CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

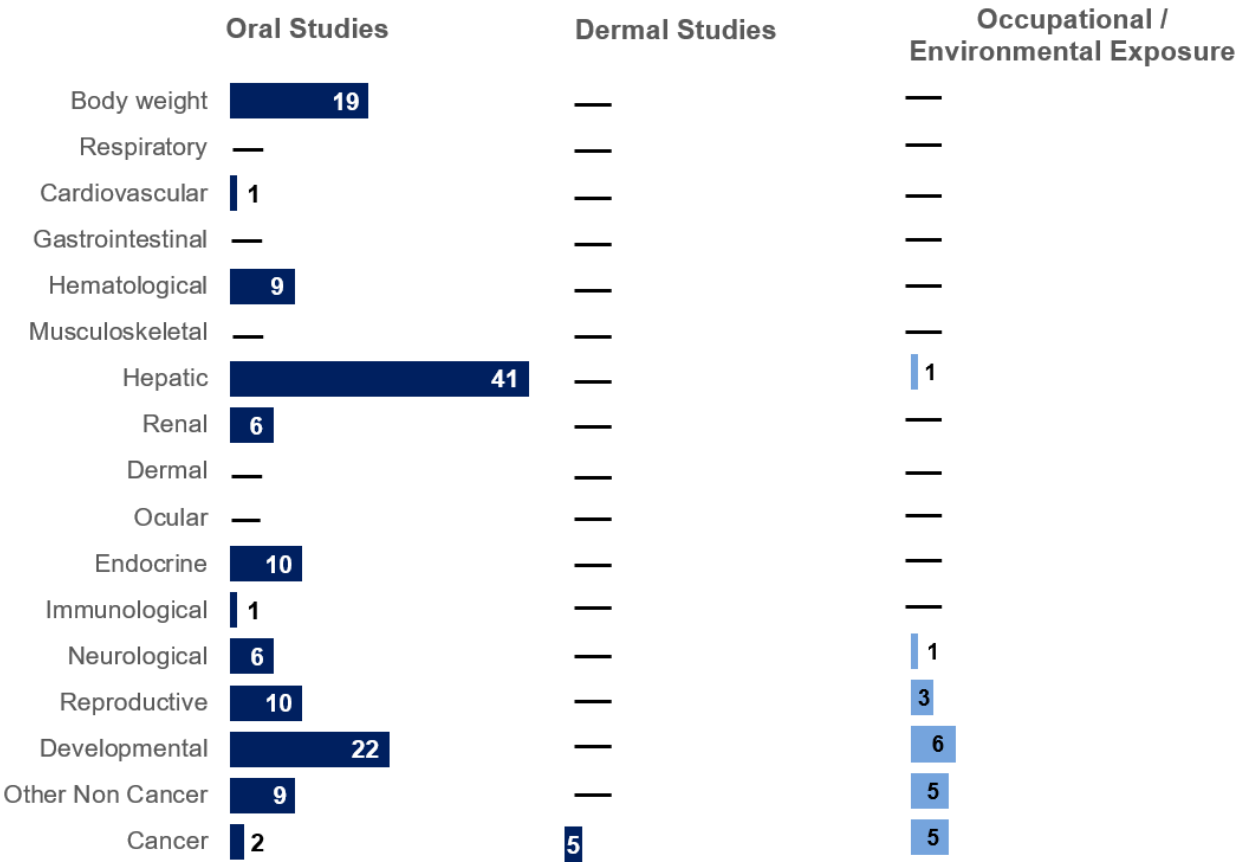
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to mirex and chlordecone that are discussed in Chapter 2 are summarized in Figures 6-1 and 6-2, respectively. The purpose of these figures is to illustrate the information concerning the health effects of mirex and chlordecone. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

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

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

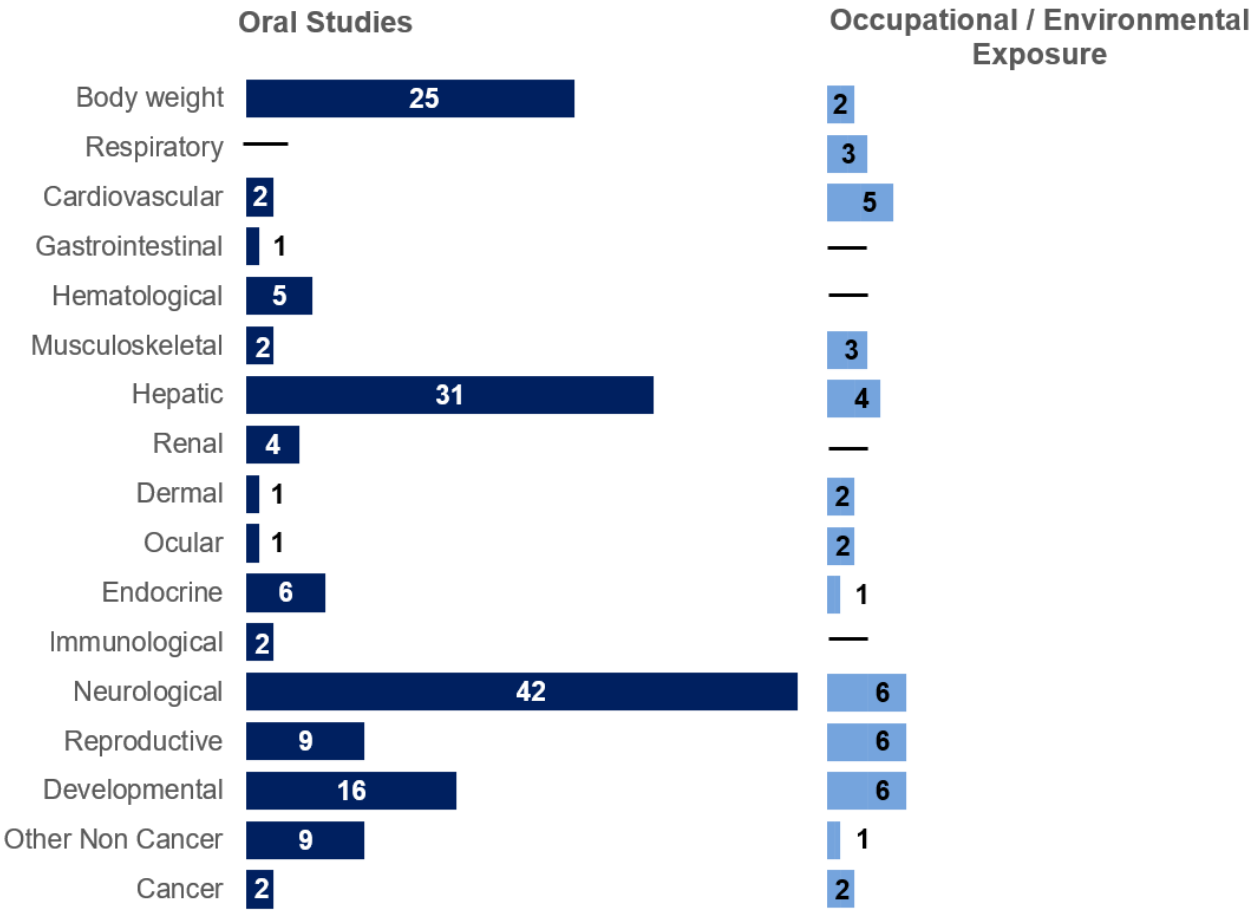
Potential body weight, liver, and developmental effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



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

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

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



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

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

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

6.2 Identification of Data Needs

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

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

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

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

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

Health Effects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Ongoing Studies

No ongoing studies were identified for mirex or chlordecone.