potential for accumulation in tissues. The preferential distribution of chlordecone to the liver rather than to the fat tissue is due to its association with plasma proteins.

### 2.3.1 Absorption

#### 2.3.1.1 Inhalation Exposure

No data were located regarding absorption of mirex in humans after inhalation exposure.

Very limited data show that inhaled mirex can be rapidly absorbed into the blood of rats (Atallah and Dorough 1975; Dorough and Atallah 1975). The fate of [$^{14}$C] mirex in cigarette smoke in rats was assessed using a smoking device (Atallah and Dorough 1975; Dorough and Atallah 1975). Eight 5-mL puffs were administered to the trachea of rats at 15-second intervals. Two to four minutes after inhalation, 47% of the radiolabel was exhaled, 36% was found in the lung, 11% was in the blood, and 1% was in the heart. No quantitative conclusions regarding absorption in humans following inhalation can be drawn from this assay since the relationship of the inhalation parameters of the rat to normal human breathing was not determined.

Chlordecone is absorbed following occupational exposure (Cannon et al. 1978; Cohn et al. 1978; Taylor 1982, 1985). Mean blood levels of workers exposed to chlordecone at a manufacturing plant in Hopewell, Virginia, were 2.53 ppm for workers manifesting illness (nervousness or unfounded anxiety; pleuritic chest pain; weight loss of up to 60 pounds in 4 months; visual difficulties; skin rashes of an erythematous, macropapular nature) and 0.6 ppm for workers with no illness (Cannon et al. 1978). Two months following cessation of exposure, blood levels in workers were in excess of 2 ppm (Taylor 1982, 1985). Following exposure in humans, mean half-lives of 96 days (range of 63-148 days) (Adir et al. 1978) and 165 days (Cohn et al. 1978) in blood have been reported for chlordecone. This relatively long half-life may be due to the high degree of lipid solubility and limited metabolism of chlordecone.

No studies were located regarding absorption in animals after inhalation exposure to chlordecone.

### 2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to mirex.

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

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

Mirex rapidly entered the maternal bloodstream of pregnant rats dosed orally with 5 mg/kg of mirex on gestation days 15, 18, or 20 (Kavlock et al. 1980). Four hours after oral dosing on gestation day 15, the plasma concentration of mirex was 13 ppm. Mirex plasma concentrations were significantly affected by both the time of administration and the hour of observation ($p<0.01$). Higher plasma concentrations were found at older gestation ages (13 ppm on gestation day 15, compared to 23 ppm on gestation day 20, measured 4 hours after administration). Plasma concentrations declined with time after dosing (Kavlock et al. 1980).

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

As noted in Section 2.3.1.1, chlordecone is absorbed after occupational exposure (Cannon et al. 1978; Cohn et al. 1978; Taylor 1982, 1985). Although the route of exposure was not specified, hygiene at the workplace was extremely poor and unintentional ingestion of chlordecone was possible. For a description of the absorption of chlordecone following occupational exposure see Section 2.3.1.1.

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

### 2.3.1.3 Dermal Exposure

No data were located regarding absorption of mirex in humans or animals after dermal exposure. As noted in Section 2.3.1.1, studies have shown that chlordecone is absorbed after occupational exposure (Cannon et al. 1978; Cohn et al. 1978; Taylor 1982, 1985). Although the route of exposure was not specified in the studies, dermal exposures probably constituted a major portion of the exposure in these occupational situations. For a description of the absorption of chlordecone following occupational exposure see Section 2.3.1.1.

Chlordecone is absorbed to a limited extent following dermal exposure in rats (Hall et al. 1988; Shah et al. 1987). The percent of dose absorbed was determined by dividing the radioactivity in the body (carcass) and in the excreta by the total radioactivity recovered (in carcass, excreta, treated skin, and washes of the application materials). The results showed that fractional absorption decreased as the dose of chlordecone increased. At 72 hours after exposure to 0.29, 0.54, or 2.68 μmol $^{14}$C-chlordecone/cm$^2$, skin penetration of chlordecone in young rats was 10.17%, 7.23%, and 1.93%, respectively, of the applied dose. Skin penetration of chlordecone in adult rats at 72 hours was 9.2%, 5.96%, and 1.03% for the low-, middle-, and high-dose groups, respectively. The area of application when expressed as the percentage of the total surface area (≈2.3%) was the same in both young and adult rats. The actual amount of chlordecone absorbed per cm$^2$ (0.03 pmol/cm$^2$) was similar for all dose groups suggesting that saturation occurred at the low dose. No significant age-dependent differences in dermal absorption were seen.

## 2.3.2 Distribution

### 2.3.2.1 Inhalation Exposure

Mirex has been found in human adipose tissue (Burse et al. 1989; Kutz et al. 1974). Although the route of exposure was not specified, exposure was probably via the inhalation, oral, and dermal routes. Levels of 0.16-5.94 ppm and 0.3-l .13 ppm in males and females, respectively, were found in tissue samples taken either from postmortem examinations or during surgery (Kutz et al. 1974). The adipose tissue samples came from individuals who lived in areas in which mirex was used extensively in a

program to control fire ants. Adipose tissue levels of mirex ranging from 0.03 to 3.72 ppm have been found in residents living near a dump site in Tennessee (Burse et al. 1989).

Only very limited animal data were located regarding the distribution of mirex following inhalation exposure (Atallah and Dorough 1975; Dorough and Atallah 1975). Mirex was found in the lungs (36%), blood (11%), and hearts (1%) of rats exposed to mirex in cigarette smoke (Atallah and Dorough 1975; Dorough and Atallah 1975). The exposure concentration was not reported.

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

No studies were located regarding distribution in animals following inhalation exposure to chlordecone.

#### 2.3.2.2 Oral Exposure

Mirex has been found in human adipose tissue (Burse et al. 1989; Kutz et al. 1974). Although the route of exposure is not specified, these individuals were probably exposed via the inhalation, oral, and dermal routes. Levels of 0.16-5.94 ppm and 0.3-l .13 ppm in males and females, respectively, were found in tissue samples taken either from postmortem examinations or during surgery (Kutz et al. 1974). The adipose tissue samples came from individuals who lived in areas where mirex was used extensively in a program to control fire ants. Adipose tissue levels of mirex ranging from 0.03 to 3.72 ppm have been found in residents living near a dump site in Tennessee (Burse et al. 1989).

Following oral dosing in animals, mirex is distributed to various tissues and sequestered in the fat. Females generally accumulated greater amounts than males. Mirex demonstrated an affinity for lipids

in rats given a single oral dose of mirex (0.2 mg/kg) (Chambers et al. 1982; Gibson et al. 1972). Male and female rats given a single oral dose of 0.2 mg/kg mirex also accumulated the highest concentrations in the fat (Chambers et al. 1982; Gibson et al. 1972). The levels in fat of females were approximately two times higher than levels measured in the fat of males (Chambers et al. 1982). For females, mirex levels in the fat ranged from 338 to 944 ng/g at 7 days and increased to 483-1,043 ng/g at 14 days (Chambers et al. 1982). For males, mirex levels in fat ranged from 161 to 479 ng/g at 7 days and from 419 to 530 ng/g at 14 days (Chambers et al. 1982). Mirex also accumulated in the nervous tissue, with females accumulating higher amounts than males (Chambers et al. 1982). Accumulation of mirex in the nervous tissue in females peaked at 7 days (40-59 ng/g) and then decreased from 7 to 14 days (Chambers et al. 1982). Mirex levels in the nervous tissue of males ranged from 13.2 to 28 ng/g at 7 days post-dosing and decreased from 7 to 14 days (Chambers et al. 1982). Mirex accumulated in various other tissues of both males and females, including gastrointestinal tract, liver, lung, heart, kidney, adrenals, brain, skeletal muscle, spleen, and thymus (Chambers et al. 1982; Gibson et al. 1972).

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

Mirex was detected in the brains of male rats within 0.5-2 hours after receiving a single oral dose of 100 mg/kg mirex (Brown and Yarbrough 1988). By 96 hours, the following concentrations (μm01 $^{14}$C-mirex/g) were measured in the brain regions: cerebral cortex (0.47), cerebellum (0.50), brain stem

(0.73), and spinal cord (0.75). Mirex was also distributed to the liver, kidneys, testes, and omental fat. Peak tissue concentrations of mirex in the kidneys, testes, liver, and omental fat occurred 12, 48, 48, and 96 hours post-dosing, respectively. Following a single oral dose of 50 mg/kg mirex to mice, mirex was distributed to the brain (Fujimori et al. 1982a). Mirex levels in the striatum and medulla/pans were significantly higher than in the cortex, midbrain, or cerebellum ($p<0.05$) 48 hours post-dosing (Fujimori et al. 1982a). However, at 6, 12, and 96 hours, discrete brain area levels of mirex did not differ significantly. Mirex levels in whole brain and plasma were 3-40 times lower than levels found in chlordecone-treated mice (Fujimori et al. 1982a). Mirex showed less-specific distribution in discrete areas of the brain than did chlordecone (Fujimori et al. 1982a). Samples of brain tissue from rats fed 0, 0.089, or 0.89 mg/kg/day for 34-49 days showed that mirex accumulates in rat brain tissue in a dose-dependent manner (Thome et al. 1978). Mirex levels in brain tissue were 7-8 times higher in the high-dose group than in the low-dose group (Thorne et al. 1978).

Mirex accumulates in maternal tissues, readily crosses the placenta of animals, and accumulates in fetal tissues (Kavlock et al. 1980; Khera et al. 1976). Maximum concentrations of mirex found in the placenta of rats ranged from 3.5 to 4 ppm at 4 hours post-dosing (Kavlock et al. 1980). Mirex levels in the placenta 48 hours after dosing were less than 50% of the 4-hour level (Kavlock et al. 1980). The uptake of mirex by fetal organs was in the order of liver > brain = heart > kidney in a ratio of 3:2:2:1 (Kavlock et al. 1980). Mirex concentrations in the fetuses remained low at 4 hours after dosing, increased slightly at 24 hours, and decreased thereafter (Kavlock et al. 1980). The decline noted in the second 24-hour period was due to both organ growth and mirex elimination (Kavlock et al. 1980). Mirex accumulated in maternal and fetal tissues at all dose levels (1.5, 3, 6, 12.5 mg/kg given on gestation days 6-15) (Khera et al. 1976). Fetal brain levels were more than three times higher (31.5 ppm) than mean maternal brain levels (8.87 ppm) at 12.5 mg/kg. All other mean fetal tissue values were lower than mean maternal values (Khera et al. 1976). The highest maternal levels of mirex were found in the fat, indicating the potential for long-term sequestering of the compound (Khera et al. 1976).

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

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

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

As indicated in Section 2.3.2.1, occupational exposure studies have shown that chlordecone is absorbed and distributed to various tissues and has a long retention time in the body (Cannon et al. 1978; Cohn et al. 1978; Taylor 1982, 1985). Because of the poor hygiene practices at the workplace studied, ingestion of the chlordecone was also likely by the workers in these studies. For a more complete discussion of the distribution of chlordecone after occupational exposure see Section 2.3.2.1.

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

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

Studies show that pretreatment with an inducer (phenobarbital) or inhibitor (SKF-525A) of P-450 causes an alteration in the distribution of chlordecone in rats (Aldous et al. 1983). Following a single oral dose of chlordecone alone, the liver had the highest levels of chlordecone, followed by the adrenal gland, lung, kidney, and spinal cord (Aldous et al. 1983). Pretreatment with phenobarbital (particularly with multiple phenobarbital doses) caused an increase in the accumulation of chlordecone in the liver compared to animals given no pretreatment. This hepatic increase resulted in a significant decrease of chlordecone levels in other tissue (e.g., brain, kidney, muscle) as well as significantly reduced excretion. Pretreatment with SKF-525A caused a nonsignificant reduction in chlordecone levels in the liver and significant increases in the digestive system tissues. The results of the chlordecone distribution following SKF-525A pre-dosing must be interpreted with caution, since the effects may have resulted partly from SKF-525A-mediated decreases in absorption of the chlordecone (Aldous et al. 1983).

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

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

Chlordecone accumulates in maternal tissues, readily crosses the placenta of rats, and accumulates in fetal tissues (Chernoff et al. 1979a; Kavlock et al. 1980). Four hours following a single oral dose of 5 mg/kg, maximal concentrations of chlordecone in the placenta ranged from 3.5 to 4 ppm (Kavlock et al. 1980). Concentrations of chlordecone in the placenta remained steady for up to 48 hours postdosing. Chlordecone levels in the fetus were generally highest in the liver, followed by the brain, heart, and kidney. Concentrations increased during the first 24 hours after dosing and declined in the second 24-hour period, regardless of gestation age at the time of dosing (Kavlock et al. 1980). Chlordecone levels found in maternal and fetal tissues were slightly higher than the levels of mirex following administration of equal doses (Kavlock et al. 1980). The livers of weanling rats fed diets of 0.05 mg/kg chlordecone or mirex for 28 days accumulated higher levels of chlordecone (6.1 ppm) than mirex (0.89 ppm) (Chu et al. 1980a). Possible explanations for this are that mirex is more poorly absorbed from the feed than is chlordecone or that the absorbed dose of mirex accumulates in the liver to a lesser extent than chlordecone (Chu et al. 1980a).

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

#### 2.3.2.3 Dermal Exposure

Mirex has been found in human adipose tissue (Burse et al. 1989; Kutz et al. 1974). Although the route of exposure is not specified, exposure was probably via the inhalation, oral, and dermal routes. Levels of 0.16-5.94 ppm and 0.3-1.13 ppm in males and females, respectively, were found in tissue samples taken during postmortem examinations or during surgery (Kutz et al. 1974). The adipose tissue samples came from individuals who lived in areas in which mirex was used extensively. Levels of mirex in adipose tissue ranging from 0.03 to 3.72 ppm have been found in residents living near a dump site in Tennessee (Burse et al. 1989). No other studies were located regarding distribution in humans or animals following dermal exposure to mirex.

As indicated in Section 2.3.2.1, studies in workers occupationally exposed to chlordecone have shown that it is absorbed, distributed to various tissues, and has a long retention time in the body (Cannon et al. 1978; Cohn et al. 1978; Taylor 1982, 1985). Since dermal exposures probably constituted a major

portion of the exposure in these occupational studies, information presented in Section 2.3.2.1 is also applicable here. No studies were located regarding distribution in animals after dermal exposure to chlordecone.

### 2.3.2.4 Other Routes of Exposure

Mirex is rapidly absorbed and distributes to the plasma and liver after intraperitoneal injection. Peak concentrations were seen at 3 hours in the plasma and 6 hours in the liver following single or multiple doses of mirex (4 mg/kg) injected intraperitoneally into mice (Charles et al. 1985). Significant amounts were rapidly taken up by the liver (21-29%) within the first 3-6 hours. Plasma-to-liver ratios were low (<l) indicating an increased influx of the chemical into the tissue. Mirex decay curves for plasma and liver for 72 hours showed a biphasic pattern that consisted of a rapid phase (up to 24 hours) and a slow phase (24-72 hours) (Charles et al. 1985). For plasma, the half-lives were 9.2 and 62.8 hours for the rapid and slow phases, respectively. For liver, the half-lives for the slow and rapid phases were 12.1 and 62.4 hours, respectively (Charles et al. 1985).

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

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

## 2.3.3 Metabolism

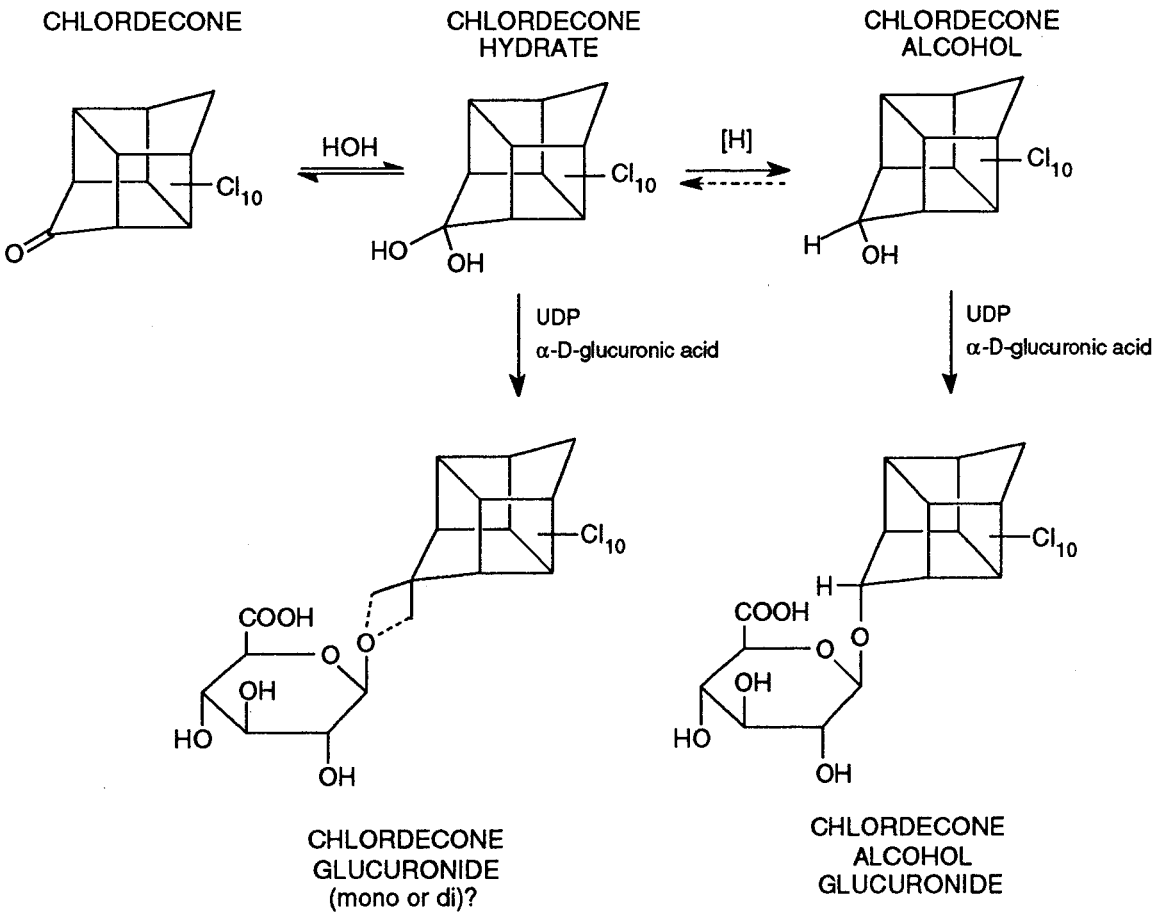
Radiolabeling experiments showed that mirex is not metabolized in humans, rodents, cows, or minipigs; the parent compound was the only radiolabeled compound present in the plasma, fat, and feces (Dorough and Ivie 1974; Gibson et al. 1972; Kutz et al. 1974; Mehendale et al. 1972; Morgan et

al. 1979). However, a monohydro derivative of mirex was identified in the feces, but not the fat or plasma, of rhesus monkeys given an oral or intravenous dose of mirex (Pittman et al. 1976; Stein et al. 1976; Wiener et al. 1976). It is believed that the suspected metabolite may have arisen as a result of bacterial action in the lower gut or in the feces (Stein et al. 1976).

The potential for *in vivo* conversion of mirex to chlordecone was also examined (Morgan et al. 1979). Chlordecone was not detected in the tissues; therefore, no evidence was found of *in vivo* conversion (Morgan et al. 1979).

The fate of chlordecone in humans involves uptake by the liver, enzymatic reduction to chlordecone alcohol, conjugation with glucuronic acid, partial conversion to unidentified polar forms, and excretion of these metabolites mainly as glucuronide conjugates into bile (Fariss et al. 1980; Guzelian et al. 1981) (see Figure 2-3). Of the total chlordecone measured in bile of occupationally exposed workers, the predominant portion (72%) was unconjugated, with only a small portion conjugated with glucuronic acid or sulfate (9%) (Fariss et al. 1980). The remaining fraction (19%) of total chlordecone measured in the bile was stable polar metabolites which were resistant to β-glucuronidase. Following treatment of bile with β-glucuronidase plus sulfatase, the ratio of total chlordecone to total chlordecone alcohol was 1:3 in human bile (Fariss et al. 1980). Bioreduction of chlordecone to chlordecone alcohol is species-specific since rats treated orally or intraperitoneally with chlordecone produced no chlordecone alcohol in the feces, bile, or liver (Fariss et al. 1980; Guzelian et al. 1981; Houston et al. 1981). Following treatment of bile with β-glucuronidase plus sulfatase, the ratio of total chlordecone to total chlordecone alcohol in rat bile was in excess of 150:l for orally exposed rats (Fariss et al. 1980; Guzelian et al. 1981). Guinea pigs and hamsters given an intraperitoneal dose of 20 mg/kg chlordecone also did not convert chlordecone to chlordecone alcohol, as indicated by the fact that no chlordecone alcohol was detected in the feces, bile, or liver (Houston et al. 1981). Therefore, rats, guinea pigs, and hamsters are not good animal models for predicting chlordecone metabolism in humans because they do not convert chlordecone to chlordecone alcohol (Fariss et al. 1980; Guzelian et al. 1981; Houston et al. 1981). Gerbils were found to be the most suitable animal model of chlordecone metabolism in humans because only gerbils converted chlordecone to its alcohol (Houston et al. 1981). Reduction of chlordecone is catalyzed in gerbil liver by a species-specific reductase, chlordecone reductase. This chlordecone reductase was characterized in gerbil liver cytosol *in vitro* and determined to be of the “aldo-keto reductase” family (Molowa et al. 1986b). It is specific to gerbils and humans (Molowa et al. 1986b). Like humans, chlordecone-treated gerbils excreted

## FIGURE 2-3. Proposed Metabolic Pathways for Chlordecone




Derived from Fariss, Blanke, Saady et al. 1980

chlordecone alcohol exclusively in the stool and not in the urine (Houston et al. 1981). Following intraperitoneal dosing of 20 mg/kg $^{14}$C-chlordecone, the ratio of chlordecone to chlordecone alcohol in the bile of gerbils was approximately 2.5: 1. No quantitative estimate of the extent to which chlordecone was metabolized was reported. Following treatment of bile with β-glucuronidase plus acid hydrolysis, the ratio of chlordecone to chlordecone alcohol in the bile was 1:2, indicating that chlordecone is present in the bile largely in the form of its glucuronide conjugate (Houston et al. 1981). Incubation of chlordecone with the cytosolic fraction of gerbil liver homogenate in the presence of NADPH produced chlordecone alcohol (Houston et al. 1981). Reduction and conjugation of chlordecone also occur in pigs (Soine et al. 1983). Chlordecone is biotransformed in pigs to conjugated chlordecone, chlordecone alcohol, and conjugated chlordecone alcohol, which are excreted in the bile and eliminated in the feces (Soine et al. 1983). The high levels of chlordecone alcohol and conjugated chlordecone alcohol in the bile and the absence of these metabolites in the plasma and liver suggest that chlordecone alcohol is formed and conjugated in the liver and excreted into the bile (Soine et al. 1983).

### 2.3.4 Excretion

#### 2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to mirex or chlordecone.

#### 2.3.4.2 Oral Exposure

Limited data indicate that mirex is excreted in human milk; it was identified in 3 of 14 human milk samples obtained from Canadians (Mes et al. 1978). The dose was not reported. However, the exposure was assumed to be chronic in nature, and the route of exposure was proposed to be through the diet or skin contact (Mes et al. 1978). No other studies were located.

In animals, mirex is excreted unchanged mainly in the feces; urinary excretion is negligible (Byrd et al. 1982; Chambers et al. 1982; Gibson et al. 1972; Ivie et al. 1974b). Female rats receiving a single oral dose of $^{14}$C-mirex (0.2 mg/kg) excreted 18% of the total administered dose in the feces (Gibson et al. 1972). Very little was excreted in the urine (0.3% of the total dose) during the 7-day period. Of

the total quantity eliminated, 85% was excreted in the feces within the first 48 hours. This percentage represents unabsorbed material. The virtual lack of urinary excretion and the fact that fecal excretion was only about 3% of the administered dose after the initial 48 hours suggest that mirex is not metabolized in rats and that the absorbed portion is only slowly excreted (Gibson et al. 1972). Cumulative fecal excretion was 18-45% 21 days after female rats were given a single oral dose of 10 mg/kg mirex (Byrd et al. 1982). Most of the fecal mirex was excreted within 48 hours and represented unabsorbed mirex (Byrd et al. 1982). A biological half-life of mirex was estimated to be 460 days by a model developed to simulate mirex pharmacokinetics after oral administration (Byrd et al. 1982). Male rats receiving a single oral dose of 6 mg/kg excreted 58.5% of the administered dose in the feces 7 days after administration (Mehendale et al. 1972). Fifty-five percent of the administered dose was excreted in the feces within the first 48 hours post-dosing and probably represented unabsorbed dose from the gut (Mehendale et al. 1972). Only 0.69% of the administered dose was excreted in the urine (Mehendale et al. 1972). Mirex was the only compound identified in the urine or feces (Mehendale et al. 1972). A half-life of 38 hours was estimated based on the first rapid elimination (Mehendale et al. 1972). A second half-life was projected to be >l00 days, indicating a very slow rate of elimination from the body (Mehendale et al. 1972).

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

Another route of elimination is via milk. The secretion of mirex in milk was a major route of elimination for nursing dams given either 1 or 10 mg/kg of mirex on days 2-5 postpartum (Kavlock et al. 1980). The dams excreted 11,000 μg of mirex via the milk during the entire lactation period. This represents 95% of the total amount of mirex administered. Mirex entered the milk supply more quickly than chlordecone. Greater amounts of mirex were excreted via the milk as compared with chlordecone because of the octanol-water partition coefficient (Kavlock et al. 1980). Mirex was also excreted in the milk of lactating goats given daily doses of 1 mg/kg for 18 or 61 weeks followed by daily doses of 10 mg/kg for 4 weeks (Smrek et al. 1977). The concentration of mirex in colostrum fat ranged from 16 to 20 ppm. Colostrum, which is fluid secreted for the first few days after parturition, is characterized by high protein and antibody content. Over 8 weeks, the levels of mirex in milk fat

decreased to less than half the amount excreted in colostrum immediately after birth of the kids. The goats eliminated more mirex in colostmm than in regular milk. A lactating Jersey cow given a daily dose equivalent to 0.005 mg/kg/day in the diet for 28 days, excreted 50% of the administered dose in the feces during the 28-day exposure period (Dorough and Ivie 1974). Only approximately 3% of the administered dose of mirex was excreted in the feces in the 28 days after treatment ended. These results show that the radioactivity in the feces represents unabsorbed mirex, and that the turnover rate of mirex stored in the tissues is very low. In this study, mirex was also found in cow's milk. About 10% of the administered dose was excreted in the milk 10 days after treatment began. Cumulative excretion in the milk was 13% after 28 days of exposure. Only 2% of the administered dose was excreted in the milk during the entire 28-day post-treatment period. The levels of mirex in milk equilibrated after 1 week of treatment, with the concentration in whole milk being 0.058 ppm. One week after treatment ended, the residues in the milk dropped to 0.006 ppm and then declined to 0.002 ppm after 28 days (Dorough and Ivie 1974). Mirex was the only compound identified in the feces and cow's milk.

Chlordecone and chlordecone alcohol (chlordecol) are excreted in the bile and eliminated via the feces of humans occupationally exposed to chlordecone (Blanke et al. 1978; Boylan et al. 1979; Cohn et al. 1978; Guzelian et al. 1981). However, a substantial enterohepatic recirculation of chlordecone exists that curtails its excretion (Boylan et al. 1979; Cohn et al. 1978; Guzelian et al. 1981). Only 5-10% of the biliary chlordecone entering the lumen of the duodenum appeared in the feces (Cohn et al. 1978; Guzelian et al. 1981). Similarly, the rate of chlordecone excretion in the bile was on the average 19 times greater than the rate of elimination of chlordecone in the stool (Cohn et al. 1978). Chlordecone was not detected in the sweat and was detected in only minor quantities in urine, saliva, and gastric juice (Cohn et al. 1978). Similarly, stool contained 11-34% of the quantities excreted in bile for workers exposed for 6 months (Boylan et al. 1979). When biliary contents were diverted, fecal excretion of chlordecone alcohol fell to low or undetectable levels; however, chlordecone excretion in feces persisted, suggesting a nonbiliary mechanism for the excretion of chlordecone into the intestine and feces (Boylan et al. 1979). Analogous experiments with rats gave similar results (Boylan et al. 1979). With no bile in the gut, the average amount of chlordecone in the human stool in two 72-hour collections was eight times as great as with the biliary circuit intact (Boylan et al. 1979). This suggests that bile may suppress nonbiliary excretion of chlordecone (Boylan et al. 1979). When bile was completely diverted from the intestines of rats, however, fecal excretion of radiolabel -was unchanged (Boylan et al. 1979).

Chlordecone, chlordecone alcohol, and their glucuronide conjugates were identified in human bile of occupationally exposed workers (Guzelian et al. 1981). Of the total chlordecone measured in bile, most (72%) is unconjugated, a small amount (9%) is conjugated with glucuronic acid, and the final portion (19%) is present as an uncharacterized “acid releasable” form (Guzelian et al. 1981). However, only a minor amount of chlordecone alcohol (<10%) was present in bile as the free metabolite. The remainder was conjugated with glucuronide (Guzelian et al. 1981).

In rats, chlordecone is slowly eliminated in the feces (Egle et al. 1978). Rats given a single oral dose of 40 mg/kg $^{14}$C-chlordecone excreted 65.5% of the administered dose in the feces and 1.6% of the dose in the urine by 84 days (Egle et al. 1978). Less than 1% of the administered dose was expired as radiolabeled carbon dioxide ($^{14}$ C-$CO^2$) (Egle et al. 1978). Rats fed $^{14}$C-chlordecone (0.2 mg/kg/day for 3 days) excreted 52.16% of the radioactivity in the feces .and 0.52% in the urine 25 days post-dosing (Richter et al. 1979).

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

Chlordecone is also excreted in the milk of nursing rats (Kavlock et al. 1980). Dams excreted 6,000 μg of chlordecone via the milk during the entire lactation period. This represents 52% of the total amount of chlordecone administered. When compared with mirex-treated rats, chlordecone entered the milk supply more slowly than mirex. More mirex was excreted via the milk than chlordecone because of a higher octanol-water partition coefficient.

### 2.3.4.3 Dermal Exposure

Mirex is excreted in human milk. Mirex was identified in 3 of 14 milk samples obtained from Canadian women (Mes et al. 1978). The dose was not reported, but exposure was assumed to be of chronic duration via the diet or via dermal contact (Mes et al. 1978).

No studies were located regarding excretion of mirex in animals following dermal exposure.

Chlordecone and chlordecone alcohol (chlordecol) are excreted in the bile and eliminated in the feces of humans occupationally exposed to chlordecone (Blanke et al. 1978; Boylan et al. 1979; Cohn et al. 1978; Guzelian et al. 1981). See Section 2.3.4.2 for more details.

No studies were located regarding excretion of chlordecone in animals following dermal exposure.

### 2.3.4.4 Other Routes of Exposure

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

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

Chlordecone appeared in the bile within l-3 hours after intravenous dosing of rats (0.1, 1, or 10 mg/kg) (Bungay et al. 1981). The average concentration of chlordecone in the bile varied linearly with dose: 0.051, 0.50, and 5 μg/g in the low-, middle-, and high-dose groups, respectively (Bungay et

al. 1981). Rats given a single intravenous dose of 1 mg/kg had a chlordecone excretion rate in the bile of 0.22% of the dose per hour (Bungay et al. 1981).

### 2.3.5 Mechanisms of Action

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 1ipid:water partition coefficient (HSDB 1994a, 1994b), so it partitions readily to fat and demonstrates a very high potential for accumulation in tissues (Chambers et al. 1982; Ivie et al. 1974b).

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 verylow-density lipoproteins (VLDL) and low-density lipoproteins (LDL) and distribute preferentially to fat (Soine et al. 1982).

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. 1980a, 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 to 100 mg/kg/day and 50 to 100 mg/kg/day, respectively) thereby inhibiting the biliary excretion of substances. The inhibition does not appear to be due to inhibition of the metabolism of the substance to be excreted in the bile or to decreased bile flow (Mehendale 1977c). 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 mg2+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 (CNS) dopaminergic or a-noradrenergic activity in expression of hypothermia. The decrease in body temperature produced by chlordecone was mimicked by intracistemal norepinephrine (Cook et al. 1988a, 1988b) and was blocked by administration of a-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).

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 dichlorodiphenyldichloroethane (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, 1986b). 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 tremongenic doses of chlordecone (Brown et al. 1991; Chen et al. 1985; Hong et al. 1984; Tilson et al. 1986b; Uphouse and Eckols 1986). However, dopamine (Desaiah 1985; Fujimori et al. 1982b) 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, 1989c; Vig et al. 1990b, 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. 1980a, 1980b; Folmar 1978; Jinna et al. 1989; Singh et al. 1984), oligomycin-sensitive $mg^{2+}$ATPase (Chetty et al. 1983b; Desaiah et al. 1980a, 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 coincident with the changes in intracellular calcium.

The mechanism underlying many of the adverse effects of chlordecone on reproductive function is believed to be due 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). The differential sensitivity of these tissues may explain the failure of chlordecone to completely mimic estrogen in functions mediated by central nervous system estrogen receptors.

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).

In animal studies, mirex (a nonmutagenic hepatocarcinogen) promoted mouse skin squamous carcinomas and papillomas after initiation with 7,12-dimethyl-benz[a]anthracene (DMBA) for 1 week. Mirex, also, potentiated the promotional potency of the phorbol ester tumor promoter, 12-*O*-tetradecanoylphorbol- 13-acetate (TPA). There was a 90% incidence (activation) of the c-Ha-ras tumor gene in these co-promoted tumors. When both mirex and TPA 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. Thus, 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 (Meyer et al. 1993, 1994; Moser et al. 1992, 1993).

## 2.4 RELEVANCE TO PUBLIC HEALTH

People living in areas surrounding hazardous waste sites may be exposed to mirex or chlordecone primarily via dermal contact with or ingestion of contaminated soil since these compounds bind to soil particles. The other major means of exposure for people living near hazardous waste sites is ingestion of indigenous wildlife since mirex and chlordecone are bioconcentrated in fish and animals. Although mirex or chlordecone can be found adsorbed to soil particles suspended in uncontaminated water, ingestion of these chemicals in drinking water is unlikely because of their limited solubility in water. Similarly, inhalation exposure to mirex or chlordecone following volatilization from contaminated

media is not likely to be a major route of exposure since these chemicals are essentially nonvolatile. For the general population, the most likely route of exposure to mirex or chlordecone is via ingestion of residues on contaminated food. Both of these chemicals are excreted very slowly and bioaccumulate in the body after exposure.

Although mirex and chlordecone are structurally very similar (differing only in the replacement of two bridgehead chlorine atoms on the mirex molecule with a carbonyl oxygen on the chlordecone molecule), significant differences exist in the toxicity profiles of these two chemicals. Therefore, mirex and chlordecone will be discussed separately below.

No information was located regarding toxicity of mirex in humans, but animal studies indicate that mirex exposure may result in a variety of adverse health effects in exposed populations. The primary organs affected by mirex in experimental animals are the liver, kidneys, eyes, and thyroid. In the liver, mirex causes adaptive changes similar to those seen with other chlorinated hydrocarbon insecticides as well as decreased hepatobiliary function and decreased glycogen storage. In the kidneys, an increase in glomerulosclerosis and proteinuria have been observed. Ocular lesions include the development of cataracts in the eyes of the young if exposure occurs during a critical period immediately after birth. In the thyroid, an increase in cystic follicles or a collapse of follicles has been observed. Decreased fertility and marked developmental toxicity have been observed following exposure to mirex. Mirex exposure results in testicular atrophy and reproductive failure. Adverse developmental effects seen in fetuses following maternal exposure to mirex include cataracts, cardiovascular disturbances, visceral anomalies, increased resorptions, and increased stillbirths. Also, mirex is a liver carcinogen in animals.

Studies in humans exposed occupationally to chlordecone demonstrate toxic effects on the nervous system, liver, and reproductive system. Tremors, unfounded anxiety or irritability, blurring of vision, headache, and increases in cerebrospinal fluid pressure were found in workers exposed to high levels of chlordecone during its manufacture. In addition, several workers had hepatomegaly, evidence of increased microsomal enzyme activity, mild inflammatory changes, and fatty degeneration. Reproductive toxicity consisted of decreased sperm and sperm motility. Studies in animals have supported these findings and, in addition, have demonstrated adverse effects of chlordecone on the kidney and thermoregulation. Animal studies also show effects on the female estrous cycle, uterus, and ovaries and decreased viability and development of fetuses. Liver cancer has also been observed

in animal studies. Animal studies have also demonstrated the potential for greatly potentiated hepatotoxicity of haloalkanes such as carbon tetrachloride after exposure to chlordecone.

## Minimal Risk Levels for Mirex and Chlordecone

### *Inhalation MRLs*

No inhalation MRLs were derived for either mirex or chlordecone because of the absence of reliable data following inhalation exposure.

### *Oral MRLs*

No acute-duration oral MRL was derived for mirex because serious effects (arrhythmias in neonatal pups from maternal exposure during gestation) were observed at the lowest dose tested (0.1 mg/kg/day) (Grabowski 1983a).

- An MRL of 0.01 mg/kg/day has been developed for acute-duration oral exposure (14 days or less) to chlordecone.

This MRL for chlordecone is based on a NOAEL of 1.25 mg/kg for neurological effects (increased startle response) in offspring Fischer 344 rats in a 10-day study conducted by EPA (1986c). This study was part of a toxicity screen performed at EPA in which male Fischer 344 rats received gavage doses of chlordecone for 10 consecutive days. At 2.5 mg/kg/day and above, the amplitude of the acoustic startle response was significantly increased. At the other two doses, the amplitude was increased with all decibel stimuli. Motor activity in a figure-8 maze was decreased at the highest dose tested. Startle response, as a measure of adverse neurological effects, and other parameters such as tremors and abnormal gait have been reported in studies with animals following acute exposure to chlordecone (Egle et al. 1979; Jordan et al. 1981; Klingensmith and Mehendale 1982a; Mactutus et al. 1984a; Maier and Costa 1990; Swanson and Wooley 1982; Tilson et al. 1985).

Intermediate-duration oral studies in humans for mirex are lacking. A review of the animal oral intermediate toxicity data for mirex indicates that the available studies are not adequate to derive intermediate oral MRL for mirex. The most suitable study provides a LOAEL of 0.25 mg/kg/day for

endocrine effects-dilation of rough endoplasmic reticulum cistemae of the thyroid of weanling Sprague-Dawley rats (Singh et al. 1985). Adjusting the LOAEL of 0.25 mg/kg/day determined from this study with a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for interspecies variability) yields an intermediate oral MRL of 0.0003 mg/kg/day, which is lower than the chronic-duration oral MRL of 0.0008 mg/kg/day derived from an NTP (1990) study in rats (see chronic-duration MRL). Therefore, no oral intermediate-duration MRL was developed for mirex.

- An MRL of 0.0005 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to chlordecone.

The MRL is based on a NOAEL of 0.05 mg/kg/day for renal effects in rats at a LOAEL of 0.25 mg/kg/day. In the study by Larson et al. (1979b) in which the NOAEL was derived, groups of Wistar strain rats of both sexes were administered 0, 0.05, 0.25, 0.5, 1.25, 2.5, or 4.0 mg/kg/day for a period of one year. After one year (in a 2-year feeding study), 5 rats/sex/dose group were sacrificed. Additionally, 3 to 5 rats of each sex receiving 0.25 or 0.5 mg/kg/day and 3 males receiving 1.25 mg/kg/day were returned to the control diet for 4 weeks and then sacrificed. Proteinuria was noted in all treatment groups at all intervals after 3 months except in males at 21 and 24 months when control levels were elevated, and in females at 24 months when the levels in only the 0.5 and 1.25 mg/kg/day groups were elevated. The severity of observed glomemlosclerosis was increased in both males and females at $\geq$0.25 mg/kg/day. Increase in kidney weight relative to body weight was reported, but was not considered seriously adverse (Larson et al. 1979b).

- An MRL of 0.0008 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to mirex.

This MRL for mirex was derived using a NOAEL of 0.075 mg/kg/day for dose-dependent hepatic changes from a study by NTP (1990). The dose-dependent changes included increased fatty metamorphosis (cytoplasmic vacuoles consistent with intracellular fat accumulation) and necrosis of hepatocytes (focal and/or centrilobular) in F344/N rats of both sexes at a dose of 0.7 mg/kg/day following a 2-year oral exposure to mirex doses of 0-7.7 mg/kg/day (males: 0, 0.007, 0.075, 0.7, 1.8, 3.8; females: 0, 3.9, 7.7). Dilation of the sinusoids (by blood or proteinaceous material) was also observed in males at $\geq$0.7 mg/kg/day and in females at 3.9 mg/kg/day. Increased nephropathy was

also observed in male rats at ≥0.7 mg/kg/day and in female rats at ≥2 mg/kg/day. Epithelial hyperplasia of the renal pelvis and parathyroid hyperplasia were increased in males at 0.7 mg/kg/day and above; these lesions were probably secondary to the nephropathy. Cystic follicles of the thyroid were increased in male rats at ≥0.7 mg/kg/day. Body weight was decreased in males and females by more than 10% in males (ll-18%) at 3.8 mg/kg/day and in females (15-17%) at 3.9 mg/kg/day (NTP 1990). In another chronic animal study, hepatobiliary changes-which included dose-dependent focal biliary hyperplasia and hepatic pericentral cytoplasmic vacuolization and lobular pattern with mild anisokaryosis at a mirex dose of 0.07 mg/kg/day and marked hepatic panlobular cytoplasmic vacuolization with loss of basophilia, fatty infiltration, and marked anisokaryosis at higher doses-were reported in Sprague-Dawley rats following chronic oral exposure to mirex. At 0.07 mg/kg of mirex, significant increases in the hepatic microsomal aniline hydroxylase (AH) and aminopyrine-N-demethylase (APDM) were observed; however, at 0.32 mg/kg of mirex only APDM increased significantly. Mirex tended to increase slightly, but insignificantly, the liver weight of over the control rats at doses ≥0.07. The thyroids of the rats also exhibited dose-dependent degenerative and proliferative changes in the follicular epithelium but without alteration in the colloidal density at doses ≥0.07 mg/kg/day (Chu et al. 1981c). Several other chronic feeding studies of rodents with mirex reported a variety of adverse hepatic effects which included hepatic lesions (fatty metamorphosis, cystic degeneration, necrosis, and biliary hyperplasia with periportal fibrosis) in CD rats (Ulland et al. 1977a); enlarged and mottled surfaces of the liver and some discoloration on gross necropsy, centrilobular hypertrophy of hepatocytes, increased glucose 6-phosphatase in the centrilobular region and decreased acid phosphatase in the centrilobular region of the liver, increased activity in Kupffer cells, and extensive proliferation of smooth endoplasmic reticulum with nuclear changes and lipid accumulation (Fulfs et al. 1977) in CD-l mice; and significantly increased total liver DNA and microsomal enzyme activity in CD-l mice (Byard et al. 1975). Several intermediateduration studies in rats also indicate that the thyroid is a target organ for mirex toxicity (Chu et al. 1981a, 1981b; Singh et al. 1982, 1985). These studies showed reduced colloid, thickening of the follicular epithelium, angular collapse of the follicles, and dilation of the rough endoplasmic reticulum of thyroid cells at 0.25 mg/kg/day for 28 days. Reproductive toxicity (a sensitive end point in acuteand intermediate-duration studies) was tested at doses higher than the LOAEL from this study, and inhibition of reproduction was observed (Wolfe et al. 1979).

- An MRL of 0.0005 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to chlordecone.

The MRL is based on a NOAEL of 0.05 mg/kg/day for renal effects in rats at a LOAEL of 0.25 mg/kg/day. In the study by Larson et al. (1979b) in which the NOAEL was derived, groups of Wistar strain rats of both sexes were administered 0, 0.05, 0.25, 0.5, 1.25, 2.5, or 4.0 mg/kg/day for a period of 2 years. After one year (in a 2-year feeding study), 5 rats/sex/dose group were sacrificed. Additionally, 3 to 5 rats of each sex receiving 0.25 or 0.5 mg/kg/day and 3 males receiving 1.25 mg/kg/day were returned to the control diet for 4 weeks and then sacrificed. Proteinuria was noted in all treatment groups at all intervals after 3 months except in males at 21 and 24 months when control levels were elevated, and in females at 24 months when the levels in only the 0.5 and 1.25 mg/kg/day groups were elevated. The severity of observed glomerulosclerosis was increased in both males and females at $\geq$0.25 mg/kg/day. Increase in kidney weight relative to body weight was reported, but was not considered seriously adverse (Larson et al. 1979b).

**Death.** No reports of mirex- or chlordecone-related deaths in humans were located in the literature. Animal studies regarding death have been limited to oral, dermal, and parenteral studies. Studies examining exposure in animals by the oral route indicate that large single oral doses of mirex are necessary to cause death, with dogs less sensitive to the lethal effects of mirex than rats (Gaines 1969; Gaines and Kimbrough 1970; Larson et al. 1979a). However, with repeated exposures, death is observed at much lower doses (Fujimori et al. 1983; Gaines and Kimbrough 1970; Khera et al. 1976; Larson et al. 1979a; Mehendale et al. 1973; Ware and Good 1967). Substantial differences were also observed in the magnitude of single versus multiple doses of chlordecone that resulted in death (Desaiah et al. 1980a; Kavlock et al. 1985; Larson et al. 1979b; Simmons et al. 1987). In longer-term studies, juvenile animals appeared more sensitive to the lethal effects of chlordecone than adults (Huber 1965). No cause of death was identified in these studies. Based on the relatively high doses of mirex and chlordecone necessary to cause death in animal studies and the absence of reports of death due to these chemicals after high occupational exposures, it is unlikely that death would occur in persons exposed to mirex or chlordecone at hazardous waste sites.

### Systemic Effects

*Respiratory Effects.* No studies were located regarding the respiratory toxicity of mirex in humans or animals. Thus, insufficient information is available to determine whether persons exposed to mirex at hazardous waste sites might experience adverse respiratory effects.

Studies of workers exposed to high levels of chlordecone indicated that pleuritic chest pain was a relatively common complaint (Cannon et al. 1978; Taylor 1982, 1985). Examination of workers with this complaint revealed no cause for the pains. Since oral exposure studies in animals did not identify any respiratory end points that may have been affected following ingestion of chlordecone (Larson et al. 1979b) and no inhalation exposure studies were located, a possible physiological basis for the workers' complaints has not been identified. Insufficient information is available to determine whether persons exposed to low levels of chlordecone at hazardous waste sites would experience adverse respiratory effects, but the possibility cannot be discounted.

*Cardiovascular Effects.* No studies were located regarding the cardiovascular effects of mirex in humans. A study in animals suggested that ingestion of mirex has a transient effect on cardiac output and alters flow to essential internal organs (Buelke-Sam et al. 1983), but the toxicological significance of this finding is unclear. No increase in lesions of the heart or vasculature was observed upon histological examination (Larson et al. 1979a), and biochemical changes in the heart following ingestion were slight (Desaiah 1980). Thus, persons at hazardous waste sites would not be likely to experience adverse effects from low-level exposures to mirex.

The available information indicates that chlordecone is not markedly cardiotoxic in humans (Cannon et al. 1978; Taylor 1982, 1985; Taylor et al. 1978). Rat studies with chlordecone have shown that chronic low-dose ingestion does not cause histologically evident cardiac lesions (Larson et al. 1979b), but acute-duration exposure to higher doses results in inhibition of a number of biochemical parameters in the heart involved in contractility and energy production (Desaiah 1980; Kodavanti et al. 1990a). Also, intermediate-duration exposure to moderate doses results in vasodilation (Larson et al. 1979b). The vasodilatory effect may be due to central nervous system effects on the noradrenergic mechanism controlling body temperature (Cook et al. 1988a, 1988b). Thus, the possibility that persons exposed to chlordecone may experience adverse cardiovascular effects cannot be discounted.

*Gastrointestinal Effects.* No information on the gastrointestinal effects of mirex in humans was located. Animal studies indicate that mirex is not highly toxic to the gastrointestinal tract, but diarrhea has been observed in animals following acute high-level oral exposure and longer-term lower-level oral exposure (Dietz and McMillan 1979; Fujimori et al. 1983; Gaines and Kimbrough 1970; Kendall 1974a; Khera et al. 1976; Mehendale 1981b). Gross pathologic examination of gastrointestinal tissues from one of these studies (Fujimori et al. 1983) showed intestinal lesions, suggesting that the diarrhea

may have been a direct effect of the mirex on the gastrointestinal tract. However, a neurologic component of the diarrhea cannot be eliminated. It is possible that humans exposed to high levels of mirex at hazardous waste sites may experience some diarrhea.

No information was located regarding the gastrointestinal toxicity of chlordecone in humans. Only very limited evidence of gastrointestinal effects has been observed in oral studies in experimental animals (Fujimori et al. 1983; Larson et al. 1979b). Thus, it is unlikely that chlordecone exposure would result in adverse effects on the gastrointestinal tracts of persons exposed to low levels at hazardous waste sites.

***Hematological Effects.*** No studies were located regarding hematological effects of mirex or chlordecone in humans. Limited information was located regarding the hematological effects of mirex and chlordecone in experimental animals, but the results reported in the studies were predominantly negative for adverse effects for both mirex (Chu et al. 1980a; Ervin and Yarbrough 1983; Larson et al. 1979a; Yarbrough et al. 1981) and chlordecone (Chu et al. 1980a; Larson et al. 1979b). Thus, it is unlikely that persons exposed to low levels of mirex or chlordecone at hazardous waste sites would experience adverse hematological effects.

***Musculoskeletal Effects.*** No information was located regarding musculoskeletal effects in humans or animals exposed to mirex. Thus, insufficient information is available to determine whether persons exposed to mirex at hazardous waste sites may experience adverse musculoskeletal effects.

Workers exposed to high levels of chlordecone experienced tremors, muscle weakness, gait ataxia, and incoordination (Cannon et al. 1978; Taylor 1982, 1985). Although these effects may be attributable to adverse effects of chlordecone on the nervous system, muscle biopsies obtained from six of the workers showed evidence of a myopathic condition (Martinez et al. 1978). Animal studies have not extensively examined the effects of chlordecone on muscle; however, weakness that increased in severity with time was observed in rats following a single large oral dose of chlordecone (Egle et al. 1979). Histopathological analyses of muscle taken from rats after parenteral administration of chlordecone showed mitochondrial damage and glycogen and lipid depletion (Phillips and Eroschenko 1982). The authors speculated that the effects on muscle were the result of altered mitochondrial oxidative metabolism and membrane calcium permeability. In support of this hypothesis, biochemical analyses of sarcoplasmic reticulum from muscle of exposed rats showed inhibition of $mg^{2+}$ATPase

(Mishra et al. 1980). Additional *in vitro* studies showed inhibition of sarcoplasmic $Ca^{2+}$ATPase and $mg^{2+}$ATPase (Mishra et al. 1980) and inhibition of muscle lactate dehydrogenase (Anderson and Noble 1977; Anderson et al. 1978), although the inhibition of the lactate dehydrogenase may have been an artifact (Meany and Packer 1979). These data suggest that chlordecone may have a direct toxic effect on muscle. Therefore, the possibility that persons exposed to sufficiently high concentrations of chlordecone at hazardous waste sites may experience adverse muscular effects cannot be discounted.

***Hepatic Effects.*** Although human data on the hepatic effects of mirex are minimal, animal studies have shown that the liver undergoes both adaptive and toxic changes following oral exposure. The primary toxic effects of mirex are inhibition of hepatobiliary excretion (Berrnan et al. 1986; Davison et al. 1976; Mehendale 1976, 1977c; Teo and Vore 1991) and depletion of hepatic glycogen stores (Elgin et al. 1990; Ervin and Yarbrough 1983; Fujimori et al. 1983; Jovanovich et al. 1987; Kendall 1979). The precise mechanism for the inhibition of hepatobiliary excretion is unclear but may involve a combination of decreased uptake of substances from the blood by hepatocytes (Teo and Vore 1990), decreased transfer of chemicals from the hepatocyte to the bile (Berman et al. 1986), and leaking from the bile duct via a paracellular pathway (Curtis and Hoyt 1984) (see also Section 2.3.5, Mechanism of Action). A 28-day study in Sprague-Dawley rats reported a decrease in hepatic microsomal aniline hydroxylase. Histopathological findings in this study included fatty vacuolation, panlobular ballooning of hepatocytes, moderate lobular pattern with perinuclear clear zone and perivenous cytoplasmic ballooning with anisokaryosis in liver (Chu et al. 1980b, 1981b). A 21-month study in Sprague-Dawley rats reported a decrease in hepatic rnicrosomal aniline hydroxylase. Histopathological findings in this study included panlobular cytoplasmic vacuolation with loss of basophilia, fatty infiltration, and anisokaryosis in liver (Chu et al. 1981c). F344/N male and female rats fed mirex doses (males = 0.007, 0.07, 0.7, 1.8, 3.8 mg/kg/day; females = 0.007, 0.08, 0.7, 2.0, 3.9 mg/kg/day) for 2 years developed histopathological changes, which included hepatocytomegaly with eosinophilic cytoplasm observed in males and females at $\geq$0.7 mg/kg/day. Fatty metamorphosis (cytoplasmic vacuoles consistent with intracellular fat accumulation) and necrosis of hepatocytes (focal and centrilobular) were increased in males and females at $\geq$0.7 mg/kg/day. Dilation of the sinusoids (by blood or proteinaceous material) was observed in males at $\geq$0.7 mg/kg/day and in females only at the highest dose tested (NTP 1990). A chronic-duration MRL of 0.0008 mg/kg/day for mirex is based on hepatic effects in rats observed in this study. Based on the animal data, persons exposed to sufficiently high concentrations of mirex at hazardous waste sites may suffer liver damage.

Examination of workers exposed to high levels of chlordecone has shown adaptive changes (increased liver size, proliferation of the smooth endoplasmic reticulum, and increased microsomal enzyme activity) but only limited evidence of hepatotoxicity (increased serum alkaline phosphatase, lipofuscin accumulation, mild inflammatory changes, mild portal fibrosis, fatty infiltration, and/or paracrystalline mitochondrial inclusions) (Guzelian et al. 1980). Sulfobromophthalein clearance was unaffected. The results of animal studies support these findings and indicate that exposure to moderate or high concentrations of chlordecone may also result in decreased hepatobiliary function (Curtis and Hoyt 1984; Curtis and Mehendale 1979; Curtis et al. 1979b, 1981; Mehendale 1977b, 1981b; Teo and Vore 1991); decreased hepatic glycogen (Fujimori et al. 1983); and increased serum nonprotein nitrogen compounds and enzymes, decreased serum tnglycerides and LDL cholesterol chlordecone (Chetty et al. 1993a, 1993b). Given the extremely poor hygiene at the plant where the workers were employed and the high levels of exposure that occurred, it is unlikely that persons living in the vicinity of hazardous waste sites would experience more severe effects than the workers who were examined. However, the possibility of mild hepatobiliary dysfunction among exposed persons at hazardous waste sites cannot be dismissed.

***Renal Effects***. No studies were located regarding renal effects of mirex or chlordecone in humans. However, studies in animals indicated an increase in the severity of renal lesions observed in rats following chronic-duration oral exposures to both mirex (NTP 1990) and chlordecone (Larson et al. 1979b). Intermediate- and chronic-duration MRLs of 0.0005 mg/kg/day were derived for oral exposure to chlordecone based on the NOAEL of 0.05 mg/kg/day for histopathological evidence of renal damage from this study. Thus, it is possible that persons exposed to sufficiently high concentrations of mirex or chlordecone for long periods may experience adverse renal effects.

***Endocrine Effects*** No studies were located regarding thyroid or adrenal effects in humans after oral exposure to mirex or chlordecone. Result of studies in rats indicate that mirex is toxic to the thyroid. Reversible reduction in colloid density, a thickening of follicular epithelium, and angular collapse of the follicles, but no effect on serum levels of $T_3$ or $T_4$ were reported in rats following oral exposure to mirex (Chu et al. 1980a, 1981a, 1981b). In other studies, ultrastructural analyses of thyroids from rats treated for 28 days showed dilation of the rough endoplasmic reticulum and increased columnar cells with irregularly shaped lysosomal bodies, dilation of cistemae, and increased vacuolization (Singh et al. 1982, 1985). Similar effects were observed following dietary exposure for 148 days (Chu et al. 1981a). Dietary exposure for 2 years also resulted in an increase in cystic follicles in male rats (NTP

1990). Mirex had no effect on the adrenal medulla (Baggett et al. 1980). No studies were located regarding thyroid effects in animals following oral exposure to chlordecone. Studies in animals also indicate that the adrenal gland hypertrophies and releases increased levels of corticosterone in response to mirex exposure (Ervin and Yarbrough 1985; Jovanovich et al. 1987; Williams and Yarbrough 1983). Other studies in animals have demonstrated increased adrenal weight; increased cholesterol, lipid, and protein content (Williams and Yarbrough 1983); increased adrenal weight and increased serum adrenocorticotropic hormone (Ervin and Yarbrough 1985; Jovanovich et al. 1987); and decreased body fats (Jovanovich et al. 1987). Less information is available regarding the effects of chlordecone on the adrenal glands of animals. Increased relative adrenal weight was observed following a single oral dose of chlordecone in rats (Swanson and Wooley 1982). Enlargement of the adrenal gland, with hyperplasia and hypertrophy of the cortical cells, was observed in a 30-day dietary study in rats (Cannon and Kimbrough 1979); decreased adrenal lipid was observed in a 90-day dietary study in rats (Larson et al. 1979b). Consistent with a corticosterone-induced increase in lipid utilization, decreased body fat was observed following a dietary exposure in rats for 16 days (Mehendale et al. 1977b, 1978b), and 15 or 20 days (Klingensmith and Mehendale 1982a), or exposure of mice for 33 days (Fujimori et al. 1983). In contrast to the absence of effects of mirex on the adrenal medulla, oral exposure to chlordecone for 8 days resulted in a decrease in the medullary content of epinephrine in rats (Baggett et al. 1980). The evidence indicates that human exposure to mirex or chlordecone can result in endocrine toxicity.

*Dermal Effects*. No studies were located regarding dermal effects in humans after exposure to mirex. A study using rabbits showed slight erythema and scaling resulting from dermal exposure to an unspecified amount of chlordecone (Larson et al. 1979a). Therefore, the possibility exists that persons exposed dermally to mirex in the vicinity of hazardous waste sites may also experience some skin irritation.

Workers exposed to high levels of chlordecone reported a high incidence of skin rashes (Cannon et al. 1978; Taylor 1982, 1985; Taylor et al. 1978). Acute-duration dermal exposure of rabbits to chlordecone resulted in no signs of irritation (Larson et al. 1979b), but the experience of workers suggests that skin irritation or rashes from exposure at hazardous waste sites are possible.

*Ocular Effects.* No studies were located regarding ocular effects in humans after exposure to mirex. However, studies using neonatal animals have demonstrated that cataracts and other lesions of the lens

may be induced if exposure to mirex occurs during a critical period (between postpartum days 1 and 8) (Chernoff et al. 1979b; Gaines and Kimbrough 1970; Rogers and Grabowski 1984; Scotti et al. 1981). While it is unclear whether lens development in human infants parallels that in rats and mice, the possibility exists that cataracts may develop in infants as a result of mirex exposure.

***Body Weight Effects***. Animal studies show decreases in serum glucose (Chu et al. 1981b; Ervin and Yarbrough 1983; Fujimori et al. 1983; Jovanovich et al. 1987; Robinson and Yarbrough 1978a; Williams and Yarbrough 1983; Yarbrough et al. 1981) and decreases in body weight or body weight gain (Buelke-Sam et al. 1983; Byrd et al. 1981; Chadwick et al. 1977; Chernoff et al. 1979a, 1979b; Chu et al. 1981a; Curtis and Hoyt 1984; Davison et al. 1976; Elgin et al. 1990; Fujimori et al. 1983; Jovanovich et al. 1987; Khera et al. 1976; Larson et al. 1979a; Mehendale et al. 1973; NTP 1990; Ritchie and Ho 1982; Rogers and Grabowski 1984; Villeneuve et al. 1977).

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

***Other Systemic Effects.*** No studies were located regarding other systemic effects in humans exposed to mirex or chlordecone. However, animal studies in which mirex and chlordecone exposure resulted in loss of body fat (Fujimori et al. 1983; Klingensmith and Mehendale 1982a; Mehendale et al. 1977b, 1978b) and decreased serum glucose levels (Fujimori et al. 1983), combined with the observation that both chemicals cause depletion of hepatic glycogen levels, suggest an increased utilization of fat and glucose. *In vitro* studies with chlordecone suggest that it stimulates cellular respiration (Carmines et

al. 1979) and uncouples oxidative phosphorylation (Manring and Moreland 1981), as well as supporting the hypothesis that the increased utilization of substrates for energy production may result from the failure of oxidative phosphorylation to produce energy. A similar phenomenon may occur with mirex. In addition to the possible metabolic dysfunction, chlordecone has also been demonstrated to cause hypothermia following oral (Swanson and Wooley 1982) and parenteral administration (Cook et al. 1988a, 1988b; Hong et al. 1984; Hsu et al. 1986). Although the hypothermia has been proposed to be a result of decreased metabolic heat production (Hsu et al. 1986), recent studies manipulating brain neurotransmitter levels have shown that the decrease in body temperature may be due to noradrenergic stimulation of peripheral vasodilation (Cook et al. 1988a, 1988b). This explanation would help explain the paradoxical increase in tail temperature seen concomitant with the decrease in core temperature (Cook et al. 1988a, 1988b). These data suggest that persons exposed to sufficiently high concentrations of chlordecone at hazardous waste sites may experience some decrease in body temperature.

**Immunological Effects.** No data on immunotoxicity of mirex in were located. The only information about the immunological effects of mirex exposure in animals was provided by one acute oral study in rats in which decrease spleen weight was reported (Buelke-Sam et al. 1983). Thus, it is uncertain whether persons exposed to mirex at hazardous waste sites might experience adverse effects on the immune system.

It is not known if the immune system is the target of chlordecone toxicity in humans. In rats that received high oral doses of chlordecone, adverse immunological effects included reductions in spleen and thymus weights, numbers of neutrophils, and natural killer cell activity (EPA 1986c; Smialowicz et al. 1985). However, these effects were most likely due to general toxicity rather than a direct toxic effect on the immune system. One study with rats fed calcium-deficient diets found an increase in plaque-forming cells at the lowest dose tested (0.5 mg/kg/day). The effect on plaque-forming cells was found to be more severe in calcium-sufficient animals than in calcium-deficient animals (Chetty et al. 1993c).

Because of the lack of human data and the limited animal data on the immunologic effects of chlordecone, it is not known whether low concentrations of chlordecone would induce immunotoxic effects in populations living in the vicinity of hazardous waste sites.

**Neurological Effects.** No studies were located regarding neurological effects in humans following exposure to mirex, but animal studies have demonstrated lethargy, weakness, diarrhea, hyperexcitability, tremors, and convulsions as a result of mirex exposure (Chu et al. 1981a; Curtis and Hoyt 1984; Fujimori et al. 1983; Gaines and Kimbrough 1970; Kendall 1974a; Larson et al. 1979a; Mehendale 1981b). Although the lethargy and diarrhea may be attributable to other systemic effects, the hyperexcitability, tremors, and convulsions are probably of neural ongin. However, no information was located that might explain the mechanism for these effects.

Strong evidence for neurotoxicity of chlordecone has been obtained in human studies. Interviews of workers exposed to high levels of chlordecone during its manufacture revealed a high percentage of workers with histories of tremors, unfounded nervousness or anxiety, and visual difficulties (Cannon et al. 1978). The tremors were characterized as resembling intention tremors and occurred mainly in the upper extremities (Taylor 1982, 1985). In more severe cases, the lower extremities were involved and gait disturbances were apparent. Nerve biopsies of the more severely affected workers showed decreases in small myelinated and unmyelinated neurons (Martinez et al. 1978). Although mood and memory disturbances were reported by many workers, testing revealed active encephalopathy in only one subject (Taylor 1982, 1985). Reports of blurring of vision were found to be associated with an opsoclonus-like phenomenon, in which rapid random eye movements followed horizontal saccades (Taylor 1982, 1985). This was attributed to a loss of inhibitory control of saccadic activity. Headaches were also reported by a number of workers (Taylor 1982, 1985). Cerebrospinal fluid pressure was elevated in three of these individuals, and relief of cerebrospinal fluid pressure resulted in amelioration of the headaches (Sanbom et al. 1979).

Studies in animals have shown similar effects (tremor, exaggerated startle response, gait disturbances) (Albertson et al. 1985; Aldous et al. 1984; Baggett et al. 1980; Chang-Tsui and Ho 1979; Desaiah et al. 1980a; Egle et al. 1979; End et al. 1981; Fujimori et al. 1982b; Hoskins and Ho 1982; Huang et al. 1980; Hwang and Van Woert 1979; Jordan et al. 1981; Klingensmith and Mehendale 1982b; Maier and Costa 1990; Mishra et al. 1980; Smialowicz et al. 1985; Swanson and Wooley 1982; Uzodinma et al. 1984a). Numerous studies have been conducted in animals to determine the underlying cause for the tremoring. From these studies, it has been concluded that the tremors are induced in the central nervous system at a level above the spinal cord (Hwang and Van Woert 1979) and that the central nervous system effects are unlike those of other chlorinated hydrocarbons (Bloomquist et al. 1986; Chang-Tsui and Ho 1979; Lawrence and Casida 1984; Seth et al. 1981). In addition, the tremors are

unlike those produced by DDT (Hong et al. 1986; Tilson et al. 1985, 1986b). Also, animal studies indicate that more than one neurotransmitter system may be involved in expression of the tremors (Aronstam and Hong 1986; Brown et al. 1991; Chen et al. 1985; Desaiah 1985; Fujimori et al. 1982b; Gerhart et al. 1982, 1983, 1985; Herr et al. 1987; Hong et al. 1984; Hwang and Van Woert 1979; Tilson et al. 1986b; Uphouse and Eckols 1986). Experiments at the cellular level have indicated effects on calcium regulation of neuronal function (Bondy and Halsall 1988; Bondy and McKee 1990; Bondy et al. 1989; End et al. 1979, 1981; Kodavanti et al. 1988, 1989c; Komulainen and Bondy 1987; Vig et al. 1990b, 1991) and several enzymes involved in maintenance of ionic gradients (Bansal and Desaiah 1982; Chetty et al. 1983b; Desaiah 1981; Desaiah et al. 1980a, 1980b, 1991; Folmar 1978; Jinna et al. 1989; Mishra et al. 1980; Singh et al. 1984). For a further description of these studies see Section 2.3.5, Mechanisms of Action.

Studies in animals have also examined the peripheral nerve damage associated with chlordecone exposure and have shown that the damage is to unmyelinated axons and consists of vesiculation of the Schwann cell cytoplasm and swelling of unmyelinated axons with dissolution of microtubules and inclusion of paracrystalline material in mitochondria (Phillips and Eroschenko 1982). The effects of chlordecone on the cerebrospinal fluid have also been further studied in animals, and results show degenerative changes in the choroid plexus, the tissue responsible for production of cerebrospinal fluid and regulation of its flow (Schumacher and Eroschenko 1985). These results suggest that persons exposed to mirex or chlordecone at hazardous waste sites might also experience adverse neurological effects if they are exposed to sufficiently high concentrations. An acute MRL of 0.01 mg/kg/day has been developed for chlordecone based on a NOAEL of 1.25 mg/kg for neurological effects (increased startle response) in Fischer 344 rats in a 10-day study conducted by EPA (1986c).

**Reproductive Effects.** No human studies are available to assess the reproductive effects of mirex. The available studies involving human exposure to chlordecone suggest that adverse reproductive effects can occur in males as a result of occupational exposure to chlordecone (Guzelian 1982a; Taylor 1982, 1985; Taylor et al. 1978). However, these studies did not quantify the exposure levels of chlordecone. Mammalian studies indicate that testicular atrophy can occur at low doses of chlordecone in the diet for 3 months, a dose well below the level that causes overt maternal toxicity (Larson et al. 1979b). Dietary exposure at twice the higher levels for 3 months resulted in complete reproductive failure of female mice (Huber 1965). Chlordecone is well known for its estrogenic effects on mammalian reproductive organs when administered by oral or parenteral routes. A single

intraperitoneal injection of chlordecone to ovariectomized rats with an implanted progesteronereleasing source was found to decrease progesterone levels (Johnson et al. 1990), and a single injection of chlordecone also induced persistent vaginal estrus when administered intraperitoneally or subcutaneously in female rats (Sierra and Uphouse 1986; Uphouse et al. 1984). Young females exposed to the same levels of chlordecone developed persistent vaginal estrus and anovulation, as did the mature females when treated with chlordecone (Hammond et al. 1978). A single intraperitoneal injection of chlordecone to hypophysectomized female rats followed by daily administration of progesterone doses induced a normal number of implantation sites by acting as an estrogen substitute (Johnson et al. 1992). When exposure to chlordecone was delayed until the day following ovulation, decreased fertility and inhibition of implantation occurred (Pinkston and Uphouse 1988). The effects of neonatal exposure to chlordecone on reproductive function in rats and mice are similar to those seen after prenatal exposure. Multiple injections of chlordecone to neonatal female rats increased uterotropic response (Gellert 1978); uterine weights increased in a dose-related manner (Gellert 1978; Hammond et al. 1979). Parenteral administration of a daily dose of chlordecone to l-day-old female mouse pups produced cellular proliferation and hypertrophy in the entire reproductive tract and keratinization of the vagina within 4 days of treatment in a dose-dependent manner (Eroschenko and Mousa 1979). In neonatal male mice, daily dietary administration of chlordecone was less effective than estradiol in suppressing spermatogenesis (Huber 1965).

The mechanism by which chlordecone acts possibly involves direct binding to estrogen receptors. Chlordecone may act at the neuroendocrine level to influence gonadotrophin release (Bulger and Kupfer 1985). Chlordecone affects the male reproductive capacity following prenatal exposure and produces postnatal functional changes in the reproductive capacity of female offspring at even lower levels of exposure during the prenatal and/or neonatal period (Gellert and Wilson 1979). After longer exposure (in utero and lactational), the offspring showed reduced fertility (Good et al. 1965). Thus, the potential hazard of chlordecone to the progeny that survive prenatal and/or neonatal treatment is an adverse effect on the subsequent reproductive capacity of females, and therefore, cannot be ruled out. The effect observed is similar to that seen following neonatal steroid-induced sterility and, thus, may reflect an estrogenic action of chlordecone on the developing brain. Unlike chlordecone, mirex is not uterotropic in rats (Hammond et al. 1979). However, mirex has estrogenic potential because it undergoes degradation to chlordecone in nature (Carlson et al. 1976), and therefore, its potential to produce reproductive toxicity cannot be ignored. Chlordecone has demonstrated an estrogen-like action in animals (Huber 1965; Uphouse et al. 1984). Abnormal spermatogenesis has been observed

among workers exposed at a chemical plant (Guzelian 1982a, 1982b). Possible detrimental effects on the reproductive processes of workers or populations inadvertently exposed to chlordecone at hazardous waste sites cannot be excluded.

**Developmental Effects.** No human studies.are available to assess the developmental effects of mirex. The available studies of chlordecone in humans have not addressed whether adverse developmental effects can occur as a result of paternal exposure to chlordecone. Transplacental and lactational transfer of chlordecone has been demonstrated in animals (Huber 1965). Animal studies demonstrated that prenatal exposure to mirex can induce a high incidence of dysrhythmias that can persist into the postnatal period (Grabowski 1983a). These problems are sufficiently severe to cause some fetal deaths (Grabowski and Payne 1983a). Following gestational exposure of rats and mice to chlordecone, significant embryo/fetotoxicity and teratogenicity were seen at doses (≥10 mg/kg/day) that were severely toxic to dams (Byrd et al. 1981). Reduction in fetal body weight, delayed ossification, and increased incidence of malformations (cataract and edema) at doses below 10 mg/kg/day were also observed in rat fetuses (Gaines and Kimbrough 1970); other malformations seen were undescended testes and enlarged cerebral ventricles which often indicate developmental delays (Chernoff et al. 1979a; Grabowski 1983a). Thus, chlordecone also appears to be a teratogen. However, lower doses of chlordecone also caused tremors and reduced body weight gain in dams and increased fetal and neonatal mortality (Rogers and Grabowski 1983). The mechanism by which these effects occur is not known. No human data exist to establish whether exposure to mothers at hazardous waste sites may cause adverse developmental effects in the progeny, but the possibility that parental exposure to sufficiently high amounts of mirex or chlordecone may cause adverse effects on offspring cannot be excluded.

**Genotoxic Effects.** No genotoxicity studies involving the inhalation, oral, or dermal exposure of humans to mirex or chlordecone were found. Mirex was not mutagenic in the single assay that used a human cell line (Tong et al. 1981). In this test system, the ability of mirex (purity not specified) to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in cultured human foreskin fibroblasts (Detroit-550) was investigated in the absence of an exogenous metabolic activation system and in the presence of metabolic activation provided by primary Fischer rat hepatocytes. At log doses below the cytotoxic level ($10^{-4}$ and $10^{-5}$ molar), no significant increase in the mutation frequency was observed in the human cells exposed either in the presence or absence of hepatocytes.

There has been very little testing of mirex and chlordecone in whole-animal genotoxicity assays. In the available *in vivo* animal studies, mirex and chlordecone were not clastogenic for male rat germinal cells in well-conducted dominant lethal assays (Khera et al. 1976; Simon et al. 1986). Although both mirex and chlordecone clearly increased ornithine decarboxylase activity (indicative of cellular proliferation) in rat livers following oral exposure, neither agent induced DNA damage in the target organ (Kitchin and Brown 1989; Mitra et al. 1990).

Mirex does appear to be capable of selectively reducing the proportion of tetraploid hepatocytes in adult rat livers (Abraham et al. 1983). There is also evidence from an *in vitro* assay that mirex (purity not specified) preferentially binds to freshly prepared polyploid mouse hepatocytes (Rosenbaum and Charles 1986). While binding of increasing concentrations of $^{14}$C-mirex (0.2-1 micromolar) to both diploid and polyploid cells gradually attained saturation at doses between 0.4 and 0.8 micromolar, polyploid cells were saturated by relatively low concentrations (two to three times lower than for diploid cells). Regardless of hepatocyte class, the response was partially $Na^{2+}$ dependent and completely $Ca^{2+}$ dependent. The inhibition or enhancement of normal hepatic cell ploidy in animals may prove to be important in understanding the mechanism of mirex-induced tnmongenesis; however, the pathogenic implications of ploidy alteration in carcinogenesis are not well characterized. Additionally, the overall results of these studies tend to suggest that polyploid cells in rodent livers may be predisposed to ploidy alterations because of the high percentage of tetraploids. In contrast, hepatocyte populations in humans, other species, or young animals are predominantly diploid. Approximately 99% of human liver cells are diploid. Support for the assumption that tetraploid hepatocytes may be preferentially at risk from mirex exposure was provided by the results of the study by Carlson and Abraham (1985) who investigated the effects of mirex (99%) on the distribution of ploidy cells in neonatal rats (5 days of age at initiation of treatment) exposed to 4.5 mg/kg mirex (route of exposure not specified but presumed to be intraperitoneal injection). The results indicated that mirex had no effect on the relative frequency of hepatic diploids or tetraploids, there were no significant differences in $^{3}$H-thymidine incorporation into the DNA of either class of hepatocytes, and there were no clear effects on the mitotic index. The findings of this study are noteworthy because young rodents have a preponderance of diploid hepatocytes. It has been established that neonatal rodent livers contain = 80-85% diploid cells, while polyploid hepatocytes make their appearance and increase in an orderly and time-related manner at = 21 days of age (Carriere 1969). Refer to Table 2-5 for a further summary of the *in vivo* results and Table 2-6 for the *in vitro* results.

## TABLE 2-5. Genotoxicity of Mirex and Chlordecone *In Vivo*

| Species (test system) | End point | Results | Reference |
|---|---|---|---|
| ***Mirex*** | | | |
| Mammalian cells: | | | |
| Male rat germinal cells | Dominant lethal mutations | – | Khera et al. 1976 |
| Rat hepatocytes | DNA damage (alkaline elution) | – | Mitra et al. 1990 |
| Rat hepatocytes | Selective reduction of polyploid cells | + | Abraham et al. 1983 |
| ***Chlordecone*** | | | |
| Mammalian cells: | | | |
| 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

## TABLE 2-6. Genotoxicity of Mirex and Chlordecone *In Vitro*

| Species (test system) | End point | Results | | Reference |
|---|---|---|---|---|
| | | With activation | Without activation | |
| ***Mirex*** | | | | |
| Prokaryotic organisms: | | | | |
| *Salmonella typhimurium* | | | | |
| TA1535, TA1537, TA98, TA100 | Gene mutation | – | – | Mortelmans et al. 1986 |
| TA1535, TA1537, TA98, TA100 | Gene mutation | –[a] | – | Schoeny et al. 1979 |
| *S. typhimurium* G46, TA1535, TA100, C3076, TA1537, D3052, TA1538, TA98 | 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 |
| Mammalian cells: | | | | |
| Human foreskin fibroblasts (Detroit-550 cells) | Gene mutation | –[b] | – | 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 ?? | NA | + | Tsushimoto et al. 1982 |

## TABLE 2-6. Genotoxicity of Mirex and Chlordecone *In Vitro* (continued)

| Species (test system) | End point | Results | | Reference |
|---|---|---|---|---|
| | | With activation | Without activation | |
| ***Chlordecone*** | | | | |
| Prokaryotic organisms: | | | | |
| *S. typhimurium* | | | | |
| TA1535, TA1537, TA98, TA100 | Gene mutation | – | – | Mortelmans et al. 1986 |
| TA1535, TA1537, TA98, TA100 | Gene mutation | –[c] | – | Schoeny et al. 1979 |
| *S. typhimurium* G46, TA1535, TA100, C3076, TA1537, D3052, TA1538, TA98 | Gene mutation | – | – | Probst et al. 1981 |
| *Escherichia coli* WP2, WP2uvrA⁻ | Gene mutation | – | – | Probst et al. 1981 |
| Mammalian cells: | | | | |
| Rat liver epithelial cells | Gene mutation | –[b] | – | Williams 1980 |
| Chinese hamster ovary cells | Structural chromosome aberrations | – | – | Galloway et al. 1987 |
| | Sister chromatid exchange | – | + | Galloway et al. 1987 |
| Chinese hamster M3-1 cells | Structural chromosome aberrations | NR | +/– | Bale 1983 |

## TABLE 2-6. Genotoxicity of Mirex and Chlordecone *In Vitro* (continued)

| Species (test system) | End point | Results | | Reference |
|---|---|---|---|---|
| | | With activation | Without activation | |
| Rat, mouse, and/or hamster hepatocytes | Unscheduled DNA synthesis | NA | – | Maslansky and Williams 1981; Probst et al. 1981 |
| Chinese hamster lung fibroblasts (V79) | Inhibition of metabolic cooperation | NA | + | Tsushimoto et al. 1982 |

[a]Liver enzymes induced by Aroclor 1254 and also by mirex
[b]Metabolic activation provided by primary Fischer rat hepatocytes
[c]Liver enzymes induced by Aroclor 1254 and also by chlordecone

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

Neither mirex nor chlordecone have been extensively tested in *in vitro* genotoxicity assays. In microbial systems, mirex (10-10,000 μg/plate) was not mutagenic in *Salmonella typhimurium* TA1535, TA1537, TA98, or Tal00 in the absence or presence of S9 fractions prepared from induced rat or hamster livers (Mortelmans et al. 1986). In another study, Schoeny et al. (1979) found that mirex (0.1-100 μg/plate) was devoid of mutagenic activity in the same *S. typhimurium* strain, with or without conventional microsomal activation; or when the S9 liver fraction was prepared from rats induced with mirex. Using a battery of eight histidine auxotrophs of *S. typhimurium* and two tryptophan auxotrophs of *Escherichia coli* (WP2 and $WP_2$ $uvrA^-$), no evidence of mutagenesis was uncovered when mirex was tested in a concentration agar gradient assay (Probst et al. 1981). Mirex was also negative for the induction of prophage in *E. coli* at eight nonactivated and S9-activated doses which included soluble levels (0.04 and 0.07 millimolar) and insoluble levels (0.14-4.55 millimolar) (Houk and DeMarini 1987).

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). Similarly, chlordecone alcohol, the major metabolite of chlordecone in humans, is not mutagenic in *S. typhimurium* (Mortelmans et al. 1986).

With the exception of the human cell line gene mutation assay, mirex has not been investigated for possible mutagenic or clastogenic effects in mammalian cell lines. However, chlordecone ($10^{-5}$ and $10^{-6}$ molar) did not increase the frequency of mutations at the HGPRT locus in adult rat liver epithelial cells cocultivated with freshly dissociated adult male Fischer-344 hepatocytes which served as the feeder system for metabolism (Williams 1980). Chlordecone and chlordecone alcohol were also investigated for potential clastogenic activity in Chinese hamster ovary (CHO) cells. Chlordecone did not increase the frequency of CHO cells with abnormal chromosome morphology over a nonactivated concentration range of 10-20 mg/L or over an Aroclor 1254-induced rat liver S9-activated concentration range of 5-15 mg/L (Galloway et al. 1987). Chlordecone alcohol caused a slight increase in chromosome aberrations in CHO cells at 4, 8, and 16 mg/L +S9; however, the suggestive evidence of clastogenesis was not reproducible. Similarly, the 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.

Chlordecone (1.67-10.00 mg/L) increased the frequency of sister chromatid exchange in CHO cells but only in the absence of S9 activation and only in the presence of cell-cycle delay; the results were confirmed in a repeat trial (Galloway et al. 1987). By contrast, chlordecone alcohol was negative for sister chromatid exchange induction both with and without S9 activation (Galloway et al. 1987). 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. Chlordecone was also uniformly negative in unscheduled DNA synthesis assays of primary rat hepatocytes (Probst et al. 1981; Williams 1980).

Metabolic cooperation between 6-thioguanine-resistant (6-$TG^r$) mutants ($HGPRT^-$) and 6-thioguanine-insensitive (6-$TG^s$) wild-type ($HGPRT^+$) Chinese hamster lung fibroblasts (V79) was, however, inhibited by both mirex and chlordecone (Tsushimoto et al. 1982). 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 survivol 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 doserelated 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). These results provide persuasive evidence that both mirex and chlordecone interfere with cell-to-cell communication.

Refer to Table 2-6 for a further summary of the *in vitro* results.

Mirex and chlordecone have not been extensively tested in *in vivo* and *in vitro* genetic toxicology test systems. Nevertheless, the picture that emerges for both compounds, which differ only in the placement of an oxygen atom on carbon 2, provides compelling evidence that neither mirex nor chlordecone are genotoxic. There are also 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 omithine 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 (20 mg/kg), was given orally to partially hepatectomized Sprague-Dawley rats followed by two subcutaneous doses of 3 or 9 mg/kg chlordecone per week for 27 weeks (0.86 or 2.6 mg/kg/day). The higher dose resulted in hyperplastic liver nodules in seven of eight initiated males and hepatocellular carcinomas in five of six initiated females. No tumor initiation activity was seen with a single oral dose of 30 mg/kg chlordecone 24 hours after hepatectomy followed by phenobarbital promotion (Sirica et al. 1989).

The steady-state liver concentrations of chlordecone were similar in male and female rats and mice at each of the doses. These levels may, therefore, be important for interspecies comparisons since chlordecone is not metabolized in rats but is metabolized in humans.

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.

**Cancer.** No studies have been conducted in human populations to determine whether mirex or chlordecone causes cancer. However, studies in mice and rats have demonstrated the ability of mirex to cause liver tumors (Innes et al. 1969; NTP 1990; Ulland et al. 1977a), pheochromocytomas (NTP 1990), and rare renal tumors (NTP 1990). A study in mice and rats also showed the ability of chlordecone to increase liver tumors (NCI 1976). As indicated above, available data on the genotoxicity of mirex and chlordecone indicate that these chemicals do not cause cancer by a mutagenic mechanism but rather by tumor promotion. Both mirex and chlordecone are considered by the DHHS to be substances that may reasonably be anticipated to be carcinogens and by IARC to be possible human carcinogens. EPA has not classified mirex or chlordecone as to their carcinogenicity.

As indicated above in the section on "Genotoxic Effects", it is likely that mirex and chlordecone are tumor promoters and not tumor initiators. Initiators irreversibly alter DNA by a mutation, chromosomal aberration, or other alteration. Promoters act by facilitating the proliferation of previously initiated preneoplastic cells. One of the mechanisms for promotion is believed to involve suppression of inhibitory proliferative control through inhibition of gap-junctional-mediated intercellular communication as well as enzyme induction (Trosko et al. 1983). The results of studies to evaluate the promotional activity potential of mirex in mice indicate that mirex is a mouse skin cancer promoter but exerts this toxicity through a hitherto unknown mechanism that is different from that of phorbol esters, such as TPA (Meyer et al. 1993, 1994; Moser et al. 1992, 1993). Unlike initiation, promotion is a reversible process to a point. This implies, at least in theory, that there may be justification for setting NOAELs for promoters.

## 2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The

body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to mirex and chlordecone are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by mirex and chlordecone are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

### 2.5.1 Biomarkers Used to Identify or Quantify Exposure to Mirex or Chlordecone

The primary biomarkers of exposure to mirex include mirex concentrations in blood (Byrd et al. 1982; Kavlock et al. 1980; Smrek et al. 1977; Wiener et al. 1976), fat (Burse et al. 1989; Kutz et al. 1974), feces (Byrd et al. 1982; Chambers et al. 1982; Gibson et al. 1972; Ivie et al. 1974b), or milk (Dorough and Ivie 1974; Kavlock et al. 1980; Mes et al. 1978; Smrek et al. 1977). Since mirex is not metabolized, it is the only biomarker to be measured in these biological media. Since mirex is retained in the body for long periods of time and only slowly excreted, its measurement is useful as a biomarker of acute, intermediate, or chronic exposures to both low and high levels.

The biomarkers of exposure to chlordecone include blood or saliva concentrations of chlordecone, and fecal or bile concentrations of chlordecone, chlordecone alcohol, and/or their glucuronide conjugates. Blood samples are the most useful tool for epidemiological studies of exposure to chlordecone (Guzelian et al. 1981). The unusually high concentration of chlordecone in blood compared with its concentration in fat (1:7 in humans), which is due to chlordecone's association with plasma proteins, and its long half-life make chlordecone in blood (a readily sampled tissue) a good biomarker of exposure (Guzelian et al. 1981). The blood concentration of chlordecone serves as an accurate reflection of total body content of chlordecone (Guzelian et al. 1981). Blood is the best biological material to monitor and to use for determining acute, intermediate, and chronic exposures to both low and high levels of chlordecone.

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

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

### 2.5.2 Biomarkers Used to Characterize Effects Caused by Mirex or Chlordecone

Microsomal enzyme induction has been shown to be increased by both mirex and chlordecone in humans and/or experimental animals. Serum levels of chlordecone associated with enzyme induction in exposed workers were estimated to range from 100 to 500 μg/L (Guzelian 1985). Urinary D-glucaric acid levels have been shown to be a sensitive indicator of microsomal enzyme induction in workers exposed to chlordecone (Guzelian 1985). However, other substances such as barbiturates,

phenytoin, chlorbutanol, aminopyrine, phenylbutazone, and contraceptive steroids as well as other organochlorinated pesticides also cause microsomal enzyme induction and cause changes in urinary D-glucaric acid (Morgan and Roan 1974).

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

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

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

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

## 2.6 INTERACTIONS WITH OTHER SUBSTANCES

Both mirex and chlordecone are microsomal enzyme inducers, and as such enhance the metabolism of compounds oxidized or reduced by the mixed function oxygenase system. For example, the metabolism of lindane was enhanced in rats previously exposed to chlordecone (Chadwick et al. 1979). For chemicals that undergo a loss of activity with metabolism, a decrease in effectiveness would be likely in mirex- or chlordecone-exposed persons. For example, pretreatment of rats with chlordecone reduced the cholinesterase inhibition produced by a subsequent dose of methyl parathion (Tvede et al. 1989). In this study, methyl parathion was apparently metabolized to its active metabolite, methyl paraoxon, and the methyl paraoxon was further metabolized to an inactive metabolite. For chemicals that undergo a transformation to an active or toxic metabolite, enhanced activity/toxicity would be likely in mirex- or chlordecone-exposed persons. An example of this type of interaction was shown in the enhancement of acetaminophen toxicity by 30 mg/kg of mirex or chlordecone (Fouse and Hodgson 1987). Acetaminophen causes hepatic necrosis as the result of the binding of the reactive intermediate, postulated to be N-acetylquinoneimine, formed by the microsomal cytochrome P-450-dependent monooxygenase system. Mirex and chlordecone increased the activity of this system, and as a result, the toxicity of the acetaminophen was increased.

By far the most extensively studied interaction of mirex or chlordecone is the ability of chlordecone to markedly potentiate the hepatotoxicity of halomethanes such as carbon tetrachloride (Agarwal and Mehendale 1983c; Bell and Mehendale 1985; Chaudhury and Mehendale 1991; Curtis et al. 1979b, 1981; Davis and Mehendale 1980; Klingensmith and Mehendale 1981, 1982b, 1983a, 1983b; Klingensmith et al. 1983a, 1983b; Kodavanti et al. 1989a, 1990a, 1991; Lockard et al. 1983a, 1983b; Mehendale and Klingensmith 1988; Soni and Mehendale 1993), bromotrichloromethane (Agarwal and Mehendale 1982; Faroon and Mehendale 1990; Faroon et al. 1991; Klingensmith and Mehendale 1981), and chloroform (Cianflone et al. 1980; Hewitt et al. 1979, 1983, 1986a, 1986b, 1990; Iijima et al. 1983; Mehendale et al. 1989; Purushotham et al. 1988). For example, pretreatment of rats with 5 mg/kg chlordecone resulted in a 67-fold increase in carbon tetrachloride-induced lethality due to liver failure (Klingensmith and Mehendale 1982b). The increase in hepatotoxicity is characterized by increased serum enzymes, extensive necrosis, increased destruction of cytochrome P4.50 isozymes, and decreased biliary function. The potentiation of hepatotoxicity does not appear to be due solely to increased metabolism of the haloalkanes to toxic intermediates ($CCl_3$, free radical and phosgene) and as such is distinct from the potentiation of halomethane toxicity by phenobarbital (Agarwal and

Mehendale 1984a, 1984d; Bell and Mehendale 1987; Klingensmith and Mehendale 1983a, 1983b; Mehendale and Klingensmith 1988; Mehendale et al. 1990) or mirex (Bell and Mehendale 1985; Cianflone et al. 1980; Hewitt et al. 1979, 1986a; Mehendale and Klingensmith 1988; Mehendale et al. 1989; Purushotham et al. 1988).

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

A number of pharmacological agents have been shown to decrease the tremors produced in rats by chlordecone (Gerhart et al. 1983, 1985; Herr et al. 1987). Agents shown to be effective in at least one study include yohimbe or phenoxybenzamine ($\alpha$-noradrenergic antagonists), mecamylamine (a nicotinic antagonist), chlordiazepoxide ($\alpha$ benzodiazepine), muscimol (a GABA agonist), and mephenesin (a centrally acting muscle relaxant). These pharmacological agents were administered subcutaneously in animals at the following doses: yohimbe (an a-noradrenergic antagonist) = 0.5 or

1 mg/kg; phenoxybenzamine (an α-noradrenergic antagonists) = 5 mg/kg; mecamylamine (a nicotinic antagonist) = 1 mg/kg; chlordiazepoxide (a benzodiazepine) = 10 mg/kg; muscimol (a GABA agonist) = 1 mg/kg; and mephenesin (a centrally acting muscle relaxant) = 100 mg/kg. Persons being treated therapeutically with any of these drugs are likely to experience diminished tremors following exposure to chlordecone. In contrast, treatment with quipazine (a serotonergic agonist) was shown to potentiate chlordecone-induced tremors (Gerhart et al. 1983). It is possible that persons being treated for depression with quipazine or with Prozac® (a serotonin uptake inhibitor) may experience enhanced tremors.

Pretreatment of rats with difluoromethylomithine (DFMO), an inhibitor of ornithine decarboxylase, prior to exposure to a tremongenic dose of chlordecone, also resulted in inhibition of the tremor (Tilson et al. 1986b). DFMO was more effective if given 5 hours prior to the chlordecone than if given 24 hours prior to exposure. The DFMO was ineffective if given 19 hours after chlordecone exposure. These results suggest an interaction of the polyamine synthetic pathway with tremors produced by chlordecone. The mechanism of the interaction is unclear but may involve effects of polyamines on intracellular calcium homeostasis. Persons being treated with DFMO for cancer or protozoa1 infections would be likely to have reduced tremor severity after exposure to chlordecone.

In contrast to the reduction of tremors by DFMO, pretreatment of rats with diphenylhydantoin results in exacerbation of chlordecone-induced tremors (Hong et al. 1986; Tilson et al. 1985, 1986b). The mechanism for the exacerbation of the tremors is unknown. Therefore, if persons receiving diphenylhydantoin treatment for epilepsy were exposed to sufficiently high concentrations of chlordecone at a hazardous waste site, increased tremor severity would be likely to occur.

Cholestyramine, a chelating agent, binds chlordecone present in the gastrointestinal tract and limits its enterohepatic recirculation (Boylan et al. 1978; Cohn et al. 1978). This interaction leads to increased excretion of the chlordecone and decreased toxicity. Thus, persons being treated with cholestyramine to lower plasma cholesterol may experience increased excretion of chlordecone and decreased toxicity. The use of cholestyramine as a therapeutic agent in cases of chlordecone poisoning is discussed more fully in Section 2.8.2, Reducing Body Burden.

## 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to mirex and chlordecone than will most persons exposed to the same level of mirex or chlordecone in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting endproduct metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

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

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

Studies in rats have demonstrated that certain treatments exacerbate the tremors associated with chlordecone exposure. These include pretreatment with the anticonvulsant, diphenylhydantoin (Hong et al. 1986; Tilson et al. 1985, 1986b), and treatment with the serotonergic agonist, quipazine (Gerhart et al. 1983). Therefore, persons being treated with diphenylhydantoin for epilepsy or quipazine for

depression may be likely to experience more severe tremors upon exposure to high levels of chlordecone. Extrapolating from the effects seen in animals with quipazine, it might be likely that persons taking the prescription drug Prozac@, a serotonin uptake inhibitor used to treat depression, will also experience more severe tremors. Furthermore, the elderly may be a susceptible population because serotonin metabolism is increased during aging (Walker and Fishman 1991).

Studies in animals have also shown that juvenile animals experience a higher death rate than adults following exposure to chlordecone at equivalent mg/kg doses (Huber 1965). No explanation was given for these findings, but similar sensitivities may exist in children. Furthermore, although inhibition of $Na^{+}$-$K^{+}$ATPase, $mg^{2+}$ATPase, and $Ca^{2+}$ATPase activities have not been definitively shown to be the mechanism underlying chlordecone toxicity, sufficient evidence exists to suggest that their inhibition may be involved in a number of adverse effect (see Section 2.3.5, Mechanism of Action). Neonatal rats have shown a greater inhibition of these enzymes than adult rats (Jinna et al. 1989). This provides additional support for the suggestion that infants and young children may represent a susceptible population to the toxic effects of chlordecone.

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

## 2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to mirex or chlordecone. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposure to mirex and chlordecone. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

### 2.8.1 Reducing Peak Absorption Following Exposure

General recommendations reported for reducing absorption following acute, high-dose exposure to mirex and chlordecone include removing the individual from the source of the exposure and removing contaminated clothing (Haddad and Winchester 1990; Morgan et al. 1979). It has been suggested that the skin and hair be washed with soap and copious amounts of water. Most organochlorine pesticides are lipid soluble and are efficiently absorbed through the skin, so decontamination attempts should be accomplished quickly (Ellenhorn and Barceloux 1988). If the exposure has occurred by ingestion of chlordecone or mirex, several approaches have been proposed to limit the gastrointestinal absorption. One method is to induce emesis, provided the patient is conscious (HSDB 1994a, 1994b). However, the procedure is not without certain drawbacks. There is a risk of causing chemical pneumonitis in the patient by the aspiration of hydrocarbon solvent associated with the pesticide. Another suggested approach to reduce absorption is the administration of an activated charcoal slurry and a saline or sorbitol cathartic (HSDB 1994a, 1994b; Morgan et al. 1979). This technique has been found to increase the excretion of chlordecone twofold. If a patient has decreased levels of consciousness, gastric lavage has been suggested along with the use of a cuffed endotracheal tube to decrease the chance of aspiration (Morgan et al. 1979). The lipophilic properties of the halogenated hydrocarbons indicate that these chemicals will readily cross cell membranes such as the skin or the gastrointestinal epithelium.

### 2.8.2 Reducing Body Burden

Chlordecone, which is excreted mainly in the feces, appears to undergo enterohepatic recirculation, which limits its excretion (Boylan et al. 1978). Analysis of the amount of chlordecone excreted in the bile compared to the amount found in the stool has indicated that only 5-10% of the bile level of the pesticide is eliminated in the feces (Boylan et al. 1978). Approximately equal fractions of chlordecone and its metabolite, chlordecone alcohol, are excreted in the stool (Cohn et al. 1978). Like most halogenated hydrocarbon pesticides, very little of the chlordecone or its metabolites is excreted via the urine. Because of the apparent enterohepatic recirculation of chlordecone and chlordecone alcohol, most experimental approaches to chlordecone detoxification have focused on limiting reabsorption from the gastrointestinal tract using cholestyramine (Boylan et al. 1978; Cohn et al. 1978), liquid paraffin (Richter et al. 1979), and chlorella and chlorella-derived sporopollenin (Pore 1984). No

information was found that indicated that mirex undergoes enterohepatic recirculation, so it is not known whether use of these therapies would be effective in reducing absorption of mirex.

The use of cholestyramine in reducing the body burden of chlordecone has been investigated in humans and rats. In the human study, 32 workers who had been heavily exposed to chlordecone over a period of from 3 to 16 months were treated for 5 months with cholestryramine (Cohn et al. 1978). Cholestyramine treatment resulted in a sevenfold increase in the fecal excretion of chlordecone. Similarly, a study using rats demonstrated a doubling of fecal excretion and a 30-50% decrease in tissue levels of chlordecone after 2 weeks treatment with cholestyramine following a single oral dose of chlordecone (Boylan et al. 1978).

Cholestyramine use is not without limitations. It does not bind chlordecone alcohol, a metabolite of chlordecone that is also excreted in the bile (Guzelian 1981). It has a gritty texture in the mouth, and it causes several gastrointestinal disturbances, which may limit the willingness of patients to take it. It may also interfere with the absorption of fat-soluble vitamins and interact with other medications (Goldfrank 1990).

Two other compounds have been examined for therapeutic action in animal (rat) models of chlordecone poisoning. Sporopollenin, a carotenoid polymer derived from the cell walls of the alga *Chlorella prothecoides,* was reported to bind to chlordecone (Pore 1984). In animal studies using rats, sporopollenin decreased the half life of chlordecone from 40 days to 19 days. The excretion rate in control animals fed a-cellulose, in the same bulk amount as sporopollenin, did not change. Prevention of enterohepatic recirculation of chlordecone was also evaluated with liquid paraffin. Rats exposed to $^{14}$C-chlordecone for 3 days and then to diets containing 8% liquid paraffin for 24 days excreted approximately 20% more of the labelled compound in the feces than did control animals (Richter et al. 1979). Fourteen of 18 tissues examined had significantly less radioactivity than control tissues.

Hemoperfusion has been tried experimentally without success (Guzelian 1981). In a study in which a 16-unit plasmaphoresis was performed in one patient, chlordecone blood levels dropped during treatment but then returned to and even exceeded pretreatment levels. Although the fraction of chlordecone present in the blood relative to fat (1:7) was higher than that of halogenated pesticides (1:300 or greater) and indicated that hemoperfusion might be successful, the equilibrium was such that the compound moved readily from the fat to the blood, thus limiting the effect of a short duration

hemoperfusion. Dialysis is also not recommended because of the nature of the equilibrium of pesticide between the fat and the blood (HSDB 1994a, 1994b). One reason for the high blood levels of chlordecone is that it binds to plasma proteins (Guzelian 1981).

## 2.8.3 Interfering with the Mechanism of Action for Toxic Effects

No standard therapies have been reported for interfering with the mechanisms of mirex or chlordecone toxicities and, therefore, therapy has been directed towards supportive care. However, limited anecdotal information is available regarding treatments used to ameliorate the effects caused by chlordecone in the workers from the plant in Hopewell, Virginia. The administration of propranolol appeared to reduce tremor somewhat (Taylor 1982, 1985). The cause for effectiveness of this therapy is unclear; propranolol was ineffective in ameliorating tremor in rats (Gerhart et al. 1983). In experimental animals, phenoxybenzamine (an a-noradrenergic antagonist), pizotifen (a serotonin antagonist), mecamylamine (a nicotinic antagonist), trihexyphenidyl (a muscarinic antagonist), chlordiazepoxide (a benzodiazepine), muscimol (a GABA agonist), and mephenesin (a centrally acting muscle relaxant) resulted in attenuation of chlordecone-induced tremor (Gerhart et al. 1982, 1983, 1985; Herr et al 1987; Hwang and Van Woert 1979). Mephenesin was the most effective agent. It is unclear whether these agents would be effective if administered to humans following chlordecone exposure.

Prednisolone was observed to be effective in ameliorating the headache seen in 3 workers with elevated cerebral spinal fluid pressure and papilledema resulting from exposure to high levels of chlordecone (Sanbom et al. 1979). However, when prednisolone therapy was stopped, the headaches returned and did not dissipate until serum chlordecone levels were reduced. It is possible that the prednisolone blocked the headache by increasing vasoconstriction and decreasing intracranial cerebral spinal fluid volume.

Pretreatment of rats with α-noradrenergic antagonists blocked the hypothermia induced by chlordecone (Cook et al. 1988b). It is possible that if similar effects are observed in humans, α-antagonists may be capable of blocking the hypothermia.

## 2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of mirex or chlordecone is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of mirex and chlordecone.

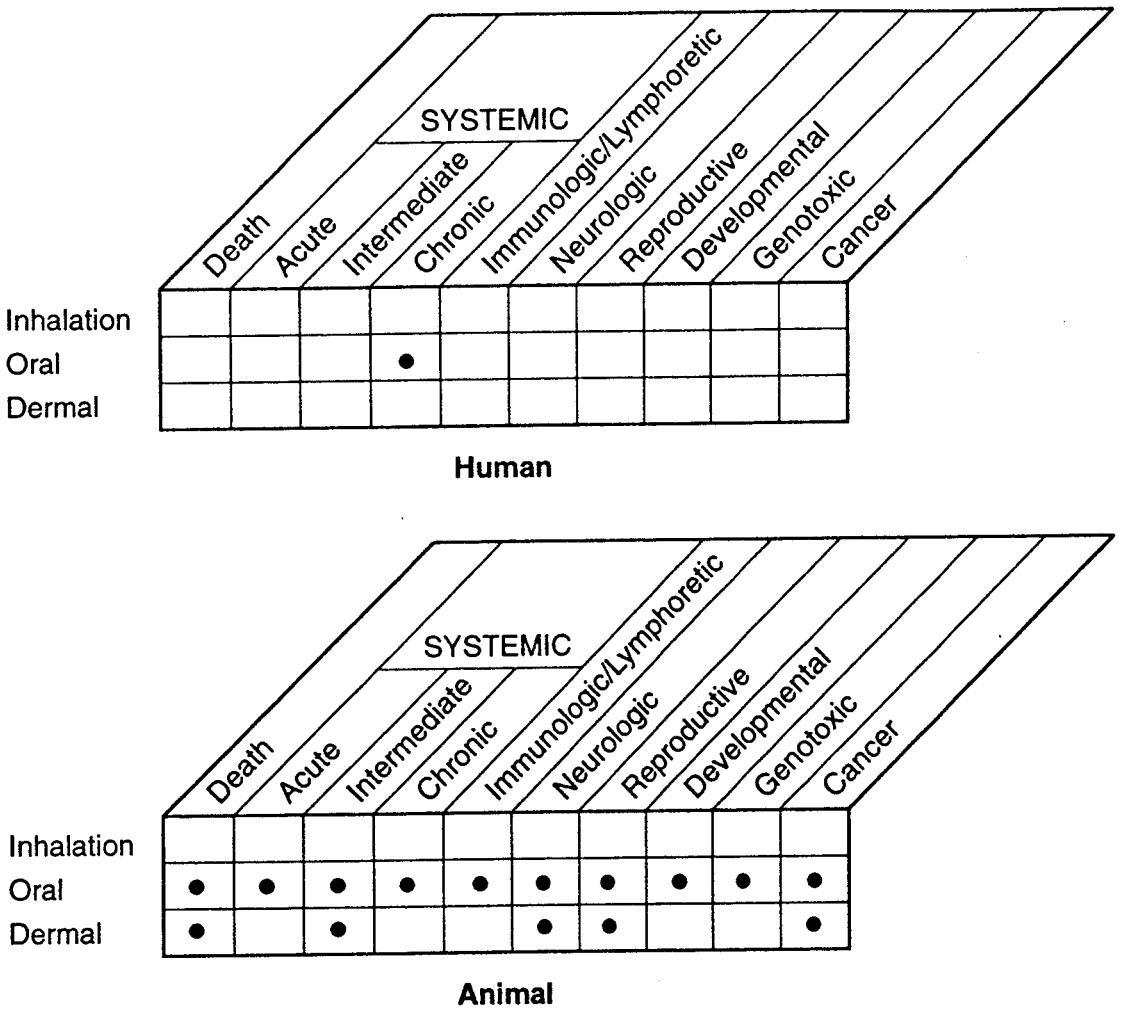
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be fulfilled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 2.9.1 Existing Information on Health Effects of Mirex and Chlordecone

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to mirex and chlordecone are summarized in Figures 2-4 and 2-5, respectively. The purpose of the figures is to illustrate the existing information concerning the health effects of mirex and chlordecone. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in figures should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision *Guide for Identifying Substance-Specific Data Needs Related to Toxicological Projiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

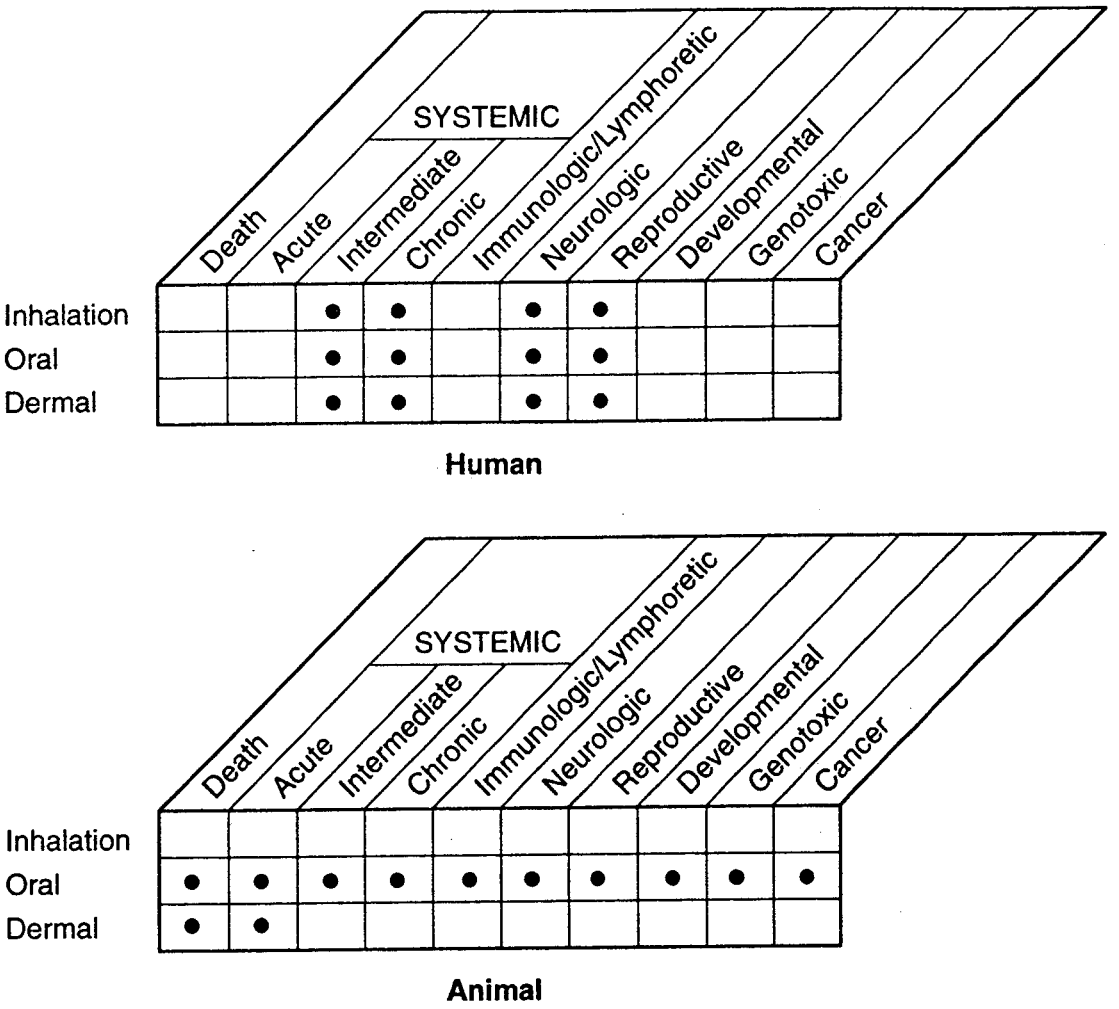
There are no epidemiological or case reports of mirex-exposed individuals. The literature reviewed for the health effects of chlordecone in humans came from reports of one occupational cohort of workers exposed to chlordecone in a manufacturing plant. This exposure was classified as intermediate-tochronic; no precise duration or level of exposure to chlordecone could be quantified from these reports. A single route of exposure could not be established for this worker population; poor hygiene

## FIGURE 2-4. Existing Information on Health Effects of Mirex




● Existing Studies

**FIGURE 2-5. Existing Information on Health Effects of Chlordecone**




● Existing Studies

in the plant made inhalation, oral, and dermal exposure routes likely to occur. The information on human exposure in this study is extremely limited because of the possible contamination with the precursor used to manufacture chlordecone, hexachloropentadiene. Therefore, information on human exposure to both mirex and chlordecone is limited.

The database for the health effects of mirex and chlordecone following oral administration in experimental animals is more substantial. However, as can be seen in Figures 2-4 and 2-5, no information is available on the health effects of inhalation and dermal exposure to mirex or chlordecone in animals.

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

### 2.9.2 Identification of Data Needs

**Acute-Duration Exposure.** No information is available regarding the effects of acute-duration exposure to mirex in humans following inhalation, oral, or dermal exposure. A large number of studies have been published for acute-duration oral exposure of rats and mice to mirex (Baggett et al. 1980; Berman et al. 1986; Buelke-Sam et al. 1983; Chernoff et al. 1979a, 1979b; Chu et al. 1981a, 1981b; Davison et al. 1976; Desaiah et al. 1980a; Elgin et al. 1990; Ervin and Yarbrough 1983, 1985; Fouse and Hodgson 1987; Fujimori et al. 1983; Gaines 1969; Gaines and Kimbrough 1970; Hewitt et al. 1979, 1986a; Jovanovich et al. 1987; Kendall 1974a, 1979; Khera et al. 1976; Larson et al. 1979a; Mehendale 1976, 1977c; Mehendale et al. 1973; Mitra et al. 1990; NTP 1990; Plaa et al. 1987; Rogers and Grabowski 1984; Scotti et al. 1981; Singh et al. 1982, 1985; Teo and Vore 1990, 1991; Williams

and Yarbrough 1983), many of them addressing interactions with other chemicals, such as the halogenated hydrocarbons, and adaptive liver effects (Abston and Yarbrough 1976; Baker et al. 1972; Byard et al. 1975; Chadwick et al. 1977; Chambers and Trevethan 1983; Chu et al. 1981a, 1981b; Cianflone et al. 1980; Curtis.and Hoyt 1984; Curtis et al. 1981; Davison et al. 1976; Elgin et al. 1990; Ervin and Yarbrough 1983; Fabacher and Hodgson 1976; Fujimori et al. 1983; Fulfs et al. 1977; Gaines and Kimbrough 1970; Hewitt et al. 1979; Iverson 1976; Jovanovich et al. 1987; Karl and Yarbrough 1984; Klingensmith and Mehendale 1983b; Kocarek et al. 1991; Larson et al. 1979a; Madhukar and Matsumura 1979; Mehendale 1981b; Mehendale et al. 1973, 1989; NTP 1990; Peppriell 1981; Pittz et al. 1979; Plaa et al. 1987; Purbshotham et al. 1988; Ritchie and Ho 1982; Robacker et al. 1981; Robinson and Yarbrough 1978c; Stevens et al. 1979; Teo and Vore 1991; Thottassery and Yarbrough 1991; Ulland et al. 1977a; Villeneuve et al. 1977; Warren et al. 1978; Williams and Yarbrough 1983; Yarbrough et al. 1981, 1984, 1986a, 1986b). However, no information could be located for acute-duration inhalation or dermal exposure.

Mirex may lead to death after oral exposure, depending upon dose (Fujimori et al. 1983; Gaines 1969; Gaines and Kimbrough 1970; Khera et al. 1976; Larson et al. 1979a; Mehendale et al. 1973); some evidence exists that pregnant rats may be more sensitive to the lethal effects of mirex (Mehendale et al. 1973). The main targets of mirex toxicity following acute exposure by the oral route are the liver, nervous system, developing fetus, and eyes. Impaired hepatobiliary excretion (Berman et al. 1986; Davison et al. 1976; Fouse and Hodgson 1987; Hewitt et al. 1986a; Kendall 1979; Mehendale 1976, 1977c, 1981b; Mitra et al. 1990; Teo and Vore 1990, 1991) and hepatic glycogen depletion (Elgin et al. 1990; Ervin and Yarbrough 1983; Fujimori et al. 1983; Jovanovich et al. 1987; Kendall 1979) have been described as the major hepatic effects. Tremors, hyperactivity or lethargy, and weakness were observed following acute-duration oral exposure to large doses of mirex (Gaines and Kimbrough 1970; Kendall 1974a). Prenatal acute-duration exposure to mirex resulted in cardiac and visceral anomalies, cataracts, increased resorptions, and lethality of offspring (Buelke-Sam et al. 1983; Byrd et al. 1981; Chernoff and Kavlock 1982, 1973; Chernoff et al. 1979a, 1979b; Gaines and Kimbrough 1970; Grabowski 1983a; Grabowski and Payne 1983a; Gray and Kavlock 1984; Gray et al. 1983; Kavlock et al. 1982; Khera et al. 1976; Roger and Grabowski 1983, 1984). Cataract formation in newborns occurs after early postnatal exposure (Chernoff et al. 1979b; Gaines and Kimbrough 1970; Rogers and Grabowski 1984; Scotti et al. 1981). Diarrhea (resulting from gastric irritation) has also been found with acute-duration oral mirex administration, especially in dying animals; however, the dose at which this effect occurs is not clear (Gaines and Kimbrough 1970; Kendall 1974a; Khera et al. 1976).

Alterations in blood flow (Buelke-Sam et al. 1983), in addition to changes in membrane-bound enzymes responsible for electrolyte flux in cardiac cells, occurs after acute oral exposure (Desaiah 1980). The physiological significance of these changes to the experimental animal is not known. Thyroid toxicity has also been documented in rats (Chu et al. 1981a, 1981b; NTP 1990; Singh et al. 1982, 1985), in addition to adrenal hypertrophy and hyperfunction (Ervin and Yarbrough 1985; Jovanovich et al. 1987; Williams and Yarbrough 1983). There was no indication that mirex was genotoxic in a dominant lethal assay (Khera et al. 1976). It is not possible to determine the target organ for mirex toxicity after inhalation or dermal exposure due to the complete lack of data in these areas for this duration of exposure.

No acute-duration inhalation MRL could be derived for mirex because no inhalation data could be located. No acute-duration oral MRL was derived for mirex because serious effects (heart block and arrhythmias in fetuses from dams exposed during gestation) were observed at the lowest dose tested (Grabowski 1983a). Studies examining the effects of mirex and chlordecone after acute-duration dermal exposure would be helpful since persons at hazardous waste sites may be exposed dermally to mirex. Additional dermal studies are certainly necessary because skin absorption of chlordecone appears to be an important route of exposure (Taylor et al. 1978). However, populations at hazardous waste sites are unlikely to be exposed via inhalation since these substances are virtually nonvolatile, so future studies using this route of exposure are not essential.

No information is available regarding the effects of acute-duration exposure to chlordecone in humans following inhalation, oral, or dermal exposure. Some information is available regarding the effects of acute-duration exposure to chlordecone in animals by the oral route of administration (Cannon and Kimbrough 1979; Chernoff and Rogers 1976; Davis and Mehendale 1980; Desaiah 1980; Egle et al. 1979; Fujimori et al 1983; Glende and Lee 1985; Huber 1965; Iijima et al. 1983; Kavlock et al. 1985; Khera et al. 1976; Klingensmith and Mehendale 1983b; Kodavanti et al. 1990a; Larson et al. 1979b; Mehendale 1977b; Mishra et al. 1980; Plaa et al. 1987; Seidenberg et al. 1986; Simmons et al. 1987; Swanson and Wooley 1982; Swartz et al. 1988; Teo and Vore 1991; Uzodinma et al. 198ia; Yarbrough et al. 1981), but no information was located for the inhalation or dermal exposure routes. Chlordecone may lead to death after oral administration, depending on dose (Larson et al. 1979b; Simmons et al. 1987); pregnant animals may be more sensitive to lethal effects of chlordecone (Chernoff and Rogers 1976; Kavlock et al. 1985; Seidenberg et al. 1986).

The main toxic effects of acute-duration oral chlordecone administration are reproductive, neurological, musculoskeletal, and hepatic. Studies in laboratory animals exposed orally to chlordecone have demonstrated reproductive effects such as decreased fertility or fecundity and litter size, reduced sperm count, and testicular atrophy in animals (Khera et al. 1976; Uzodinma et al. 1984a; Yarbrough et al. 1981). Neurotoxicity is a well-studied toxic effect of chlordecone in rats and mice (Albertson et al. 1985; Aldous et al. 1984; Baggett et al. 1980; Chang-Tsui and Ho 1979; Desaiah et al. 1980a; Egle et al. 1979; End et al. 1981; Fujimori et al. 1982b; Hoskins and Ho 1982; Huang et al. 1980; Hwang and Van Woert 1979; Jordan et al. 1981; Klingensmith and Mehendale 1982b; Maier and Costa 1990; Mishra et al. 1980; Smialowicz et al. 1985; Swanson and Wooley 1982; Uzodinma et al. 1984a). Toxicity to the musculoskeletal system of rats has been observed after single oral doses of chlordecone (Egle et al. 1979). Biochemical changes were also found in the muscle of rats after multiple chlordecone doses (Mishra et al. 1980). There are few studies which examine the musculoskeletal system after oral administration. Chlordecone has been found in rats and mice to result in impaired biliary excretion and/or other signs of liver toxicity in some studies (Fujimori et al. 1983; Mehendale 1977b, 1981b; Teo and Vore 1991) but not in all (Davis and Mehendale 1980; Glende and Lee 1985; Iijima et al. 1983; Klingensmith and Mehendale 1983b; Plaa et al. 1987).

Cardiovascular effects of chlordecone in rats after acute-duration exposure to chlordecone are limited to biochemical changes in cardiac tissue, such as membrane enzyme inhibitions and altered protein phosphorylation (Desaiah 1980; Kodavanti et al. 1990a). These effects may impact electrolyte balance across the cell; however, additional studies must be conducted to ascertain the functional effect of enzyme changes. Chlordecone has also been found to have an affect on thermoregulation in rats (Swanson and Wooley 1982). In contrast to mirex, chlordecone induced less serious developmental effects. Common developmental effects included decreased fetal weight and delayed skeletal ossification (Chernoff and Rogers 1976; Gellert and Wilson 1979; Gray and Kavlock 1984; Squibb and Tilson 1982a; Swartz et al. 1988). At higher doses, decreased viability occurred (Gray and Kavlock 1984; Seidenberg et al. 1986). Chlordecone did not result in dominant lethal effects in acute *in vivo* genotoxicity assays (Simon et al. 1986).

No acute-duration inhalation MRL could be derived for chlordecone because no data could be located using this route of exposure. Since there are no animal data that examine gastrointestinal, hematological, respiratory, thyroid, or adrenal effects of acute-duration chlordecone administration, additional studies would be useful to establish chlordecone's toxicity. Human studies for the acute

duration are completely lacking; therefore, it would be helpful if populations exposed to this substance were carefully monitored in order to better understand the toxic effects of humans exposed to chlordecone.

**Intermediate-Duration Exposure.** No information is available regarding the toxicity of intermediate-duration exposure of humans to mirex by any route of administration. Information regarding exposure of animals to mirex for an intermediate duration is available for the oral route (Bell and Mehendale 1985; Chu et al. 1980a, 1981a, 1981b; Curtis and Hoyt 1984; Davison et al. 1976; Dietz and McMillan 1979; Fujimori et al. 1983; Gaines and Kimbrough 1970; Klingensmith and Mehendale 1982a, 1982b; Larson et al. 1979a; Mehendale 1981b; Mehendale et al. 1977a, 1978b; NTP 1990; Singh et al. 1982, 1985; Ware and Good 1967). Animals exposed orally to mirex for an intermediate period of time demonstrated increased lethality according to dose (Gaines and Kimbrough 1970; Larson et al. 1979a; Mehendale 1981b) and species (mice and dogs may be more sensitive) (Ware and Good 1967). Data from inhalation or dermal exposure to mirex could not be located; therefore, the concentration or dose that would be likely to cause death after these exposure routes cannot be established. The target organs of toxicity to orally administered mirex appear to be the liver, gastrointestinal system, and thyroid. Liver toxicity with intermediate-duration oral exposure to mirex is similar to that occurring after acute-duration exposure, with the exception that lower doses cause hepatotoxicity. The most prominent hepatic effects are impaired biliary excretion (Bell and Mehendale 1985; Curtis and Hoyt 1984; Larson et al. 1979a; Mehendale 1981b; Teo and Vore 1991) and liver histopathology (Davison et al. 1976). Mild diarrhea occurred in two studies in rats (Dietz and McMillan 1979; Mehendale 1981b); in one study with mice, severe diarrhea and hemorrhage of the intestines indicated a gastrointestinal ongin for the disturbance (Fujimori et al. 1983). Histopathological changes in the thyroid have been reported after intermediate-duration oral exposure of animals; however, no change in serum thyroid hormone levels was found (Chu et al. 1981a, 1981b; NTP 1990; Singh et al. 1982, 1985).

Adrenal effects have been seen (Larson et al. 1979b) that are consistent with increased lipid utilization (Fujimori et al. 1983; Klingensmith and Mehendale 1982a; Mehendale et al. 1977a, 1978b). Body weight decreases have been found in intermediate-duration oral studies using mirex (Chu et al. 1981b; Larson et al. 1979a). No adverse cardiovascular effects were found in one study (Larson et al. 1979a); however, the data reported from this study were limited. No renal toxicity was found after intermediate-duration oral exposure to mirex (Chu et al. 1980a; Larson et al. 1979a), but these studies

are flawed. No reports could be located describing the musculoskeletal effects of intermediateduration oral mirex administration. Well-conducted studies in animals to evaluate these end points for mirex following acute- and intermediate-duration inhalation, oral, and dermal exposures, and for chlordecone following inhalation and dermal exposures would be helpful. In addition, there is a lack of intermediate-duration human mirex exposure studies; therefore, populations exposed to this substance should be carefully monitored in order to better understand the toxic effects on humans exposed to it.

The only information available for humans exposed to chlordecone pertains to a study of intermediateto-chronic occupational exposures (exact durations not recorded) of one group of individuals employed at a facility in Hopewell, Virginia. Chlordecone was manufactured in this facility for 21-22 months; because of poor hygiene at the facility, exposure by all routes was likely. In addition, concomitant exposure to a precursor was possible. Several studies have been published to describe the toxicity in this human population (Cannon et al. 1978; Taylor 1982, 1985), and results of these studies will be considered here. These results pertain to the chronic-duration exposure also. No deaths were reported (Cannon et al. 1978; Taylor et al. 1978). Skeletal muscle biopsy was conducted on six workers who experienced adverse neurological clinical signs (such as tremors) as well as muscle weakness and incoordination (Martinez et al. 1978). Abnormal histological and biochemical indices were revealed in this tissue. Joint pain was also reported (Taylor 1982, 1985). Liver toxicity (Guzelian et al. 1980), skin rashes, and weight loss (described as severe in some individuals) occurred (Cannon et al. 1978; Taylor et al. 1978). Respiratory effects included pleuritic chest pains but no lung pathology (Taylor 1982, 1985). Cardiovascular abnormalities were not observed on electrocardiographic study (Taylor 1982, 1985). No data could be located regarding gastrointestinal, hematological, or renal effects in this population of individuals exposed to chlordecone for intermediate or chronic durations.

There are no data for intermediate-duration inhalation or dermal exposure of animals to chlordecone, but there are several oral exposure studies (Agarwal and Mehendale 1983a, 1983c; Agarwal et al. 1983; Bell and Mehendale 1985; Cannon and Kimbrough 1979; Chu et al. 1980a, 1981a, 1981b; Curtis and Hoyt 1984; Curtis and Mehendale 1979, 1980; Curtis et al. 1979b, 1981; Fabacher and Hodgson 1976; Fujimori et al. 1983; Huber 1965; Klingensmith and Mehendale 1982a, 1982b; Larson et al. 1979b; Mehendale 1981b; Mehendale et al. 1977a, 1978b; NTP 1990; Pryor et al. 1983; Singh et al. 1982, 1985; Squibb and Tilson 1982b). Oral exposure of animals to chlordecone can result in lethality; mortality is affected by dose (Fujimori et al. 1983; Mehendale 1981b; Pryor et al. 1983) and

age (Huber 1965). In animals, the major targets of intermediate-duration oral exposure to chlordecone are the liver and adrenal gland. Other major effects include neurological (exaggerated startle response), developmental (Ali et al. 1982; Rosecrans et al. 1982; Squibb and Tilson 1982a), and reproductive effects (testicular atrophy) (Larson et al. 1979b; Squibb and Tilson 1982b), which are discussed in the appropriate sections below. Impaired hepatobiliary excretion was found in intermediate-duration exposure studies (Curtis and Mehendale 1979; Curtis et al. 1979b; Mehendale 1981b), in addition to inhibition of exogenous taurocholate (Curtis and Hoyt 1984) and histopathological findings (Cannon and Kimbrough 1979; Chu et al. 1980a; Curtis et al. 1979b, 1981; Huber 1965; Larson et al. 1979b). An intermediate-duration MRL of 0.0005 mg/kg/day was derived for oral exposure to chlordecone based on a NOAEL of 0.05 mg/kg/day for histopathological evidence of renal damage from the Larson et al. (1979b) study in rats. Thyroid ultrastructure was altered after intermediate-duration exposure (Chu et al. 1981a, 1981b; NTP 1990; Singh et al. 1982, 1985); this effect was reversible after discontinuation of the exposure. Although few studies are available, decreased adrenal lipid (Larson et al. 1979b) and increased lipid utilization, possibly mediated by corticosterone (Fujimori et al. 1983; Klingensmith and Mehendale 1982a; Mehendale et al. 1977a, 1978b), occurred. Decreased body weight was also observed, perhaps by a similar mechanism (Cannon and Kimbrough 1979; Curtis and Mehendale 1979; Fabacher and Hodgson 1976; Larson et al. 1979b; Klingensmith and Mehendale 1982a; Mehendale et al. 1977a, 1978b; Pryor et al. 1983). Limited data were located regarding the cardiovascular effects of chlordecone; vasodilation has been measured and may have been associated with thermoregulation (Larson et al. 1979b). No renal toxicity was found after intermediate-duration oral exposure to chlordecone (Agarwal et al. 1983; Larson et al. 1979b). The musculoskeletal effects observed in acute-duration exposures were not found in histopathological examination of skeletal muscle from intermediate-duration exposures (Larson et al. 1979b). It is unknown if the lower dose or some other factor contributed to the lack of an effect.

Further human data should be gathered for intermediate-duration exposure to chlordecone by all routes. Human data were either absent (gastrointestinal, hematological, or renal effects) or limited to a population study with major restrictions (Cannon et al. 1978; Guzelian 1982a; Landngen et al. 1980; Martinez et al. 1978; Sanbom et al. 1979; Taylor 1982, 1985; Taylor et al. 1978). The toxicity of chlordecone after intermediate-duration exposure in animals is absent for inhalation and dermal routes. Additional information for this duration of exposure would be useful. Additional dermal studies are certainly necessary because skin absorption of chlordecone appears to be an important route of

exposure (Taylor et al. 1978). However, populations at hazardous waste sites are unlikely to be exposed via inhalation since these substances are virtually nonvolatile, so future studies using this route of exposure are not essential.

**Chronic-Duration Exposure and Cancer.** No information is available regarding the toxicity of chronic-duration exposure of humans to mirex by the inhalation or dermal route of administration. Animal studies have not been located for chronic mirex administration by the inhalation or dermal routes; however, oral studies exist (Chu et al. 1981a; Gaines and Kimbrough 1970; NTP 1990; Ulland et al. 1977a; Wolfe et al. 1979). Chronic exposure to mirex by the oral route results in mortality in animals, especially at higher doses and for longer durations (NTP 1990; Wolfe et al. 1979). The major target organs for mirex after chronic-duration exposures appear to be the kidney, nervous system, reproductive system, liver, cardiovascular system, and thyroid. Although acute- and intermediate-duration exposures to mirex are without renal effects, chronic-duration exposure results in kidney toxicity. Sufficient data exist to speculate that the kidney is a primary site of mirex toxicity. Nephrotoxicity as characterized by histological changes (necrosis, nephritis) was documented (NTP 1990). Chronic-duration exposures to mirex have been shown to increase excitability, hypoactivity, irritability, and tremors in treated rats (Chu et al. 1981a), as was found in shorter-term oral exposures. Reproductive effects of chronic-duration mirex exposure included cataract formation and decreased survivol in offspring (Gaines and Kimbrough 1970), and inhibition of reproduction (Wolfe et al. 1979). No data were located regarding the hepatobiliary effects of chronic-duration mirex administration, but histopathological examination of chronic exposure studies revealed hepatic necrosis (NTP 1990; Ulland et al. 1977a). Thyroid effects (histopathological) occurred in chronic-duration exposure to mirex (Chu et al. 1981c; NTP 1990). Several intermediate-duration studies in rats also indicate that the thyroid is a target organ for mirex toxicity (Chu et al. 1981a, 1981b; Singh et al. 1982, 1985). These studies showed reduced colloid, thickening of the follicular epithelium, angular collapse of the follicles, and dilation of the rough endoplasmic reticulum of thyroid cells at 0.25 mg/kg/day for 28 days. A chronic-duration oral MRL was derived using a NOAEL for hepatic, renal, and thyroid toxicity in a 2-year feeding study in rats (NTP 1990). This is supported by data from other studies (Chu et al. 1981c; Fulfs et al. 1977; Ulland et al. 1977a) that indicated that the liver and kidney were target organs following chronic-duration exposure to mirex. Reproductive toxicity was tested at doses higher than the NOAEL from this study, and only less serious effects (nonsignificant decrease in litter size) were observed (Wolfe et al. 1979). No chronic-duration inhalation MRL was derived for mirex because no data could be located for this duration and route. No reports could be located that

addressed the effects of chronic-duration exposure to mirex regarding gastrointestinal, hematological, musculoskeletal, dermal, or adrenal toxicity. Well-conducted studies in animals to evaluate these end points for mirex following acute- and intermediate-duration inhalation, oral, and dermal exposures would be helpful. As with the shorter duration exposures, monitoring humans who are chronically exposed to mirex by any route would be useful.

The only information available for humans exposed to chlordecone pertains to the intermediate-tochronic occupational exposure study previously discussed in the intermediate-duration section (see the above section for a description of intermediate-to-chronic toxicity of chlordecone in humans). These studies are limited in usefulness because the exposures were to more than one substance in a facility where exposure by all routes was likely (Cannon et al. 1978; Taylor 1982, 1985). These and other available human studies described respiratory (Cannon et al. 1978; Landngen et al. 1980; Sanborn et al. 1979), hepatic (Guzelian 1982a; Guzelian et al. 1980; Landngen et al. 1980), renal (Larson et al. 1979b), musculoskeletal (Landngen et al. 1980; Martinez et al. 1978; Taylor 1982, 1985), dermal (Cannon et al. 1978; Landngen et al. 1980), body weight (Cannon et al. 1978), neurological (Cannon et al. 1978; Landngen et al. 1980; Martinez et al. 1978; Sanborn et al. 1979; Taylor 1982, 1983, and reproductive (Cannon et al. 1978; Guzelian 1982a; Landngen et al. 1980; Taylor 1982, 1985) effects following chronic exposure to chlordecone. There are no inhalation or dermal data for chronicduration exposure to chlordecone in animals; however, there are a few oral studies (Larson et al. 1979b; NCI 1976). Two chronic-duration animal studies exist that present survivol data (Larson et al. 1979b; NCI 1976). Effects on mortality after inhalation or dermal exposure cannot be evaluated due to the lack of information. The target organs of chronic-duration oral exposure appear to be the kidney, nervous system, and male reproductive system. Like mirex, chlordecone caused significant renal toxicity only for chronic-duration oral exposures. Renal histopathological changes (eosinophilic inclusions, glomernlosclerosis) and increased urinary protein excretion occurred in rats (Larson et al. 1979b). Other available human studies described hematological (Larson et al. 1979b; NCI 1976), hepatic (Larson et al. 1979b; NCI 1976), renal (Larson et al. 1979b), dermal (NCI 1976), body weight (Chu et al. 1981c; Larson et al. 1979b), neurological (Larson et al. 1979b; NCI 1976), reproductive (NCI 1976), endocrine (Chu et al. 1981c), and cancer (NCI 1976) effects following chronic exposure to chlordecone. A chronic-duration MRL of 0.0005 mg/kg/day was derived for oral exposure to chlordecone based on a NOAEL of 0.05 mg/kg/day for histopathological evidence of renal damage from the Larson et al. (1979b) study in rats. There may be a difference in species sensitivity because chronically exposed dogs did not have renal effects (Larson et al. 1979b). The neurotoxicity of

chlordecone (e.g., exaggerated startle response) has been documented after chronic-duration exposure (Larson et al. 1979b). Testicular atrophy has been reported in dogs (Larson et al. 1979b). Limited data could be located regarding respiratory effects of chronic-duration oral exposure to chlordecone; routine histopathology in a few animal samples revealed no adverse lung effects in two species (Larson et al. 1979b). Similar examination of heart and gastrointestinal tissues in this study did not reveal adverse effects (Larson et al. 1979b). An independent review of the histopathological evidence from the cancer bioassay tissues reported polyarteritis in arteries and arterioles; however, no data were presented to support these conclusions (Reuber 1979b). Hematological effects were not found in one chronic-duration study in rats and dogs (Larson et al. 1979b). An independent review of this study reported anemia; however, no data were presented to support this conclusions (Reuber 1979b). Body weight was found to decrease, with concomitantly increased food consumption (Larson et al. 1979b). This indicated a decreased food efficiency. No adverse histopathological effects were reported on musculoskeletal, hepatic, or dermal tissues after oral exposure to mirex for 2 years (Larson et al. 1979b). Data from laboratory animals indicate that chronic exposure to chlordecone adversely affects the thyroid gland (Chu et al. 1981c). No chronic-duration inhalation MRL was derived because of the absence of reliable data following inhalation exposure to chlordecone. Additional studies would be helpful to verify the effects seen in the existing studies. Additional dermal studies are certainly necessary because skin absorption of chlordecone appears to be an important route of exposure (Taylor et al. 1978). However, populations at hazardous waste sites are unlikely to be exposed via inhalation since these substances are virtually nonvolatile, so future studies using this route of exposure are not essential.

No evidence for carcinogenicity in exposed humans was found in the available literature. Animal studies provide sufficient evidence that mirex and chlordecone are carcinogenic after oral exposure (Innes et al. 1969; NTF’ 1990; NCI 1976; Reuber 1978a, 1979b, 1979c; Ulland et al. 1977a). Carcinogenic potential has not been tested by the inhalation or dermal routes. Effects after inhalation exposure are unlikely because of low volatility. A carcinogenicity study in animals exposed by the dermal route would be desirable but comparison of steady-state levels of the chemicals in rat liver after repeated dermal or oral exposure may suffice to extrapolate to likely carcinogenicity concern by dermal exposure. Evidence suggests that chlordecone and mirex are epigenetic carcinogens (see the section on Genotoxicity below), and a two-stage initiation-promotion study in rats provides strong evidence for liver tumor promotion activity of chlordecone (Sirica et al. 1989). A similar evaluation

of mirex including measurement of levels of mirex in the liver at carcinogenic doses would allow comparisons and would be useful to elucidate mechanism of action and possible relevance to humans.

**Genotoxicity.** Although neither mirex nor chlordecone have been extensively evaluated in *in vivo* or *in vitro* genetic toxicology test systems, the existing studies provide convincing evidence that neither compound is genotoxic. Both compounds were negative in microbial (Mortelmans et al. 1986; Probst et al. 1981; Schoeny et al. 1979) and mammalian cell (Tong et al. 1981; Williams 1980) gene mutation assays, and neither compound showed signs of clastogenesis in male rats in well-conducted dominant lethal assays (Khera et al. 1976; Simon et al. 1986). Further genetic toxicology testing would be unlikely to provide additional useful information. However, data from a metabolic cooperation assay (Tsushimoto et al. 1982) and a dye-transfer assay (Caldwell and Loch-Caruso 1992) indicate that mirex and chlordecone interfere with cell-to-cell communication, a characteristic of many tumor promoters. Chlordecone has been shown to be a tumor promoter *in vivo* (Sirica et al. 1989); however, a more comprehensive evaluation is necessary to determine the level at which no *in vivo* promotion occurs. A similar experiment should be conducted with mirex to confirm suspected tumor promoting activity and to ascertain the threshold level for promotion. Finally, the evidence suggesting that mirex selectively reduces the proportion of rat tetraploid hepatocytes (Abraham et al. 1983) and preferentially binds to mouse polyploid hepatocytes *in vitro* (Rosenbaum and Charles 1986) should be investigated further. Similar assays involving alterations in ploidy of rodent hepatocyte populations should be undertaken with chlordecone. Information regarding effects on normal hepatic cell ploidy in animals may provide important clues regarding the mechanism(s) for the epigenetic/promoter activity of mirex and/or chlordecone, and perhaps suggest a target subpopulation of cells. However, it is emphasized that the population of hepatocytes that appear to be at risk (tetraploids) occurs in human livers at an exceedingly low frequency (Adler et al. 1981), so the relevance to human health of effects on ploidy is not clear.

**Reproductive Toxicity.** Studies in humans have attempted to correlate blood levels of chlordecone with the severity of loss of sperm motility (Guzelian 1982a; Taylor 1982, 1985; Taylor et al. 1978); however, these studies are limited by the lack of quantification of airborne concentrations of chlordecone, failure to examine the changes in sperm morphology, and a lack of control for confounding variables. No other human data regarding reproductive effects of chlordecone and mirex were located. Therefore, well-controlled epidemiological studies would be useful. Studies in laboratory animals exposed orally to chlordecone have demonstrated reproductive effects similar to

those produced by mirex in animals. Oral administration of these compounds decreased the fertility or fecundity and litter size, reduced the sperm count, and caused testicular atrophy in animals (Khera et al. 1976; Linder et al. 1983; Uzodinma et al. 1984a; Yarbrough et al. 1981). In a study performed in rabbits, dermal application of chlordecone produced testicular atrophy (Epstein 1978); however, the study was limited because of lack of dose response. No other studies in animals were found regarding reproductive effects of chlordecone or mirex via inhalation or dermal routes. Thus, studies examining effects on reproduction by these routes would be useful. Additional dermal studies are certainly necessary because skin absorption of chlordecone appears to be an important route of exposure (Taylor et al. 1978). However, populations at hazardous waste sites are unlikely to be exposed via inhalation since these substances are virtually nonvolatile, so future studies using this route of exposure are not essential. Studies conducted by the parenteral routes of exposure indicate that mirex is stable in the biological system. Animal studies performed via parenteral routes have demonstrated the estrogenic effects of chlordecone in female rats and mice (Eroschenko and Mousa 1979; Gellert 1978; Hammond et al. 1978; Johnson et al. 1992). The mechanism involving interaction with estrogen receptors has been postulated (Huber 1965). Additional studies would be useful in elucidating the mechanism of action of chlordecone. Mirex is not uterotropic in rats (Hammond et al. 1979); however, it has a potential to degrade to chlordecone in nature (Carlson et al. 1976). Therefore, studies examining the estrogenic effects of mirex would be useful.

**Developmental Toxicity.** No human studies are available on developmental effects of chlordecone or mirex in humans for any exposure route. Similarly, no studies are available for animals via the inhalation or dermal routes. Placental transfer and lactational transfer of chlordecone have been demonstrated in mice after oral exposure, though in a very limited number of animals (Huber 1965). Developmental effects of chlordecone and mirex via oral exposure have been well documented in animals (Buelke-Sam et al. 1983; Chernoff and Kavlock 1973; Chernoff et al. 1979a, 1979b; Grabowski 1983a; Gray and Kavlock 1984; Kavlock et al. 1982; Swartz et al. 1988). Therefore, additional studies via inhalation and dermal routes would be useful to examine the postnatal developmental effects of prenatal exposure to chlordecone and mirex. Additional dermal studies are certainly necessary because skin absorption of chlordecone appears to be an important route of exposure (Taylor et al. 1978). However, populations at hazardous waste sites are unlikely to be exposed via inhalation since these substances are virtually nonvolatile, so future studies using this route of exposure are not essential.

**Immunotoxicity.** No information is available regarding immunological effects of mirex or chlordecone in humans following inhalation, oral, or dermal exposures. The only information about the immunological effects of mirex exposure in animals was provided by one acute oral study in rats in which decreased spleen weight was reported (Buelke-Sam et al. 1983). Oral chlordecone treatment caused decreased spleen and thymus weights, leukocyte counts, natural killer cell activity, and mitogenic responsiveness (EPA 1986c; Smialowicz et al. 1985; Swanson and Wooley 1982); decreased natural killer cell activity (Smialowicz et al. 1985); and significant increase in plaque-forming cells (Chetty et al. 1993c). Consequently, there is a need for confirmatory information on whether these chemicals affect cell-mediated and/or humoral immunity in humans. Skin absorption of chlordecone appears to be an important route of exposure (Taylor et al. 1978). Therefore, dermal sensitization tests done on exposed workers would provide information on the likelihood of an allergic response in humans following chlordecone exposure. An indication for this testing is the development of skin rashes in workers who worked in chlordecone-manufacturing plants (Cannon et al. 1978; Taylor 1982; Taylor et al. 1978). As with many of the occupational exposure studies, the routes of exposure, dose, and duration were not precisely defined in these studies.

No studies were located that examined the immunotoxicity of mirex in experimental animals. The information available from one acute study in rats indicates that the immune system is not a target of chlordecone toxicity. There is a need for information from animal model systems on cell-mediated and humoral immunity following inhalation, oral, and dermal exposures to mirex and chlordecone. The results from these studies would help elucidate whether there are thresholds of chlordecone immunotoxicity after acute, intermediate, and chronic exposures via these routes.

Diethylstilbestrol, a nonsteroidal compound with estrogenic activity, has been shown to suppress immune responsiveness in a number of experiments (Dean et al. 1980). The immunosuppression is suggested to be mediated, at least in part, through interactions with estrogen receptors on thymic epithelial and lymphoid cells. Chlordecone has been shown to interact with estrogen receptors (Bulger et al. 1979; Hammond et al. 1979) and to mimic estrogen in a number of reproductive parameters; therefore, it is possible that chlordecone may also adversely affect immune function. Studies designed to test this hypothesis would be useful.

**Neurotoxicity.** Information on the neurotoxicity of mirex in humans following exposure by the inhalation, oral, or dermal routes was not located. Several reports regarding a single group of workers exposed to chlordecone during its manufacture noted a high incidence of nervous system toxicity (Cannon et al. 1978; Martinez et al. 1978; Sanbom et al. 1979; Taylor 1982, 1985; Taylor et al. 1978). Exposure of this population occurred by a combination of inhalation, oral, and dermal exposures, although the dermal route was suggested to be the predominant route. The toxicity was manifested as tremors, visual difficulties, muscle weakness, gait ataxia, incoordination, headache, and increased cerebrospinal fluid pressure. A few studies indicate that ingestion of mirex may also cause tremors, hyperexcitability, and/or convulsions (Chu et al. 1981a; Gaines and Kimbrough 1970; Kendall 1974a; Larson et al. 1979a). Studies directed at examining the mechanism of mirex-induced neurotoxicity would be helpful for determining whether mirex is acting by a mechanism similar to chlordecone. Several studies in animals have been undertaken in an attempt to elucidate the mechanism underlying the effects observed (Aronstam and Hong 1986; Bansal and Desaiah 1982; Bloomquist et al. 1986; Bondy and Halsall 1988; Bondy and McKee 1990; Bondy et al. 1989; Chetty et al. 1983b; Desaiah 1981, 1985; Desaiah et al. 1980a, 1980b, 1991; End et al. 1979, 1981; Folmar 1978; Gerhart et al. 1982, 1983; Herr et al. 1987; Hong et al. 1984, 1986; Hwang and Van Woert 1979; Jinna et al. 1989; Kodavanti et al. 1988, 1989c; Komulainen and Bondy 1987; Mishra et al. 1980; Singh et al. 1984; Tilson et al. 1985, 1986b; Vig et al. 1990b, 1991). However, the precise neurotoxic mechanism of chlordecone remains unclear. Additional toxicokinetic studies directed at assessing the mechanism of neurotoxicity of chlordecone would be helpful for the development of treatment strategies.

**Epidemiological and Human Dosimetry Studies.** No epidemiological studies are available for mirex exposure. Individuals living in areas that have been treated for fire ants or near hazardous waste sites containing mirex or chlordecone are the most likely exposed subpopulation because of the relatively long half-lives of these substances-estimated half-life of 10 years-(Carlson et al. 1976; La1 and Saxena 1982). A single epidemiological cohort was located for occupational exposure to chlordecone (Cannon et al. 1978; Guzelian et al. 1980; Sanbom et al. 1979; Taylor 1982, 1985). The routes of exposure in this study were probably mixed because of the poor hygiene in the chlordecone manufacturing plant (Taylor 1982, 1985). The most likely identifiable subpopulation exposed to chlordecone would be individuals who live in the Hopewell, Virginia, vicinity who may consume wildlife in which the chemical is bioconcentrated. Well-designed epidemiological studies of these subpopulations specifically examining neurological, hepatic, reproductive, developmental,

thyroid, and musculoskeletal toxicity and carcinogenicity would be useful to verify effects seen in the limited human and animal studies.

## Biomarkers of Exposure and Effect

*Exposure.* The biomarkers of exposure to mirex and chlordecone are well established and specific to each compound. The known biomarkers of exposure to mirex are mirex concentrations in blood, fat, feces, and milk (Burse et al. 1989; Byrd et al. 1982; Chambers et al. 1982; Dorough and Ivie 1974; Gibson et al. 1972; Ivie et al. 1974b; Kavlock et al. 1980; Kutz et al. 1974; Smrek et al. 1977; Wiener et al. 1976). All these biological materials are useful and can be monitored to determine the acute, intermediate, and chronic exposures to mirex. The known biomarkers of exposure for chlordecone include chlordecone concentrations in blood, saliva, and tissues, and concentrations of chlordecone or its metabolite in feces or bile (Borzelleca and Skalsky 1980; Bungay et al. 1981; Cannon et al. 1978; Cohn et al. 1978; Egle et al. 1978; Guzelian et al. 1981; Hewitt et al. 1986b; Skalsky et al. 1980; Plaa et al. 1987; Taylor 1982, 1985). Of the biomarkers of exposure listed for chlordecone, the blood is the most useful biological material to monitor in order to determine acute, intermediate, and chronic exposure to chlordecone. No relationship has been established between mirex or chlordecone exposure levels, levels of mirex or chlordecone in the biological fluids, and their associated health effects for all exposure durations. Data identifying the correlations between these parameters would be useful.

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

**Absorption, Distribution, Metabolism, and Excretion.** No data were located regarding absorption of mirex in humans following inhalation, oral, or dermal exposure. Limited epidemiological data were located regarding the distribution and excretion of mirex following inhalation, oral, and dermal exposure (Burse et al. 1989; Kutz et al. 1974; Mes et al. 1978). Mirex is not metabolized by humans or animals (Dorough and Ivie 1974; Gibson et al. 1972; Kutz et al. 1974; Mehendale et al. 1972; Morgan et al. 1979). There are a number of animal studies describing absorption, distribution, metabolism, and excretion of mirex following oral exposure (Brown and Yarbrough 1988; Byrd et al. 1982; Chambers et al. 1982; Gibson et al. 1972; Ivie et al. 1974b; Kavlock et al. 1980; Mehendale et al. 1972; Morgan et al. 1979; Plaa et al. 1987; Smrek et al. 1977; Wiener et al. 1976). Information is available to assess the relative rates and extent of these toxicokinetic parameters by the oral route. Based on the available data, saturation phenomena do not appear to affect absorption, distribution, metabolism, or excretion of mirex. Most of the toxicokinetic data, however, involve acute exposures to mirex; only very limited data deal with intermediate or chronic exposures. Additional intermediate and chronic data are needed in order to adequately assess the rates and extent of the toxicokinetic parameters for these durations. Limited animal data were located regarding the absorption, distribution, and excretion of mirex following inhalation exposure (Atallah and Dorough 1975; Dorough and Atallah 1975). More acute, intermediate, and chronic data are needed to adequately assess the relative rates and extent of the toxicokinetic parameters by this route. No animal data were located for the toxicokinetic parameters by the dermal exposure route.

Limited occupational data exist regarding absorption, distribution, metabolism, and excretion of chlordecone by humans following all three routes of exposure (Adir et al. 1978; Blanke et al. 1978; Boylan et al. 1978; Cannon et al. 1978; Cohn et al. 1978; Guzelian et al. 1981; Taylor 1982, 1985). There are a number of animal studies describing the absorption, distribution, metabolism, and excretion of chlordecone following oral exposure (Blanke et al. 1978; Borzelleca and Skalsky 1980; Boylan et al. 1979; Cohn et al. 1978; Egle et al. 1978; Fujimori et al. 1982a; Guzelian et al. 1981; Hewitt et al. 1986b; Kavlock et al. 1980; Plaa et al. 1987; Richter et al. 1979; Skalsky et al. 1980; Wang et al. 1981). Most of these data concern acute exposures. However, the available data are sufficient to assess the relative rates and extent of the pharmacokinetics following oral exposure. Dermal absorption does occur, but to a limited extent (Hall et al. 1988; Shah et al. 1987). No studies were located regarding distribution, metabolism, or excretion following dermal exposure. No animal data were located regarding absorption, distribution, metabolism, or excretion of chlordecone following

inhalation exposure. Additional data (acute, intermediate, and chronic) for both humans and animals are needed to adequately compare the toxicokinetic parameters across all routes of exposure.

**Comparative Toxicokinetics.** The absorption, distribution, metabolism, and excretion of mirex have been studied in animals (Atallah and Dorough 1975; Brown and Yarbrough 1988; Byrd et al. 1982; Chambers et al. 1982; Dorough and Atallah 1975; Gibson et al. 1972; Ivie et al. 1974b; Kavlock et al. 1980; Mehendale et al. 1972; Morgan et al. 1979; Plaa et al. 1987; Smrek et al. 1977; Wiener et al. 1976). However, information on the toxicokinetics of mirex in humans is very limited (Burse et al. 1989; Kutz et al. 1974; Mes et al. 1978). The target organs identified in animals include the liver, kidney, eyes, thyroid, reproductive tract, and fetus. Since the human data are so limited, no target organs have been identified. Therefore, no comparisons can be made between humans and animals at this time. Based on the available data in both humans and animals, mirex accumulates and is retained in the tissues, particularly in the fat. It is not metabolized and is slowly excreted in the feces. Limited information is available regarding interspecies differences in kinetics. Most of the toxicokinetic studies have been conducted using rats. A few studies using monkeys, goats, and cows yielded similar results. Therefore, based on the available data, humans would be expected to handle mirex similarly (i.e., they would probably have similar target organs).

The absorption, distribution, metabolism, and excretion of chlordecone have been studied in animals (Blanke et al. 1978; Borzelleca and Skalsky 1980; Boylan et al. 1979; Cohn et al. 1978; Egle et al. 1978; Fariss et al. 1980; Fujimori et al. 1982a; Guzelian et al. 1981; Hall et al. 1988; Hewitt et al. 1986b; Kavlock et al. 1980; Plaa et al. 1987; Richter et al. 1979; Shah et al. 1987; Skalsky et al. 1980; Wang et al. 1981). However, information on the toxicokinetics of chlordecone in humans is limited (Adir et al. 1978; Blanke et al. 1978; Boylan et al. 1978; Cannon et al. 1978; Cohn et al. 1978; Guzelian et al. 1981; Taylor 1982, 1985). Human and animal data indicate similar target organs (liver, central nervous system, reproductive system) for the toxic effects of chlordecone, suggesting some similarities of kinetics. Appropriate assessment of potential adverse human health consequences of chronic exposure to chlordecone in the environment should take into account interspecies differences in chlordecone metabolism (Guzelian et al. 1981). Toxicokinetic studies have been performed on multiple species. Based on the available data, rats, guinea pigs, and hamsters are not good animal models for studying chlordecone metabolism in humans because they do not convert chlordecone to chlordecone alcohol (Fariss et al. 1980; Guzelian et al. 1981; Houston et al. 1981). On the other hand, gerbils and pigs were found to be the most practical animal models of chlordecone metabolism in

humans because they converted chlordecone to chlordecone alcohol (Houston et al. 1981; Soine et al. 1983).

**Methods for Reducing Toxic Effects.** Methods used to reduce absorption immediately after exposure to mirex and chlordecone include removal from the source of exposure; cleansing of contaminated parts; and in cases of ingestion, speeding the removal of the unabsorbed material from the gastrointestinal tract (Haddad and Winchester 1990; HSDB 1994a, 1994b; Morgan et al. 1979). Chlordecone and chlordecone alcohol, which are excreted mainly in the feces, undergo enterohepatic recirculation, which limits their excretion (Boylan et al. 1978). Because of this, detoxification has focused on limiting reabsorption of chlordecone from the gastrointestinal tract using cholestyramine (Boylan et al. 1978; Cohn et al. 1978), liquid paraffin (Richter et al. 1979), chlorella, and chlorelladerived sporopollenin (Pore 1984). Since cholestyramine did not interact with chlordecone alcohol (Guzelian 1981), other anion exchange resins or test compounds that bind to chlordecone alcohol need to be further investigated. No information was available to indicate that mirex undergoes enterohepatic recirculation; therefore, it is not known whether use of these therapies would be effective in reducing absorption of mirex. Studies investigating whether mirex undergoes enterohepatic recirculation are needed to determine if the three therapies listed above would be effective in reducing absorption. Since mirex and chlordecone have long retention times in the body and are only slowly excreted, studies aimed at reducing body burden would be useful. Additional studies directed toward developing effective therapies for blocking the neurotoxicity of chlordecone would be helpful, but the development of such therapies may be dependent on a more complete understanding of the mechanism for neurotoxicity than are currently available. Use of antibodies to block the effects of mirex and chlordecone *in vivo* should be examined further, either to develop antibodies that are well tolerated, or to more closely study the interaction that blocks the effects and develop drugs based on that interaction.

## 2.9.3 Ongoing Studies

No ongoing studies regarding the health effects of mirex and/or chlordecone were found.