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 endrin 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 endrin.

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.

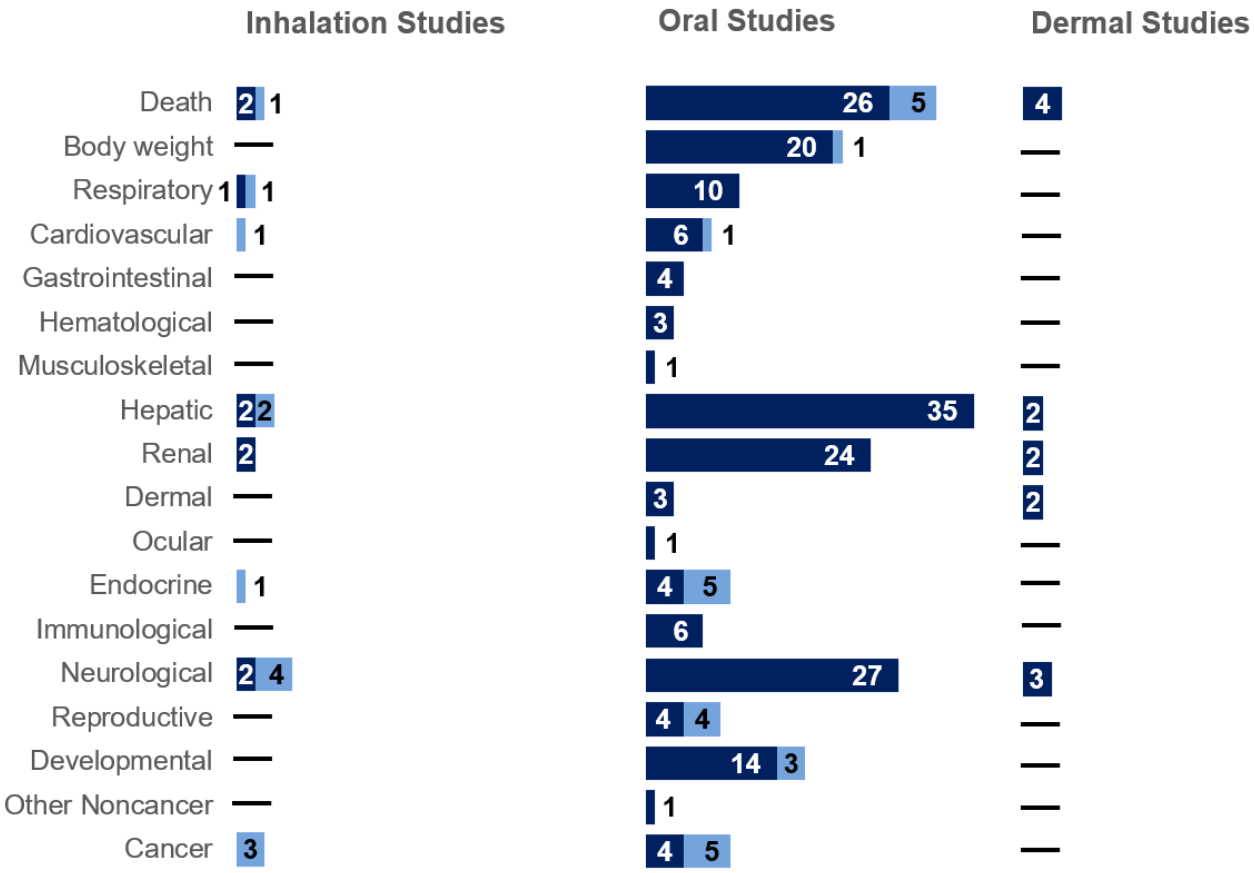
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to endrin that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of endrin. 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.

As illustrated in Figure 6-1, most of the data on the toxicity of endrin come from oral studies in laboratory animals. The most examined endpoints were neurological, hepatic, renal, body weight, and developmental effects. The available human studies include occupational health surveys, population-based studies, and case series predominantly focused on neurological effects and cancer. However, more recent human studies evaluated potential endocrine, reproductive, and developmental effects. For the purposes of Figure 6-1, all occupational studies were classified as inhalation studies and all population-based studies were classified as oral studies; however, it is acknowledged that humans were likely exposed via multiple exposure routes in both occupational and environmental settings. The laboratory animal inhalation and dermal toxicity database consists of a small number of studies evaluating limited endpoints. Only one study (Young and Mehendale 1986) was found on the health effects of endrin aldehyde or endrin ketone in animals following oral exposure; all other animal studies in Figure 6-1 evaluate endrin.

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

Most studies examined the potential hepatic and neurological effects of endrin
The majority of the studies examined oral exposure in **animals** (versus **humans**)



Includes studies discussed in Chapter 2. A total of 95 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints. All occupational studies were classified as inhalation studies and all population-based studies were classified as oral studies to avoid double counting these studies; however, it is acknowledged that humans were likely exposed via multiple exposure routes in both occupational and environmental settings.

6.2 Identification of Data Needs

Missing information in Figure 6-1 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. The inhalation database is inadequate to derive an acute-duration inhalation MRL; available human studies do not provide exposure data and the animal database is limited to a single study reporting lethality and histological alterations in the brain of a single cat (Ressang et al. 1959). Well-designed acute studies evaluating a comprehensive set of endpoints, including neurotoxicity, could potentially identify a point of departure (POD) to use as the basis for an acute inhalation MRL. The oral database is adequate to derive an acute-duration oral MRL based on neurobehavioral changes in rats. Additional well-designed, low-dose acute studies designed to evaluate a wide-array of neurological endpoints, including neurobehavior, could potentially identify a NOAEL for neurological effects following acute exposure and decrease the uncertainty in the acute oral MRL.

Intermediate-Duration MRLs. The inhalation database is not adequate to derive an intermediate-duration inhalation MRL; there are no available human studies and the animal database is limited to a single study evaluating mice and rabbits exposed to lethal concentrations (Treon et al. 1955). The oral database is also inadequate to derive an intermediate-duration oral MRL due to inadequate low-dose information; however, the acute-duration oral MRL was adopted as the intermediate-duration oral MRL. Well-designed, intermediate-duration inhalation and oral studies designed to evaluate a wide array of endpoints at low exposure levels, particularly neurological endpoints, could potentially identify an appropriate POD to use as the basis for intermediate-duration MRLs.

Chronic-Duration MRLs. The inhalation database is inadequate to derive a chronic-duration inhalation MRL; available human studies do not provide exposure data and there are no animal studies. Low-exposure inhalation studies designed to identify a NOAEL for neurological effects could potentially identify a POD to use as the basis for a chronic-duration inhalation MRL. The oral database is adequate to derive a chronic-duration oral MRL. Additional well-designed, low-dose chronic studies designed to evaluate a wide-array of neurological endpoints, including neurobehavior, could decreased the uncertainty in the chronic oral MRL.

Health Effects.

Neurotoxicity. While overt neurological effects are well characterized following oral exposures and, to a lesser extent, inhalation and dermal exposures, additional studies specifically to evaluate a wide array of neurological endpoints, including neurobehavior, would be helpful to establish dose-response relationships. Studies in humans indicate that endrin causes changes in the nervous system after occupational and oral exposure. Clinical symptoms including twitching and jerking of muscles, seizures, dizziness, and mental confusion within 2 hours following occupational exposure. Studies in animals confirm the neurotoxic potential of endrin.

Hepatic Toxicity. Additional low-exposure studies may better define the dose-response relationships. There is limited evidence of changes in liver function in endrin-exposed workers. Animal studies confirm that hepatotoxicity occurs following exposure at or near lethal doses. Hepatotoxicity has been observed following chronic exposure to sublethal doses.

Renal Toxicity. Additional low-exposure studies may better define the dose-response relationships. There are no data in humans regarding changes in renal function in endrin-exposed individuals. Inhalation, oral, and dermal exposure at or near lethal levels of endrin caused diffuse degenerative lesions in the kidneys of various species. There is limited evidence of renal effects (cloudy swelling of tubule epithelial cells) at nonlethal doses from one chronic study in rats (Deichmann et al. 1970); however, this finding was not confirmed in rats or mice at sublethal chronic doses in an NCI (1979) bioassay.

Respiratory Toxicity. Additional epidemiological studies and low-exposure animal studies in several species may better define potential respiratory effects and inform the dose-response relationships. No clear associations have been observed between altered respiratory function or disease and occupational endrin exposure in humans; however, human data are limited to two studies. In animals, most respiratory tract effects were associated with lethal exposure levels, and were attributed to widespread systemic failure. However, one chronic rat study reported focal hemorrhage and congestion of the lungs at sublethal levels.

Cardiovascular Toxicity. Additional epidemiological studies and low-exposure animal studies in several species may better define potential cardiac effects and inform the dose-response

relationships. No clear associations have been observed between environmental or occupational endrin exposure in humans; however, available human data are extremely limited. In dogs, diffuse degenerative lesions have been reported at lethal doses and elevated heart weight has been reported at sublethal doses. These findings have not been observed in other animal species.

Endocrine Toxicity. Additional epidemiological studies and low-exposure animal studies in several species may better define potential endocrine effects and inform the dose-response relationships. No clear associations have been observed between environmental exposure to endrin and endocrine effects in humans. In animals, chronic exposure to sublethal dietary doses caused thyroid hyperplasia and pituitary cysts in rats, but not mice.

Immunotoxicity. *In vivo* studies designed specifically to assess immune function (inhalation, oral, and dermal exposure routes), as well as additional *in vitro* testing involving humoral mediated immunity and nonspecific immunity, could be useful in assessing the immunotoxic potential of endrin. No *in vivo* studies evaluating immune function are available in humans or animals following exposure to endrin after inhalation, oral, or dermal exposure. Results of *in vitro* assays evaluating inhibition of lymphocyte responses and neutrophilic chemotaxis were negative. Animal studies are limited to oral studies reporting inconsistent organ weight changes in immune organs; the only study evaluating immune organ histopathology did not observe any histopathological lesions after chronic exposure.

Reproductive Toxicity. Additional, well-designed reproductive assays evaluating various species and several dose levels via the oral route (and other routes as well) would be useful in assessing the potential reproductive toxicity of endrin. No clear associations have been observed between environmental endrin exposure and preterm labor or birth outcomes in humans; however, there is limited evidence of a potential association between delayed female physical and sexual development in adolescents living in a highly contaminated region in Kazakhstan. Additional well-designed epidemiological studies with appropriate statistical power and control for confounding variables would be useful to further evaluate this potential association. No studies are available on the reproductive effects of endrin in animals after inhalation or dermal exposure. Reproductive toxicity data in animals are limited to two 1-generation studies, one in mice limited to a single dose level (Good and Ware 1969) and one in dogs with several experimental flaws (Kettering 1971), and a low-dose 3-generation study in rats (Eisenlord et al. 1968). Only the mouse study indicated potential reproductive effects (decreased litter size).

Developmental Toxicity. Additional low-exposure studies could determine if any additional developmental effects occur at oral doses below maternal toxicity or following inhalation or dermal exposure. Conducting these studies in multiple species could be helpful in identifying potential species differences. Limited evidence in humans indicate that endrin is not associated with adverse birth outcomes or impaired male reproductive development; however, one study reported an association between endrin exposure and cord blood thyroid hormone levels. Offspring of mice and hamsters exposed to endrin during gestation showed statistically significant increases in the incidence of fused ribs, cleft palate, exencephaly, and meningoencephaloceles at maternally toxic doses. In rats, only delayed ossification was observed at maternally toxic doses. However, perinatal studies in rats suggest altered neurobehavior in offspring at doses below those associated with maternal toxicity.

Epidemiology and Human Dosimetry Studies. Additional quantitative exposure data obtained from individuals occupationally exposed to low levels of endrin would be useful in evaluating potential risk to people living near hazardous waste sites. There are reports on the adverse effects of endrin in humans. These reports involve acute exposures in people who ingested endrin-contaminated food, occupational surveys and case reports, and population-based studies. Most studies have poor control for confounding variables, particularly exposure to other organochlorine pesticides, and/or have low statistical power. Despite limitations, existing studies identify the nervous system as a major target associated with exposure to endrin. However, reliable quantitative exposure levels that lead to these effects are lacking.

Biomarkers of Exposure and Effect. Measurement of endrin and its metabolites can be useful indicators of exposure. Since endrin is cleared from the blood rapidly, such measurements are suitable only for recent exposures. Changes in the nervous system appear to be the main effect associated with human exposure to endrin. Effects on the nervous system can be monitored in exposed individuals by measuring the incidence of signs and symptoms such as myoclonic jerking, seizures, convulsions, dizziness, and mental confusion. Because these effects also occur following exposure to other organochlorine pesticides and drugs, the development of more specific biomarkers of endrin exposure would be useful for studying potential endrin-related adverse health effects.

Absorption, Distribution, Metabolism, and Excretion. Additional studies are needed to determine absorption rates following exposure by all routes. There are limited data on the absorption of

endrin in humans and animals. Limited studies provide qualitative evidence that endrin is absorbed following inhalation, oral, and dermal exposures; however, no information is available on the rate or extent of absorption that occurs by any of these routes.

Data are sparse on the distribution of endrin. Limited data in humans indicate that significant amounts of endrin residues are found in adipose tissue of people acutely exposed to high levels, but not typically in the general population. However, endrin has been detected in breast milk and placental tissues. Low levels of endrin are found in the liver, kidneys, and brain in people exposed to endrin or endrin-contaminated food. The time of sample collection is critical since endrin residues in tissues decline rapidly after exposure has ceased.

Additional studies in different species, as well as inhalation and dermal exposure studies, would be helpful. No studies were found regarding the metabolism of endrin in humans, excretion patterns in workers show metabolites similar to those identified in animal studies. Metabolism following oral exposure in animals has been fairly well characterized and shows some species differences.

Additional studies on the excretion of endrin and its metabolites via the dermal route would be useful since differences in urinary metabolite profiles have been observed following exposure to endrin by other routes. Excretion patterns following oral and inhalation exposure have been fairly well characterized.

Comparative Toxicokinetics. Additional studies using all three potential routes of human exposure would be useful in understanding differences in species and in determining which animal species is the most appropriate model for human exposure. There are limited data on the kinetics of endrin in humans. Studies in animals suggest that metabolism and urinary metabolite profiles vary among species.

Children's Susceptibility. Developmental effects have not been evaluated in animals following inhalation or dermal exposure. Studies in young animals and/or epidemiological data for children would be useful to address these data gaps. Data are inadequate to determine if children are more susceptible to acute toxic effects of endrin. In an endrin poisoning episode in Pakistan (of unknown origin), children 1–9 years old represented about 70% of the cases of convulsions (Rowley et al. 1987). The causative factor responsible for the outbreak was not identified, however, so it is unclear whether the age distribution of cases was due to increased susceptibility in children or age-specific exposure situations. Available data from oral developmental studies in animals do not indicate that developing animals are uniquely susceptible to toxicity following exposure to endrin.

Physical and Chemical Properties. More complete information on the physical and chemical properties of endrin aldehyde and endrin ketone would be useful. However, the physical and chemical properties of endrin have been sufficiently documented to permit estimation of its environmental fate.

Production, Import/Export, Use, Release, and Disposal. Information as to whether endrin is currently being produced and the export volumes for endrin are needed to evaluate existing routes of exposure for the general population and occupationally exposed individuals. Endrin is no longer registered for use and is not likely to be imported into the United States. Consequently, the risk of human exposure to endrin (and to endrin aldehyde and endrin ketone, which occur as impurities or transformation products of endrin) from these activities is expected to be minimal. However, recent information suggests that several organochlorine pesticides that have been banned from use or have been voluntarily cancelled in the United States are still being manufactured in large quantities for export abroad.

Environmental Fate. Anaerobic biodegradation, which may occur in river bottoms and in Superfund sites, has been studied in the laboratory, but not under natural conditions. Further information on these processes, including identification of degradation products, would be useful in determining potential mechanisms and the potential for contamination of groundwater by endrin released from soils. The partitioning of endrin released to the environment and the potential for bioaccumulation is well characterized. Information on biodegradation of endrin in soil under aerobic conditions exists, but degradation products have not been identified.

Bioavailability from Environmental Media. Additional information regarding the bioavailability of endrin from both ingestion of soil-bound endrin and dermal contact with endrin-contaminated soils would be helpful, particularly for populations living near hazardous waste sites. Information on absorption following inhalation and oral exposure, however, is well characterized under most conditions.

Food Chain Bioaccumulation. Data on bioaccumulation and bioconcentration of endrin generally appear to be adequate, particularly since endrin has not been registered for use in the United States since the mid-1980s. Although bioconcentration data are available for several species, it may be useful to obtain information on bioconcentration in the species with the highest BCF factor (snail) since data are only available in the pouch snail.

Exposure Levels in Environmental Media. There are possibilities of exposure from foodstuffs imported from countries that still use endrin and potential localized risks from exposures near waste disposal sites or from groundwater contaminated with endrin. Additional data on environmental concentrations of endrin, endrin aldehyde, and endrin ketone from these possible sources of exposure would be useful. In addition, reliable monitoring data for the levels of endrin, endrin aldehyde, and endrin ketone in contaminated media at hazardous waste sites are needed so that the information obtained on levels of these substances in the environment can be used in combination with their known body burdens to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Endrin has been reported to occur at very low levels in food and air. It has only rarely been detected in a number of national and regional surveys of drinking water supplies. Because endrin is no longer commercially used in the United States, future levels of endrin, endrin aldehyde, and endrin ketone in environmental media are expected to be low.

Exposure Levels in Humans. No studies specifically evaluating levels of endrin, endrin aldehyde, or endrin ketone in blood and other tissues of people near hazardous waste sites were located. This information is necessary for assessing the need to conduct health studies on these populations. Data on the concentrations of endrin in breast milk from U.S. women would be particularly useful, given that it has been detected in the milk of lactating women in other countries. However, metabolism of endrin in humans is relatively rapid compared with other organochlorine pesticides. Thus, levels in human blood and tissue may only be useful for acute exposures or very high occupational exposures. Endrin was not found in adipose tissue samples of the general U.S. population, or in adipose breast tissue from breast cancer patients in the United States.

Exposures of Children. Children may be exposed to endrin through the same routes as adults, as well as via placental transfer and breastfeeding. Monitoring of children's exposure to endrin would be useful, particularly in heavily contaminated areas, in combination with children's health and susceptibility information, to assess the potential risk for deleterious effects.

6.3 Ongoing Studies

No ongoing studies were identified for endrin.