3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of aldrin/dieldrin. 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.

Aldrin and dieldrin are structurally similar pesticides. The only difference between the structures of aldrin and dieldrin is the presence, in dieldrin, of an epoxied ring at the site of one of the carbon-carbon double bonds in aldrin (see Chapter 4). Because aldrin is rapidly metabolized to dieldrin in the body and converted to dieldrin in the environment, these two compounds are discussed together throughout Chapter 3 and the rest this document.

3.2 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 users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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 (LOAEL) 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 aldrin and dieldrin are indicated in Tables 3-1 and 3-2, respectively, and Figures 3-1 and 3-2, respectively. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-2 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for aldrin and dieldrin. 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 1990d), 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 B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Virtually all of the studies presented in this section on inhalation exposure are either epidemiological reports of occupational exposure or case reports of either accidental or intentional poisonings. Extremely limited information was located regarding the effects of inhalation exposures of animals to aldrin or dieldrin. In many of the human and animal studies, inhalation exposure may occur simultaneously with dermal exposure. Thus, many of the effects reported in this section may be due, in part, to dermal exposure to aldrin or dieldrin. Furthermore, in occupational studies and case reports of poisonings, precise levels of exposure are not known. Thus, the results in this section are not presented in an LSE table and figure.

No studies were located regarding cardiovascular, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after inhalation exposure to aldrin/dieldrin.

3.2.1.1 Death

No increase in mortality from any cause was reported in workers who had been employed in the manufacture of aldrin, dieldrin, endrin, and/or telodrin at a facility in the Netherlands for >4 years (cohort=233 workers) (van Raalte 1977; Versteeg and Jager 1973). Furthermore, in a 20-year follow-up of this population and expansion of the cohort to include workers exposed for at least 1 year between 1954 and 1970 (cohort=570 workers), a lower than expected overall incidence of mortality was observed (de Jong 1991). Although the workers described by de Jong represented a unique population because they had been under observation for an average of 25.86 years, all of the studies described above are limited because of the small number of subjects used (#570 workers), uncertainty regarding exposure levels, and the potential exposure of the subjects to more than one of these pesticides and/or to other chemicals at the chemical manufacturing complex. Several of these studies have attempted to estimate

exposures using blood levels. However, blood levels were not obtained for approximately 10 years (during what is expected to have been the period of heaviest exposures) and extrapolations were based on data obtained in a study using constant daily low-level oral dosing (Hunter and Robinson 1967). It is unclear whether such extrapolations accurately reflect exposure levels in the occupational situation. Only two case studies were located regarding deaths that may have been attributable to occupational exposure to aldrin or dieldrin (Muirhead et al. 1959; Pick et al. 1965). One of these studies concerned a farmer with multiple exposures to insecticides that contained dieldrin. The farmer died in hemolytic crisis after developing immunohemolytic anemia (Muirhead et al. 1959). Immunologic testing revealed a strong antigenic response to red blood cells coated with dieldrin. The other study concerned a worker from an orange grove who developed aplastic anemia and died following repeated exposures to aldrin during spraying (Pick et al. 1965). In the latter study, the relationship between aldrin exposure and the aplastic anemia is considerably more tenuous, being linked only in that the onset of symptoms corresponded with spraying and the condition deteriorated upon subsequent exposure.

Only very limited data were located regarding death in animals following inhalation exposure to aldrin or dieldrin. Cats, guinea pigs, rats, rabbits, and mice were exposed to aldrin vapors and particles generated by sublimating aldrin at 200 EC (Treon et al. 1957b). Aldrin levels of 108 mg/m^3 for 1 hour resulted in death in 9 out of 10 rats, 3 out of 4 rabbits, and 2 out of 10 mice. Cats and guinea pigs were less sensitive. One out of 1 cat and no guinea pigs died following exposure to 215 mg/m^3 for 4 hours. Interpretation of the results of this study are limited in that sublimation may have resulted in the generation of atmospheres containing a higher proportion of volatile contaminants and thermal decomposition products than would be expected in atmospheres typical of most occupational exposures.

3.2.1.2 Systemic Effects

Respiratory Effects. Extremely limited information is available regarding the respiratory effects of aldrin and dieldrin in humans after inhalation exposure. A study of workers with at least 4 years of employment in the manufacture of aldrin, dieldrin, endrin, or telodrin found no new pulmonary disease or deterioration of existing pulmonary disease (Jager 1970). Similarly, no increase in mortality from respiratory diseases was noted in workers employed for at least 1 year at the same plant during 1954–1970 when these workers were followed for at least 20 years (de Jong 1991). In contrast, in another study that examined workers involved in the manufacture of aldrin, dieldrin, and/or endrin for at least a year, a significantly increased incidence of pneumonia and other pulmonary diseases was found when compared to the incidence in U.S. white males (Ditraglia et al. 1981). However, all of these studies

are limited by small sample size and the possible exposure of the workers to other chemicals and/or pesticides.

Extremely limited data were located regarding respiratory effects in animals after inhalation exposure to aldrin or dieldrin. Cats, guinea pigs, rats, rabbits, and mice exposed to aldrin vapors and particles generated by sublimating aldrin at 200 EC were reported to have exhibited symptoms indicative of mucous membrane irritation (Treon et al. 1957b). However, the exposure levels associated with these effects were not reported, and the contribution of thermal decomposition products or other volatile contaminants other than aldrin cannot be eliminated.

Cardiovascular Effects. Very limited information is available regarding the cardiovascular effects of aldrin and dieldrin in humans after inhalation exposure. Suggestive evidence of an association between dieldrin and hypertension was obtained in a study examining disease incidence in patients with elevated fat levels of dieldrin (Radomski et al. 1968). However, the number of patients with hypertension in this study was low (eight cases), and elevated fat levels of other pesticide residues also correlated with hypertension. Furthermore, other studies did not support the correlation of hypertension with dieldrin exposure. For example, a study examining disease incidence in 2,620 pesticide-exposed workers reported no increase in the incidence of hypertension in workers with elevated serum dieldrin (Morgan et al. 1980). Also, workers involved in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years had normal blood pressure (Jager 1970). Similarly, no increased mortality from circulatory system diseases was observed in the mortality study by de Jong (1991). All of these studies are limited because the subjects were exposed to a variety of other chemicals.

A slight, but significant, increase in serum cholesterol was observed in pesticide-exposed workers with elevated serum dieldrin (Morgan and Lin 1978). However, this study was limited in that the workers were occupationally exposed to a number of different pesticides and other chemicals including hydrocarbon solvents.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to aldrin or dieldrin.

Gastrointestinal Effects. No increased mortality from digestive system causes was observed in a mortality study of workers employed in the manufacture of aldrin and dieldrin for at least 1 year between 1954 and 1970 (de Jong 1991).

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to aldrin or dieldrin.

Hematological Effects. No abnormal values for hemoglobin, white blood cells, or erythrocyte sedimentation rate were found in workers who had been employed in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years (Jager 1970). Similarly, no increase in blood diseases was observed in a morbidity study of workers employed at the plant described by Jager (1970) over the period of 1979–1990 (de Jong 1991). Also, workers who had been involved in either the manufacture or application of pesticides and who had elevated blood levels of dieldrin, had no hematological effects of clinical significance (Morgan and Lin 1978; Warnick and Carter 1972). These studies are limited by either potential exposure to other chemicals (de Jong 1991; Jager 1970; Morgan and Lin 1978) or by known exposure to other pesticides as demonstrated by elevated blood levels of "β-benzine [sic] hexachloride" (β-benzene hexachloride), heptachlor epoxied, 1,1,1-trichloro-2,2-bis(*p*-chloro-phenyl)ethane (*p,p*'-DDT), 1,1,1-trichloro-2-(*o*-chlorophenyl)2-(*p*-chlorophenyl)ethane (*o,p*'-DDT), and 1,1-dichloro-2,2-bis(*p*-chloro-phenyl) ethene (*p,p*'-DDE) (Warnick and Carter 1972).

A case of immunohemolytic anemia attributable to multiple dieldrin exposures was reported (Muirhead et al. 1959). Also, a worker from a grove where aldrin was sprayed developed aplastic anemia (Pick et al. 1965) and one person employed in the manufacture of aldrin and dieldrin between 1954 and 1970 died from aplastic anemia (de Jong 1991). However, it is unclear whether these cases of aplastic anemia were directly due to aldrin or dieldrin exposures because exposure to a variety of other chemicals was possible. Also, three cases of pancytopenia and one case of thrombocytopenia associated with exposure to dieldrin were reported during 1961 (AMA 1962). However, no assessment of whether dieldrin was the causative agent was provided in the report.

No studies were located regarding hematologic effects in animals after inhalation exposure to aldrin or dieldrin.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to aldrin or dieldrin.

Hepatic Effects. Although a slight increase in serum hepatic enzymes (serum alanine aminotransferase [ALT] and serum aspartate aminotransferase [AST]) has been observed to correlate with serum dieldrin levels in one study of pesticide-exposed workers (Morgan and Lin 1978), no evidence of any hepatic effects of aldrin or dieldrin exposure have been observed in other studies of workers involved in either the manufacture (de Jong 1991; Hoogendam et al. 1965; Hunter et al. 1972; Jager 1970; van Sittert and de Jong 1987) or the manufacture or application (Morgan and Roan 1974; Warnick and Carter 1972) of these pesticides. Parameters that have been examined in the negative studies include serum hepatic enzyme activity (Hoogendam et al. 1965; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987; Warnick and Carter 1972), hepatic enlargement (Jager 1970), and tests intended to detect microsomal enzyme induction (Hunter et al. 1972; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987). All of the studies are limited by the potential exposure of the workers to other chemicals and/or organochlorine pesticides.

No studies were located regarding hepatic effects in animals after inhalation exposure to aldrin or dieldrin.

Renal Effects. No evidence of renal damage was seen in workers employed for four or more years in the manufacture of aldrin or dieldrin (Jager 1970). This study is limited by the potential exposure of the workers to other chemicals.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals after inhalation exposure to aldrin or dieldrin.

Dermal Effects. No evidence of dermatitis was seen in workers employed for four or more years in the manufacture of aldrin, dieldrin, endrin, or telodrin (Jager 1970). This study is limited by the possible exposure of the workers to other chemicals.

Extremely limited data were located regarding dermal/ocular effects in animals after inhalation exposure to aldrin or dieldrin. Cats, guinea pigs, rats, rabbits, and mice exposed to aldrin vapors and particles generated by sublimating aldrin at 200 EC were reported to have exhibited symptoms indicative of mucous membrane irritation (Treon et al. 1957b). However, the exposure levels associated with these

effects were not reported and the contribution of thermal decomposition products or other volatile contaminants other than aldrin cannot be eliminated.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after inhalation exposure to aldrin or dieldrin.

3.2.1.3 Immunological and Lymphoreticular Effects

Limited information is available regarding the immunological effects of aldrin or dieldrin in humans after inhalation exposure. A case report was located concerning a pesticide sprayer who developed immunohemolytic anemia after multiple exposures to dieldrin, heptachlor, and toxaphene (Muirhead et al. 1959). Antibodies for dieldrin-coated or heptachlor-coated red blood cells were found in the subject's serum. However, this study is limited because of the exposure of the subject to other pesticides.

No studies were located regarding immunological effects in animals after inhalation exposure to aldrin or dieldrin.

3.2.1.4 Neurological Effects

Central nervous system excitation culminating in convulsions was the principal adverse effect noted in occupational studies of workers employed in either the application or manufacture of aldrin or dieldrin. In many cases, convulsions appeared suddenly and without prodromal signs (Hoogendam et al. 1965; Kazantzis et al. 1964; Patel and Rao 1958). Electroencephalograms (EEGs) taken shortly after the convulsions revealed bilateral irregular alpha rhythms interrupted by spike and wave patterns (Avar and Czegledi-Janko 1970; Kazantzis et al. 1964). In one case study of dieldrin sprayers who developed convulsions, the convulsive episodes did not follow known accidental overexposures (Patel and Rao 1958). Rather, the convulsions developed anywhere from 14 to 154 days after the first exposure to dieldrin. The time to onset was more rapid for those sprayers using the more concentrated spray. An accumulative type of intoxication was also reported in workers involved in the manufacture of aldrin, dieldrin, telodrin, or endrin (Jager 1970). In this report, convulsions were believed to have been caused by either accumulating levels of dieldrin in the blood or modest overexposures in the presence of subconvulsive accumulations of dieldrin.

Other central nervous system symptoms reported by workers involved in the manufacture or application of aldrin and/or dieldrin included headaches (Jager 1970; Patel and Rao 1958), dizziness (Jager 1970), hyperirritability (Jager 1970; Kazantzis et al. 1964), general malaise (Jager 1970), nausea and vomiting (Jager 1970; Kazantzis et al. 1964), anorexia (Jager 1970), muscle twitching (Jager 1970; Patel and Rao 1958), and myoclonic jerking (Jager 1970; Kazantzis et al. 1964). The more severe symptoms were accompanied by EEG patterns with bilateral spike and wave complexes and multiple spike and wave discharges in the alpha region (Jager 1970; Kazantzis et al. 1964). Less severe symptoms were accompanied by bilateral theta (Jager 1970; Kazantzis et al. 1964) and/or delta (Kazantzis et al. 1964) wave discharges.

In all cases in which follow-up of the subjects was reported, removal from the source of exposure caused a rapid physical recovery and a slower recovery of the EEG activity (within a year) to normal levels (Avar and Czegledi-Janko 1970; Hoogendam et al. 1962, 1965; Jager 1970; Kazantzis et al. 1964).

A morbidity study of workers employed in the manufacture of aldrin and dieldrin between 1979 and 1990 noted no degenerative disorders of the nervous system (de Jong 1991). However, this study reported significant increases in mental diseases among those <30 years old and in those 46–50 years old. The diseases were classified as stress reactions, short-term depression, or sleep disorders. It is unclear whether these effects were the result of aldrin/dieldrin exposure.

Results from a comprehensive neurological workup of 27 workers involved in either the manufacture or application of dieldrin were compared to those of a group of unexposed workers (Sandifer et al. 1981). Scores on five psychological tests were significantly different from those of the unexposed controls; however, the importance of the results was questioned by the authors because of differences in the degree of literacy between the two groups. Also, three exposed workers had abnormal electromyograms (EMGs) suggesting a peripheral neuropathy. However, EMGs were not obtained in the control group; thus, the significance of these results is unknown.

No studies were located regarding neurological effects in animals after inhalation exposure to aldrin or dieldrin.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to aldrin or dieldrin.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to aldrin or dieldrin.

3.2.1.7 Cancer

Selected Mortality Studies. Aldrin and dieldrin were manufactured at two sites worldwide in plants at the Rocky Mountain Arsenal in Denver, Colorado, and at Pernis in the Netherlands. Workers from these plants have been included in two series of retrospective cohort mortality studies which have been updated several times. Exposure to dibromochloropropane (DBCP) and several organophosphates may also have occurred in the Denver plant. Cancer mortality findings of the studies at the Denver plant (Amoateng-Adjepong et al. 1995; Brown 1992; Ditraglia et al. 1981; Ribbens 1985) and the Pernis plant (de Jong 1991; de Jong et al. 1997; Jager 1970; Ribbens 1985; van Raalte 1977) are inconclusive, as summarized below.

The first study of the Denver plant found no significant increase in cancer mortality, but concluded that additional follow-up was necessary due to a small number of deaths (173) and the relatively short period of observation (Ditraglia et al. 1981). In the follow-up by Brown (1992), 1,158 workers who were employed for at least 6 months prior to 1965 and were followed through 1987 were investigated. Cause-specific mortality analysis of 337 deaths showed an increase in liver and biliary tract cancer (five cases observed) that was statistically significant when compared to state and local rates (Standardized mortality ratios [SMRs] of 5.10 and 4.86, respectively), but not the national rate (SMR=3.93). All of these five deaths (three from biliary tract/bile duct cancer, one from gall bladder cancer, and one from hepatoma) occurred after 15 years of latency (SMR=4.85). The cohort in the most recent study of the Denver plant (Amoateng-Adjepong et al. 1995) was expanded to 2,384 subjects and followed through 1990 (median 29 years). The median age at hiring was 26 years and the median tenure was 2 years. The increase in hepatobiliary cancer was of a lower magnitude than in the previous study and was no longer statistically significant, although no additional cases had occurred (5 cases observed/2.0 expected based on state rates,

SMR=249). Based on this information and findings that the cancers were not limited to any particular production unit, did not display duration-response trends, and essentially occurred in the biliary tract or gall bladder (rather than liver), the investigators concluded that the hepatobiliary cancer excess was not due to occupational exposures at the plant.

No indications of a carcinogenic effect were found in the early mortality studies of the Dutch (Pernis) workers (Jager 1970; Ribbens 1985; van Raalte 1977). Similarly, in the follow-up study by de Jong (1991), there were no increases in cause-specific mortality among 76 deaths in 570 workers who were employed for at least 1 year between 1954 and 1970 and followed-up until 1987. Follow-up of this cohort until 1993 (118 deaths) showed a significant increase in mortality from rectal cancer (6 deaths observed versus 1.5 expected compared to Netherlands national rates, SMR=390.4) and an insignificant increase in liver cancer deaths (2 observed versus 0.9 expected, SMR=225.0) (de Jong et al. 1997). Stratification by dose level (low, moderate, or high exposure based on blood levels of dieldrin) did not disclose any indications of a dose-response relation for either of these causes of death.

Equivocal evidence exists for an association between dieldrin and breast cancer risk from three human epidemiologic studies (Dorgan et al. 1999; Høyer et al. 1998, 2000). In these studies, while dieldrin exposure was verified through blood sampling, and exposure by inhalation, as well as by ingestion and dermal contact, was possible, no specific route of exposure was identified or estimated with any certainty.

The potential of dieldrin to affect breast cancer risk was evaluated in a prospective nested case control study of women in Denmark (Høyer et al. 1998). Serum samples were obtained from 7,712 women from 1976 to 1978. In 1996–1997, serum samples from 240 women who had developed invasive breast cancer and 477 matched breast cancer-free controls were analyzed for levels of dieldrin and 17 other organochlorine pesticides or metabolites and 28 PCB congeners. Controls and cases were matched for age, date of examination, and vital status at the examination. Irrespective of breast cancer status, dieldrin was detected in 78% of the women enrolled in the study, with median levels at 24.4 ng/g lipid. Dieldrin was the only organochlorine compound of those tested associated with a significant increase in breast cancer risk. Women in the highest quartile of the serum dieldrin range had double the risk of breast cancer compared to women in the lowest quartile (odds ratio [OR] 2.25, 95% confidence interval [CI] 1.32–3.84, p trend=0.003). Relative risk (RR) did not change significantly when adjusted for potential confounders of weight and number of full-term pregnancies (OR 2.05, 95% CI 1.17–3.57, p trend=0.01).

A subsequent study using the same cohort of Danish women investigated whether breast cancer survival was affected by past exposure to dieldrin (Høyer et al. 2000). Dieldrin, at blood concentrations >57.6 ng/g, representative of the highest quartile, was found to have a significant adverse effect on overall survival and breast cancer specific survival compared to the lowest quartile levels of <12 ng/g lipid (RR 2.78, 95% CI 1.38–5.59, p trend<0.01; RR 2.61, 95% CI 0.97–7.01, p trend<0.01) in this case-control study of Danish women between 20 and 80 years of age. A total of 195 breast cancer cases, who each provided two blood samples that were taken in 1976–1978 and 1981–1983, respectively, were included in the survival analysis. The median duration of follow-up with regard to death was 86 months after the first examination (1976–1978) and 79 months after the second examination (1981–1983). Relative risk was adjusted for number of positive lymph nodes and tumor size and grade. When the analysis was performed using an average of the blood concentrations from the two collections, the association was even stronger, with a 5-fold higher risk of death in women from the highest quartile compared to the lowest quartile (RR 5.76, 95% CI 1.86–17.92, p trend<0.01) and a clear dose-response relationship. Potential confounders as body mass index, age at menopause, and hormone replacement therapy did not influence the results. This study was limited by small size, 6–39 women per quartile.

A cohort study of women from Missouri failed to find an association between serum dieldrin levels and breast cancer risk (Dorgan et al. 1999). Blood samples were collected from 7,224 women from 1977 to 1987. During the 9.5-year follow-up period, 105 women developed breast cancer; each was matched to two controls based on age and date of blood collection. Dieldrin was detected in serum in 56.2% of the cases and 61.8% of the controls. The relative risk of cancer in the highest dieldrin serum concentration range quartile was moderately lower compared to the lowest quartile (RR 0.7, 95% CI 0.3–1.3, p=0.44).

Animal Cancer Studies. No studies were located regarding cancer in animals after inhalation exposure to aldrin or dieldrin. As summarized in Section 3.2.2.7, EPA derived carcinogenic potency estimates for oral exposure to aldrin and dieldrin using liver tumor responses in mice. Based on the oral data, unit risk estimates for inhalation exposures (the excess cancer risk associated with lifetime exposure to 1µg/m^3) of 4.9x10^{-3} and 4.6x10^{-3} were calculated for aldrin and dieldrin, respectively (EPA 1986; IRIS 2002a, 2002b). Based on these unit risk values, aldrin and dieldrin cancer risk levels of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} correspond to 70 years of continuous exposure to 0.02, 0.002, 0.0002, and 2.0x10^{-5} µg/m^3, respectively (1.3, 1.3x10^{-1}, 1.3x10^{-2}, and 1.3x10^{-3} ppt). The predicted cancer risks are considered conservative upper estimates. The actual risk of cancer is unlikely to be higher and may be substantially lower.

3.2.2 Oral Exposure

3.2.2.1 Death

A 2-year-old child died a short time after consuming an unknown quantity of a 5% solution of dieldrin (Garrettson and Curley 1969). It is unclear from this report whether the child died during the severe convulsions produced by the dieldrin or during the postictal period (the period immediately following a seizure that is characterized by central nervous system depression). This child's 4-year-old brother, who also consumed an unknown quantity of the 5% dieldrin solution, experienced severe convulsions but recovered completely.

Of several persons who consumed wheat that had been mixed with aldrin and lindane for a period of 6–12 months, an infant female child died within a few hours after experiencing a severe generalized convulsion (Gupta 1975).

The doses at which aldrin is acutely lethal in experimental animals are quite similar to lethal dieldrin doses. Oral LD_{50} values for single doses of aldrin in rats ranged from 39 to 64 mg/kg (Gaines 1960; Treon et al. 1952). Oral LD_{50} values for single doses of dieldrin in adult rats ranged from 37 to 46 mg/kg/day (Gaines 1960; Lu et al. 1965; Treon et al. 1952). Aldrin was lethal in females at a slightly lower dose when it was administered in solution in oil (LD_{50}=48 mg/kg) than when it was administered in a kerosene vehicle (LD_{50}=64 mg/kg) (Treon et al. 1952).

The age of the animals appeared to influence the acute toxicity of a single administration of dieldrin. Newborn rats had a relatively high LD_{50} (168 mg/kg) (Lu et al. 1965); whereas 2-week-old rats had an LD_{50} of 25 mg/kg, which is somewhat lower that the adult LD_{50} value (Lu et al. 1965). When aldrin was widely used as an insecticide, several incidents were reported in which livestock died as the result of accidental mixing of unspecified amounts of aldrin with livestock feed (Buck and Van Note 1968). In an incident in which both calves and adult cattle were exposed, mortality occurred exclusively among the calves.

Decreased survival in animals consuming aldrin and/or dieldrin over longer periods was seen at lower doses. All rats consuming 15 mg/kg/day aldrin or dieldrin in the diet died by the end of the second week of exposure (Treon et al. 1951a). Rats exposed to aldrin or dieldrin for 6 weeks exhibited increased mortality at estimated doses of 8 and 16 mg/kg/day, respectively (NCI 1978a). When exposed for 2 years

or more, rats exhibited decreased survival at doses of 0.5–2.5 mg/kg/day aldrin or dieldrin (Deichmann et al. 1970; Fitzhugh et al. 1964; Harr et al. 1970; NCI 1978a).

In intermediate- and chronic-duration studies, dogs and mice appeared to have a sensitivity to the lethal effects of aldrin and/or dieldrin that is similar to that of rats. All dogs given aldrin at doses of 0.89–1.78 mg/kg/day or dieldrin at doses of 1.95–4.24 mg/kg/day died or were killed in a moribund condition in a 9-month dietary study (Treon et al. 1951b). Dogs appeared to survive for longer periods if the dog was larger or older at the start of the study. Decreased survival in dogs exposed for 25 months was also observed at 1 mg/kg/day aldrin or 0.5 mg/kg/day of dieldrin (Fitzhugh et al. 1964). In mice, decreased survival was seen at 1.3 mg/kg/day dieldrin (Thorpe and Walker 1973; Walker et al. 1972). In contrast, hamsters appeared to be less sensitive to dieldrin. Exposure to 14.9 mg/kg/day dieldrin for 120 weeks had no effect on hamster survival (Cabral et al. 1979).

The highest NOAEL values, all LD_{50} values, and all reliable LOAEL values for death in each species and duration category are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding dermal/ocular effects in humans or animals after oral exposure to aldrin or dieldrin.

The highest NOAEL values and all reliable LOAEL values for each study for each end point for dieldrin are recorded in Table 3-2 and plotted in Figure 3-2.

Table 3-1. Levels of Significant Exposure to Aldrin - Oral

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
	ACUTE EXPOSURE						
	Death						
1	Rat	1 x (GO)				39[d] (LD_{50}, male) 60 (LD_{50}, female)	Gaines 1960
2	Rat	2 wk ad lib (F)				15 (10/10 died)	Treon et al. 1951a
3	Rat	1 d (G)				63.6 (LD_{50})	Treon et al. 1952
4	Rat	1 d (GO)				48.3 (LD_{50})	Treon et al. 1952
	Neurological						
5	Rat	3 d 1x/d (GO)		5		10 (convulsions)	Mehrotra et al. 1989
	Reproductive						
6	Mouse	5 d 1x/d (G)		1.0			Epstein et al. 1972
	Developmental						
7	Mouse	5-7 d (GO)			2[b] (decreased body weight and increased seizure threshold in offspring)		Al-Hachim 1971

Table 3-1. Levels of Significant Exposure to Aldrin - 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)		
8	Mouse	1 x Gd 9 (GO)				25	(webbed feet)	Ottolenghi et al. 1974
9	Hamster	1 x Gd 7, 8, or 9 (GO)				50	(increased fetal mortality)	Ottolenghi et al. 1974

Table 3-1. Levels of Significant Exposure to Aldrin - 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
	INTERMEDIATE EXPOSURE								
	Death								
10	Rat	6 wk ad lib (F)					8	(2/10 died)	NCI 1978a
11	Mouse	6 wk ad lib (F)					2.6	(2/10 died)	NCI 1978a
12	Dog	9 mo ad lib (F)					0.89-1.78	(2/2 died)	Treon et al. 1951b
13	Dog	5 wk 5d/wk (C)					1.5	(3/3 pre-weanlings died)	Treon et al. 1955b
	Systemic								
14	Rat	27 wk ad lib (F)	Hepatic Renal Bd Wt	1.25 1.25 0.63	1.25	(decreased body weight gain)			Treon et al. 1953b
15	Dog	9 mo ad lib (F)	Gastro Hepatic		0.89-1.78 0.89-1.78	(vomiting) (moderate hepatocellular degeneration)			Treon et al. 1951b

Table 3-1. Levels of Significant Exposure to Aldrin - 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)		
Neurological								
16	Dog	9 mo ad lib (F)				0.89-1.78	(hypersensitivity; tremors; convulsions; neuronal degeneration)	Treon et al. 1951b

Table 3-1. Levels of Significant Exposure to Aldrin - 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
CHRONIC EXPOSURE									
Death									
17	Rat	31 mo 7d/wk (F)					2.5	(33% reduced survival in females)	Deichmann et al. 1970
18	Rat	2 yr ad lib (F)					2.5	(58% reduced survival)	Fitzhugh et al. 1964
19	Mouse	80 wk ad lib (F)					0.78	(34% reduced survival)	NCI 1978a
Systemic									
20	Rat	25 mo ad lib (F)	Hemato	0.25					Deichmann et al. 1967
			Hepatic		0.25	(slight liver degeneration)			
			Renal		0.25	(hyaline casts)			
21	Rat	2 yr ad lib (F)	Hepatic		0.025[c]	(hepatocellular enlargement and vacuolation, bile duct proliferation)			Fitzhugh et al. 1964; Reuber 1980
			Renal	0.1	0.5	(nephritis)	2.5	(bladder distension and hemorrhages)	
22	Dog	15.7 mo 7 d/wk 1-3x/d (F)	Hepatic	0.04-0.09	0.12-0.25	(hyaline droplet degeneration)			Treon et al. 1955b
			Renal		0.04-0.09	(vacuolation of renal tubules)			

Table 3-1. Levels of Significant Exposure to Aldrin - 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)		
	Neurological								
23	Rat	74-80 wk ad lib (F)					1.5	(convulsions)	NCI 1978a
24	Mouse	80 wk ad lib (F)			0.39	(hyperexcitability)			NCI 1978a
	Reproductive								
25	Rat	3 gen ad lib (F)					0.63	(decreased number of litters)	Treon et al. 1954a
	Developmental								
26	Rat	3 gen ad lib (F)					0.125	(increased mortality of offspring)	Treon et al. 1954a
	Cancer								
27	Rat	74-80 wk ad lib (F)					1.5	(CEL - thyroid)	NCI 1978a
28	Mouse	2 yr 7d/wk (F)					1.3	(CEL - liver)	Davis and Fitzhugh 1962

Table 3-1. Levels of Significant Exposure to Aldrin - 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)		
29	Mouse	80 wk ad lib (F)				0.52	(CEL - liver)	NCI 1978a

[a]The number corresponds to entries in Figure 3-1.
[b]Used to derive an acute oral Minimal Risk Level (MRL) of 0.002 mg/kg/day; LOAEL (2 mg/kg/day) divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive a chronic oral Minimal Risk Level (MRL) of 0.00003 mg/kg/day; LOAEL (0.025 mg/kg/day) divided by an uncertainty factor of 1,000 (10 for used of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[d]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

ad lib = ad libitum; (C) = capsule; CEL = cancer effect level; d = day(s); (F) = feed; (G) = gavage (not specified); Gastro = gastrointestinal; Gd = gestation day(s); gen = generation(s); (GO) = gavage (oil); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to Aldrin - Oral

Acute (≤14 days)

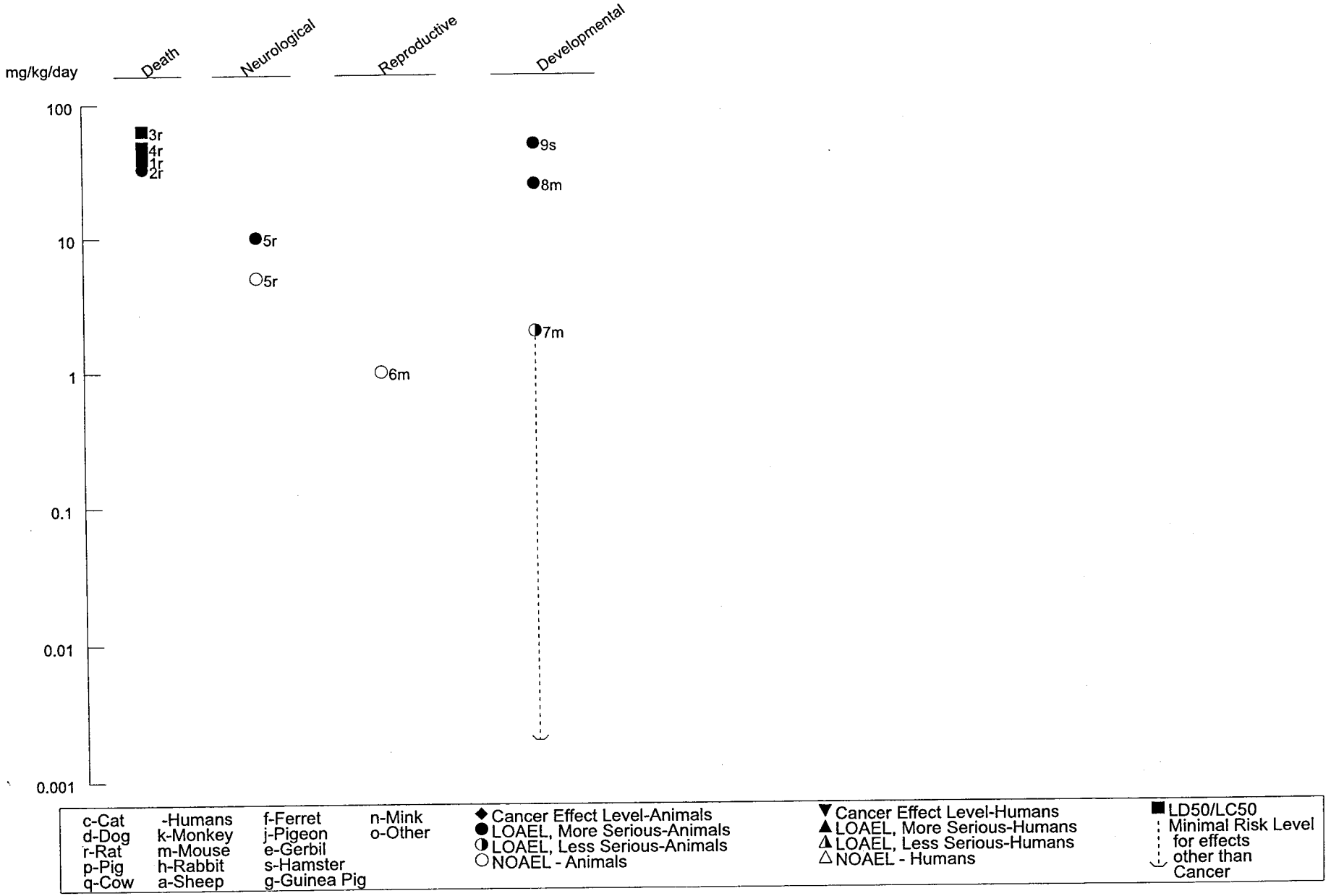


Figure 3-1. Levels of Significant Exposure to Aldrin - Oral (*Continued*)

Intermediate (15-364 days)

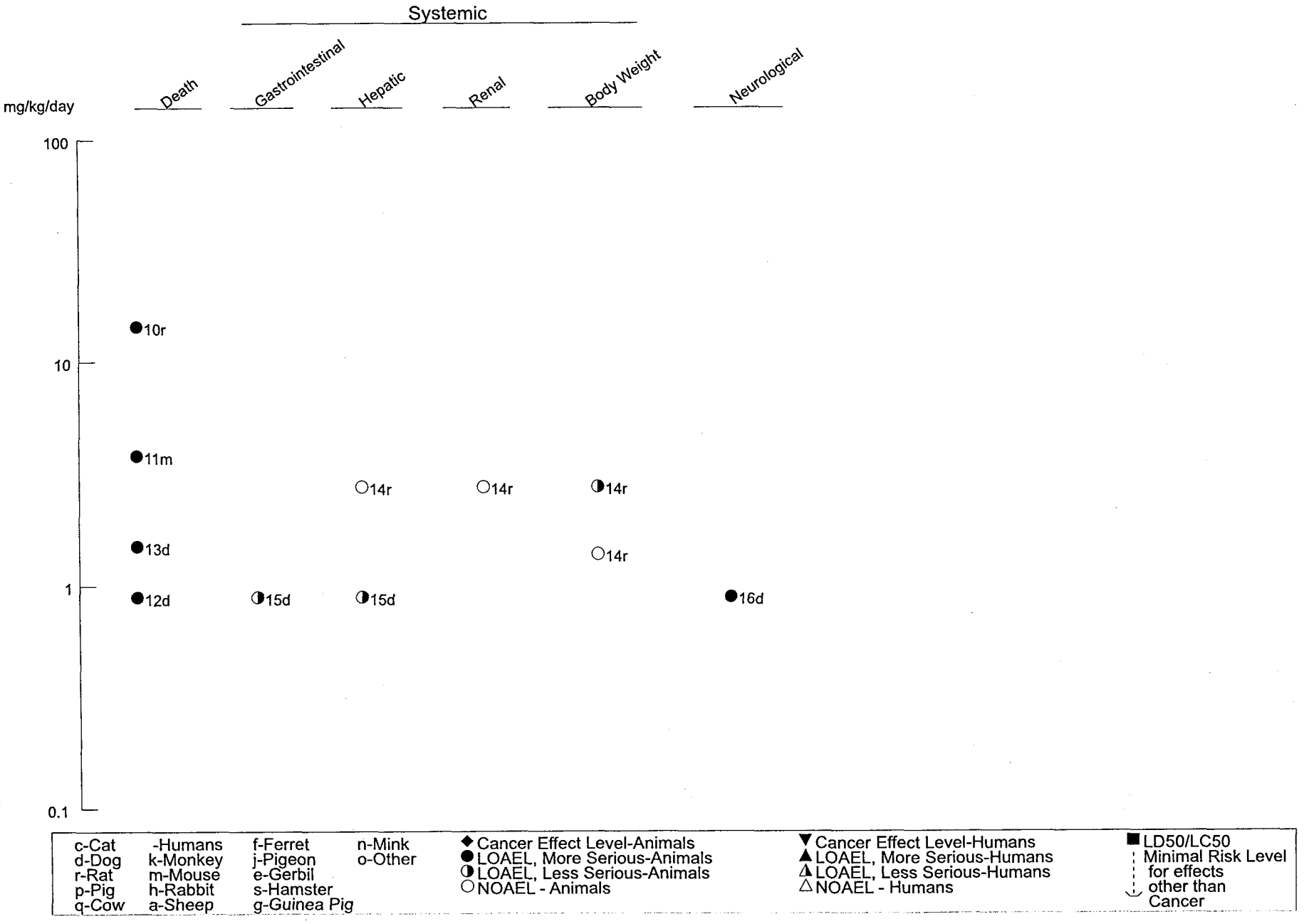


Figure 3-1. Levels of Significant Exposure to Aldrin - Oral (*Continued*)

Chronic (≥365 days)

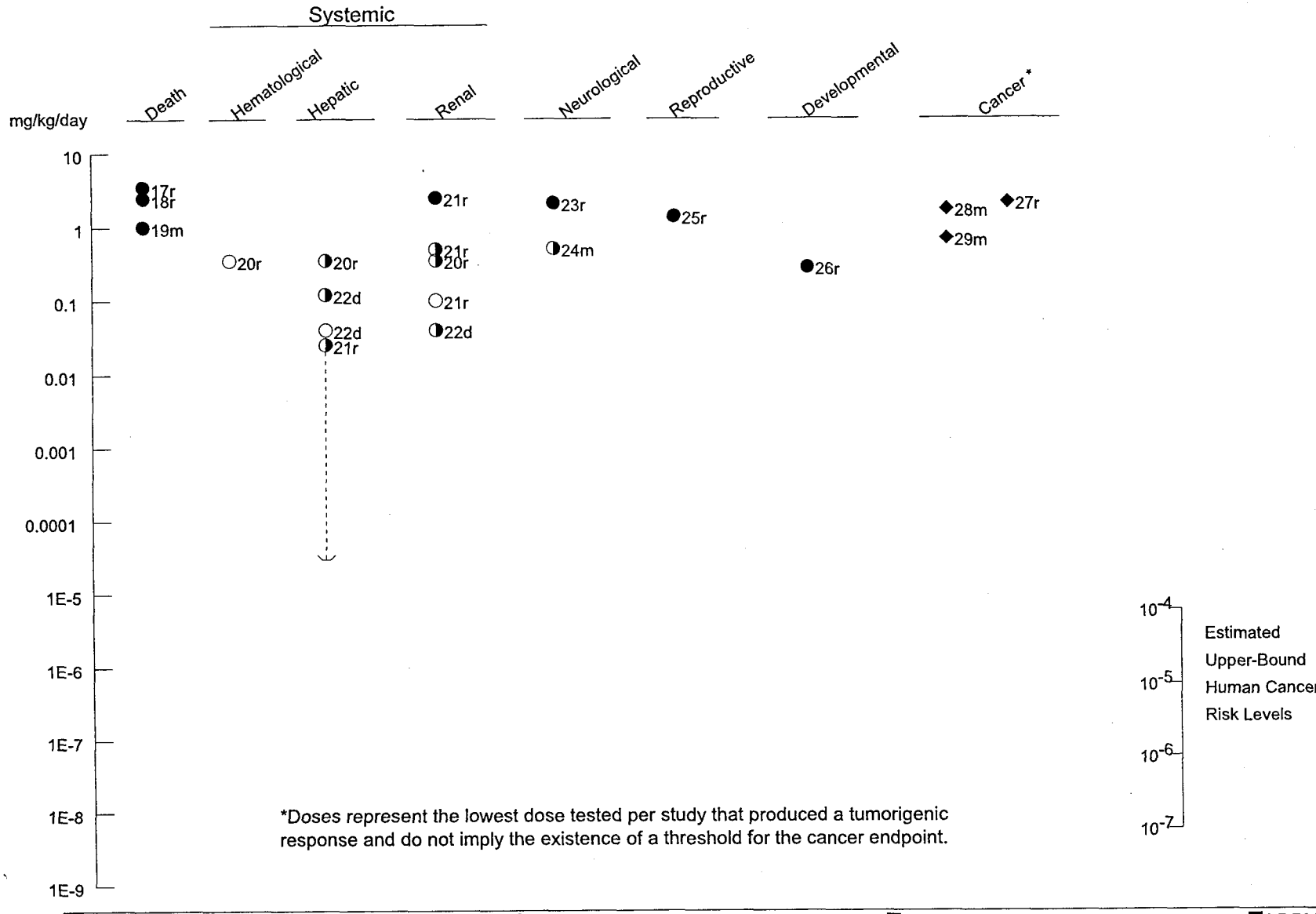


Table 3-2. Levels of Significant Exposure to Dieldrin - Oral

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
	ACUTE EXPOSURE							
	Death							
1	Rat	10 d 1x/d Gd7-16 (GO)		3		6	(13/32 dams died)	Chernoff et al. 1975
2	Rat	1 x (GO)				46	(LD_{50})	Gaines 1960
3	Rat	1 x (GO)				168	(LD_{50}, newborn)	Lu et al. 1965
4	Rat	1 x (GO)				37	(LD_{50}, young adult)	Lu et al. 1965
5	Rat	4 d 1 x (GO)				9	(LD_{50}, 14-16 day old)	Lu et al. 1965
6	Rat	1 x (GO)				25	(LD_{50}, 14-16 day old)	Lu et al. 1965
7	Rat	4 d 1x/d (GO)				54.8	(LD_{50}, young adult)	Lu et al. 1965
8	Rat Carworth	2 wk ad lib (F)				15	(10/10 died)	Treon et al. 1951a
9	Rat	1 d (GO)				38.8	(LD_{50})	Treon et al. 1952

Table 3-2. Levels of Significant Exposure to Dieldrin - 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							
10	Rat	1 x (GO)	Hepatic		26 (increased lipid peroxidation)		Goel et al. 1988
11	Rat	1 x (GO)	Hepatic		30 (decreased lipid peroxidation)		Kohli et al. 1977
12	Rat	3 d 1x/d (GO)	Cardio	10			Mehrotra et al. 1989
13	Mouse	1-2 wk ad lib (F)	Hepatic	1.6			Wright et al. 1972
Immunological/Lymphoreticular							
14	Mouse	2 x (GO)			16.6 (impaired T-cell activity)		Fournier et al. 1988
15	Mouse	1 x (GO)		12		18 (increased lethality following viral infection)	Krzystniak et al. 1985
16	Mouse	2 wk ad lib (F)			0.065 (impaired antigen processing by macrophages)		Loose et al. 1981
Neurological							
17	Rat	1 x (GO)		8.4		16.7 (disrupted operant behavior)	Burt 1975
18	Rat	1 x (GO)				2.5 (disrupted operant behavior)	Burt 1975

Table 3-2. Levels of Significant Exposure to Dieldrin - 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
19	Rat	1 x (GO)				0.5 (*impaired behavior*)	Carlson and Rosellini 1987
20	Rat	1 x (GO)			40 (hypothermia)	50 (convulsions)	Wagner and Greene 1978
21	Rat	1 x (GO)				25 (increased evoked potentials)	Woolley et al. 1985
22	Sheep	4 d (C)				20 (impaired operant behavior; EEG changes)	Sandler et al. 1969
	Developmental						
23	Rat	10 d 1x/d Gd7-16 (GO)		6			Chernoff et al. 1975
24	Mouse	10 d 1x/d Gd7-16 (GO)		1.5		3 (supernumerary ribs)	Chernoff et al. 1975
25	Mouse	13 d Gd6-18 (GO)			2 (low blood glucose level in neonates)		Costella and Virgo 1980
26	Mouse	1 x (GO)				15 (webbed foot; cleft palate)	Ottolenghi et al. 1974
27	Hamster	1 x Gd 7, 8, or 9 (GO)				30 (open eye; webbed foot; cleft palate; increased resorptions; increased fetal mortality)	Ottolenghi et al. 1974

Table 3-2. Levels of Significant Exposure to Dieldrin - 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)		
INTERMEDIATE EXPOSURE									
Death									
28	Rat	6 wk ad lib (F)					16	(7/10 died)	NCI 1978a
29	Mouse	6 wk ad lib (F)					2.6	(7/10 died)	NCI 1978a
30	Mouse	74 d ad lib (F)					2.6	(17% increased mortality)	Virgo and Bellward 1975
31	Mouse	40 wk (F)					7.5	(4/4 died)	Wright et al. 1972
32	Dog	9 mo ad lib (F)					1.95-4.24	(3/3 died)	Treon et al. 1951b
Systemic									
33	Rat	6 mo ad lib (F)	Hepatic Renal		10 10	(hepatocellular necrosis) (epithelial cell degeneration)			Ahmed et al. 1986a
34	Rat	15 d (GO)	Hepatic Renal		5 5	(diffuse necrosis) (glomerulonephritis; renal tubular nephrosis)			Bandyopadhyay et al. 1982b
35	Rat (Fischer- 344)	90d (F)	Hepatic	0.5					Kolaja et al. 1996a

Table 3-2. Levels of Significant Exposure to Dieldrin - 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
36	Rat	1-6 mo (F)	Hepatic		2	(decreased hepatic protein; areas of necrosis)			Shakoori et al. 1982
37	Rat	27 wk ad lib (F)	Hepatic Renal	1.25 1.25					Treon et al. 1953b
38	Mouse (B6C3F1)	90d (F)	Hepatic	1.3					Kolaja et al. 1996a
39	Mouse (B6C3F1)	28d (F)	Hepatic	1.3					Stevenson et al. 1995a
40	Mouse	40 wk (F)	Hepatic	1.6					Wright et al. 1972
41	Dog	9 mo ad lib (F)	Gastro Hepatic	0.73-1.85	1.95-4.24 0.73-1.85	(vomiting) (moderate hepatocellular degeneration)			Treon et al. 1951b
Immunological/Lymphoreticular									
42	Mouse	10 wk ad lib (F)					0.13	(increased lethality following protozoan infection)	Loose 1982
43	Mouse	3, 6, 18 wk, 7d/wk, 1x/d (F)					0.13	(increased lethality following tumor implant)	Loose et al. 1981

Table 3-2. Levels of Significant Exposure to Dieldrin - 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
	Neurological							
44	Monkey	55-109 d 1x/d (F)		0.01[b]		0.1	(learning deficit)	Smith et al. 1976
45	Rat	6-120 d (F)		0.025		0.25	(disrupted operant behavior)	Burt 1975
46	Rat	60 d ad lib (GO)				0.5	(tremors)	Mehrotra et al. 1989
47	Dog	9 mo ad lib (F)				0.73-1.85	(neuronal degeneration convulsions)	Treon et al. 1951b
	Reproductive							
48	Mouse	120 d 1x/d (F)				0.65	(decreased litter size)	Good and Ware 1969
49	Mouse	74 d ad lib (F)		0.65		1.3	(decreased fertility)	Virgo and Bellward 1975
50	Mouse	74 d ad lib (F)		0.65	1.3 (long latency to nursing)			Virgo and Bellward 1975
	Developmental							
51	Mouse	74 d ad lib (F)		0.325		0.65	(increased pup mortality)	Virgo and Bellward 1975

Table 3-2. Levels of Significant Exposure to Dieldrin - 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
	CHRONIC EXPOSURE								
	Death								
52	Rat	31 mo (F)					1.5	(11% reduced survival in females)	Deichmann et al. 1970
53	Rat	2 yr ad lib (F)					2.5	(58% reduced survival)	Fitzhugh et al. 1964
54	Mouse	80 wk ad lib (F)					0.65	(10% increased mortality)	NCI 1978a
55	Mouse	132 wk 1x/d (F)					1.3	(50% mortality reached at 15 months versus 20-24 months *in controls*)	Walker et al. 1972
	Systemic								
56	Human	18 mo (C)	Hemato	0.003					Hunter and Robinson 1967
			Hepatic	0.003					
57	Monkey	69 mo 1x/d (F)	Hepatic	0.1					Wright et al. 1978
58	Rat	2 yr ad lib (F)	Hepatic		0.025	(hepatocellular enlargement and vacuolation, bile duct proliferation)			Fitzhugh et al. 1964; Reuber 1980
			Renal	0.5	2.5	(*nephritis*)	5	(bladder distension and hemorrhages)	

Table 3-2. Levels of Significant Exposure to Dieldrin - 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
59	Rat	2 yr ad lib (F)	Resp	0.5			Walker et al. 1969
			Cardio	0.5			
			Gastro	0.5			
			Hemato	0.5			
			Musc/skel	0.5			
			Hepatic	0.005[c] F	0.05 F (increased liver weight with parenchymal cell changes including focal hyperplasia at a higher dose)		
			Renal	0.5			
			Endocr	0.5			
			Dermal	0.5			
			Bd Wt	0.5			
60	Mouse	92 wk 7d/wk ad lib (F)	Hepatic	1.3			Tennekes et al. 1981
61	Mouse	2 yr (F)	Hepatic		1.3 (liver hyperplasia)		Thorpe and Walker 1973
62	Dog	15.7 mo 7 d/wk 1-3x/d (F)	Hepatic	0.14-0.26			Treon et al. 1955b
			Renal		0.14-0.26 (vacuolation of renal tubules)		

Table 3-2. Levels of Significant Exposure to Dieldrin - 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
63	Dog	2 yr 1x/d (C)	Resp	0.05			Walker et al. 1969
			Cardio	0.05			
			Gastro	0.05			
			Hemato	0.05			
			Musc/skel	0.05			
			Hepatic	0.05			
			Renal	0.05			
			Endocr	0.05			
			Dermal	0.05			
			Ocular	0.05			
			Bd Wt	0.05			
	Neurological						
64	Human	18 mo (C)		0.003			Hunter and Robinson 1967
65	Rat	59-80 wk ad lib (F)			1.45 (hyperexcitability)		NCI 1978a
66	Rat	104-105 wk ad lib (F)		0.5		2.5 (convulsions)	NCI 1978b
67	Rat	2 yr ad lib (F)		0.05		0.5 (tremors and occasional convulsions)	Walker et al. 1969
68	Mouse	80 wk ad lib (F)				0.33 (tremors)	NCI 1978a

Table 3-2. Levels of Significant Exposure to Dieldrin - 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
69	Dog	2 yr 1x/d (C)		0.05				Walker et al. 1969
	Reproductive							
70	Rat	3 gen ad lib (F)				0.125	(decreased number of litters)	Treon et al. 1954a
	Developmental							
71	Rat	3 gen ad lib (F)				0.125	(increased mortality of offspring)	Treon et al. 1954a
	Cancer							
72	Mouse	2 yr 7d/wk (F)				1.3	(CEL - liver)	Davis and Fitzhugh 1962
73	Mouse	75 wk ad lib (F)				1.3	(CEL - liver)	Lipsky et al. 1989
74	Mouse	85 wk ad lib (F)				1.3	(CEL - liver)	Meierhenry et al. 1983
75	Mouse	80 wk ad lib (F)				0.65	(CEL - liver)	NCI 1978a

Table 3-2. Levels of Significant Exposure to Dieldrin - 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)		
76	Mouse	92 wk 7d/wk ad lib (F)				1.3	(CEL - liver)	Tennekes et al. 1981
77	Mouse	132 wk 1x/d (F)				1.3	(CEL- liver)	Walker et al. 1972
78	Mouse	128 wk 1x/d (F)				0.33	(CEL - liver)	Walker et al. 1972

[a]The number corresponds to entries in Figure 3-2.
[b]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.0001 mg/kg/d; NOAEL (0.01 mg/kg/day) divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic oral Minimal Risk Level (MRL) of 0.00005 mg/kg/d; NOAEL (0.005 mg/kg/day) divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); EEG = electroencephalogram; (F) = feed; Gastro = gastrointestinal; Gd = gestation day(s); gen = generation(s); (GO) = gavage oil; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Dieldrin - Oral

Acute (≤14 days)

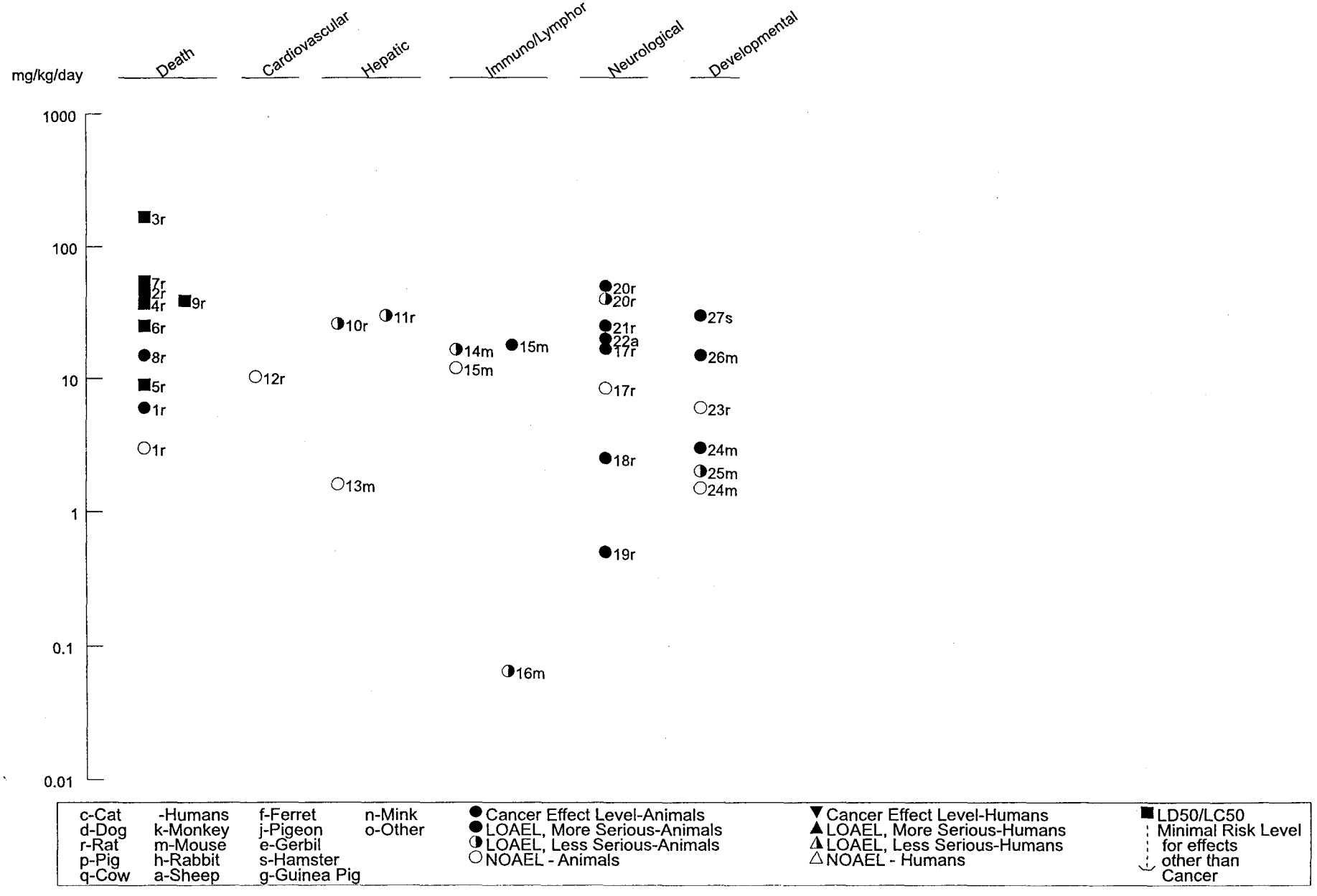


Figure 3-2. Levels of Significant Exposure to Dieldrin - Oral (*Continued*)

Intermediate (15-364 days)

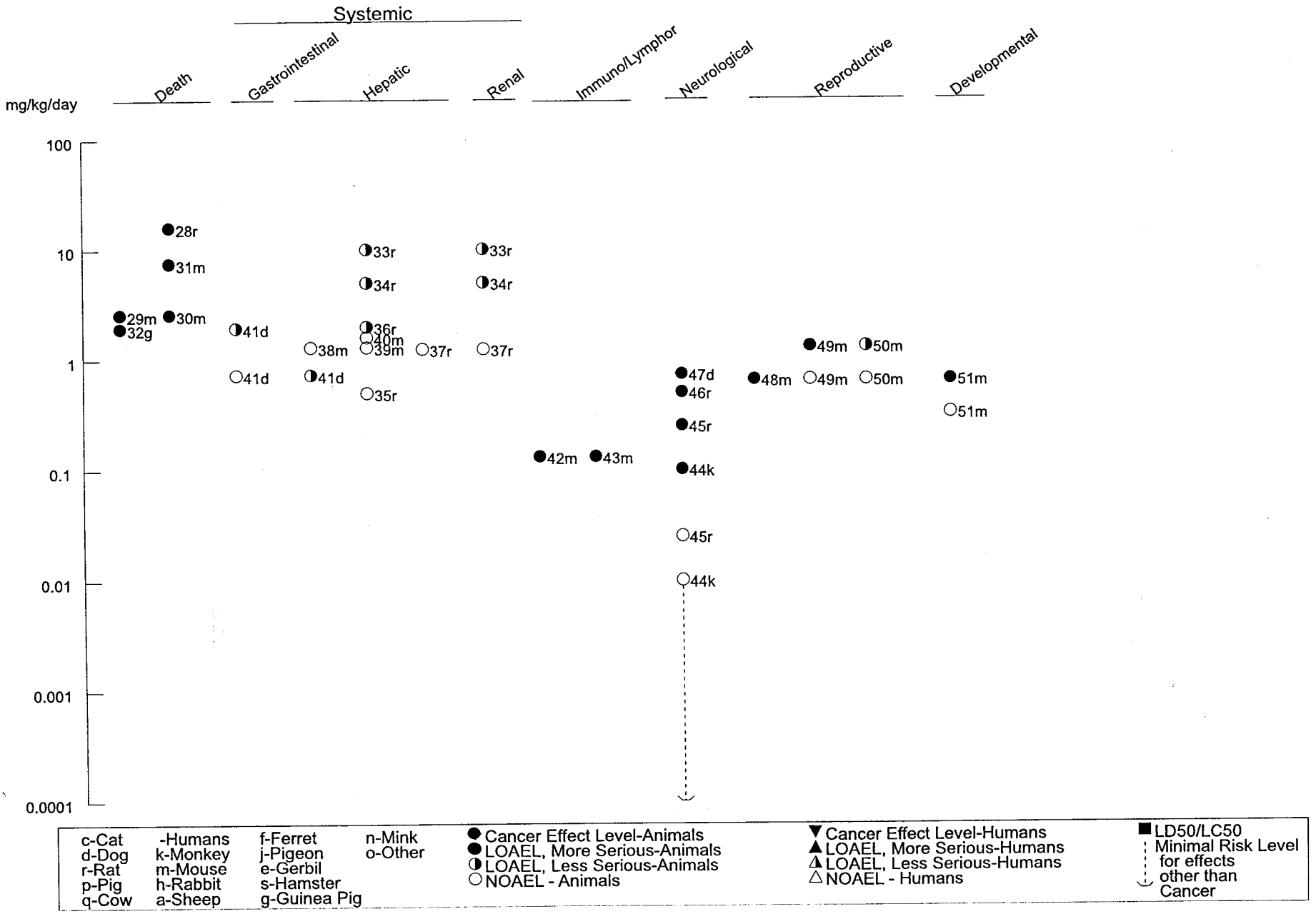


Figure 3-2. Levels of Significant Exposure to Dieldrin - Oral (*Continued*)

Chronic (≥365 days)

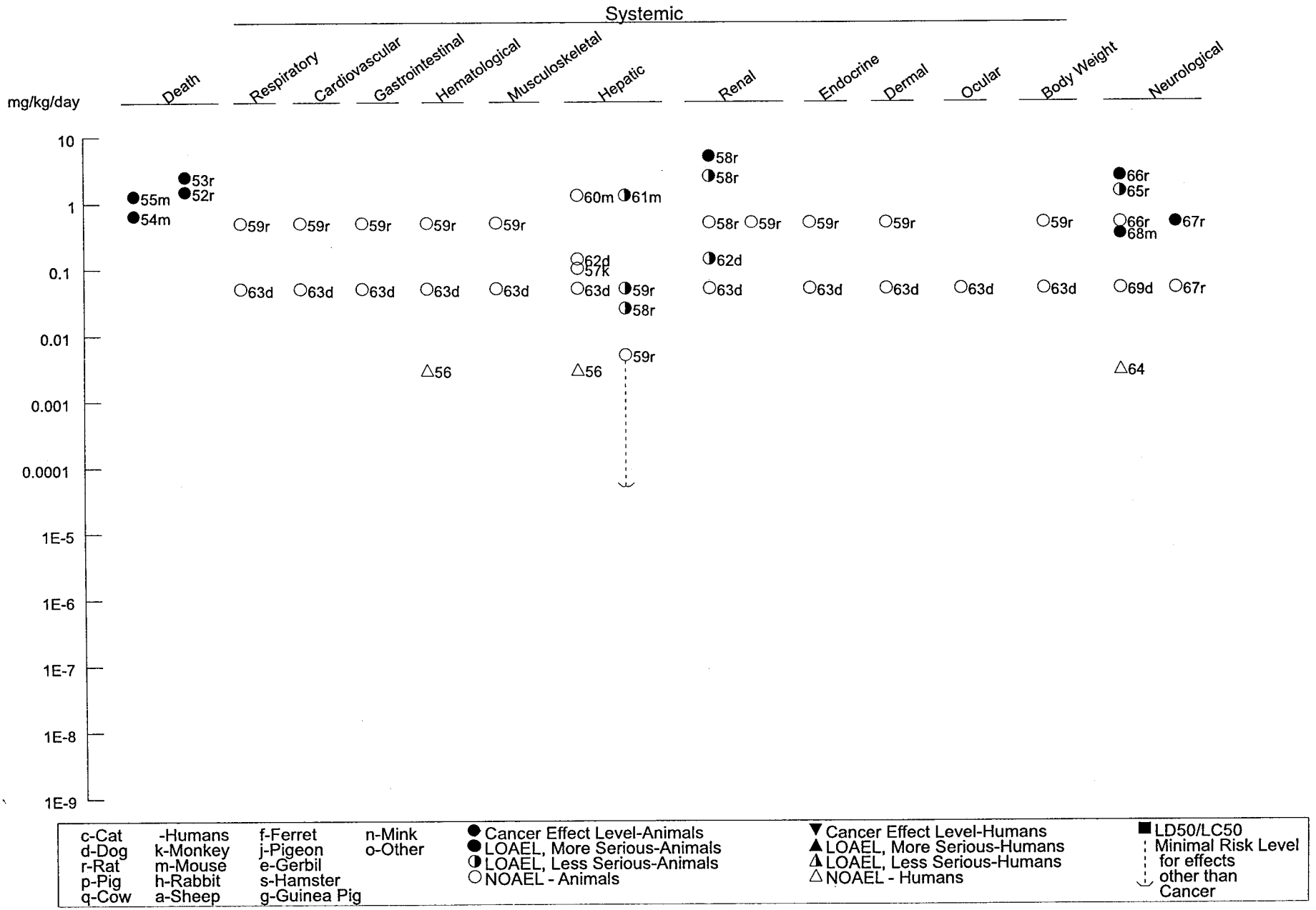
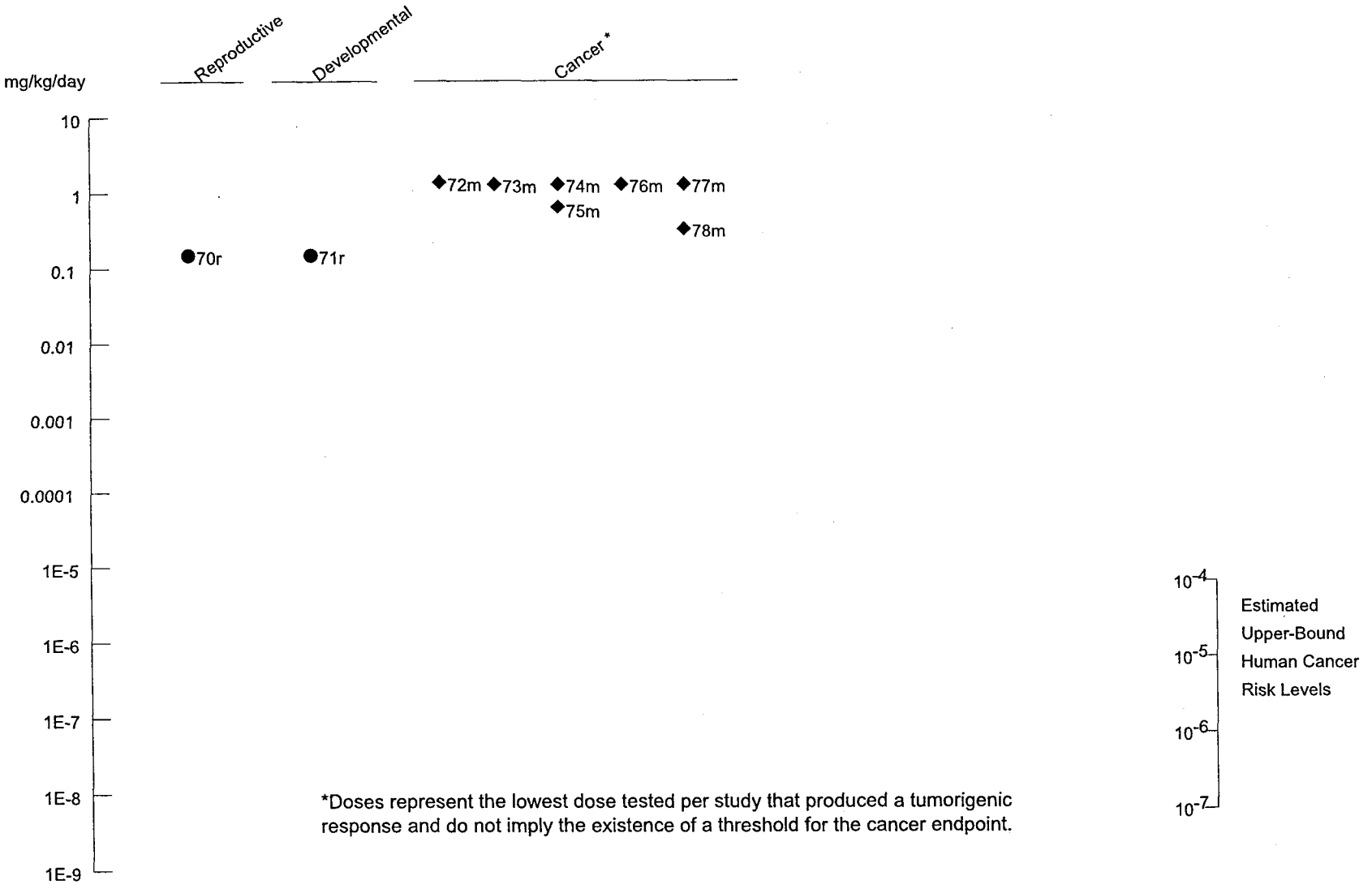


Figure 3-2. Levels of Significant Exposure to Dieldrin - Oral (*Continued*)

Chronic (≥365 days)



*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 endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to aldrin or dieldrin.

Routine gross and microscopic examinations showed no adverse effects in the lungs of rats exposed to #3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), #3 mg/kg/day aldrin or #3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a, 1978b), or #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to #1.04 mg/kg/day aldrin or #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Cardiovascular Effects. A young man who attempted suicide by consuming approximately 25.6 mg/kg of aldrin had extremely labile blood pressure upon admission to the hospital (Spiotta 1951). His electrocardiogram was normal. Another man who ingested 120 mg/kg of dieldrin had tachycardia and elevated blood pressure at the time of his admission to the hospital (Black 1974). Both men were suffering from convulsions at the time that these effects were observed; thus, it is possible that these cardiovascular effects may have been the result of altered activity in the central nervous system. In the case of the man who ingested 120 mg/kg of dieldrin, the cardiovascular effects were controlled with β-adrenergic blocking drugs, suggesting that the effects were due to increased sympathetic output (Black 1974).

A correlation between adipose tissue levels of dieldrin and the incidence of hypertension was reported in a study of terminal hospital patients (Radomski et al. 1968). However, interpretation of these results is limited by the small number of cases of hypertension (eight cases) and the observation that the levels of a number of other pesticides in adipose tissues also correlated with the incidence of hypertension.

Acute oral administration of aldrin and dieldrin inhibited Ca^{2+}-pump activity in the heart (and brain) of rats (Mehrortra et al. 1989). Treatment by gavage for 3 days caused significantly decreased cardiac calmodulin levels at doses as low as 1 mg/kg/day dieldrin and 5 mg/kg/day aldrin, and significant inhibition of Ca^{2+}ATPase activity in heart sarcoplasmic reticulum at 10 mg/kg/day aldrin or dieldrin. The authors suggested that such changes could adversely affect cardiac contractility by altering calmodulin-regulated Ca^{2+}-pump activity in neurons, but no measurement of cardiac function were performed to support this hypothesis.

Routine gross and microscopic examinations showed no adverse effects in the heart of rats exposed to #3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), #3 mg/kg/day aldrin or #3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to #1.04 mg/kg/day aldrin or #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969). Examination of the vascular system does not appear to have been performed in these studies.

Chronic exposure of rats to dieldrin at dietary doses as low as 0.016 mg/kg/day was reported to cause fibrinoid degeneration, inflammation, endothelial proliferation, and perivascular edema in small-to-medium-size arteries (Harr et al. 1970). However, this condition is known to occur spontaneously, no dose-response information was provided, and statistical analyses of these data were not presented. Also, the study by Harr et al. (1970) utilized a semisynthetic diet rather than standard rodent chow, and it is unclear whether such a diet may have affected the outcome of this study. Thus, the significance of this finding is unknown.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to aldrin or dieldrin.

Dogs that ingested lethal doses of aldrin (as low as 0.89–1.78 mg/kg/day over a period of 5–6 months) or dieldrin (as low as 1.95–4.24 mg/kg/day over a period of 11 days–1.3 months) during a 9-month study vomited and became emaciated several days prior to death (Treon et al. 1951b). It is unclear whether the vomiting was directly due to gastrointestinal irritation. Routine gross and microscopic examinations showed no adverse effects in the stomach or intestines of rats exposed to #3 mg/kg/day aldrin or #3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to #1.04 mg/kg/day aldrin or #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Hematological Effects. Limited information is available on hematological effects in orally-exposed humans. Groups of 3–4 volunteers who consumed dieldrin in capsules at doses as high as 0.003 mg/kg/day over a period of 18 months experienced no adverse effects on cellular components of the blood (hemoglobin, packed cell volume, total and differential white blood cell count) or plasma proteins (Hunter and Robinson 1967). Blood coagulation tests were normal in the case of a man who ingested 120 mg/kg of dieldrin followed by repeated stomach lavage in an effort to limit absorption (Black 1974).

One case of immunohemolytic anemia attributable to ingestion of dieldrin was reported (Hamilton et al. 1978). Three cases of pancytopenia and one case of thrombocytopenia have also been associated with exposure to dieldrin, but no assessment regarding whether dieldrin was the causative agent was provided in the report (AMA 1962).

Routinely-examined hematological indices were normal in dietary studies of rats exposed to 0.25 mg/kg/day aldrin for up to 25 months (Deichmann et al. 1967), rats exposed to #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969), and dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969). Some histological changes in blood-forming tissues of exposed animals have been reported. The rats that were exposed to 0.25 mg/kg/day aldrin for 25 months had moderate to marked congestion of the red pulp with slight hemolysis in the spleen (Deichmann et al. 1967), but the significance of these findings is unclear due to a lack of incidence data and the normal hematology indices. Dogs given doses as low as 1 mg/kg/day of either aldrin or dieldrin for 25 months had a reduced number of mature granulocytes and erythroid cells in the bone marrow (Fitzhugh et al. 1964), but these data are limited by small numbers of animals (1–2 males and 1–2 females per dose).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to aldrin or dieldrin.

Muscular lesions, including focal edema, coagulative necrosis, and chronic myositis (inflammation), were observed in rats that were fed aldrin in doses of 0.016 mg/kg/day for 750 days or 0.032 mg/kg/day for 546 days (Harr et al. 1970). Although these effects were not observed in controls, interpretation of the findings is complicated by study limitations, which include small numbers of animals (two per sex per dose), lack of incidence data, and use of a semisynthetic diet rather than standard rodent chow. Additionally, no gross or histopathological changes in muscle were reported in other studies at higher oral doses, including rats exposed to #3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), #3 mg/kg/day aldrin or #3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969), mice exposed to #1.04 mg/kg/day aldrin or #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Treatment of rats with 1.25 mg/kg/day of dieldrin for 60 days was reported to impair the performance of rats who had been trained to pull a weight up an inclined plane in order to receive food (Khairy 1960). Although the author attributed the impaired performance to a decrease in muscular efficiency, no attempt

was made to determine whether the effect was neurological or muscular in origin. Thus, this effect cannot be established as a musculoskeletal effect.

Hepatic Effects. Healthy male subjects who consumed up to 0.003 mg/kg/day of dieldrin in capsules for 18 months showed no clinical signs and had no adverse hepatic effects as indicated by normal serum levels of liver enzymes (alanine and aspartate aminotrasferases, and alkaline phosphatase); however, no liver function tests or biopsies were performed (Hunter and Robinson 1967). However, a child who drank an unknown quantity of a 5% dieldrin solution and who experienced severe convulsions had evidence of liver dysfunction (Garrettson and Curley 1969). The half-life of phenobarbital in the child was greatly increased shortly after the initial intoxication, indicating a decreased ability of the liver to metabolize phenobarbital. Six months later, the phenobarbital half-life had returned to normal levels. However, serum alkaline phosphatase and thymol turbidity test results were elevated above normal levels. Evidence of liver damage (elevated serum aminotransferases) was also observed in a man 5 days after ingesting 120 mg/kg of dieldrin despite vigorous intervention to limit absorption (Black 1974). In the study by Black (1974), the dieldrin was a 15% solution in toluene. It is likely that the solution ingested by the child described by Garrettson and Curley (1969) also contained solvents and possibly emulsifiers. It is possible that the other ingredients in the dieldrin solutions contributed to the hepatic toxicity that was observed.

A number of adaptive changes characteristically produced by halogenated hydrocarbon pesticides were observed in livers of dogs, mice, and rats exposed to aldrin and/or dieldrin. These changes include an increase in liver weight and/or size (Bandyopadhyay et al. 1982b; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; Kohli et al. 1977; Olson et al. 1980; Tennekes et al. 1981; Treon et al. 1951a, 1953b, 1955b; Walker et al. 1969; Walton et al. 1971; Wright et al. 1972), liver cell enlargement (Olson et al. 1980; Treon et al. 1951a, 1954b; Walker et al. 1972), cytoplasmic eosinophilia with migration of basophilic granules (Fitzhugh et al. 1964; Treon et al. 1951a, 1954b; Walker et al. 1969, 1972), an increase in the smooth endoplasmic reticulum (Wright et al. 1972), an increase in microsomal protein (Wright et al. 1972), an increase in cytochrome P-450 content (Walton et al. 1971; Wright et al. 1972, 1978), and/or an increase in microsomal enzyme activity (Den Tonkelaar and van Esch 1974; Kohli et al. 1977; Tennekes et al. 1981; Walton et al. 1971; Wright et al. 1972, 1978).

Within 1 week, alterations of liver cell ultrastructure (an increase in cytoplasmic vacuoles and smooth endoplasmic reticulum) and increased microsomal protein and mixed-function oxidase activity were observed in rats exposed to 8 mg/kg/day or mice exposed to 1.6 mg/kg/day of dieldrin (Wright et al.

1972). After 4 weeks of exposure to 2 mg/kg/day of dieldrin, similar effects were observed in dogs. In addition, liver cell enlargement and increased levels of cytochrome P-450 were apparent in rats and mice 4 weeks after exposure to 8 and 1.6 mg/kg/day, respectively (Wright et al. 1972). Cessation of dosing with dieldrin allowed the reversal of these changes in these animals (Wright et al. 1972). The lowest dose at which an increase in liver-to-body-weight ratio was observed in rats was 0.00035 mg/kg/day of dieldrin for 85 days (Olson et al. 1980). However, this study was limited in that only one dose of dieldrin was tested and animals received limited rations during the last 15 days of the study to maintain their body weights below normal. Monkeys exposed to dieldrin for between 5 and 6 years had a more limited response than dogs, mice, or rats. Exposure to concentrations as high as 0.1 mg/kg/day of dieldrin produced increased mixed-function oxidase activity and cytochrome P-450 content in livers but no histologic changes in the liver that were observable by light or electron microscopy (Wright et al. 1972, 1978). In virtually all of these studies no other evidence of hepatic toxicity was reported; thus, these adaptive changes were not considered to be adverse.

Mixed results regarding changes in hepatic lipid peroxidation have been observed. A single oral dose of 30 mg/kg was reported to decrease hepatic lipid peroxidation in male rats (Kohli et al. 1977). In contrast, a single oral dose of 26 mg/kg was reported to increase hepatic lipid peroxidation in female rats (Goel et al. 1988). It is unclear whether the contrasting results of these two studies are attributable to sex-related differences in metabolism.

Limited evidence for adverse hepatic effects has been observed in rats in intermediate-duration studies following 1–6 months of exposure to 2 mg/kg/day of dieldrin (Shakoori et al. 1982) or 6 months of exposure to 10 mg/kg/day of dieldrin (Ahmed et al. 1986a). At 2 mg/kg/day dieldrin, adverse effects were limited to decreased hepatic protein and some instances of necrosis (Shakoori et al. 1982). At 10 mg/kg/day, there was an increase in serum hepatic enzyme activity (alkaline phosphatase and/or alanine aminotransferase) with decreases in hepatic protein and areas of necrosis (Ahmed et al. 1986a). The statistical significance of the incidence of necrotic areas was not presented. Both of these studies are limited because only one dose of dieldrin was used. No histopathological changes were observed in the livers of rats exposed to #3.75 mg/kg/day aldrin or dieldrin for 6 months, although small numbers of animals were examined (Treon et al. 1951a). Dogs that ingested doses as low as 0.89–1.78 mg/kg/day of aldrin or 0.73–1.85 mg/kg/day of dieldrin for 9 months had moderate parenchymatous degeneration (Treon et al. 1955b). Although the degeneration appeared to increase in severity with dose, this study is limited by a small number of animals.

Evidence for adverse hepatic effects has also been observed in chronic studies. Hyaline droplet degeneration was observed in the livers of dogs that ingested 0.12–0.25 mg/kg/day of aldrin for 15.7 months (Treon et al. 1955b). Similar effects were not observed in dogs that ingested 0.14–0.26 mg/kg/day of dieldrin over the same period. In dogs exposed to 1 mg/kg/day of aldrin or dieldrin for 25 months, slight-to-moderate fatty degeneration was observed (Fitzhugh et al. 1964). Also, in dogs given doses as low as 0.2 mg/kg/day of dieldrin for up to 1 year, degeneration was observed (Kitselman 1953). The degree of necrosis increased with dose. However, these studies are limited in that too few animals were tested (Fitzhugh et al. 1964; Kitselman 1953; Treon et al. 1955b). Both male and female dogs exposed to 0.05 mg/kg/day of dieldrin for 2 years had elevated serum alkaline phosphatase levels, and males at this dose had decreased serum proteins (Walker et al. 1969). The origin of the increased serum alkaline phosphatase activity was unknown, but not believed to be due to bone disorders or biliary obstruction (i.e., the usual clinical interpretation of elevated serum alkaline phosphatase in dogs [Cornelius 1970; Walker et al. 1969]). The decrease in total serum proteins was slight and considered to have no clinical or toxicological significance since the electrophoretic pattern of the proteins was unchanged. The possibility that increased serum alkaline phosphatase may not necessarily represent hepatic damage in dogs was also raised by El-Aharaf et al. (1972), who showed that dogs exposed to 0.05–0.20 mg/kg/day of dieldrin for 1 year had increased serum alkaline phosphatase of hepatic origin but no increase in serum levels of 5'-nucleotidase (a hepatic membrane enzyme that should be elevated in the serum as a result of hepatic damage). Because hepatic levels of alkaline phosphatase increased in parallel with serum levels of alkaline phosphatase, these authors suggested that alkaline phosphatase may be transferred directly from the hepatocyte to the sinusoidal blood.

Rats exposed to doses of dieldrin ranging from 0.016 to 0.063 mg/kg/day throughout their lifetime were reported to have developed hepatic lesions consisting of centrilobular degeneration and peripheral hyperplasia (Harr et al. 1970). Pyknosis of hepatocellular nuclei was also reported; however, no statistics, dose-response data, or incidence data were presented to support this conclusion. Also, the rats in this study received dieldrin in a semisynthetic diet, and it is unclear whether such a diet may have affected the study outcome.

Rats exposed via their diets to aldrin or dieldrin for 2 years at doses as low as 0.025 mg/kg/day had increases in liver-to-body-weight ratio and hepatic histopathological changes consistent with exposure to chlorinated hydrocarbons (Fitzhugh et al. 1964). At 2.5 mg/kg/day, gross enlargement of the liver was observed, and the histopathological changes were considered to be marked and included an increase in the severity of hepatic cell vacuolation. The hepatic lesions that were seen at the aldrin dose of

0.025 mg/kg/day were characterized by hypertrophy of centrilobular hepatocytes, cytoplasmic eosinophilia, and peripheral migration of basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation, changes consistent with a marked hepatic adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. No NOAEL for liver effects of chronic aldrin exposure was identified. Based on the LOAEL of 0.025 mg/kg/day (Fitzhugh et al. 1964) and considering the evidence for dose-related progression of hepatotoxicity in this and other studies, a chronic oral MRL of $3.0x10^{-5}$ mg/kg/day was calculated for aldrin as described in the footnote in Table 3-1.

Rats that were exposed to 0.005, 0.05, or 0.5 mg/kg/day dieldrin in the diet for 2 years similarly had increased absolute and relative liver weights at $0.05 mg/kg/day, and at the highest dose of 0.5 mg/kg/day, liver parenchymal cell changes characteristic of organochlorine exposure, as well as indications of focal hyperplasia (Walker et al. 1969). Based on the 0.005 mg/kg/day NOAEL for liver effects (Walker et al. 1969) and considering the evidence for dose-related progression of hepatotoxicity, a chronic oral MRL of $5.0x10^{-5}$ mg/kg/day was calculated for dieldrin as described in the footnote in Table 3-2.

Mice exposed to 1.3 mg/kg/day dieldrin for 2 years had livers with occasional necrotic areas (Thorpe and Walker 1973); however, this study is limited because it is unclear whether the necrotic areas were secondary to tumor development, the incidence of these areas was not reported, and only one dose of dieldrin was tested. Routine histological examinations in other chronic studies showed no nonneoplastic liver changes in mice exposed to #1.04 mg/kg/day aldrin for 80 weeks (NCI 1978a), #0.65 mg/kg/day dieldrin for 80 weeks (NCI 1978a), or 1.3 mg/kg/day dieldrin for 92 weeks (Tennekes et al. 1981), although the emphasis in these studies was on detection of carcinogenicity.

Renal Effects. A man who attempted suicide by consuming approximately 25.6 mg/kg of aldrin had elevated blood urea nitrogen, gross hematuria, and albuminuria upon admission to the hospital (Spiotta 1951). By 17 days after admission, levels of nitrogen, blood, and protein in the urine had returned to normal. Six weeks after the suicide attempt, the ability to concentrate the urine was determined to be poor. In contrast, a man who ingested 120 mg/kg of dieldrin had no evidence of renal damage (Black 1974). In both of these case reports, the actual dose available for absorption was unknown because efforts were made to limit absorption of the chemicals from the gastrointestinal tract.

Adverse effects on the kidneys have been observed following exposure of rats and dogs to aldrin and/or dieldrin. Exposure of rats to 5 mg/kg/day of dieldrin for 15 days resulted in membranous glomerulonephritis, nephrosis in the proximal convoluted tubules, vacuolated cytoplasm, necrotic cells in the tubular lumen, and large intertubular spaces (Bandyopadhyay et al. 1982b). Similarly, exposure of rats to 10 mg/kg/day of dieldrin for 6 months in a single–dose level study resulted in degenerative changes in the epithelial cells of the kidney and lymphocyte and macrophage infiltration (Ahmed et al. 1986a). Rats exposed to 0.25 mg/kg/day of dieldrin for 25 months in a single-dose level study showed slight lymphocyte infiltration, vascular congestion in the renal cortex, and hyaline casts in the renal tubules (Deichmann et al. 1967). Increases in the incidence and severity of nephritis were also observed in male rats exposed to doses as low as 0.5 mg/kg/day of aldrin or 0.125 mg/kg/day of dieldrin for 2 years (Fitzhugh et al. 1964; Harr et al. 1970; Reuber 1980). However, these studies are limited because no statistical analyses were presented to support these conclusions. Dogs exposed to doses of aldrin or dieldrin as low as 0.2 mg/kg/day also had degeneration of the renal tubules (Fitzhugh et al. 1964; Kitselman 1953), but these studies are limited by the absence of sufficient experimental detail, the lack of histopathological data on many of the animals, and the small number of animals tested. In the study by Fitzhugh et al. (1964), only one or two males and females were used per dose; in the study by Kitselman (1953), three dogs were used per dose. Slight vacuolation of the renal tubules was also reported in dogs exposed to doses as low as 0.14–0.26 mg/kg/day of dieldrin or 0.04–0.09 mg/kg/day of aldrin for 15.7 months, but this study was also limited by the small number of dogs used (Treon et al. 1955b). Routine gross and microscopic examinations showed no adverse effects in the kidneys of rats exposed to #3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), #3 mg/kg/day aldrin or #3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a, 1978b), or #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to #1.04 mg/kg/day aldrin or #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Endocrine Effects. No information was located regarding effects of aldrin or dieldrin on the endocrine system in humans following oral exposure.

Histological examination of nonreproductive endocrine tissues in intermediate- and chronic-duration studies showed no aldrin- or dieldrin-related non-neoplastic changes in animals. Tissues that were examined in these studies included adrenal, thyroid, parathyroid, pancreas, and/or pituitary in rats exposed to #3.75 mg/kg/day of aldrin or dieldrin for 6 months (Treon et al. 1951a), rats exposed to #3.75 mg/kg/day aldrin for up to 80 weeks (NCI 1978a), mice exposed to #1.04 mg/kg/day aldrin for up

to 80 weeks (NCI 1978a), rats exposed to #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969), rats exposed #3.25 mg/kg/day dieldrin for 80–104 weeks (NCI 1978a), mice exposed to #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), and dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969). Animal fertility studies indicate that the testis is a target of aldrin and dieldrin in males (see Section 3.2.2.5, Reproductive Effects).

The ability of chlorinated hydrocarbons to disrupt estrogen homeostatis, by up-regulating selected gene transcription, has been hypothesized to be responsible for their oncogenic effects. While dieldrin alone did not show any evidence of estrogenicity when administered to rats by intragastric intubation at a dose of 7.5 µmol/kg/day, 5 days/week, for 9 months, when administered with toxaphene (30 µmol toxaphene/kg/day and 7.5 µmol/kg/day), bone mass density was significantly increased (Syversen et al. 2000). A single dose of dieldrin (37 mg/kg) administered to female rats by gavage significantly increased expression of cytochrome P450 CYP1A1, CYP1A2, and CYP1B1, which are involved in estrogen metabolism, in the liver, kidney, and mammary tissues (Badawi et al. 2000).

Dermal Effects. Routine histological examinations showed no adverse effects in the skin of rats exposed to #3 mg/kg/day aldrin or #3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to #1.04 mg/kg/day aldrin or #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

Ocular Effects. Routine histological examinations showed no adverse effects in the eyes of rats exposed to #3 mg/kg/day aldrin or #3.25 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a), or #0.5 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969); mice exposed to #1.04 mg/kg/day aldrin or #0.65 mg/kg/day dieldrin for up to 80 weeks (NCI 1978a); or dogs exposed to #0.05 mg/kg/day dieldrin for up to 2 years (Walker et al. 1969).

3.2.2.3 Immunological and Lymphoreticular Effects

Limited information was located regarding immunological effects in humans after oral exposure to aldrin or dieldrin. A case report was located concerning a man who developed immunohemolytic anemia after eating fish that contained high levels of dieldrin (Hamilton et al. 1978). Testing of the patient's serum revealed a positive antibody test for dieldrin-coated red blood cells.

An epidemiological study of 98 breast-fed and 73 bottle-fed Inuit infants from Nunavik (Arctic Quebec, Canada) indicated that the RR of experiencing otitis media (three or more episodes) over the first year of life increased with prenatal exposure to dieldrin (Dewailly et al. 2000). The RR for 4–7-month-old infants in the highest exposure group (>43 µg/kg dieldrin in maternal breast milk) as compared to infants in the lowest exposure group (<21 µg/kg) was 1.75 (95% CI 1.05–2.91). The RR of infants experiencing three or more episodes of otitis media over the first year of life was 3.5 (95% CI 0.95–12.97). No clinically relevant differences were noted between breast-fed and bottle-fed infants with regard to immunologic parameters, nor were any of the immunologic parameters associated with prenatal dieldrin exposure.

Immunosuppression by dieldrin has been reported in a number of studies in mice. An increase in lethality of mouse hepatitis virus three and a decrease in the antigenic response to the virus were observed in mice given a single oral dose of dieldrin ($18 mg/kg) (Krzystyniak et al. 1985). Similarly, an increase in lethality of infections with the malaria parasite, *Plasmodium berghei*, or *Leishmania tropica* in mice was produced by treatment of the mice with dieldrin in the diet at doses as low as 0.13 mg/kg/day for 10 weeks (Loose 1982). Also, a decrease in tumor cell killing in mice was observed after dieldrin treatment with doses as low as 0.13 mg/kg/day for 3, 6, or 18 weeks (Loose et al. 1981).

Since resistance to intracellular organisms and tumor cell killing require induction of cell-mediated immunity through thymus-derived lymphocyte (T-lymphocyte) interactions with macrophages, the effects of dieldrin consumption on the activity of these components of the response were tested. A decrease in antigen processing by alveolar macrophages was observed in mice following consumption of dieldrin for 2 weeks (Loose et al. 1981). Macrophages that ingested sheep red blood cell antigen manifested a significantly impaired ability to transfer an adequate immunogen to naive control mice. Splenic and alveolar macrophages were the most sensitive cell types as the decrease occurred following exposure to dieldrin doses as low as 0.065 mg/kg/day (lowest tested dose). Peritoneal macrophage antigen processing was significantly depressed at 0.65 mg/kg/day, and Kupffer cell antigen processing was depressed at

6.5 mg/kg/day. This effect was observed in the absence of effects on macrophage respiration, phagocytic activity or capacity, or microbicidal activity. In addition, macrophages from dieldrin-treated (0.65 mg/kg/day for 10 weeks) mice were found to produce a soluble factor that induced T-lymphocyte suppressor cells (Loose 1982). Inhibition of lymphocyte proliferation was also seen in a mixed lymphocyte reaction test in which splenic cells from mice treated twice with 16.6 mg/kg dieldrin were combined with stimulator cells from control animals (Fournier et al. 1988). However, this study is limited because only one dose level of dieldrin was tested.

All reliable LOAEL values for immunologic effects of dieldrin in mice in acute- and intermediate-duration studies are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Case reports regarding accidental poisonings or suicide attempts provide the majority of the information on the neurological effects of aldrin and dieldrin by the oral route. Two children who consumed an unknown amount of a 5% dieldrin solution began to salivate heavily and developed convulsions within 15 minutes (Garrettson and Curley 1969). In the surviving child, the seizure episode lasted for 7.5 hours before being controlled by phenobarbital. EEG recordings taken from this child showed bursts of synchronous high-voltage slow waves. Both the child's condition and the EEG recordings returned to normal with time. Convulsions also developed rapidly in a man who attempted suicide by consuming an estimated 25.6 mg/kg of aldrin (Spiotta 1951) and in a man who ingested 120 mg/kg of dieldrin (Black 1974). Anticonvulsants were given to control the seizures, but one man exhibited motor hyperexcitability and restlessness for several days (Spiotta 1951), and the other required muscle paralysis to sufficiently control the convulsions to allow artificial respiration (Black 1974). EEGs taken a few days after admission showed epileptiform activity, but the EEGs returned toward normal with time.

A small group of persons who consumed wheat that had been mixed with aldrin and lindane over a period of 6–12 months developed a variety of central nervous system symptoms (Gupta 1975). These included bilateral myoclonic jerks, generalized seizures, auditory and visual auras, hyperexcitability, and irritability. In some cases, the onset of symptoms was abrupt. EEGs showed spike and wave activity and abnormal bursts of slow delta-wave discharges. After exposure was discontinued, the symptoms slowly improved. However, 1 year after exposure, infrequent myoclonic jerks were observed in several of the subjects. One subject also complained of memory loss and irritability, and a 7-year-old child was believed to have developed mild mental retardation as a result of the exposure. Although both aldrin and

lindane had been mixed with the wheat, the author concluded that the effects observed were due to the aldrin exposure because in previous years wheat had been routinely mixed with lindane and consumed with no apparent adverse effects. Persistent headaches, irritability, and short-term memory loss were also reported following recovery from convulsions in a man who ingested 120 mg/kg of dieldrin (Black 1974).

Dieldrin administered to volunteers daily for 18 months at doses as high as 0.003 mg/kg/day had no effect on central nervous system activity (as measured by EEG), peripheral nerve activity, or muscle activity (Hunter and Robinson 1967).

Ingestion of aldrin and dieldrin most likely was not a significant route of exposure and therefore probably did not contribute significantly to the neurological effects observed in many of the occupational studies presented in Section 3.2.1.4. However, in the study by Patel and Rao (1958), the authors could not eliminate oral exposure by dieldrin since workers reportedly mixed the dieldrin solutions with their bare hands and some time later consumed food using their hands.

Convulsions were also observed in rats given single doses of dieldrin ranging from 40 to 50 mg/kg (Wagner and Greene 1978; Woolley et al. 1985). When aldrin or dieldrin was administered to rats for 3 days, convulsions were observed at a dose of 10 mg/kg/day (Mehrotra et al. 1989). Transient hypothermia and anorexia were also observed following a single dose of 40 mg/kg (Woolley et al. 1985). Long-term potentiation of limbic evoked potentials was observed following a single dose of 25 mg/kg, and subthreshold limbic stimulation caused convulsions following a single dose of 40 mg/kg (Woolley et al. 1985). Neurotoxic signs observed in cattle poisoned with unspecified dietary concentrations of aldrin included tremors, running, hyperirritability, and seizures (Buck and Van Note 1968).

Operant behavior was disrupted in rats following single doses of dieldrin ranging from 0.5 to 16.7 mg/kg. The simpler paradigms of fixed interval responding and maze training were both impaired at doses as low as 16.7 mg/kg, whereas differential responding to low rates of reinforcement was impaired at 2.5 mg/kg (Burt 1975). Responses in an inescapable foot shock stress paradigm were impaired at doses as low as 0.5 mg/kg (Carlson and Rosellini 1987). In sheep, operant responding was decreased 38–76% during a 4-day treatment with 20 mg/kg/day dieldrin (Sandler et al. 1969). EEGs obtained during exposure showed high-voltage, slow wave activity.

In studies of intermediate duration, operant behavior was disrupted at somewhat lower doses of dieldrin. Following 60–120 days of exposure of rats to 0.25 mg/kg/day, dieldrin significantly impaired maze

training (Burt 1975). In a study which was used as the basis for an intermediate-duration oral MRL (Smith et al. 1976), monkeys orally administered 0.1 mg dieldrin/kg/day for 55 days demonstrated impaired learning (difficulty learning a successive discrimination reversal task); this effect was not seen in monkeys administered 0.01 mg/kg/day, a dose considered to be a NOAEL for impaired learning. No effect on operant behavior in rats was observed following 0.025 mg/kg/day for 60–120 days. Sheep appeared to be somewhat less sensitive to the effects of dieldrin on behavior, although a small number of animals was used in these studies (Van Gelder 1975). The lowest dose at which sheep had impaired operant behavior was 2.5 mg/kg/day for 12 weeks. This was determined using an auditory signal detection test. Visual discrimination was not impaired until doses of 10 mg/kg/day were administered, and maze training and extinction of a conditioned avoidance response were not impaired at 15 mg/kg/day (Van Gelder 1975).

Physical signs of neurotoxicity were observed in two single-dose level, intermediate-duration studies in rats. Tremors were observed in rats at a dose of 0.5 mg/kg/day for 60 days (Mehrotra et al. 1988) and hyperexcitability was observed at 2.5 mg/kg/day in an 8-week study (Wagner and Greene 1978). Exposure to 1.25 mg/kg/day aldrin or dieldrin for 6 months caused degenerative histological changes in brain cells of rats (Treon et al. 1951a). Dogs given aldrin at 0.89–1.78 mg/kg/day or dieldrin at 0.73–1.85 mg/kg/day for up to 9 months experienced neuronal degeneration in the cerebral cortex and convulsions (Treon et al. 1951b). At this dose, aldrin-treated dogs also exhibited hypersensitivity to stimulation, twitching, and tremors. At higher doses, the basal ganglia and cerebellum also exhibited degenerative changes.

Irritability, tremors, and/or convulsions were observed in rats exposed to aldrin or dieldrin in doses ranging from 0.65 to 3.25 mg/kg/day, but not #0.05 mg/kg/day, for 1.5–2 years (NCI 1978a, 1978b; Walker et al. 1969). Mice experienced hyperexcitability, fighting and/or tremors at 0.39 mg/kg/day aldrin or 0.33 mg/kg/day dieldrin in 80-week bioassays (NCI 1978a).

EEGs taken from dogs exposed to 0.05 mg/kg/day for 2 years were normal (Walker et al. 1969). However, dogs were reported to develop convulsions when given 0.5 mg/kg/day for 25 months (Fitzhugh et al. 1964), and slight neuronal degeneration was reported following 1 year of exposure to aldrin or dieldrin at 0.2 mg/kg/day (Kitselman 1953). However, both of these studies are limited by the small number of animals tested. The only other study that noted histopathological evidence of central nervous system damage was a 2-year study of the effects of dieldrin in rats (Harr et al. 1970). Cerebral edema and small foci of degeneration were reported in rats exposed to dieldrin at 0.016 mg/kg/day, but no statistical

analysis of these results was presented. Also, the study by Harr et al. (1970) used a semisynthetic diet, and it is unclear whether the use of such a diet may have affected the study outcome.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

3.2.2.5 Reproductive Effects

Aldrin levels in blood and placental tissues of women who had premature labor or spontaneous abortions were significantly higher than in women with normal deliveries (Saxena et al. 1980). However, interpretation of this study is limited because levels of six other organochlorine pesticides were also significantly elevated and because other potential distinctions between the two groups that might have contributed to premature labor or abortion, such as smoking or alcohol consumption, were not addressed. Nevertheless, this observation suggests that aldrin can pass through the human placenta and accumulate in the developing fetus. Similarly, accumulation of dieldrin in the amniotic fluid and in the developing fetus has been reported by Polishuk et al. (1977b).

Acute exposure of male mice to aldrin or dieldrin produced no adverse effects on reproduction. Male mice treated with doses of aldrin up to 1 mg/kg/day for a period of 5 days showed no significant effects in a dominant lethal study (Epstein et al. 1972). Similarly, single oral doses of dieldrin ranging from 12.5 to 50 mg/kg had no significant effect on the number of pregnancies produced by male mice in a dominant lethal assay (Dean et al. 1975).

A significant but slight decrease in fertility was observed in female mice exposed to 1.3 or 1.95 mg/kg/day of dieldrin from 4 weeks prior to mating through weaning (Virgo and Bellward 1975). In this study, males were exposed to test material only during the 2-week mating period. Similarly, male and female rats receiving diet containing aldrin or dieldrin at doses of aldrin as low as 0.63 mg/kg/day and dieldrin as low as 0.125 mg/kg/day from the time they were 28 days old had decreased fertility (decreased number of litters) during the first mating of the parental generation in a three-generation reproduction study (Treon et al. 1954a). A subsequent mating of the parental rats receiving aldrin showed no reproductive effects, and those receiving dieldrin failed to show a consistent dose-related effect on fertility. At matings of the offspring, no effect on fertility (number of litters) was observed at 0.125 mg/kg/day; however, effects on fertility due to higher doses were difficult to assess because few

offspring survived to be mated. In contrast, no consistent effect of doses of dieldrin as high as 2 mg/kg/day was found on the conception rate of male and female rats exposed from the time they were 28 days old through the period of mating (initiated when the rats were 146 days old) (Harr et al. 1970). These results are limited in that no statistical analysis of the data was presented. In addition, male and female mice exposed to 0.65 mg/kg/day of dieldrin for 30 days prior to mating and then for 90 days thereafter experienced no adverse effects on fertility, fecundity, or the length of gestation (Good and Ware 1969). The only adverse reproductive effect observed in this study was a slight decrease in litter size. However, this study is limited in that only one dose level of dieldrin was tested.

A number of adverse reproductive effects were observed in dogs following exposure of males and females to 0.15 or 0.30 mg/kg/day for 14 months prior to mating (Deichmann et al. 1971). These included delayed estrus, reduced libido, lack of mammary function and development, and an increased number of stillbirths. However, this study is limited by the small number of animals tested.

Maternal behavior was adversely affected by dieldrin when mice were treated from 4 weeks prior to delivery until weaning. At 1.3 mg/kg/day, Virgo and Bellward (1975) observed a delay in the time before mice nursed their pups. Also, at doses of 1.95 mg/kg/day and above, some dieldrin-treated maternal animals violently shook the pups, ultimately killing them, and others neglected their litters (Virgo and Bellward 1975). At doses of dieldrin above 1.95 mg/kg/day, high maternal mortality was also observed in this study.

The highest NOAEL for dieldrin and all reliable LOAEL values for reproductive effects in animals after oral exposure to aldrin or dieldrin are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to aldrin or dieldrin. However, a study of dieldrin levels in women and their fetuses during labor revealed detectable levels of dieldrin in the placenta, amniotic fluid, and fetal blood (Polishuk et al. 1977b). These results suggest that dieldrin can pass through the human placenta and accumulate in the developing fetus.

Conflicting results have been obtained in animal studies examining the ability of aldrin and dieldrin to cause external malformations or skeletal anomalies. Such effects have been observed in mice and hamsters following a single very large dose of aldrin or dieldrin in mid-gestation (Ottolenghi et al. 1974). Significant increases in cleft palate and webbed foot were observed in mice following a dose of 15 mg/kg of dieldrin or 25 mg/kg of aldrin on gestation day 9. Significant increases in cleft palate, open eye, and webbed foot were seen following a dose of 30 mg/kg of dieldrin or 50 mg/kg of aldrin on gestation days 7, 8, and/or 9 in hamsters. Fetal mortality was also significantly increased, and fetal weight was significantly decreased in hamsters. No information was provided regarding the health of maternal animals in this study. Also, this study is limited in that only a single dose of aldrin and dieldrin was tested. A significant increase in supernumerary ribs was observed in mice from dams exposed to 3 or 6 mg/kg/day dieldrin on gestation days 7–16 (Chernoff et al. 1975). In this study, these doses of dieldrin also caused an increase in the maternal liver-to-body-weight ratio. However, other studies examining developmental effects of aldrin and/or dieldrin have failed to observe similar malformations or anomalies. No developmental defects were observed in rats exposed to concentrations of dieldrin as high as 6 mg/kg/day from gestation day 7 to 16 (Chernoff et al. 1975). Also, no significant developmental effects were observed in mice exposed to doses of dieldrin as high as 4 mg/kg/day from gestation day 6 to 14 (Dix et al. 1977), although the number of litters tested in this study was somewhat low.

Offspring of mice treated for 5–7 days during the third trimester of pregnancy with 2 or 4 mg/kg/day of aldrin had 18% decreased body weight and a significantly increased electroconvulsive shock brain seizure threshold, although there was no disruption of the acquisition of a conditioned avoidance response (Al-Hachim 1971). Based on the 2 mg/kg/day LOAEL for developmental effects, an acute oral MRL of 0.002 mg/kg/day was calculated for aldrin as described in the footnote in Table 3-1. Rat pups that were exposed to 0.00035 mg/kg/day dieldrin from gestation day 5 until the pups were 70 days old showed a significant improvement in swimming and maze running performance (Olson et al. 1980). This dose of dieldrin is several orders of magnitude below any other dose at which developmental effects have been

observed. Interpretation of these results is difficult because the significance of improved performance in behavioral paradigms is unknown, and the study is limited because only one dose of dieldrin was tested.

Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin. Mice exposed to dieldrin in the diet at doses as low as 1 mg/kg/day from 4 weeks prior to mating through weaning had significantly decreased pup survival (Virgo and Bellward 1975). Maternal mortality was unaffected in this study at doses below 2.6 mg/kg/day. A similar decrease in postnatal survival has been observed in rats and dogs exposed to aldrin and/or dieldrin by the oral route. Increased mortality of offspring during the first 5 days of life was observed at 0.125 mg/kg/day of either aldrin and dieldrin in the first mating of a three-generation reproduction study in rats (Treon et al. 1954a). Maternal mortality was unaffected at doses as high as 1.25 mg/kg/day of either aldrin or dieldrin. Similarly, rats exposed to dieldrin from the time that they were 28 days old to when they were mated at 146 days old had decreased postnatal pup survival at doses as low as 0.125 mg/kg/day (Harr et al. 1970). Maternal mortality in this study was unaffected at doses below 0.5 mg/kg/day. This study is limited, however, in that no statistical analysis of the data was presented to confirm this assertion. Also, the rats in this study received a semisynthetic diet, and it is unclear whether such a diet may have affected the study outcome. Dogs exposed to doses of aldrin as low as 0.2 mg/kg/day or dieldrin at doses as low as 0.6 mg/kg/day for up to 1 year had poor litter survival (Kitselman 1953). In some instances, apparently normal puppies were born but died after a few days of nursing. Although maternal toxicity was not specifically addressed in this study, dogs receiving similar doses of aldrin and dieldrin had histopathological evidence of hepatic and renal toxicity. This study is also limited because too few dogs were tested, pregnancies were incidental to the study protocol, and thus adequate controls were not used. Dogs mated 2 weeks to 9 months after a 14-month exposure to doses of aldrin as low as 0.15 mg/kg/day also had high mortality among the offspring (Deichmann et al. 1971). However, this study was also limited by the small number of animals tested.

A number of studies have been undertaken to assess the cause of the decreased pup survival. To test whether the decrease in pup survival was dependent on maternal postnatal care, a cross-fostering experiment was performed (Virgo and Bellward 1977). Mice born to dieldrin-exposed dams were nursed by untreated dams. Significantly decreased pup survival was also observed in this study at 1 mg/kg/day irrespective of whether pups were nursed by birth or foster maternal animals. In a single-dose level study of mice that were exposed to 2 mg/kg/day dieldrin between 6 and 18 days of gestation, pups that were examined at varying times after birth had a rapid decrease in blood glucose and depletion of tissue glycogen stores that were significant when compared to controls (Costella and Virgo 1980). These

decreases occurred despite apparently normal gluconeogenesis. Cardiac failure, secondary to cardiac glycogen depletion, has been proposed as the cause of death (Costella and Virgo 1980).

Histopathological examination of pups born to treated maternal animals was performed in two studies. Rat pups born to dams treated with dieldrin at doses as low as 0.004–0.008 mg/kg/day had neural lesions consisting of cerebral edema, internal and external hydrocephalus, and focal neuronal degeneration. Hepatic degeneration was seen in the pups of dams fed doses of dieldrin as low as 0.016 mg/kg/day (Harr et al. 1970). However, no information regarding the dose-dependency of these effects or the relative numbers of animals affected was reported. Also, the rats in this study received a semisynthetic diet, and it is unclear whether such a diet may have affected the study outcome. Offspring from dogs that had been treated with doses of aldrin as low as 0.2 mg/kg/day or dieldrin as low as 0.6 mg/kg/day had degeneration of hepatic and renal tissues (Kitselman 1953). Both of these studies are limited by the lack of supporting clinical chemistry data and the absence of statistical analyses of the histopathological data. Furthermore, in the study by Kitselman (1953), not all offspring were examined histopathologically.

The highest NOAEL values and all reliable LOAEL values for developmental effects in animals after acute- or intermediate-duration exposure to dieldrin are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

A few epidemiological studies have examined cancer mortality in workers employed in the manufacture of aldrin and dieldrin. The results of these studies may be found in Sections 3.2.1.7 and 3.2.3.7. However, although possible, ingestion of aldrin or dieldrin is not thought to have been a significant source of exposure in these studies because manufacturing practices limit such exposures (Jager 1970).

Equivocal evidence exists for an association between dieldrin and breast cancer risk from three human epidemiologic studies (Dorgan et al. 1999; Høyer et al. 1998, 2000). In these studies, while dieldrin exposure was verified through blood sampling, and exposure by ingestion, as well as by inhalation and dermal contact, was possible, no specific route of exposure was identified or estimated with any certainty.

The potential of dieldrin to affect breast cancer risk was evaluated in a prospective nested case control study of women in Denmark (Høyer et al. 1998). Serum samples were obtained from 7,712 women from 1976 to 1978. In 1996–1997, serum samples from 240 women who had developed invasive breast cancer

and 477 matched breast cancer-free controls were analyzed for levels of dieldrin and 17 other organochlorine pesticides or metabolites and 28 PCB congeners. Controls and cases were matched for age, date of examination, and vital status at the examination. Irrespective of breast cancer status, dieldrin was detected in 78% of the women enrolled in the study, with median levels at 24.4 ng/g lipid. Dieldrin was the only organochlorine compound of those tested associated with a significant increase in breast cancer risk. Women in the highest quartile of the serum dieldrin range had double the risk of breast cancer compared to women in the lowest quartile (OR 2.25, 95% CI 1.32–3.84, p trend=0.003). Relative risk did not change significantly when adjusted for potential confounders of weight and number of full-term pregnancies (OR 2.05, 95% CI 1.17–3.57, p trend=0.01).

A subsequent study using the same cohort of Danish women investigated whether breast cancer survival was affected by past exposure to dieldrin (Høyer et al. 2000). Dieldrin at blood concentrations >57.6 ng/g, representative of the highest quartile, was found to have a significant adverse effect on overall survival and breast cancer specific survival compared to the lowest quartile levels of <12 ng/g lipid (RR 2.78, 95% CI 1.38–5.59, p trend<0.01; RR 2.61, 95% CI 0.97–7.01, p trend<0.01) in this case-control study of Danish women between 20 and 80 years of age. A total of 195 breast cancer cases, who each provided two blood samples that were taken in 1976–1978 and 1981–1983, respectively, were included in the survival analysis. The median duration of follow-up with regard to death was 86 months after the first examination (1976–1978) and 79 months after the second examination (1981–1983). Relative risk was adjusted for number of positive lymph nodes and tumor size and grade. When the analysis was performed using an average of the blood concentrations from the two collections, the association was even stronger, with a 5-fold higher risk of death in women from the highest quartile compared to the lowest quartile (RR 5.76, 95% CI 1.86–17.92, p trend<0.01) and a clear dose-response relationship. Potential confounders as body mass index, age at menopause, and hormone replacement therapy did not influence the results. This study was limited by small size, 6–39 women per quartile.

A cohort study of women from Missouri failed to find an association between serum dieldrin levels and breast cancer risk (Dorgan et al. 1999). Blood samples were collected from 7,224 women from 1977 to 1987. During the 9.5-year follow-up period, 105 women developed breast cancer; each was matched to two controls based on age and date of blood collection. Dieldrin was detected in serum in 56.2% of the cases and 61.8% of the controls. The relative risk of cancer in the highest dieldrin serum concentration range quartile was moderately lower compared to the lowest quartile (RR 0.7, 95% CI 0.3–1.3, p=0.44).

Several bioassays indicate that the response in mice to prolonged ingestion of aldrin or dieldrin differs from that in other species in that a generalized hepatomegaly observed in several species (rat [Cleveland 1966; Fitzhugh et al. 1964; Hodge et al. 1967; Treon and Cleveland 1955; Walker et al. 1969], dog [Fitzhugh et al. 1964; Hodge et al. 1967; Walker et al. 1969], and mouse [Davis and Fitzhugh 1962; Walker et al. 1972]) appears to be uniquely followed in mice, after about 1 year with threshold levels of aldrin or dieldrin in the diet, by an increase in liver tumors. With respect to aldrin, studies in two strains of mice (C3HeB/Fe and $B6C3F_1$) show an increase in hepatic tumors with chronic exposure (Davis and Fitzhugh 1962; NCI 1978a). A significant increase in the incidence of hepatocellular carcinoma was reported in males receiving 0.52 mg/kg/day of aldrin for 80 weeks (NCI 1978a). An increase in the incidence of hepatic cell adenomas at 1.3 mg/kg/day was also reported in a 2-year study by Davis and Fitzhugh (1962). Reevaluation of the histopathology data by Reuber (1980) and other pathologists indicated that most tumors classified by Davis and Fitzhugh (1962) as hepatic cell adenomas were hepatocellular carcinomas (Epstein 1975).

With respect to dieldrin, bioassays in Balb/c, CF_1, $B6C3F_1$, C3HeB/Fe, C3H/He, and C57BL/6J mice have also shown an increase in the incidence of hepatocellular adenoma and/or carcinomas with chronic exposure. A study in $B6C3F_1$ mice by NCI (1978a) showed a significant increase in the incidence of hepatocellular carcinoma with exposure of males to 0.65 mg/kg/day for 80 weeks. Increased incidences of hepatocellular carcinomas were also reported in male C3H/He, $B6C3F_1$, and C57BL/6J mice exposed to 1.3 mg dieldrin/kg/day for 85 weeks (Meierhenry et al. 1983) and in male CF_1 mice exposed to 1.3 mg dieldrin/kg/day for 92 weeks (Tennekes et al. 1981). An increase in both hepatocellular adenomas (Type A tumors) and hepatocellular carcinomas (Type B tumors) in CF_1 mice that ingested 1.3 mg/kg/day for 2 years was identified by Thorpe and Walker (1973). Similarly, a significant increase was observed in the incidence of hepatocellular carcinomas and combined incidence of both hepatocellular adenomas and carcinomas in a 132-week study at 1.3 mg/kg/day and of combined incidence of both hepatocellular adenomas and carcinomas in a 128-week study at 0.33 mg/kg/day in CF_1 mice (Walker et al. 1972). In a 75-week study in Balb/c mice (Lipsky et al. 1989) and a 2-year study in C3HeB/Fe mice, (Davis and Fitzhugh 1962) increases in the incidence of hepatic cell adenoma were observed at 1.3 mg/kg/day. However, reexamination of the histopathology data by Reuber (1980) and other pathologists showed an increase in the incidence of hepatocellular carcinomas (Epstein 1975). Although reanalysis of the data presented in the Walker et al. (1972) study by Reuber also indicated a significant increase in pulmonary adenomas and carcinomas in female mice at 0.013 and 0.13 mg/kg/day and a significant increase in lymphoid and other tumors in female mice at 0.13 mg/kg/day (Epstein 1975), these conclusions were

based on errors in the reporting of the number of females examined at 0.013 and 0.13 mg/kg/day (Hunt et al. 1975).

In addition to producing an increase in the incidence of hepatocellular carcinomas in mice, dieldrin was also shown to significantly decrease the time to tumor development in mice at doses as low as 0.013 mg/kg/day in females and 0.13 mg/kg/day in males (Tennekes et al. 1982).

Carcinogenicity studies of aldrin and/or dieldrin in rats and hamsters have produced mostly negative results (Cabral et al. 1979; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; NCI 1978b; Walker et al. 1969). However, several of these studies have been determined to be flawed based on limited microscopic examination of animals (Fitzhugh et al. 1964; Walker et al. 1969), too few animals being used (Fitzhugh et al. 1964; NCI 1978b), and/or high levels of early mortality with insufficient numbers of animals surviving until termination of the study (Deichmann et al. 1970; Fitzhugh et al. 1964). Furthermore, reanalysis of the data from the study by Fitzhugh et al. (1964) revealed a significant increase in multiple- site tumors when doses of aldrin and dieldrin at or below 0.5 mg/kg/day were combined and an increased incidence of liver carcinomas at 5 mg/kg/day when data from both sexes were combined (Epstein 1975).

A carcinogenic response was also observed in rats exposed to 1.5 mg/kg/day of aldrin for 80 weeks (NCI 1978a). These animals had a significantly increased incidence of follicular cell adenoma and carcinoma of the thyroid. Also, a significant increase in adrenal cortical adenomas was seen in female rats at this dose. However, these effects were not dose-dependent. Similarly, a significant increase in the combined incidence of adrenal cortical adenomas and carcinomas was observed in females given 1.5 mg/kg/day for 59 weeks but not at 3 mg/kg/day (NCI 1978a). This result was, however, discounted by the study authors because of the historical variability of this result in control animals.

There is evidence that dieldrin can act as a liver tumor promoter in mice, but not in rats (Kolaja et al. 1996c). Preneoplastic focal hepatic lesions were initiated by intraperitoneal treatments with diethylnitrosamine (two injections separated by two weeks in male F344 rats, two injections per week for 8 weeks in male B6C3F1 mice). After the preneoplastic lesions developed, dieldrin was administered in the diet for 7, 30, or 60 days at estimated doses of 0.05, 0.15 or 0.5 mg/kg/day in the rats and 0.013, 0.13, or 1.3 mg/kg/day in the mice. Dieldrin induced significant increases in the number, volume, and deoxyribonucleic acid (DNA) labeling index of the DEN-induced preneoplastic foci in mice at the highest dose after 30 and 60 days. The lower doses (#0.13 mg/kg/day) did not produce these promotional effects

at any time point. The results of this study are consistent with findings of other studies of generally similar design by the same investigators (Kolaja et al. 1995a, 1995b, 1998).

The lowest dose that produced a tumorigenic response (Cancer Effect Levels, CELs) for each species and duration category of exposure to aldrin and dieldrin are recorded for aldrin in Table 3-1 and for dieldrin in Table 3-2 and plotted for aldrin in Figure 3-1 and for dieldrin in Figure 3-2.

The EPA reviewed the carcinogenicity data on aldrin and dieldrin and calculated human potency estimates using liver tumor responses in mice (EPA 1986l; IRIS 2002a, 2002b). The potency estimates (q_1^*) represent a 95% upper confidence limit of the extra lifetime human risks. Using potency estimates calculated from three data sets in two mouse strains and both sexes (Davis 1965; Epstein 1975; NCI 1978a), a geometric mean of 17 $(mg/kg/day)^{-1}$ was chosen for the oral cancer risk estimate for aldrin (IRIS 2002a). The unit risk estimate for drinking water exposures (the excess cancer risk associated with lifetime exposure to 1 µg/L) is $4.9x10^{-4}$. Using potency estimates calculated from 13 data sets in five mouse strains and both sexes (Davis 1965; Epstein 1975; Meierhenry et al. 1983; NCI 1978a, 1978b; Tennekes et al. 1981; Thorpe and Walker 1973; Walker et al. 1972), a geometric mean of 16 $(mg/kg/day)^{-1}$ was chosen for the oral cancer risk estimate for dieldrin (IRIS 2002b). The unit risk estimate for drinking water exposures to dieldrin is $4.6x10^{-4}$. Based on the unit risk values for aldrin and dieldrin, cancer risk levels of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} correspond to 70 years of continuous drinking water exposure to 0.2, 0.02, 0.002, and 0.0002 µg/L, respectively (0.006, 0.0006, $6.0x10^{-5}$, and $6.0x10^{-6}$ µg/kg/day). The predicted cancer risks are considered conservative upper estimates. The actual risk of cancer is unlikely to be higher and may be substantially lower. These values are recorded in Figures 3-1 and 3-2.

3.2.3 Dermal Exposure

As indicated in the section on inhalation exposure, it is often difficult to clearly separate dermal from inhalation exposures in many occupational studies. Thus, many of the findings described in the section on inhalation exposure are repeated here.

3.2.3.1 Death

No increase in mortality from any cause was found in studies of workers who had been employed in the manufacture of aldrin, dieldrin, endrin, and/or telodrin at a facility in the Netherlands for >4 years (cohort=233 workers) (van Raalte 1977; Versteeg and Jager 1973). Furthermore, in a 20-year follow-up of this population and expansion of the cohort to include workers employed for at least 1 year during 1954–1970 (cohort=570 workers), a lower than expected overall mortality was observed (de Jong 1991). Although the group of workers described by de Jong (1991) represents a unique population because they have been under medical supervision for an average of 25.86 years, all of the studies described above are limited because of the small number of subjects used (#570 workers) and the potential exposure of the subjects to more than one of these pesticides and/or to other chemicals at the chemical manufacturing complex. Several of these studies have attempted to estimate exposure levels using blood levels. However, blood levels were not obtained for approximately 10 years (during what is expected to have been the period of heaviest exposure) and extrapolations were based on data obtained in a study using constant daily low-level oral dosing (Hunter and Robinson 1967). It is unclear whether such extrapolations accurately reflect exposure levels in the occupational situation. Only two case studies were located regarding deaths that may have been attributable to occupational exposure to aldrin or dieldrin (Muirhead et al. 1959; Pick et al. 1965). One concerned a farmer with multiple exposures to insecticide containing dieldrin. The farmer died in hemolytic crisis after developing immunohemolytic anemia (Muirhead et al. 1959). Immunologic testing revealed a strong antigenic response of blood cells coated with dieldrin. The other concerned a worker from an orange grove who developed aplastic anemia and died following repeated exposures to aldrin during spraying (Pick et al. 1965). In the latter study, the relationship between aldrin exposure and the aplastic anemia is considerably more tenuous, being linked only in that the onset of symptoms corresponded with spraying and the condition deteriorated upon subsequent exposure.

In rats, a single dermal application of aldrin in xylene was reported to produce death in 50% of the animals tested at 98 mg/kg/day (Gaines 1960). Dieldrin in xylene produced an LD_{50} value of 60 mg/kg/day in female rats and 90 mg/kg/day in male rats (Gaines 1960). However, this study is limited because the rats were not restrained, oral intake could not be eliminated, and the xylene vehicle has intrinsic dermal toxicity. A single 24-hour dermal exposure of rabbits to dry crystallized aldrin or dieldrin resulted in LD_{50} values between 600 and 1,250 mg/kg for both chemicals (Treon et al. 1953a). Similar results were obtained when these chemicals were prepared as oil solutions and maintained in contact with the skin for 24 hours. Also, sheep dipped in a solution of 200 mg/L of dieldrin (twice the

recommended dose) experienced an 11% mortality rate within the 1st month following exposure (Glastonbury et al. 1987). This study is limited because the preparation of dieldrin used was unsuitable for use in emulsions and may have been stripped from the bath during the dipping of the first sheep resulting in much higher doses for some animals than others. In addition, wool biting was observed among these sheep; this type of oral exposure may have contributed to the lethal effects.

Dermal exposure of rabbits to aldrin or dieldrin (2 hours/day, 5 days/week, for 10 weeks) resulted in slightly greater lethality when these chemicals were prepared as solutions in oil and much greater lethality when the chemicals were administered as suspensions in kerosene than when crystallized material was placed directly in contact with the skin (Treon et al. 1953a). In the case of aldrin, three out of three rabbits survived exposure to average doses of 34–39 mg/kg/day during the 10-week period; one out of three died after exposure to 19–26 mg/kg/day in oil; and three out of three died after exposure to 19–27 mg/kg/day in kerosene. Crystallized dieldrin exposures of 39–41 mg/kg/day were survived by three out of three rabbits; but all rabbits died at 43–57 mg/kg/day in oil and 24–26 mg/kg/day in kerosene. The greater lethality of the kerosene suspensions may have been associated with greater absorption as a result of skin damage caused by the kerosene.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded for aldrin in Table 3-3 and for dieldrin in Table 3-4.

3.2.3.2 Systemic Effects

The highest NOAEL values for each study for dermal/ocular effects are recorded for aldrin in Table 3-3 and for dieldrin in Table 3-4.

Respiratory Effects. Conflicting reports were located regarding the respiratory effects of aldrin and dieldrin in humans after dermal exposure. In a study of workers with at least 4 years of employment in the manufacture of aldrin, dieldrin, endrin, or telodrin, no new pulmonary disease or deterioration of existing pulmonary disease were observed (Jager 1970). Similarly, no increase in mortality from respiratory diseases was noted in workers employed for at least 1 year at the same facility during 1954–1970 when these workers were followed for at least 20 years (de Jong 1991). In contrast, however, in another study that examined workers involved in the manufacture of aldrin, dieldrin, and/or endrin for

Table 3-3. Levels of Significant Exposure to Aldrin - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg/day)	LOAEL			Reference
				Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE							
Death							
Rabbit	1 d 24hr/d				1250	(4/4 died)	Treon et al. 1953a
INTERMEDIATE EXPOSURE							
Death							
Rabbit	10 wk 5d/wk 2hr/d				120-125 19-26 4-5	(2/3 died-dry) (1/3 died-oil solution) (2/4 died-kerosene suspension)	Treon et al. 1953a
Systemic							
Rabbit	10 wk 5d/wk 2hr/d	Dermal	221-320				Treon et al. 1953a

d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s)

Table 3-4. Levels of Significant Exposure to Dieldrin - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
ACUTE EXPOSURE							
Death							
Rabbit	1 d 24hr/d				360 600	(1/4 died - dry) (1/4 died - oil solution)	Treon et al. 1953a
Systemic							
Human	4 d 24hr/d	Dermal	0.5%				Suskind 1959
Immunological/Lymphoreticular							
Human	4 d 24hr/d		0.5%				Suskind 1959
INTERMEDIATE EXPOSURE							
Death							
Rabbit	10 wk 5d/wk 2hr/d				97-174 43-57 4-5	(3/3 died-dry) (3/3 died-oil solution) (2/3 died-kerosene suspension)	Treon et al. 1953a
Systemic							
Rabbit	10 wk 5d/wk 2hr/d	Dermal	97-174				Treon et al. 1953a
Neurological							
Human	180 d 5.5d/wk 6hr/d		1.8				Fletcher et al. 1959

d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s)

at least a year, a significantly increased incidence of pneumonia and other pulmonary diseases was observed when the incidence in the exposed workers was compared to the incidence in U.S. white males (Ditraglia et al. 1981). Both studies are limited by the small sample size and the possible exposure of the workers to other chemicals and/or pesticides. In addition, inhalation exposure may have contributed to the production of these effects since exposures by both inhalation and dermal absorption are likely in these populations of workers.

No effects on lung weight or pathology were found in a study in which rabbits were wrapped with material containing up to 0.04% dieldrin for up to 52 weeks (Witherup et al. 1961). However, this study is limited in that some animals from the study were treated with a variety of drugs to control "extraneous" diseases.

Cardiovascular Effects. Limited information was available regarding the cardiovascular effects of aldrin or dieldrin in humans after dermal exposure. Suggestive evidence of an association between dieldrin and hypertension was obtained in a study examining the incidence of certain diseases in patients with elevated fat levels of dieldrin (Radomski et al. 1968). However, elevated fat levels of other pesticide residues also correlated with hypertension in this study. Furthermore, a study examining disease incidence in 2,620 workers exposed to a number of pesticides reported no increase in the incidence of hypertension in workers with elevated serum dieldrin (Morgan et al. 1980). The lack of a correlation between hypertension and aldrin or dieldrin exposure is also supported by the observation that workers involved in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years had normal blood pressure (Jager 1970). Similarly, no increase in mortality from circulatory system diseases was observed in a mortality study by de Jong (1991). All of these studies are limited because the subjects were exposed to a variety of other chemicals.

A slight, but significant, increase in serum cholesterol was observed in pesticide-exposed workers with elevated serum dieldrin (Morgan and Lin 1978). However, this study was limited in that the workers were occupationally exposed to a number of different pesticides and other chemicals including hydrocarbon solvents.

No effects on heart weight or pathology were found in a study in which rabbits were wrapped with material containing up to 0.04% dieldrin for up to 52 weeks (Witherup et al. 1961). However, this study is limited in that some animals from the study were treated with a variety of drugs to control "extraneous" diseases.

Gastrointestinal Effects. No increased mortality from digestive system causes was observed in a mortality study of workers employed in the manufacture of aldrin and dieldrin for at least 1 year between 1954 and 1970 (de Jong 1991).

No studies were located regarding gastrointestinal effects in animals after dermal exposure to aldrin or dieldrin.

Hematological Effects. No abnormal values for hemoglobin, white blood cells, or erythrocyte sedimentation rate were found in workers who had been employed in the manufacture of aldrin, dieldrin, endrin, or telodrin for at least 4 years (Jager 1970). Similarly, no increase in blood diseases was observed in a morbidity study of workers employed at the same facility for at least 1 year (de Jong 1991). Also, workers who had been involved in either the manufacture or application of pesticides and who had significantly elevated blood levels of dieldrin compared to controls not employed in pesticide-related jobs had no hematological effects of clinical significance (Warnick and Carter 1972). These studies are limited by either potential exposure to other chemicals (Jager 1970) or by known exposure to other pesticides as demonstrated by elevated blood levels of β-benzine [sic] hexachloride (β-benzene hexachloride), heptachlor epoxied, *p,p*'-DDT, *o,p*'-DDT, and *p,p*'-DDE (Warnick and Carter 1972).

A case of immunohemolytic anemia attributable to dieldrin exposure was reported (Muirhead et al. 1959). Also, a worker from a grove where aldrin was sprayed developed aplastic anemia (Pick et al. 1965), and one person employed in the manufacture of aldrin and dieldrin between 1954 and 1970 died from aplastic anemia (de Jong 1991). However, it is unclear whether these cases of aplastic anemia were directly due to aldrin or dieldrin exposures because exposure to a variety of other chemicals was possible. Three cases of pancytopenia and one case of thrombocytopenia associated with exposure to dieldrin were reported during 1961 (AMA 1962). However, no assessment regarding whether dieldrin was the causative agent was provided in the report.

No studies were located regarding hematologic effects in animals after dermal exposure to aldrin or dieldrin.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after dermal exposure to aldrin or dieldrin.

Hepatic Effects. Although a slight increase in serum hepatic enzymes (alanine and aspartate aminotransferases) has been observed to correlate with serum dieldrin levels in pesticide-exposed workers (Morgan and Lin 1978), no evidence of any hepatic effects of aldrin or dieldrin exposure have been observed in other studies of workers involved in either the manufacture (de Jong 1991; Hoogendam et al. 1965; Hunter et al. 1972; Jager 1970; van Sittert and de Jong 1987) or the manufacture or application (Morgan and Roan 1974; Warnick and Carter 1972) of these pesticides. Parameters that have been examined in the negative studies include serum hepatic enzyme activity (Hoogendam et al. 1965; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987; Warnick and Carter 1972), hepatic enlargement (Jager 1970), and tests intended to detect microsomal enzyme induction (Hunter et al. 1972; Jager 1970; Morgan and Roan 1974; van Sittert and de Jong 1987). All of the studies are limited by the potential exposure of the workers to other chemicals and/or organochlorine pesticides.

No effects on liver weight, serum proteins, thymol turbidity, serum alkaline phosphatase, or pathology were found in a study in which rabbits were wrapped with material containing up to 0.04% dieldrin for up to 52 weeks (Witherup et al. 1961). However, this study is limited in that some animals from the study were treated with a variety of drugs to control "extraneous" diseases.

Renal Effects. No evidence of renal damage was seen in workers employed for four or more years in the manufacture of aldrin, dieldrin, endrin, or telodrin (Jager 1970). However, this study is limited by the potential exposure of these workers to other chemicals.

No studies were located regarding renal effects in animals after dermal exposure to aldrin or dieldrin.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals after dermal exposure to aldrin or dieldrin.

Dermal Effects. Contact dermatitis was observed in police recruits wearing socks that had been moth-proofed with a solution containing dieldrin (Ross 1964). Several recruits had a positive patch test when tested against the moth-proofing agent. The outbreak of the dermatitis appeared to have been exacerbated by the presence of the particular dye used in the socks and by the fact that the recruits' feet had sweated heavily. In contrast, no evidence of dermatitis was seen in volunteers who wore patches of cotton broadcloth or wool flannel impregnated with up to 0.5% dieldrin by weight for 4 days (Suskind 1959) or in workers employed for four or more years in the manufacture of aldrin, dieldrin, endrin, or telodrin

(Jager 1970). The study by Jager (1970) is limited by the potential exposure of these workers to other chemicals.

Application of up to 6,000 mg/kg of aldrin or 3,600 mg/kg of dieldrin as either the crystalline material or as a solution in oil to the skin of rabbits for 24 hours was reported to result in occasional very slight erythema, but the lowest doses associated with this effect were not reported (Treon et al. 1953a). In contrast, no irritation was observed following application of 221–320 mg/kg/day aldrin or 97–174 mg/kg/day of dieldrin to the skin of rabbits for 2 hours/day, 5 days/week, for up to 10 weeks (Treon et al. 1953a). Also, no treatment-related effects were observed after microscopic examination of the skin of rabbits wrapped with wool fabric containing up to 0.04% dieldrin by weight for 52 weeks (Witherup et al. 1961).

Ocular Effects. No studies were located regarding ocular effects in humans or animals after dermal exposure to aldrin or dieldrin.

3.2.3.3 Immunological and Lymphoreticular Effects

Limited information is available regarding the immunological effects of aldrin and dieldrin in humans after dermal exposure. No sensitization was observed in volunteers who were reexposed to fabric containing up to 0.5% dieldrin 2 weeks following a 4-day exposure (Suskind 1959). However, a case report was located concerning a man who developed immunohemolytic anemia after multiple exposures to dieldrin, heptachlor, and toxaphene while spraying cotton fields (Muirhead et al. 1959). Antibodies for dieldrin-coated or heptachlor-coated red blood cells were found in the subject's serum. However, this study is limited because of the exposure of the subject to other pesticides.

No studies were located regarding immunological effects in animals after dermal exposure to aldrin or dieldrin.

All reliable LOAEL values for immunologic effects of dieldrin in humans in acute-duration dermal studies are recorded in Table 3-4.

3.2.3.4 Neurological Effects

Central nervous system excitation culminating in convulsions was the principal toxic effect noted in occupational studies of workers employed in either the manufacture or application of aldrin or dieldrin. In many cases, convulsions appeared suddenly and without prodromal signs (Hoogendam et al. 1965; Kazantzis et al. 1964; Patel and Rao 1958). EEGs taken shortly after the convulsions revealed bilateral irregular alpha rhythms interrupted by spike and wave patterns (Avar and Czegledi-Janko 1970; Kazantzis et al. 1964). In the case of dieldrin sprayers who developed convulsions, the convulsive episodes did not follow known accidental overexposures (Patel and Rao 1958). Rather, the convulsions developed anywhere from 14 to 154 days after the first exposure to dieldrin. The time to onset was more rapid for sprayers using the more concentrated spray. An accumulative type of poisoning was also reported in workers involved in the manufacture of aldrin, dieldrin, telodrin, or endrin (Jager 1970). In this report, convulsions were believed to have been caused by either accumulating levels of dieldrin in the blood or modest overexposures in the presence of subconvulsive accumulations of dieldrin. Other central nervous system symptoms reported by workers involved in the manufacturer or application of aldrin and/or dieldrin included headaches (Jager 1970; Patel and Rao 1958), dizziness (Jager 1970), hyperirritability (Jager 1970; Kazantzis et al. 1964), general malaise (Jager 1970), nausea and vomiting (Jager 1970; Kazantzis et al. 1964), anorexia (Jager 1970), muscle twitching (Jager 1970; Patel and Rao 1958), and myoclonic jerking (Jager 1970; Jenkins and Toole 1964; Kazantzis et al. 1964). The more severe symptoms were accompanied by EEG patterns with bilateral spike and wave complexes and multiple spike and wave discharges in the alpha region (Jager 1970; Kazantzis et al. 1964). Less severe symptoms were accompanied by bilateral theta (Jager 1970; Kazantzis et al. 1964) and/or delta (Kazantzis et al. 1964) wave discharges.

In all cases in which follow-up of the subjects was reported, removal from the source of exposure caused a rapid physical recovery and a slower recovery (within a year) of the EEG activity to normal levels (Avar and Czegledi-Janko 1970; Hoogendam et al. 1962, 1965; Jager 1970; Jenkins and Toole 1964; Kazantzis et al. 1964).

No symptoms of poisoning were observed in workers who were exposed to an estimated 1.8 mg/kg/day for 6 months at 6 hours/day for 5.5 days/week based on accumulation of dieldrin on absorbent pads that were attached to various surfaces on the workers (Fletcher et al. 1959).

A morbidity study of workers employed in the manufacture of aldrin and dieldrin between 1979 and 1990 noted no degenerative disorders of the nervous system (de Jong 1991). However, this study reported significant increases in mental disorders among those <30 years old and in those 46–50 years old. The diseases were classified as stress reactions, short-term depression, or sleep disorders. It is unclear whether these effects were directly the result of aldrin or dieldrin exposure or may have had some other cause.

Results of a comprehensive neurological work-up of 27 workers involved in either the manufacture or application of dieldrin were compared to those of unexposed workers (Sandifer et al. 1981). Scores on five psychological tests were significantly different from those of the unexposed controls; however, the importance of the results was questioned by the authors because of a lack of equality in the level of literacy of the two groups. Also, three exposed workers had abnormal EMGs suggesting a peripheral neuropathy. However, EMGs were not obtained in the control group; thus, the significance of these results is unknown.

Tremors and convulsions were reported in a study examining the effects of acute dermal exposure to aldrin or dieldrin in rabbits (Treon et al. 1953a). However, the doses associated with these effects were not reported. Neurological symptoms including salivation, grinding of the teeth, and spasms were observed in rabbits that were dipped into an emulsion of dieldrin, xylene, Triton X-155®, and water, at doses as low as 70 mg/kg once a week until death or termination of the experiment (Bundren et al. 1952). This study is limited in that no vehicle control was used and some dose levels were tested on a single animal.

The highest NOAEL for neurological effects in humans in an intermediate-duration study is recorded in Table 3-4.

3.2.3.5 Reproductive Effects

No studies were located regarding reproduction effects in humans or animals after dermal exposure to aldrin or dieldrin.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to aldrin or dieldrin.

The only study located that referred to developmental effects following dermal exposure was a case report of a number of lambs that died either prior to or during parturition (Glastonbury et al. 1987). Ewes had been dipped in an aqueous emulsion of 210 mg/L of dieldrin on one occasion up to 4 months prior to giving birth. External appearance of the lambs was normal, but the lambs were small. Also, the brains of these lambs had an abnormal cerebellar structure. It is unclear whether these effects can be attributed entirely to dieldrin exposure since vitamin A deficiency was also observed in these sheep and vitamin A deficiency is known to cause fetal mortality.

3.2.3.7 Cancer

Aldrin and dieldrin were manufactured at two sites worldwide in plants at the Rocky Mountain Arsenal in Denver, Colorado, and at Pernis in the Netherlands. Workers from these plants have been included in two series of retrospective cohort mortality studies which have been updated several times. Exposure to DBCP and several organophosphates may also have occurred in the Denver plant. Cancer mortality findings of the studies at the Denver plant (Amoateng-Adjepong et al. 1995; Brown 1992; Ditraglia et al. 1981; Ribbens 1985) and the Pernis plant (de Jong 1991; de Jong et al. 1997; Jager 1970; Ribbens 1985; van Raalte 1977) are inconclusive, as summarized below.

The first study of the Denver plant found no significant increase in cancer mortality, but concluded that additional follow-up was necessary due to a small number of deaths (173) and relatively short period of observation (Ditraglia et al. 1981). In the follow-up by Brown (1992), 1,158 workers who were employed for at least 6 months prior to 1965 and were followed through 1987 were investigated. Cause-specific mortality analysis of 337 deaths showed an increase in liver and biliary tract cancer (five cases observed) that was statistically significant when compared to state and local rates (SMRs of 5.10 and 4.86, respectively), but not the national rate (SMR 3.93). All of these five deaths (three from biliary tract/ bile duct cancer, one from gall bladder cancer, and one from hepatoma) occurred after 15 years of latency (SMR=4.85). The cohort in the most recent study of the Denver plant (Amoateng-Adjepong et al. 1995) was expanded to 2,384 subjects and followed through 1990 (median 29 years). The median age at hiring was 26 years and the median tenure was 2 years. The increase in hepatobiliary cancer was of a lower

magnitude than in the previous study and was no longer statistically significant, although no additional cases had occurred (five cases observed/2.0 expected based on state rates, SMR=249). Based on this information and findings that the cancers were not limited to any particular production unit, did not display duration-response trends, and essentially occurred in the biliary tract or gall bladder (rather than liver), the investigators concluded that the hepatobiliary cancer excess was not due to occupational exposures at the plant.

No indications of a carcinogenic effect were found in the early mortality studies of the Dutch (Pernis) workers (Jager 1970; Ribbens 1985; van Raalte 1977). Similarly, in the follow-up study by de Jong (1991), there were no increases in cause-specific mortality among 76 deaths in 570 workers who were employed for at least 1 year between 1954 and 1970 and followed-up until 1987. Follow-up of this cohort until 1993 (118 deaths) showed a significant increase in mortality from rectal cancer (6 deaths observed versus 1.5 expected compared to Netherlands national rates, SMR=390.4) and an insignificant increase in liver cancer deaths (two observed versus 0.9 expected, SMR=225.0) (de Jong et al. 1997). Stratification by dose level (low, moderate, or high exposure based on blood levels of dieldrin) did not disclose any indications for a dose-response relation for either of these causes of death.

Equivocal evidence exists for an association between dieldrin and breast cancer risk from three human epidemiologic studies (Dorgan et al. 1999; Høyer et al. 1998, 2000). In these studies, while dieldrin exposure was verified through blood sampling, and exposure by dermal contact, as well as by inhalation and ingestion, was possible, no specific route of exposure was identified or estimated with any certainty.

The potential of dieldrin to affect breast cancer risk was evaluated in a prospective nested case control study of women in Denmark (Høyer et al. 1998). Serum samples were obtained from 7,712 women from 1976 to 1978. In 1996–1997, serum samples from 240 women who had developed invasive breast cancer and 477 matched breast cancer-free controls were analyzed for levels of dieldrin and 17 other organochlorine pesticides or metabolites and 28 PCB congeners. Controls and cases were matched for age, date of examination, and vital status at the examination. Irrespective of breast cancer status, dieldrin was detected in 78% of the women enrolled in the study, with median levels at 24.4 ng/g lipid. Dieldrin was the only organochlorine compound of those tested associated with a significant increase in breast cancer risk. Women in the highest quartile of the serum dieldrin range had double the risk of breast cancer compared to women in the lowest quartile (OR 2.25, 95% CI 1.32–3.84, p trend=0.003). Relative risk did not change significantly when adjusted for potential confounders of weight and number of full-term pregnancies (OR 2.05, 95% CI 1.17–3.57, p trend=0.01).

A subsequent study using the same cohort of Danish women investigated whether breast cancer survival was affected by past exposure to dieldrin (Høyer et al. 2000). Dieldrin at blood concentrations >57.6 ng/g, representative of the highest quartile, was found to have a significant adverse effect on overall survival and breast cancer specific survival compared to the lowest quartile levels of <12 ng/g lipid (RR 2.78, 95% CI 1.38–5.59, p trend<0.01; RR 2.61, 95% CI 0.97–7.01, p trend<0.01) in this case-control study of Danish women between 20 and 80 years of age. A total of 195 breast cancer cases, who each provided two blood samples that were taken in 1976–1978 and 1981–1983, respectively, were included in the survival analysis. The median duration of follow-up with regard to death was 86 months after the first examination (1976–1978) and 79 months after the second examination (1981–1983). Relative risk was adjusted for number of positive lymph nodes and tumor size and grade. When the analysis was performed using an average of the blood concentrations from the two collections, the association was even stronger, with a 5-fold higher risk of death in women from the highest quartile compared to the lowest quartile (RR 5.76, 95% CI 1.86–17.92, p trend<0.01) and a clear dose-response relationship. Potential confounders as body mass index, age at menopause, and hormone replacement therapy did not influence the results. This study was limited by small size, 6–39 women per quartile.

A cohort study of women from Missouri failed to find an association between serum dieldrin levels and breast cancer risk (Dorgan et al. 1999). Blood samples were collected from 7,224 women from 1977 to 1987. During the 9.5-year follow-up period, 105 women developed breast cancer; each was matched to two controls based on age and date of blood collection. Dieldrin was detected in serum in 56.2% of the cases and 61.8% of the controls. The relative risk of cancer in the highest dieldrin serum concentration range quartile was moderately lower compared to the lowest quartile (RR 0.7, 95% CI 0.3–1.3, p=0.44).

No studies were located regarding cancer in animals after dermal exposure to aldrin or dieldrin.

3.2.4 Other Routes of Exposure

Dieldrin, 10 mg/kg/day, injected intraperitoneally for 5 days, did not appear to have any estrogenic action in mature male rats as the serum and urinary levels of $\alpha_{2\mu}$-globulin were not significantly altered (Nagahori et al. 2001).

3.3 GENOTOXICITY

Sister chromatid exchanges and chromosomal aberrations were studied in a population of floriculturists occupationally exposed to several pesticides, including aldrin (Dulout et al. 1985). A statistically significant increase in sister chromatid exchanges, but not exchange type chromosome aberrations, was seen in workers with clinical symptoms of pesticide exposure as compared to those without symptoms. There was an increase in exchange-type chromosome aberrations in this population when compared to nonfloriculturists. Interpretations based on this study are limited because the route and dose of exposure could not be determined, since the workers could have been exposed via inhalation or dermal contact following the spraying of the greenhouses with the pesticide aerosols. In addition, there was concomitant exposure to other organophosphorus, carbamate, and organochlorine insecticides.

Lymphocytes from workers in a dieldrin manufacturing facility were examined for chromosome aberrations (Dean et al. 1975). No statistically significant differences in either chromatid-type or chromosome-type aberrations were seen in current workers when compared to former workers or to unexposed controls. While there was no occupational exposure to other pesticides in this study, the exposure could have occurred via inhalation and/or dermal contact.

No studies were located regarding genotoxic effects in animals after inhalation exposure to aldrin or dieldrin.

No studies were located regarding genotoxic effects in humans after oral exposure to aldrin or dieldrin.

Studies in a variety of mammalian species have demonstrated a unique sensitivity of the mouse liver to dieldrin-induced hepatocarcinogenicity, and mechanistic studies suggest a nongenotoxic mode of action (Stevenson et al. 1999; WHO 1989). Aldrin and dieldrin were found to induce DNA synthesis in the mouse liver (Busser and Lutz 1987; Kamendulis et al. 2001). The effects of dieldrin on changes in hepatocyte DNA synthesis, mitosis, apoptosis, and ploidy were studied in rats and mice treated with a 0, 1, 3, or 10 mg dieldrin/kg diet (Kamendulis et al. 2001). Livers from mice fed only the highest dose (10 mg dieldrin/kg) exhibited significantly increased DNA synthesis and mitosis at 14, 28, or 90 days on the diet and a significant increase in octaploid (8N) hepatocytes. No changes were observed in rat livers. The apoptotic index in the liver of mice in any treatment group did not change over a 90-day treatment and study period. In another study in which single doses of aldrin were administered orally to male rats

and male and female mice (0.016, 0.011, and 0.008 mmol/kg [5.84, 4.01, and 2.92 mg/kg], respectively), DNA synthesis in the liver was stimulated only in male mice (Busser and Lutz 1987).

Single doses of aldrin administered orally to three groups of male Swiss mice (13.0, 19.5, and 39.0 mg/kg) resulted in a statistically significant increase in the number of abnormal metaphases in dividing spermatocytes. There was also a significant increase at all doses of univalents, indicating a decreased pairing of meiotic chromosomes (Rani and Reddy 1986).

A dominant lethal assay was conducted using 40 male CF_1 mice orally dosed with 12.5 or 25 mg/kg of dieldrin (Dean et al. 1975). The results of this assay indicated that the overall mean percentage of implantations was significantly reduced in the females mated with males receiving 12.5 mg/kg dieldrin. However, a second series of experiments showed that the overall mean of successful implantations was significantly higher in the 25 mg/kg group than in the controls. Several doses of both aldrin and dieldrin were tested in a dominant lethal study conducted in mice (Epstein et al. 1972). Dieldrin did not meet any criteria for mutagenic effects. Females mated to males exposed to aldrin did show some reduction in implantations, but these were judged to be nonsignificant upon statistical analysis.

Present *in vivo* data have not established whether or not aldrin or dieldrin react directly with DNA to produce mutations in either the germ cells or in the somatic cells. The reduced meiotic pairing reported by Rani and Reddy (1986) does suggest that aldrin can cross the blood/testis barrier, but the results of Dean et al. (1975) offer no clear evidence that there are significant reactions with DNA.

No studies were located regarding genotoxic effects in animals after dermal exposure to aldrin or dieldrin.

In vitro studies assaying for genotoxicity of aldrin or dieldrin have been conducted in several species. Significant increases in chromosome aberrations have been reported in cultured human lung cells. Similar results have been observed in bone marrow cells of mice treated intraperitoneally with dieldrin (Majumdar et al. 1976). Sister chromatid exchanges were significantly increased in Chinese hamster ovary cells at doses of dieldrin that caused marked cell cycle delay when tested both with and without S9 (Galloway et al. 1987). However, no chromosome aberrations were seen in this study. In addition, only 3 of 4,800 cells from 48 Chinese hamsters exposed via intraperitoneal injection of 60 mg/kg of dieldrin showed aberrant chromosomes (Dean et al. 1975).

Mitotic gene conversion in *Saccharomyces cerevisiae* was negative in a host-mediated assay in which adult male CF_1 mice were orally dosed for 5 consecutive days with 5 or 10 mg/kg of dieldrin (Dean et al.

1975). Micronuclei formation was increased in *Tradescantia* by 3.81 ppm dieldrin, but aldrin yielded negative results (Sandhu et al. 1989). The authors speculated that the immiscibility of aldrin in water contributed to the negative findings of that chemical.

Dieldrin-induced gene mutation has been reported to be positive in Chinese hamster V79 cells (Ahmed et al. 1977b) and in *Salmonella* (Ennever and Rosenkranz 1986; Majumdar et al. 1977) but negative in *Aspergillus nidulans* (Crebelli et al. 1986). Dieldrin-induced gene mutation in several strains of *Salmonella* has also been reported to be negative, with and without activation (De Flora et al. 1984; Glatt et al. 1983; Haworth et al. 1983; Marshall et al. 1976; Moriya et al. 1983; Shirasu 1975), but weakly positive results were reported in *Salmonella* following photoactivation with ultraviolet light (De Flora et al. 1989). Dieldrin produced positive results for focus formation in the BPV-1 DNA carrying C3H/10T(½) mouse embryo fibroblast cell line (T1) (Kowalski et al. 2000). Aldrin and dieldrin were not mutagenic in a *Bacillus subtilis* rec-assay (Shirasu 1975), or in *E. coli* (Ashwood-Smith et al. 1972; Fahrig 1974; Shirasu 1975) or *Saccharomyces cerevisiae* (Fahrig 1974). Aldrin was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (Moriya et al. 1983).

The preponderance of evidence appears to indicate that aldrin and dieldrin induce a carcinogenic response through nongenotoxic mechanisms (i.e., not acting directly on the DNA). There is some evidence that the activity of several specific transfer ribonucleic acids (tRNAs) is depressed by exposure to dieldrin, but it is uncertain whether this is due to decreased synthesis or to direct inactivation (Chung and Williams 1986). Other possible mechanisms for the cellular effects of aldrin and dieldrin include increasing unscheduled DNA synthesis (UDS), since increased DNA synthesis in hepatocytes was observed in B6C3F1 mice fed $1 mg dieldrin/kg for $7 days (Klaunig et al. 1995; Stevenson et al. 1995a), and a positive effect has been reported for dieldrin in SV-40 transformed human fibroblast cells in culture with and without metabolic activation (Ahmed et al. 1977a). However, UDS assays have been negative in both Fischer 344 rat (Probst et al. 1981) and Balb/c mouse (Klaunig et al. 1984) primary hepatocyte cultures.

Another possible mechanism for the nongenotoxic action of aldrin and dieldrin involves the inhibition of metabolic cooperation and gap junctional intercellular communication. These effects have been reported in Chinese hamster cells (Jone et al. 1985; Kurata et al. 1982; Trosko et al. 1987), rat and mouse hepatocytes (Klaunig and Ruch 1987; Klaunig et al. 1990), and human teratocarcinoma cells (Wade et al. 1986; Zhong-Xiang et al. 1986). While these effects are epigenetic, rather than genotoxic, these processes may offer insight into cellular changes in metabolism and proliferation that could explain cell

cycle changes and the disparate results of genotoxicity assays. Key *in vivo* genotoxicity studies are presented in Table 3-5, and *in vitro* genotoxicity studies are presented in Table 3-6.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Studies directly measuring absorption of aldrin or dieldrin in humans following inhalation exposure of known amounts of these pesticides were not located. However, results of a survey of women in pesticide-treated homes showed a correlation between the treatment and dieldrin levels in human breast milk (Stacey and Tatum 1985). Inhalation was suggested as the most probable route of exposure because absorption by skin contact with pesticide-treated surfaces was not believed to contribute significantly to the exposures. Measurable levels of aldrin and dieldrin in indoor air have been detected several years after pesticide treatment of homes (Dobbs and Williams 1983).

In vivo studies on absorption following inhalation exposure of animals to aldrin/dieldrin were not located. In an *in vitro* study using isolated perfused rabbit lungs, aldrin (0.25, 0.50, 1.0, 1.5, 2.0, 2.5, and 3.0 µmol) was taken up by simple diffusion and then metabolized at a slower rate to dieldrin in the lung. Dieldrin was detected 3 minutes after initiation of the experiment. The rate of uptake of aldrin by the lung was biphasic consisting of a rapid phase followed by a slower phase, which could be related to the metabolic turnover of aldrin to dieldrin (Mehendale and El-Bassiouni 1975).

3.4.1.2 Oral Exposure

Volunteers were fed dieldrin at concentrations of 0.0001, 0.0007, and 0.003 mg/kg/day for 18–24 months. A dose-related increase in blood and adipose tissue levels of dieldrin was found (Hunter and Robinson 1967; Hunter et al. 1969). However, no quantitative data specifically describing absorption of aldrin/dieldrin following oral exposure were found in the literature.

Table 3-5. Genotoxicity of Aldrin/Dieldrin *In Vivo*

Species (test system)	End point	Results		Reference
		Without activation	With activation	
Human (occupational cohort)	Sister chromatid exchange	NA	+ (several pesticides including aldrin)	Dulout et al. 1985
Human (occupational cohort)	Chromosome aberrations	NA	– (dieldrin)	Dean et al. 1975
Swiss mice (oral exposure)	Increased abnormal metaphases	NA	+	Rani and Reddy 1986
	Increased number of univalents (decreased pairing of meiotic chromosomes)	NA	+	
Chinese hamsters (intraperitoneal	Chromosome aberrations	NA	– (dieldrin)	Dean et al. 1975
Mice (intraperitoneal	Chromosome aberrations	NA	+ (dieldrin)	Majumdar et al. 1976
Mice (oral exposure)	Increased hepatocyte DNA synthesis	NA	+ (dieldrin)	Kamendulis et al. 2001
	Mitosis	NA	+ (dieldrin)	
	Apoptosis	NA	– (dieldrin)	
	Ploidy	NA	+ (dieldrin)	
Rat (oral exposure)	Increased hepatocyte DNA synthesis	NA	– (dieldrin)	Kamendulis et al. 2001
	Mitosis	NA	– (dieldrin)	
	Apoptosis	NA	– (dieldrin)	
	Ploidy	NA	– (dieldrin)	

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable

Table 3-6. Genotoxicity of Aldrin/Dieldrin *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Chinese hamster ovary cells	Sister chromatid exchange	+ (dieldrin)	+ (dieldrin)	Galloway et al. 1987
	Chromosome aberrations	– (dieldrin)	– (dieldrin)	
Chinese hamster V79 cells	Gene mutation	NA	+	Ahmed et al. 1977b
Cultured human lung cells	Chromosome aberrations	NA	+	Majumdar et al. 1976
Saccharomyces cerevisiae	Mitotic gene conversation	NA	–	Dean et al. 1975; Fahrig 1974
Tradescantia	Micronuclei formation	NA	+ (dieldrin)	Sandhu et al. 1989
		NA	– (aldrin)	
Salmonella typhimurium	Gene mutation	+	+	Ennevar and Rosenkranz 1986; Majumdar et al. 1977
		–	–	De Flora et al. 1984; Glatt et al. 1983; Haworth et al. 1983; Marshall et al. 1976; Moriva et al. 1983; Shirasu 1975
			(+) (photoactivation)	De Flora et al. 1989
E. coli	Gene mutation	NA	–	Ashwood-Smith et al. 1972; Fahrig 1974; Shirasu 1975
Bacillus subtillis	Gene mutation	NA	–	Shirasu 1975
Aspergillus nidulans	Gene mutation	NA	–	Crebelli et al. 1986
SV-40 transformed Human fibroblast	Unscheduled DNA synthesis	NA	+	Ahmed et al. 1977a

Table 3-6. Genotoxicity of Aldrin/Dieldrin *In Vitro* (*continued)*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Rat hepatocyte	Unscheduled DNA synthesis	NA	–	Probst et al. 1981
Mouse hepatocyte	Unscheduled DNA synthesis	NA	–	Klaunig et al. 1984
Mouse embyro fibroblast	Focus formation	NA	+	Kowalski et al. 2000

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; NA = not applicable

Several metabolic studies indicate that dieldrin is absorbed from the gastrointestinal tract and is transported via the hepatic portal vein (Heath and Vandekar 1964). Following dosing with radiolabeled aldrin and dieldrin, high levels of radioactivity were detected in the liver, blood, and stomach and/or duodenum of dosed rats within 1–5 hours (Heath and Vandekar 1964; Iatropoulos et al. 1975). Twenty-four hours following a single oral administration to rats of 10 mg/kg, 50% of the dose was found in fat (Hayes 1974a).

3.4.1.3 Dermal Exposure

Although data are limited regarding absorption of aldrin and dieldrin following dermal exposure in humans, it appears to occur rapidly. Aldrin and dieldrin were first detected in urine 4 hours after dermal application of a single dose (0.004 mg/cm^2) of aldrin and dieldrin, radiolabeled with carbon 14 (^{14}C), to the forearm of six volunteers. Based on urinary ^{14}C excretion, it was estimated that 7.8% of aldrin and 7.7% of dieldrin was absorbed over a 5-day period (Feldmann and Maibach 1974). The accuracy of these values is questionable since the dose used was small, the ^{14}C recovery in the urine was low, the major route of excretion was in the feces (not the urine), and a large individual variation in data was reported.

Aldrin was rapidly absorbed into the skin of female rats following dermal application at doses of 0.006, 0.06, and 0.6 mg/cm^2 (Graham et al. 1987). Aldrin and dieldrin were detected in the skin 1 hour after aldrin application for all three dose levels. The amount absorbed was proportional to the dose applied. *In vitro* studies of rat skin strips incubated with aldrin showed absorption of aldrin was complete by 80 minutes (Graham et al. 1987). Absorption from fabric that had been impregnated with up to 0.04% dieldrin was also demonstrated in rabbits (Witherup et al. 1961).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution following inhalation exposure to aldrin or dieldrin in humans or animals.

3.4.2.2 Oral Exposure

Aldrin is rapidly converted to dieldrin. Distribution of dieldrin is initially general, but within a few hours it is redistributed primarily to fat. A study was conducted on volunteers who ingested dieldrin in doses of 0, 0.0001, 0.0007, or 0.003 mg/kg/day for 24 months (Hunter and Robinson 1967; Hunter et al. 1969). Dieldrin concentrations in blood and adipose tissue increased in a dose-related manner with a finite upper limit for the storage of dieldrin corresponding to a balance between the amount ingested and the amount eliminated daily. This was observed at about 15 months with the eventual body burden characteristic of a person and his particular daily intake (Hunter et al. 1969). The study also found that the concentrations of dieldrin in both adipose tissue and blood are proportional to the given daily dose (Hunter and Robinson 1967). The blood dieldrin concentrations increased by 4 and 10 times in the 0.0001- and 0.003-mg/kg/day dose groups, respectively, when compared to controls. Relationships were derived for the concentration of dieldrin in both adipose tissue and blood in terms of the given daily dosage. Using these relationships it was estimated that the exposure of the general population was equivalent to 0.025 mg/day (0.00033 mg/kg/day). For higher doses of dieldrin, a significant correlation existed between the concentration of dieldrin in blood and the concentration in adipose tissue. The average ratio of the concentration in the adipose tissue to that in the blood was 156:1 (Hunter and Robinson 1967). The existence of a functional relationship between the concentration of dieldrin in the adipose tissue and that in the blood gives strong support to the concept of a dynamic equilibrium in the distribution of dieldrin between these tissues. Animal experiments indicate that this type of equilibrium also exists between the concentrations in the blood and brain, and between those in the blood and liver. When dieldrin administration was terminated, its concentration in blood decreased exponentially following first order kinetics with an estimated half-life of approximately 369 days (range, 141–592 days) (Hunter et al. 1969).

A study of the body burden of dieldrin showed that the bioconcentration and rate of elimination of dieldrin were related to the lipid mass of the individual (Hunter and Robinson 1967, 1968). The highest concentrations of dieldrin in adipose tissue were found in the leanest subjects, and these subjects also exhibited the smallest total body burden. On the other hand, the proportion of the total exposure dose retained in the adipose tissue was highest in those subjects with the greatest total body fat (Hunter and Robinson 1968). The study also showed no increase in the concentration of dieldrin in whole blood during surgical stress or in periods of complete fasting, and it was concluded that the body burden of this compound in the general population constitutes no danger of intoxication as a result of tissue catabolism in times of illness or weight loss (Hunter and Robinson 1968).

Samples of brain, liver, and adipose tissue were collected from 29 randomly selected autopsies of people in Holland (DeVlieger et al. 1968). These people, with three exceptions, lived in an area where a plant manufacturing aldrin, dieldrin, and endrin is situated, but were not employed at that plant. The mean concentration of dieldrin in the white matter of the brain was significantly greater (0.0061 mg/kg) than that in the gray matter (0.0047 mg/kg). In comparison, the mean concentrations of dieldrin in the liver and adipose tissue were 0.03 and 0.17 mg/kg, respectively. Levels of dieldrin were detected in samples of adipose tissue taken from autopsy patients (Adeshina and Todd 1990; Ahmad et al. 1988; Holt et al. 1986). Dieldrin was detected at concentrations ranging from 0.36 to 0.13 mg/kg. No aldrin was detected.

Placental transfer of dieldrin occurs (Polishuk et al. 1977b). A study of women and their offspring during labor showed higher concentrations of dieldrin in fetal blood than in the mother's blood (1.22 mg/kg and 0.53 mg/kg, respectively). Dieldrin levels were also higher in the placenta (0.8 mg/kg) than in the uterus (0.54 mg/kg) (Polishuk et al. 1977b).

Tissue distribution of ^{14}C following single-dose oral administration of ^{14}C-dieldrin (0.43 mg/kg) to rats indicated that the initial rapid uptake of ^{14}C by the liver during the first 3 hours after dosing is followed by a biphasic decrease and redistribution of the compound among body tissues including adipose tissue, kidney, and lymph nodes, with the majority being distributed to the adipose tissue. During the redistribution process, the lymphatic system seems to be the major transport pathway; the parallel increase of lymph node and adipose tissue values indicated an equilibrium between lymph and depot fat (Iatropoulos et al. 1975). Between 24 and 48 hours after a single oral dose of dieldrin was administered to rats, the amount of dieldrin in fat increased to about 50% of the dose. Dieldrin's affinity for fat is illustrated by the ratio of its concentration in fat to that in blood (>130:1) (Hayes 1974a). In female rats fed 2.5 mg/kg/day for 6 months, the ratio of the concentrations of dieldrin in the blood, liver, and fat was 1:30:500, respectively (Deichmann et al. 1968). Most of the dieldrin absorbed through the skin of guinea pigs, dogs, and monkeys is accumulated in the subcutaneous fat (Sundaram et al. 1978a, 1978b).

Species differences in tissue distribution of dieldrin in rodents have been reported (Hutson 1976). When male rats and mice were subjected to a single dose of ^{14}C-dieldrin (3 mg/kg), liver and fat residues were higher in the mice than in the rats 8 days after ingestion. The liver concentration in mice (0.94 mg/kg) was about nine times higher than in rats (0.11 mg/kg). Fat samples in mice contained dieldrin levels (11.6 mg/kg) that were twice as high as the levels in rats (5.6 mg/kg) (Hutson 1976). Sex differences in tissue distribution of dieldrin in rodents have also been reported (Davison 1973; Walker et al. 1969). Female rats fed dieldrin (0.002, 0.01, and 0.1 mg/kg/day) in their diet for 39 weeks had a higher

proportion of the total dose in their carcasses than did male rats that were treated similarly (Davison 1973). Also, female rats fed dieldrin (0, 0.005, and 0.5 mg/kg/day) in their diet for 2 years had tissue concentrations of dieldrin between two and ten times that of male rats fed the same dietary concentration (Walker et al. 1969).

Following repeated dosing (2–104 weeks), an equilibrium or steady state is reached between the intake, storage, and excretion of dieldrin in various strains of rats and beagle dogs. Steady-state kinetics were determined by measuring both the level of radioactivity retained in fat, blood, liver, and brain and the percentage of the administered dose excreted at sublethal doses. The steady-state tissue concentration of dieldrin was dose- and time-dependent. In dogs receiving daily oral doses of 0.005 or 0.05 mg/kg/day dieldrin for 2 years, the steady-state blood residue levels were reached in 12–18 weeks or 18–30 weeks, respectively (Walker et al. 1969). In rats receiving 0.0002–2.5 mg/kg/day dieldrin in the diet, steady state was reached in 4–39 weeks; equilibrium was reached earlier in rats receiving higher doses of dieldrin (Baron and Walton 1971; Davison 1973; Ludwig et al. 1964; Walker et al. 1969). In rats receiving daily oral doses of 0.012 mg/kg/day ^{14}C-aldrin for 3 months, steady state was reached in 53 days (Ludwig et al. 1964).

In another study, the steady-state concentration in adipose tissues of rats receiving dietary concentrations of 1.25 mg/kg/day dieldrin for 8 weeks was reported to be 50 mg/kg dieldrin (Baron and Walton 1971). The elimination of dieldrin residues from the adipose tissue of rats subsequently placed on untreated diets was reasonably rapid with estimated half-lives reported to be 4.5 days (Baron and Walton 1971). The estimated half-lives for the adipose tissue and brain were 10.3 and 3 days, respectively, for rats on a basic diet for 12 weeks, following consumption of a diet containing 0.5 mg/kg/day dieldrin for 8 weeks (Robinson et al. 1969). The half-lives of dieldrin in the liver were estimated to be 1.3 and 10.2 days for the rapid and slower elimination, respectively, and similar values were estimated for the blood. The concentrations of dieldrin in adipose tissue were considerably greater than those in other tissues, with storage in the four tissues as follows: adipose tissue >> liver > brain > blood (Robinson et al. 1969).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution following dermal exposure to aldrin or dieldrin in humans.

Guinea pigs exposed dermally to dieldrin at concentrations varying from 0.0001 to 0.1% for 6 months showed the highest tissue distribution in adipose tissue, with lower concentrations in the liver and brain (Sundaram et al. 1978b). Rabbits exposed to fabric containing up to 0.04% dieldrin for 52 weeks also showed slight accumulation in the omental and renal fat (Witherup et al. 1961).

3.4.2.4 Other Routes of Exposure

The administration of dieldrin by the intraperitoneal route ensures more or less complete absorption. The ^{14}C-residues in tissues of rats dosed by intraperitoneal injection with a total dose of 0.01, 0.1, or 1.0 mg/kg were distributed among the brain, blood, liver, and subcutaneous fat with the highest levels in the fat. Radioactivity excreted by groups given dieldrin by intraperitoneal injection was not significantly different from that of orally treated groups (Lay et al. 1982).

In another study (Cooke et al. 2001) in male Sprague-Dawley rats injected intraperitoneally with 75 mg/kg ^{14}C-aldrin or 62 mg/kg ^{14}C-dieldrin once a week for 3 weeks, the highest levels of dieldrin ^{14}C-residues were also observed in the fat, whereas the distribution of aldrin ^{14}C-residues to the spleen was comparable to fat. In the reproductive organs, the testicular ^{14}C-residue content of both chemicals was always considerably lower than that of the epididymis, and the seminal vesicle fluid contained lower quantities of label than the seminal vesicles.

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

No studies were located regarding metabolism following inhalation exposure to aldrin or dieldrin in humans.

An *in vitro* study using rabbit lung perfusates showed that aldrin was metabolized to dieldrin within the endoplasmic reticulum. Aldrin metabolism was dose dependent. Up to 70% of aldrin was metabolized in 1 hour at low doses (#3 μmol) (Mehendale and El-Bassiouni 1975).

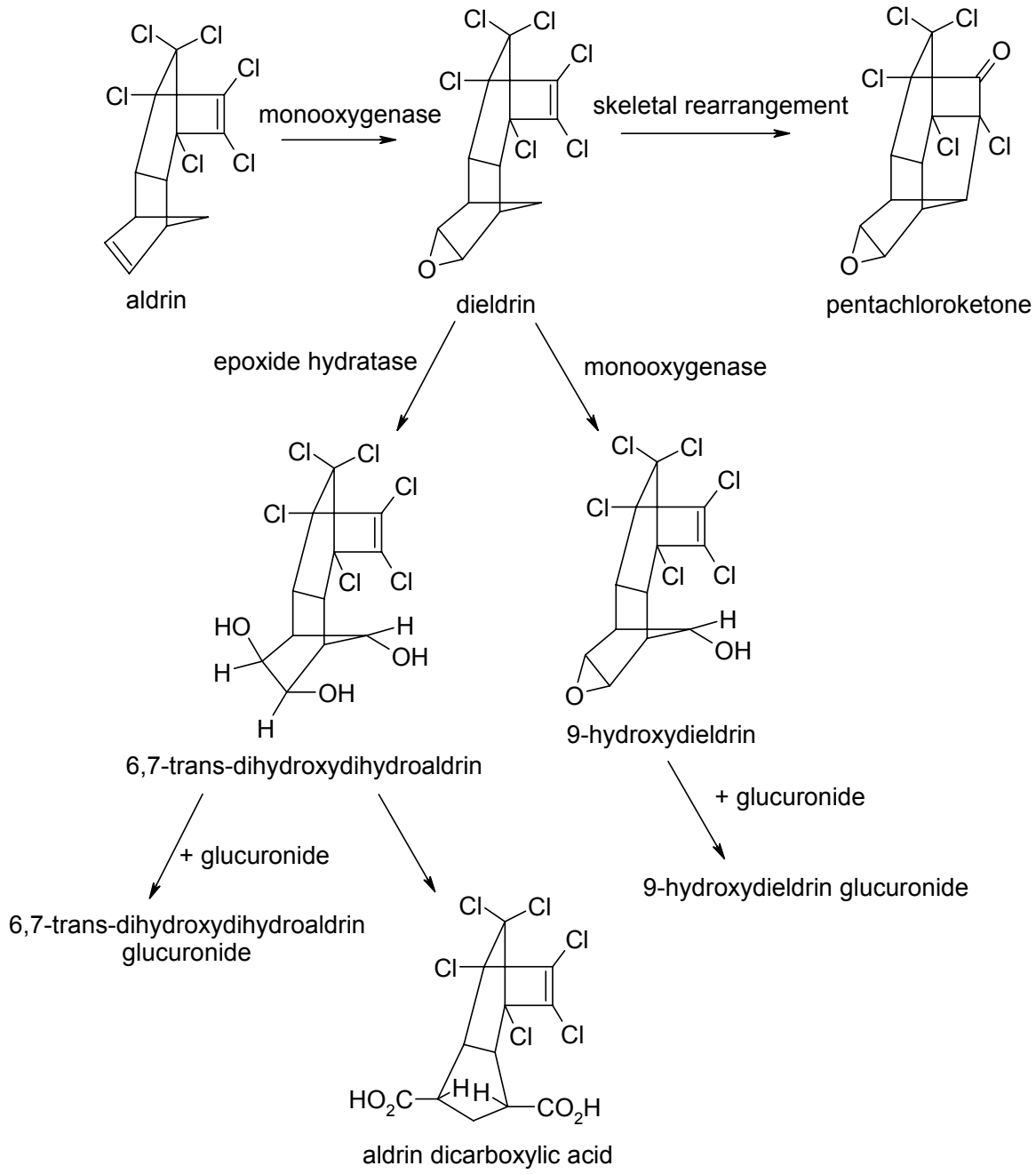
3.4.3.2 Oral Exposure

No studies were located specifically regarding metabolism following oral exposure to aldrin or dieldrin in humans.

The initial and major step in the biotransformation of aldrin in experimental animals is the formation of the corresponding epoxied dieldrin (Wong and Terriere 1965). Aldrin is readily converted to dieldrin primarily in the liver by mixed-function oxidases (Wong and Terriere 1965) and to a lesser extent in the lung (Lang et al. 1986) and skin (Graham et al. 1987; Lang et al. 1986). The known metabolic pathways of aldrin and dieldrin in laboratory animals are presented in Figure 3-3.

The formation of dieldrin by epoxidation of aldrin is a reaction catalyzed by monooxygenases in liver and lung microsomes. Aldrin epoxidation was studied in rat liver microsomes (Wolff et al. 1979). Microsomes from phenobarbital-treated rats showed a three-fold increase in dieldrin formation, whereas 3-methylcholanthrene treatment markedly depressed enzyme activity. Thus, cytochrome P-450, not cytochrome P-448, seems to be involved in epoxidation. *In vitro* studies compared the oxidation of aldrin to dieldrin in extrahepatic and hepatic tissues of rats (Lang et al. 1986). The authors tried to identify the pathway by which aldrin is metabolized in liver, lung, seminal vesicle, and subcutaneous granulation tissue. Many organs and tissues possess low cytochrome P-450 content. In these cases, an alternative oxidative pathway mediated by prostaglandin endoperoxide synthase (PES) might be more important. PES consists of a cyclooxygenase which catalyzes the bisdioxygenation of arachidonic acid to prostaglandin G_2 (PGG_2). In a second step, a reduction by hydroperoxidase to prostaglandin H_2

Figure 3-3. Proposed Metabolic Pathway for Aldrin and Dieldrin*



*Adapted from EPA 1987a

(PGH_2) occurs. The aldrin epoxidation was completely nicotine adenine dinucleotide phosphate (NADPH)-dependent in liver microsomes and hepatocytes. In lung microsomes, two pathways were involved. The NADPH-dependent activity was 1.5% and the arachidonic acid-dependent aldrin epoxidation was 0.3% of the activity found in the liver. In seminal vesicle microsomes and granulation tissue microsomes, aldrin epoxidation was stimulated by arachidonic acid and inhibited by indomethacin (a specific inhibitor of cyclooxygenase). These results suggest that aldrin was epoxidized by a prostaglandin synthase–mediated pathway in extrahepatic tissues as an alternative enzyme in the cytochrome P-450-dependent monooxygenases (Lang et al. 1986).

In mammals, two major metabolism routes of dieldrin seem to be predominant: (1) direct oxidation by cytochrome oxidases, resulting in 9-hydroxydieldrin (the Chemical Abstract Service [CAS] numbering system equivalent of 12-hydroxydieldrin), and (2) the opening of the epoxied ring by epoxied hydrases, resulting in 6,7-*trans*-dihydroxydihydroaldrin (the CAS numbering system equivalent of 4,5-*trans*-dihydroxy–dihydroaldrin) (Müller et al. 1975). Dieldrin is hydroxylated to 9-hydroxydieldrin by liver microsomal monooxygenases in rats, and the reaction is inhibited by the addition of the monooxygenase inhibitor, sesamex (Matthews and Matsumura 1969). Metabolism of dieldrin is 3–4 times more rapid in male than in female rats (Matthews et al. 1971). The difference is attributed to the greater ability of males to metabolize dieldrin to its more polar metabolites, primarily 9-hydroxydieldrin. Species differences in rates of metabolism have been observed in rats and mice. The hydroxylation reaction occurs more rapidly in rats than it does in mice as indicated by a higher ratio in rats of 9-hydroxy-^{14}C-dieldrin to ^{14}C-dieldrin (Hutson 1976).

The 9-hydroxydieldrin glucuronide is formed both *in vivo* and *in vitro*. It has been identified in the bile of rats (Chipman and Walker 1979); however, it is generally excreted in the feces in free form (Hutson 1976). The 9-hydroxydieldrin glucuronide is formed rapidly *in vitro* from dieldrin (which is hydroxylated first to 9-hydroxydieldrin) upon incubation with rat liver microsomes and uridine diphosphoglucuronic acid (Hutson 1976; Matthews et al. 1971).

Dieldrin is also metabolized by epoxide hydratase to form 6,7-*trans*-dihydroxydihydroaldrin, which was originally isolated and identified in rabbits and mice (Korte and Arent 1965) and later found also to form in other animals including Rhesus monkeys and chimpanzees (Müller et al. 1975). The 6,7-*trans*-dihydroxydihydroaldrin glucuronide is formed *in vitro* in hepatic microsomal preparations from rabbits or rats in the presence of uridine diphosphoglucuronic acid and NADPH (Matthews and Matsumura 1969).

6,7-*trans*-Dihydroxydihydroaldrin can be further oxidized to aldrin dicarboxylic acid or conjugated to glucuronic acid (Baldwin et al. 1972; Hutson 1976).

Pentachloroketone, also known as Klein's metabolite, is a major urinary metabolite in male rats, but it is only found in trace amounts in the urine of female rats and male mice (Baldwin et al. 1972; Hutson 1976; Matthews et al. 1971). Pentachloroketone is formed by molecular rearrangement. It has been suggested that pentachloroketone is the product of rearrangement of the same intermediate that leads to 9-hydroxydieldrin (Bedford and Hutson 1976).

3.4.3.3 Dermal Exposure

No studies were located regarding metabolism following dermal exposure to aldrin or dieldrin in humans.

Data show that the skin is capable of metabolizing aldrin to the stable epoxied dieldrin (Graham et al. 1987). Dieldrin was detected in the skin of rats 1 hour after aldrin application at three dose levels (0.1, 1.0, and 10 mg/kg). The amount of conversion was greatest at the lowest dose levels suggesting enzyme saturation at higher doses. The authors concluded that, following topical application, up to 10% conversion of aldrin to dieldrin by skin enzymes can occur during percutaneous absorption (Graham et al. 1987). *In vitro* studies using mouse skin microsomal preparations and rat whole skin strips also showed that metabolism of aldrin to dieldrin took place in the skin (Graham et al. 1987).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion following inhalation exposure to aldrin or dieldrin in humans or animals.

3.4.4.2 Oral Exposure

Excretion in humans is primarily in the feces via the bile. 9-Hydroxydieldrin was found in the feces of seven workers occupationally exposed to aldrin and dieldrin (Richardson and Robinson 1971). An estimated half-life for dieldrin elimination is reported to be 369 days (Hunter et al. 1969). Dieldrin is also

excreted via lactation in nursing mothers. Dieldrin concentrations of 19–26 ppb were found in breast milk (Schecter et al. 1989b).

In rats dosed with ^{14}C-aldrin at 0.012 mg/kg/day for 3 months, both aldrin and dieldrin were found in the feces, with lower concentrations of both compounds also found in the urine (Ludwig et al. 1964). Pentachloroketone was also detected in the urine of rats fed diets containing 1.25 mg/kg/day of aldrin (Klein et al. 1968).

Following administration of single oral doses of ^{14}C-dieldrin to rats, mice, monkeys, and chimpanzees, radioactivity accounting for 95, 95, 79, and 79% of the dose, respectively, was excreted in the feces, which is the main route of excretion (Hutson 1976; Müller et al. 1975). The ratio of radioactivity excreted in the feces and in the urine is 19 in rats and mice and 3.8 in monkeys and chimpanzees (Müller et al. 1975). Unchanged dieldrin and 9-hydroxydieldrin and its glucuronide are the major components in the feces of rats, monkeys, and chimpanzees, with lesser amounts of 6,7-dihydroxydihydroaldrin and aldrin dicarboxylic acid (Baldwin et al. 1972; Hutson 1976; Matthews et al. 1971; Müller et al. 1975). 9-Hydroxydieldrin has also been found in the urine of monkeys given a single dose of 0.5 mg/kg of dieldrin (Müller et al. 1975) and in mouse urine (Hutson 1976). Elimination of aldrin dicarboxylic acid occurs mainly in the urine of mice and rats (Baldwin et al. 1972; Hutson 1976) and in the feces of rats (Hutson 1976). Unchanged dieldrin was found in the feces of mice, rats, rabbits, and monkeys at concentrations ranging from 0.3 to 9.0% of the single dose administered (0.5 mg/kg) (Müller et al. 1975).

Excretion of dieldrin is 3–4 times more rapid in male than in female rats (Matthews et al. 1971). The difference was attributed to the greater ability of males to metabolize dieldrin to its more polar metabolites. An *in vitro* study using rat liver perfusates showed a sexual difference in the hepatic excretion of dieldrin. The appearance of radioactivity in the bile of livers of males was approximately three times as rapid as the appearance of radioactivity in the bile of livers of females (Klevay 1970). Species differences have been reported for the excretion of dieldrin and/or its metabolites between male CFE rats and male CF_1 or LACG mice (Baldwin et al. 1972; Hutson 1976). Excretion was more rapid in the rat than in the mouse. The ratio of 9-hydroxy-^{14}C-dieldrin to ^{14}C-dieldrin was higher in rats than in mice, indicating a slightly more rapid excretion by the rat (Hutson 1976).

In rabbits, 6,7-*trans*-dihydroxydihydroaldrin is the major metabolite excreted in the urine. Following administration of single oral doses of ^{14}C-dieldrin to rabbits, elimination was greater in urine, accounting for 81–83% of the dose (Müller et al. 1975). 6,7-*trans*-Dihydroxydihydroaldrin has also been identified

in the urine of mice (Müller et al. 1975). 6,7-*trans*-Dihydroxydihydroaldrin glucuronide has been identified in urine of rabbits and monkeys (Müller et al. 1975).

Pentachloroketone is the major component in rat urine (Baldwin et al. 1972; Hutson 1976; Matthews et al. 1971). The mouse, unlike the rat, does not appear to excrete pentachloroketone as a urinary metabolite. Pretreatment of CFE rats with dieldrin caused an enhancement of the urinary excretion of pentachloroketone, but no effect on the pattern of excretion of urinary metabolites could be detected when CF_1 mice were given similar treatments (Baldwin et al. 1972). Aldrin dicarboxylic acid, unchanged dieldrin, and 9-hydroxydieldrin glucuronide have also been found in lower concentrations in the urine of rats (Hutson 1976; Müller et al. 1975).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion following dermal exposure to aldrin or dieldrin in humans or animals.

3.4.4.4 Other Routes of Exposure

Elimination of ^{14}C following intraperitoneal or intravenous injection of ^{14}C-dieldrin to male rats was either approximately equal to or slightly less than that observed following oral dosing (between 70 and 80% of the total dose was excreted by 2 weeks postdosing) (Cole et al. 1970; Lay et al. 1982). Excretion occurred primarily in the feces (about 90%). Biliary elimination was measured experimentally following intraperitoneal administration. The rate of ^{14}C elimination in the bile increased following pretreatment of rats with phenobarbital (Chipman and Walker 1979).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

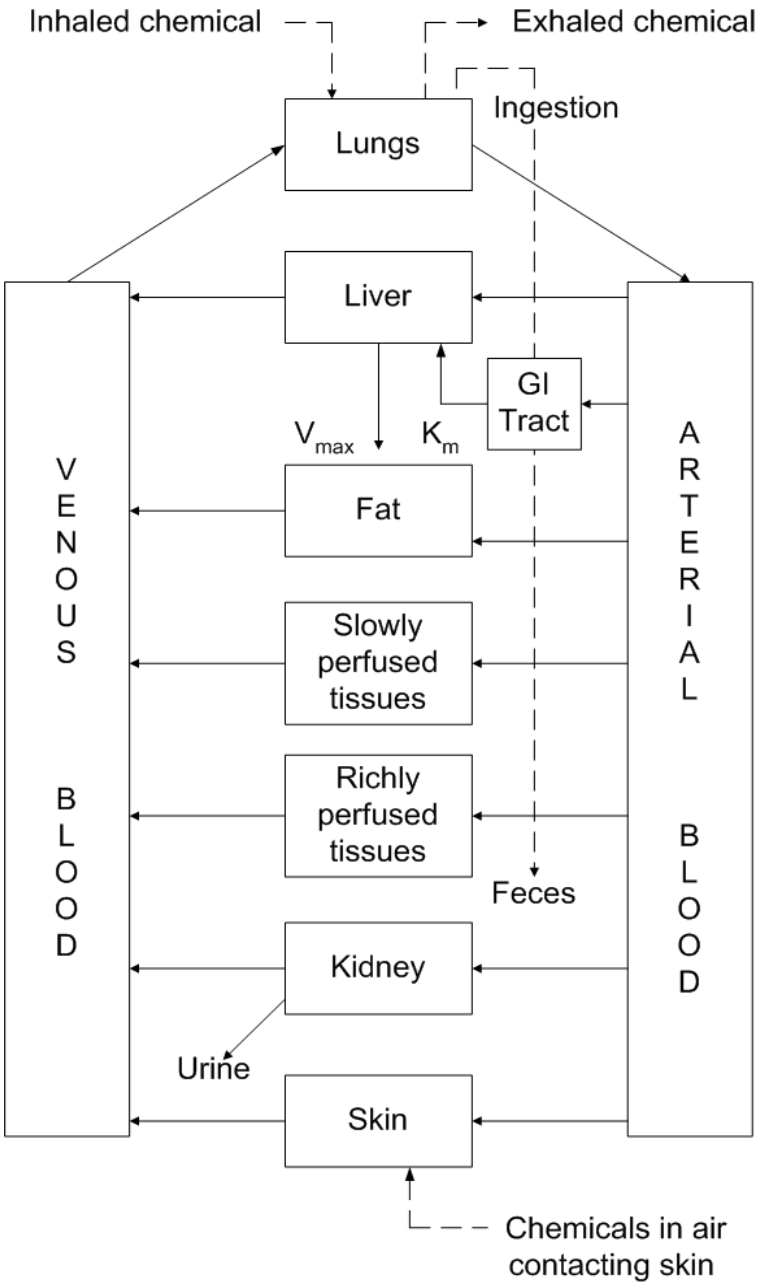
No PBPK models for aldrin or dieldrin were located.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Mechanisms of aldrin or dieldrin absorption following inhalation, oral, or dermal exposure in humans or animals were not identified. However, since both aldrin and dieldrin are lipophilic substances, absorption via passive diffusion is likely. No information was located regarding transport mechanisms in the blood. Given the high degree of solubility of aldrin and dieldrin in lipids, one might expect these chemicals to be associated with the lipid fraction of blood. In biological systems, aldrin is rapidly converted to dieldrin. Following exposure to aldrin or dieldrin, animal data indicate that dieldrin is widely distributed initially (with rapid uptake by the liver), then redistributed primarily to fat (Deichmann et al. 1968; Hayes 1974a; Hutson 1976; Iatropoulos et al. 1975). The lymphatic system appears to be the major transport pathway during redistribution (Iatropoulos et al. 1975). Animal data also indicate that epoxidation of aldrin to dieldrin is catalyzed by monooxygenases, primarily in the liver (Wong and Terriere 1965), but also in lungs (Lang et al. 1986) and skin (Graham et al. 1987; Lang et al. 1986). The study of Lang et al. (1986) provides evidence that aldrin may also be epoxidized by a prostaglandin synthetase-mediated pathway in extrahepatic tissues. Results from a dermal study indicate that the metabolism of aldrin and dieldrin may be a saturable process (Graham et al. 1987). Further metabolism, such as the hydroxylation of dieldrin to 9-hydroxydieldrin, has also been shown to occur in the liver (Matthews and Matsumura 1969). In animals administered aldrin or dieldrin, fecal excretion (via the bile) of parent compound and metabolites is the main route of elimination, with lesser amounts found in the urine (Ludwig et al. 1964). Dieldrin is also excreted in the breast milk of nursing mothers (Schecter et al. 1989b).

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

3.5.2 Mechanisms of Toxicity

A number of studies have investigated the mechanism of aldrin and dieldrin neurotoxicity. As discussed in Section 3.2.2.4, aldrin and dieldrin characteristically stimulate the central nervous system causing hyperexcitation and generalized seizures (convulsions). It is generally believed that the hyperexcitatory effects of these chemicals result from a generalized activation of synaptic activity throughout the central nervous system, although it is unclear whether aldrin and dieldrin act at the nerve terminal to facilitate neurotransmitter release, or if they cause excitation by depressing activity of inhibitory neurotransmitters within the central nervous system (Joy 1982; Shankland 1982).

Facilitation of neurotransmitter release by dieldrin has been proposed to occur as the result of the ability of aldrin or dieldrin to inhibit brain calcium ATPases (Mehrotra et al. 1988, 1989). These enzymes are involved in pumping calcium out of the nerve terminal. By inhibiting their activity, aldrin and dieldrin would cause a build-up of intracellular levels of calcium and an enhancement of neurotransmitter release.

Most recently, however, the role of aldrin and dieldrin in blocking inhibitory activity within the brain has received a great deal of attention as the probable mechanism underlying the central nervous system excitation. Based on the observed interaction of other cyclodiene insecticides with the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) (Matsumura and Ghiasuddin 1983), numerous studies were undertaken to assess the effects of aldrin and dieldrin on GABA receptor function. Both *in vitro* experiments using rat brain membranes and intravenous or intraperitoneal administration of aldrin and dieldrin to rats have shown that these agents are capable of blocking the activity of GABA by blocking the influx of chloride through the $GABA_A$ receptor-ionophore complex (Abalis et al. 1986; Bloomquist 1992, 1993; Bloomquist and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Ikeda et al. 1998; Lawrence and Casida 1984; Liu et al. 1997a, 1997b; Nagata and Narahashi 1994, 1995; Narahashi et al. 1992, 1995, 1998; Obata et al. 1988; Pomes et al. 1994). Overall, based on good correlations of effects from the molecular level to whole animal toxicity, the preponderance of evidence indicates that the convulsant and other neurotoxic effects of aldrin and dieldrin are consequent to a blocking action on the $GABA_A$ receptor-chloride channel complex.

Pesticides have been implicated in the etiology of the Lewy body diseases, which involve intracellular deposits consisting of fibrils of α-synuclein. Dieldrin has been shown to stimulate α-synuclein fibril formation *in vitro* (Uversky et al. 2001). While α-synuclein is a natively unfolded protein, dieldrin induces a conformational change in α-synuclein, a time-dependent increase in secondary structure, which

preceded the increase in fibril formation. The natively unfolded state of α-synuclein arises from the large net negative charge at neutral pH and the low intrinsic hydrophobicity. Uversky et al. (2001) proposed that nonpolar dieldrin binds to α-synuclein and shifts the equilibrium from the unfolded state to a folded intermediate conformation. The intermediate then associates, leading to fibril formation.

In a study of organochlorine compounds in human brain, there was a substantially higher concentration of dieldrin in Parkinson's disease tissue compared with Alzheimer's disease and nondemented nonparkinsonian controls tissue (Corrigan et al. 2000).

A preponderance of evidence from studies in a variety of mammalian species indicates a unique sensitivity of the mouse liver to aldrin- and dieldrin-induced hepatocarcinogenicity and mechanistic studies suggest a nongenotoxic mode of action (Stevenson et al. 1999; WHO 1989) via promotion of spontaneously initiated (background) liver cells (see Sections 3.2.2.7 and 3.3). The cellular and molecular mechanisms involved in the promotion of the liver tumors have not been fully elucidated, but appear to mainly involve species-specific susceptibility of the mouse to dieldrin-induced oxidative stress and inhibition of gap junctional communication (Jone et al. 1985; Klaunig and Ruch 1987; Klaunig et al. 1990, 1995, 1998; Kurata et al. 1982; Ruch and Klaunig 1986; Stevenson et al. 1999; Trosko et al. 1987; van Ravenzwaay and Kunz 1988; Wade et al. 1986; Zhong-Xiang et al. 1986). As discussed by Stevenson et al. (1999), the production of reactive oxygen species, depletion of hepatocyte antioxidant defenses such as vitamin E, and peroxidation of liver lipid have been shown to accompany oxidative metabolism of dieldrin in mice, apparently resulting in modulation of gene expression that favors the clonal expansion of spontaneously initiated cells.

The effects of dieldrin on changes in hepatocyte DNA synthesis, mitosis, apoptosis, and ploidy were studied in rats and mice treated with 0, 1, 3, or 10 mg dieldrin/kg diet (Kamendulis et al. 2001). No changes were observed in rat liver. Liver from mice fed only the highest dose (10 mg dieldrin/kg) exhibited significantly increased DNA synthesis and mitosis at 14, 28, or 90 days on the diet and a significant increase in octaploid (8N) hepatocytes. The apoptotic index in the liver of mice in any treatment group did not change over a 90-day treatment and study period.

The ability of chlorinated hydrocarbons to disrupt estrogen homeostatis, by up-regulating selected gene transcription, has also been hypothesized to be responsible for their oncogenic effects. Neither aldrin nor dieldrin showed evidence of estrogenicity as evidenced by lack of induction of transcriptional activation of an estrogen-responsive reported gene in transfected HeLa cells (Tully et al. 2000). There is evidence

of a synergistic estrogenic effect of dieldrin and toxaphene on the bone mass density in rats. While dieldrin alone did not show any evidence of estrogenicity when administered to rats by intragastric intubation at a dose of 7.5 µmol/kg/day, 5 days/week, for 9 months, when administered with toxaphene (30 µmol toxaphene/kg/day and 7.5 µmol/kg/day), bone mass density was significantly increased (Syversen et al. 2000). In contrast, the results of several estrogen-responsive assays in the mouse uterus, MCF-7 human breast cancer cells, and yeast-based reporter gene assays, indicate that the activities of both dieldrin and toxaphene, as well as a binary mixture of the two were minimally estrogenic (Ramamoorthy et al. 1997a).

A single dose of dieldrin (37 mg/kg), administered to female rats by gavage significantly increased expression of cytochrome P450 CYP1A1, CYP1A2, and CYP1B1, which are involved in estrogen metabolism, in the liver, kidney, and mammary tissues (Badawi et al. 2000).

3.5.3 Animal-to-Humans

Most of the available human data come from cases of acute oral exposure to relatively high levels of aldrin or dieldrin (Black 1974; Garrettson and Curley 1969; Gupta 1975; Spiotta 1951) or from chronically exposed workers (de Jong 1991; Ditraglia et al. 1981; Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; Van Raalte 1977; Van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). In both humans and animals, high doses of aldrin or dieldrin result primarily in neurotoxicity. Epidemiologic studies involving chronic exposure to aldrin and/or dieldrin similarly indicate that the central nervous system is a major organ of toxicity. Chronic animal studies additionally demonstrate adverse effects in the kidney and liver; the liver being the most sensitive target. Liver effects are indicated in limited reports of humans exposed to levels of aldrin or dieldrin that result in neurotoxic symptoms (Black 1974; Garrettson and Curley 1969). Although the human data are extremely limited, at present, there is no evidence to suggest that noncancer effects seen in animal studies would be different from those in humans. Available information is suggestive of general similarity in the metabolic pathways and disposition of aldrin and dieldrin in humans and experimental animals (Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974a; Hunter and Robinson 1967; Hunter et al. 1969; Iatropoulus et al. 1975). However, elimination rates vary among animal species and between males and females, thus contributing to uncertainty in extrapolation of toxicokinetic data from animals to humans.

Oral bioassays in animals have demonstrated that aldrin and/or dieldrin are liver carcinogens in mice, but not rats (Davis and Fitzhugh 1962; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; Meierhenry et al. 1983; NCI 1978a, 1978b; Tennekes et al. 1981; Thorpe and Walker 1973; Walker et al. 1969, 1972). Based on the results of retrospective cancer mortality studies in aldrin and dieldrin production workers, there is inconclusive evidence of carcinogenicity in occupationally-exposed humans (Amoateng-Adjepong et al. 1995; Brown 1992; de Jong 1991; de Jong et al. 1997; Ditraglia et al. 1981; Jager 1970; Ribbens 1985; van Raalte 1977). As summarized in Section 3.5.2 (Mechanisms of Toxicity), accumulating evidence indicates that the species-specificity of dieldrin-induced hepatocarcinogenicity involves susceptibility of the mouse to dieldrin-induced oxidative stress, resulting in the promotion of spontaneously initiated (background) liver tumors. Because other species, including humans, appear to be resistant to dieldrin-induced oxidative stress (Jager 1970; Stevenson et al. 1999), it does not appear that the mouse carcinogenicity data can be extrapolated to humans with a high degree of certainty.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of

affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans after exposure to aldrin or dieldrin.

In vivo studies in animals suggest that aldrin and dieldrin may disrupt normal reproductive hormone levels in male animals and be an endocrine disruptor in females. Decreased androgen production and degenerative changes in the germ cells were seen in male rats after intermediate-duration intraperitoneal exposures to aldrin. Aldrin also induced estrus changes and/or endometrial proliferation in treated dogs and ovariectomized rats. *In vitro* studies suggest that dieldrin may inhibit binding of 5α-dihydro-testosterone and 17β-estradiol to the androgen and estrogen receptors, respectively, as well as cause effects such as estrogenic induction of breast cell proliferation. Overall, *in vitro* evidence for dieldrin estrogenicity indicates weak potency compared to 17β-estradiol. Apparently contradictory results were reported in different studies for several of the assays, indicating that caution should be used in interpreting the collective *in vitro* results.

Gonadotrophic effects were observed in male rats that were treated with 0.15 mg/kg/day aldrin by intraperitoneal injection for 26 days (Chatterjee et al. 1988a, 1988b, 1988c). These effects include decreased sperm count, degeneration of germ cells, decreased weights of seminal vesicles and prostate and coagulating glands, decreased seminiferous tubule diameter, decreased plasma and testicular testosterone, decreased prostatic fructose content and acid phosphatase activity, and decreased plasma luteinizing hormone and follicular stimulating hormone. Dieldrin caused changes in testosterone production and ultrastructure in rat interstitial (Leydig) testicular cells *in vitro*; significant increases in testosterone production were observed, and the Leydig cells had increased numbers of cytoplasmic vesicles which resembled lipid droplets (Ronco et al. 1998). Dieldrin also reduced the stimulatory effect of human chorionic gonadotropin (HCG) on Leydig cell testosterone production, although dieldrin-induced ultrastructural changes in HCG-stimulated Leydig cells were similar to those found in the unstimulated cells (Ronco et al. 1998). Other *in vitro* studies showed that dieldrin significantly inhibited binding of 5α-dihydrotestosterone to the androgen receptor in rat prostate cytosol and to androgen-

binding protein in rat epididymal cytosol, although binding to human sex hormone-binding globulin was not reduced (Danzo 1997; Wakeling et al. 1973).

Estrogenic effects have been observed in some studies of aldrin and dieldrin. Changes in dogs orally exposed to 0.15 or 0.30 mg/kg/day aldrin for 14 months prior to mating included delayed estrus, reduced libido, and lack of mammary function and development (Deichmann et al. 1971), although this study is limited by small numbers of animals. Uterine weight glycogen content were increased in immature female rats and ovariectomized mature rats that were subcutaneously treated with 1 mg/kg/day aldrin for 3 days (Chatterjee et al. 1992). The increased uterine weight was due to proliferation of the endometrium and endometrial glands in both the immature and ovariectomized mature rats. A persistent vaginal estrus was additionally induced in the treated ovariectomized rats (Chatterjee et al. 1992). Immature female rats that were intraperitoneally administered 3 mg/kg/day dieldrin for 3 days showed no changes in uterine and pituitary weights, uterine peroxidase activity, circulating thyroxine levels, or levels of follicular stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, and growth hormone in the pituitary gland (Wade et al. 1997). Dieldrin slightly decreased binding of 17β-estradiol to the estrogen receptor in extracts of uterine tissue from these rats (Wade et al. 1997). There were no significant dose-related changes in uterine weight, peroxidase activity, or estrogen or progesterone receptor binding in immature (21-day-old) mice that were intraperitoneally administered approximately 1–100 mg/kg/day dieldrin for 3 days (Ramamoorthy et al. 1997a).

In *in vitro* studies, dieldrin weakly induced proliferation of MCF-7 human breast cancer cells (an estrogenic effect) at a concentration that was an order of magnitude lower than cytotoxic levels; the potency of dieldrin relative to estradiol was 0.0001 (Soto et al. 1994, 1995). Results of other MCF-7 assays similarly showed that dieldrin was a weak inducer of cell growth or did not induce proliferation (Ramamoorthy et al. 1997a; Wade et al. 1997). Levels of estrogen and progesterone receptors in MCF-7 cells were slightly increased by dieldrin (Soto et al. 1995). Dieldrin did not significantly induce chloramphenicol acetyl transferase (CAT) activity in MCF-7 cells transiently transfected with plasmids containing estrogen-responsive 5'-promoter regions from the rat creatine kinase B and human cathepsin D genes (Ramamoorthy et al. 1997a). Binding of 17β-estradiol to the estrogen receptor in human MCF-7 cells, young rabbit uterine cells, or alligator oviduct cells was not competitively decreased by dieldrin (Danzo 1997; Ramamoorthy et al. 1997a; Vonier et al. 1996). Dieldrin had minimal estrogen receptor-mediated β-galactosidase (β-gal) activity in an estrogen-responsive reporter system in yeast (Ramamoorthy et al. 1997a).

The overall *in vivo* and *in vitro* evidence indicates that aldrin and dieldrin may be disruptive of reproductive hormone levels in male animals and weakly estrogenic in females. Limited animal data further suggest that dieldrin is not disruptive of thyroid or pituitary hormone levels in females.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and

Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Neurological symptoms (for example, convulsions, abnormal EEGs, hyperexcitability, restlessness) have been reported in adults and children following ingestion (accidental or intentional) of aldrin or dieldrin (Black 1974; Garrettson and Curley 1969; Gupta 1975; Spiotta 1951). Two young children (2 and 4 years of age) experienced severe convulsions within 15 minutes after consuming an unknown quantity of a 5% solution of dieldrin; the younger child died whereas the older brother recovered completely after exhibiting evidence of liver dysfunction (Garrettson and Curley 1969). The observed effects could not be attributed solely to dieldrin because the ingested solution likely also contained solvents and emulsifiers. Among 11 people experiencing evidence of neurotoxicity associated with the consumption of wheat mixed with aldrin and lindane for a period of 6–12 months, a female infant was reported to suffer a severe convulsion, followed by death a few hours later (Gupta 1975). Since no symptoms had been observed among individuals previously consuming wheat mixed only with lindane, it was assumed that the neurotoxic effects were the result of aldrin poisoning. A 7-year-old child in this same group was thought to have developed mild mental retardation as a result of the poisoning. However, these limited oral human data do not conclusively indicate age-related differences in susceptibility to aldrin or dieldrin poisoning. Signs of neurotoxicity have also been reported in occupational studies of workers employed in the application or manufacture of aldrin or dieldrin where exposures may have been predominantly by inhalation (Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958). No data were located regarding adverse effects in humans dermally exposed to aldrin or dieldrin, although both aldrin and dieldrin have been shown to pass through the skin and enter the blood of adults (Feldman and

Maibach 1974). It is expected that children and adults would be similarly affected by dermal exposure to aldrin or dieldrin, although no data were available to substantiate this assumption.

Limited oral LD_{50} studies indicate that newborn rats may be less sensitive than adult rats to high acute doses of dieldrin, while 2-week-old rats may be somewhat more sensitive than adults (Lu et al. 1965). In a study of adult cattle and calves given feed which was accidently mixed with aldrin, mortality occurred exclusively among calves (Buck and Van Note 1968); however, information regarding the amount of aldrin in the feed, and relative consumption rates of calves and adult cattle were not available. No other information was available to suggest that children may be more susceptible than adults to aldrin or dieldrin.

It is generally believed that the neurotoxicity of both aldrin and dieldrin is based on alterations in synaptic activity within the central nervous system (Joy 1982; Shankland 1982). As discussed in Section 3.5.2, Mechanisms of Toxicity, recent *in vitro* and *in vivo* animal studies have shown that aldrin and dieldrin are capable of blocking the activity of the inhibitory neurotransmitter GABA, an indication that both chemicals may exert their neurotoxic effects via blockage of inhibitory activity within the brain. If neurological effects seen in response to aldrin and dieldrin exposure are dependent on maturation of the central nervous system, then immature nervous systems might be less sensitive to the effects elicited by aldrin and dieldrin.

There is conflicting information regarding the developmental toxicity of aldrin and dieldrin. In some cases, increased incidences of external malformations or skeletal anomalies were observed following oral exposure of pregnant laboratory animals to aldrin or dieldrin in mid-gestation (Chernoff et al. 1975; Ottolenghi et al. 1974); no significant malformations or anomalies were seen in other studies (Chernoff et al. 1975; Dix et al. 1977). These studies were limited in design and study details. A more consistently reported developmental effect was that of decreased postnatal survival in laboratory animals following *in utero* exposure to dieldrin (Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975, 1977). Dieldrin has been detected in human placenta, amniotic fluid, and fetal blood, and may be found in higher concentration in fetal blood than in the mother's blood (Polishuk et al. 1977b). Furthermore, dieldrin is excreted in the breast milk of nursing mothers (Schecter et al. 1989b). In an animal study designed to test whether decreased pup survival might be related to maternal postnatal care, mice born to dieldrin-exposed dams and then nursed by untreated dams exhibited similar survival rates to those nursed by their exposed dams, suggesting that decreased pup survival was correlated with *in utero*, rather than postnatal, exposure (Virgo and Bellward 1977). Intraperitoneal injection of aldrin in male rats

resulted in plasma decreases in luteinizing hormone, follicular hormone, and testosterone, as well as decreases in testicular testosterone (Chatterjee et al. 1988a, 1988b, 1988c). In an *in vitro* study using rat interstitial testicular cells, dieldrin caused a significant increase in testosterone production (Ronco et al. 1998). There is some evidence that aldrin and dieldrin may be estrogenic. Oral administration of aldrin resulted in delayed estrous in dogs (Deichmann et al. 1971). Subcutaneous injection of aldrin resulted in a persistent vaginal estrous in ovarectomized rats (Chatterjee et al. 1992). Dieldrin slightly decreased binding of 17β-estradiol to the estrogen receptor in extracts of uterine tissue from immature female rats intraperitoneally administered dieldrin (Wade et al. 1997). Dieldrin weakly induced both cellular proliferation and slight increases in the levels of estrogen and progesterone receptors within MCF-7 human breast cancer cells (Soto et al. 1994, 1995). The overall evidence indicates that aldrin and dieldrin may be disruptive of reproductive hormone levels in male animals and weakly estrogenic in females; the developmental significance of these findings is not clear at present.

The pharmacokinetics of aldrin and dieldrin are expected to be similar in children and adults. No studies were located to indicate any age-dependent differences in absorption rates. As discussed in detail in Section 3.4, Toxicokinetics, aldrin is rapidly converted to dieldrin. Dieldrin (either absorbed or converted from aldrin) is found mainly in the liver during the first 3 hours following absorption, but is quickly distributed to fat and eliminated primarily in the feces (via the bile) with a calculated half time of elimination of 369 days. The slow elimination may play a role in the delayed onset of neurotoxicity symptoms seen in some cases of repeated exposure to relatively low doses of aldrin or dieldrin. Although there are no data to indicate age-related differences in the pharmacokinetics of aldrin or dieldrin, any age-related increases in average body fat could conceivably result in increased susceptibility. Aldrin is readily converted to dieldrin, primarily in the liver, through epoxidation catalyzed by monooxygenases (Wong and Terriere 1965). Available information indicates that cytochrome P-450 is involved (Wolff et al. 1979); however, specific enzymes have not been identified. In the rat, it has been shown that dieldrin is largely hydroxylated to 9-hydroxydieldrin by liver microsomal monooxygenases, which is then conjugated with glucuronide, to some extent, before excretion (Matthews and Matsumura 1969). Enzyme systems responsible for these metabolic pathways may operate in the very young at levels below those in adults (Calabrese 1978). This could result in increased toxic effects due to decreased rates of excretion in the young, although no supportive data are presently available.

There is some indication that aldrin and dieldrin may impair cellular immunity (Krzystyniak et al. 1985; Loose 1982; Loose et al. 1981). Aldrin- or dieldrin-induced impairment of the immature immune system

of infants and children (Calabrese 1978) might result in a lower level of resistance to infections than adults.

There are no biomarkers of exposure or effect for aldrin or dieldrin that are unique to children or that have been validated in children or adults exposed as children. No studies were located regarding interactions of aldrin or dieldrin with other chemicals in children. Limited data concerning interactions with other chemicals in adults (see Section 3.9, Interactions With Other Chemicals) did not suggest that such interactions would be different in children. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to aldrin or dieldrin, reducing body burden, or interfering with the mechanism of action for toxic effects.

There is no information regarding possible transgenerational effects of aldrin or dieldrin exposure in humans, and limited animal data are inconclusive. Reduced meiotic pairing in dividing spermatocytes of mice orally administered single doses of aldrin indicates that aldrin can cross the blood/testis barrier (Rani and Reddy 1986). However, the mostly negative results of dominant lethal assays (Dean et al. 1975; Epstein et al. 1972) indicate little potential for significant reactions with DNA.

3.8 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 aldrin/dieldrin are discussed in Section 3.8.1.

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 aldrin are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Aldrin

Exposure to aldrin and dieldrin is measured almost exclusively by determining the level of dieldrin in the blood. Because aldrin is rapidly converted to dieldrin in the body, the detection of aldrin in body tissues is rare. Blood levels of dieldrin are specific for aldrin and dieldrin. Dieldrin levels measured in blood samples of members of the general population in the United States between 1976 and 1980 in the National Health and Nutrition Examination Survey (NHANES II) were found to be approximately 1.4 ppb (Murphy and Harvey 1985; Stehr-Green 1989). It is likely that current baseline blood levels in the general population would be lower.

Detection of dieldrin in the blood may indicate either recent or past exposure to aldrin or dieldrin. Dieldrin would be detected in the blood either immediately after inhalation, oral, or dermal absorption or as stores of dieldrin are slowly released from adipose tissue. In humans, dieldrin has a relatively long half-life in the body (Hunter and Robinson 1967; Hunter et al. 1969; Jager 1970). Hunter et al. (1969) calculated a mean half-life of 369 days, and Jager (1970) estimated a mean half life of 266 days. Thus, exposures of sufficient magnitude occurring several years earlier may still be detected in the blood. A GABA radioreceptor assay has been developed that could serve as a sensitive biomarker for exposure to dieldrin (Saleh et al. 1993). GABA (gamma aminobutyric acid) is the major inhibitory neurotransmitter in the central nervous system (see Section 3.5.2). Although potentially useful for reproducibly detecting nanogram levels of dieldrin in minute blood samples (0.1 mL), this method is not specific for aldrin and dieldrin because it would also detect other nervous system toxicants with high specific binding affinity to the chloride channel of $GABA_A$ receptor-ionophore sites (e.g., endosulfan and other cyclodiene insecticides, hexachlorocyclohexanes, pyrethroids, bicyclophosphates, and bicycloorthocarboxylate insecticides).

Because dieldrin rapidly redistributes to adipose tissue, the highest levels of dieldrin are found in fat (except immediately after exposure). Thus, fat levels of dieldrin are also a good source for identifying exposure to aldrin or dieldrin. However, obtaining fat samples requires at least minor surgery; therefore, this method is not commonly used. The 1982 Human Adipose Tissue Survey found dieldrin present in adipose tissue at a mean concentration of 458 ppb. It is likely that current levels would be lower.

Because of its high fat content, breast-milk levels of dieldrin may give some information about prior exposures and accumulation of dieldrin in fatty tissues. Breast-milk levels of dieldrin may be lowered by frequent nursing (Ackerman 1980).

Following relatively long-term exposure to constant levels of aldrin or dieldrin, a steady state of body levels of dieldrin is achieved (Hunter and Robinson 1967; Hunter et al. 1969). Thus, when repeated and regular exposure is known to have occurred, the exposure level may be calculated from blood or fat levels using the equations described by Hunter et al. (1969) (exposure level equals the blood level divided by 0.086 or the fat level divided by 0.0185).

The metabolite of dieldrin, 9-hydroxydieldrin, has been detected in human feces (Richardson and Robinson 1971). However, this metabolite has not been routinely used to identify or quantify exposure to aldrin or dieldrin.

Prior to the use of blood levels to monitor exposure to aldrin and dieldrin, EEGs were used to monitor workers for possible overexposure to these substances (Hoogendam et al. 1962, 1965; Jager 1970). However, this technique is most reliable when a baseline EEG recording from each subject has been obtained prior to exposure. Also, any centrally acting neuroexcitatory substance could produce EEG changes similar to those produced by aldrin or dieldrin, limiting the specificity of this technique.

3.8.2 Biomarkers Used to Characterize Effects Caused by Aldrin

Although none of the following effects are specific for aldrin or dieldrin, measurement of a number of parameters may provide useful information when exposure to aldrin or dieldrin is suspected. In animals, microsomal enzyme induction is one of the earliest and most sensitive effects caused by organochlorine pesticides such as aldrin and dieldrin (Wright et al. 1972). Indicators that have been used to try to assess microsomal enzyme induction in humans following exposure to aldrin or dieldrin include urinary levels of D-glucaric acid and the ratio of urinary 6-β-hydroxycortisol to 17-hydroxy-corticosteroids (Jager 1970; Morgan and Roan 1974). Other substances such as barbiturates, phenytoin, chlorbutanol, aminopyrine, phenylbutazone, progesterone, and contraceptive steroids as well as other organochlorine pesticides also cause microsomal enzyme induction and cause changes in these parameters (Morgan and Roan 1974).

Central nervous system excitation culminating in convulsions is, in some cases, the only symptom of aldrin or dieldrin intoxication. EEG changes in occupationally exposed workers have been monitored in

the past in an attempt to detect central nervous system changes prior to the onset of convulsions (Jager 1970). Characteristic changes include bilateral synchronous spikes, spike and wave complexes, and slow theta waves (Avar and Czegledi-Janko 1970; Garrettson and Curley 1969; Hoogendam et al. 1962, 1965; Jager 1970; Kazantzis et al. 1964; Spiotta 1951); however, these changes are not specific for aldrin or dieldrin overexposure and may be produced by several neuroexcitatory substances. A good correlation between blood levels of dieldrin and central nervous system toxicity has been established (Brown et al. 1964; Jager 1970). Thus, blood levels in excess of 0.2 mg/L are frequently associated with adverse central nervous system effects.

Studies of immune activity have not routinely been done in humans to assess immunosuppression caused by aldrin and dieldrin, but studies indicate that measurements of cytotoxic T-lymphocyte activity or of macrophage-antigen processing may be good indicators of the adverse effects of aldrin and dieldrin on the immune system (Loose 1982; Loose et al. 1981). However, such tests would not be specific for aldrin- or dieldrin-mediated immunosuppression.

Another potential adverse effect of aldrin and dieldrin on the immune system that has been reported only twice is the induction of immunohemolytic anemia. A Coomb's test can be used to measure the ability of the subject's serum to cause a positive immune reaction with dieldrin-coated red blood cells (Hamilton et al. 1978).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Limited information is available regarding the influence of other chemicals on the toxicity of aldrin and dieldrin. Administration of the pesticides Aramite, DDT, and methoxychlor with aldrin to rats did not cause an increase over the incidence of cancer observed in the presence of aldrin alone (Deichmann et al. 1967). However, no increase in cancer incidence was observed with any of these substances administered singly. Thus, it is unclear whether the conditions of this assay were adequate to detect an additive or synergistic effect if it existed.

Induction of microsomal enzymes by ochratoxin, a mycotoxin, was observed to enhance conversion of aldrin to dieldrin (Farb et al. 1973). Also, induction of microsomal enzymes by the pesticides hexachlorobenzene and DDT caused a decrease in storage in adipose tissue and/or an increased rate of excretion of the metabolites of aldrin and dieldrin in the feces and urine (Clark et al. 1981; Street and Chadwick 1967). However, these studies did not present information regarding the effects of these

interactions on the toxicity of aldrin or dieldrin. Thus, it is unknown whether the changes in the pharmacokinetics of aldrin and dieldrin affected their toxicity.

The ability of chlorinated hydrocarbons to disrupt estrogen homeostatis, by up-regulating selected gene transcription, has been hypothesized to be responsible for their oncogenic effects. Neither aldrin nor dieldrin showed evidence of estrogenicity as evidenced by lack of induction of transcriptional activation of an estrogen-responsive reported gene in transfected HeLa cells (Tully et al. 2000). There is evidence of a synergistic estrogenic effect of dieldrin and toxaphene on the bone mass density in rats. While dieldrin alone did not show any evidence of estrogenicity when administered to rats by intragastric intubation at a dose of 7.5 µmol/kg/day, 5 days/week, for 9 months, when administered with toxaphene (30 µmol toxaphene/kg/day and 7.5 µmol/kg/day), bone mass density was significantly increased (Syversen et al. 2000). In contrast, the results of several estrogen-responsive assays in the mouse uterus, MCF-7 human breast cancer cells, and yeast-based reporter gene assays, indicate that the activities of both dieldrin and toxaphene, as well as a binary mixture of the two were minimally estrogenic (Ramamoorthy et al. 1997a).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to aldrin than will most persons exposed to the same level of aldrin in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of aldrin, or compromised function of organs affected by aldrin/dieldrin. Populations who are at greater risk due to their unusually high exposure to aldrin are discussed in Section 6.7, Populations With Potentially High Exposures.

A susceptible population will exhibit a different or enhanced response to aldrin or dieldrin than will most persons exposed to the same level of aldrin or dieldrin in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. 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 6.7, "Populations With Potentially High Exposure."

Review of the literature regarding toxic effects of aldrin and dieldrin did not reveal any populations that are known to be unusually sensitive to aldrin or dieldrin. However, some populations that may potentially demonstrate unusual sensitivity include the very young with immature hepatic detoxification systems, persons with impaired liver function, and persons with impaired immune function.

Aldrin and dieldrin are metabolized in the liver primarily by microsomal mixed-function oxidases. To some extent, the oxidized metabolites 9-hydroxydieldrin and 6,7-*trans*-dihydroxydihydroaldrin are conjugated with glucuronide prior to excretion (Matthews and Matsumura 1969). In the very young, the microsomal enzyme system and the enzyme systems responsible for glucuronide conjugation operate at levels below those in adults (Calabrese 1978). Thus, the very young may experience increased toxic effects due to the decreased rates of excretion. Similarly, persons with impaired liver function may also experience increased toxicity because of their limited ability to fully metabolize aldrin or dieldrin. The suggestive evidence of bioconcentration of dieldrin in the fetus (Polishuk et al. 1977b) and the possibility of consumption of contaminated breast milk by infants indicate that these groups have an increased risk, because they may have higher body burdens of these pesticides than adults.

Persons suffering from compromised immune function may demonstrate an increased susceptibility to infections because of the ability of aldrin and dieldrin to impair cellular immunity (Krzystyniak et al. 1985; Loose 1982; Loose et al. 1981). Infants and children may also be susceptible because the human immune system does not reach maturity until 10–12 years of age (Calabrese 1978).

Although aldrin and dieldrin cause central nervous system excitation leading, in some cases, to convulsions, no evidence of an enhanced susceptibility to the excitatory effects of aldrin or dieldrin in persons with preexisting anomalous EEGs was observed (Jager 1970).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to aldrin/dieldrin. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to aldrin/dieldrin. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts were located that provide specific information about treatment following exposures to aldrin/dieldrin.

3.11.1 Reducing Peak Absorption Following Exposure

General recommendations reported for reducing absorption following acute high-dose exposure to aldrin and dieldrin include removing the individual from the source of exposure and decontaminating exposed skin using alcohol or soap and water (HSDB 2001a, 2001b). Dermal absorption is fairly efficient, so decontamination attempts should be accomplished quickly. An initial soap and water wash, followed by an alcohol wash, followed by a second soap and water wash have been suggested for decontaminating skin and hair after aldrin or dieldrin exposure (Hall and Rumack 1992), but it is unclear whether this represents any true improvement over thorough washing with soap and water. A number of strategies have been suggested to minimize absorption from the gastrointestinal tract. Ipecac-induced emesis has been suggested for gastric emptying, although there is a risk of pulmonary aspiration of gastric contents and resultant pneumonitis from hydrocarbon solvents due to potential early onset of unconsciousness or convulsions (HSDB 2001a, 2001b). When emesis is contraindicated, gastric lavage has been suggested as an alternative method for emptying the stomach if ingestion was recent (within 60–90 minutes) (Klaassen 1990). A cuffed endotracheal tube is recommended if hydrocarbon solvents were also ingested. Since activated charcoal can adsorb aldrin and dieldrin, it has also been commonly used as a method for reducing intestinal uptake following ingestion (HSDB 2001a, 2001b). Another method for reducing absorption is the use of a cathartic; activated charcoal is frequently given mixed as a slurry with one of the saline cathartics or sorbitol (Hall and Rumack 1992; HSDB 2001a, 2001b). The mechanism by which aldrin and dieldrin are absorbed from the gastrointestinal tract is unknown; however, their highly lipophilic nature suggests dissolution in the cell membrane.

3.11.2 Reducing Body Burden

There are no proven or accepted strategies for reducing the body burden of dieldrin. A majority of dieldrin's final metabolites are conjugated with glucuronic acid in the liver; most excretion is in the bile, with smaller amounts in the urine (Richardson and Robinson 1971). Fecal metabolites have been measured but not quantitatively compared with metabolites secreted through the bile duct; thus, it is unclear whether enterohepatic recirculation occurs. However, some biliary metabolites, such as 9-hydroxydieldrin glucuronide, seem to be deconjugated by gut microfloral glucuronidases since they are excreted in the feces in aglycone form (Chipman and Walker 1979; Hutson 1976). Deconjugation frequently favors enterohepatic recirculation (Sipes and Gandolfi 1991). If significant enterohepatic recirculation could be demonstrated, methods to interfere with the reabsorption from the gut into the systemic circulation might be effective in accelerating the excretion of aldrin and dieldrin metabolites. There are several possible strategies for reducing intestinal resorption of bile excretions; the simplest is repeated doses of activated charcoal (without cathartics) (Levy 1982). Another strategy, which has been effective in experiments with another lipophilic xenobiotic, chlordecone, is the oral administration of the anion exchange resin, cholestryamine (Boylan et al. 1978). However, it effectiveness with aldrin or dieldrin poisoning is unknown.

The pharmacokinetics of aldrin and dieldrin are not completely understood. Once absorbed by the gastrointestinal tract, these pesticides are transported to the liver via the portal vein (Heath and Vandekar 1964). They are found mainly in the liver for the first 3 hours but have also been found in the blood, lymph, kidneys, fetus, and adipose tissue (Heath and Vandekar 1964; Iatropoulos et al. 1975). The interval immediately after absorption may be a window of opportunity for removing the xenobiotic from the circulation before it partitions into adipose tissue. Potential strategies include hemodialysis and hemoperfusion (Klaassen 1990). However, the large molecular weights and lipophilic nature of these compounds argues against effective removal by hemodialysis. Another potential strategy for removal would be to attempt to increase dieldrin excretion by enhancing its metabolism. Dieldrin's metabolism to 9-hydroxydieldrin and excretion are substantially greater in male than in female rats (Matthews et al. 1971), indicating that a specific form of cytochrome P-450 may be more prevalent in male rats. If the specific form(s) of cytochrome P-450 responsible for the more rapid metabolism and excretion could be identified, specific inducers could be used to speed dieldrin's excretion in humans (Sipes and Gandolfi 1991). Long-term storage is in adipose tissue, primarily in the form of dieldrin (Hutson 1976), but initially some residues are also found in the liver and brain. It is unclear whether detrimental effects would be expected from this storage, although there is equilibrium between dieldrin in fat and blood.

Release of dieldrin from fat has not resulted in a significant health hazard in people with low body burdens of dieldrin (Hunter and Robinson 1968).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism for aldrin and dieldrin toxicity is not equally well understood for all target organs. The central nervous system is the most sensitive target for acute toxicity; aldrin and dieldrin are stimulants that can cause excitation, convulsions, and seizures (Wagner and Greene 1978; Woolley et al. 1985). There are multiple theories about the mechanism of action; it is unclear whether dieldrin facilitates excitatory neurotransmitter release or interferes with inhibitory neurotransmitter action.

One hypothesis is that the majority of dieldrin's neurotoxicity is due to its interactions with a receptor for the inhibitory neurotransmitter GABA (see Section 3.5.2). Dieldrin is thought to be a competitive inhibitor of binding to the $GABA_A$ receptor t-butylbicyclophosphorothionate (TBPS) binding site (Lawrence and Casida 1984), and *in vitro* experiments have shown that it blocks the chloride channel in $GABA_A$- receptor complex (Abalis et al. 1986; Bloomquist and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Lawrence and Casida 1984; Obata et al. 1988). Administration of benzodiazepines, which act at the GABA receptor to potentiate GABA binding (Bloom 1990), has been suggested as a method for treating aldrin- or dieldrin-induced seizures (HSDB 2001a, 2001b). This standard method of reducing central nervous system excitation might be acting at the same molecular site as dieldrin and, thus, specifically interfering with its mechanism of action. If $GABA_A$- receptor interactions are the major mechanism of central nervous system toxicity, potential research approaches for interfering with the mechanism of action would include the use of agonists such as muscimol or GABA to compete for binding at the receptor, inhibitors of GABA re-uptake such as guvacine or nipecotic acid, and blocking GABA catabolism with aminooxyacetic acid (Bloom 1990). Although benzodiazepines are safer, barbiturates also act at the GABA receptor to potentiate GABA binding and might reduce the central nervous system toxicity of dieldrin (Bloom 1990). Phenytoin has been used for seizures refractory to treatment with diazepam or barbiturate (Hall and Rumack 1992).

Adrenergic β-blockers were used effectively to control blood pressure in a dieldrin-poisoned individual (Black 1974), suggesting that such treatment may be effective in other dieldrin-poisonings where elevated blood pressure occurs.

A potential investigative strategy to reduce aldrin toxicity might be to channel aldrin metabolism to the liver where it is more likely to immediately continue to be metabolized to less toxic metabolites. While most conversion of aldrin to dieldrin occurs in the liver, some aldrin is converted to dieldrin outside of the liver. Since further metabolism and conjugation of dieldrin for excretion take place mainly in the liver, any dieldrin created outside the liver has a greater chance of causing toxic effects. Aldrin is converted to dieldrin outside the liver by the more ubiquitous prostaglandin endoperoxidase synthetase. A possible method for reducing the extrahepatic transformation of aldrin to dieldrin would be to inhibit the activity of prostaglandin endoperoxidase synthetase with the cyclooxygenase inhibitors aspirin and indomethacin. Also, ascorbic acid supplementation during dieldrin treatment has been observed to partially reduce the hepatic and renal toxicity of dieldrin treatment in experimental animals (Bandyopadhyay et al. 1982b). However, the reproducibility, effectiveness in humans, and potential mechanism for the reduction in toxicity are unknown.

Mitigation strategies that may be developed in the future for other lipophilic pesticides should be considered for their applicability to aldrin and dieldrin.

3.12 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 aldrin/dieldrin 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 aldrin/dieldrin.

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 filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

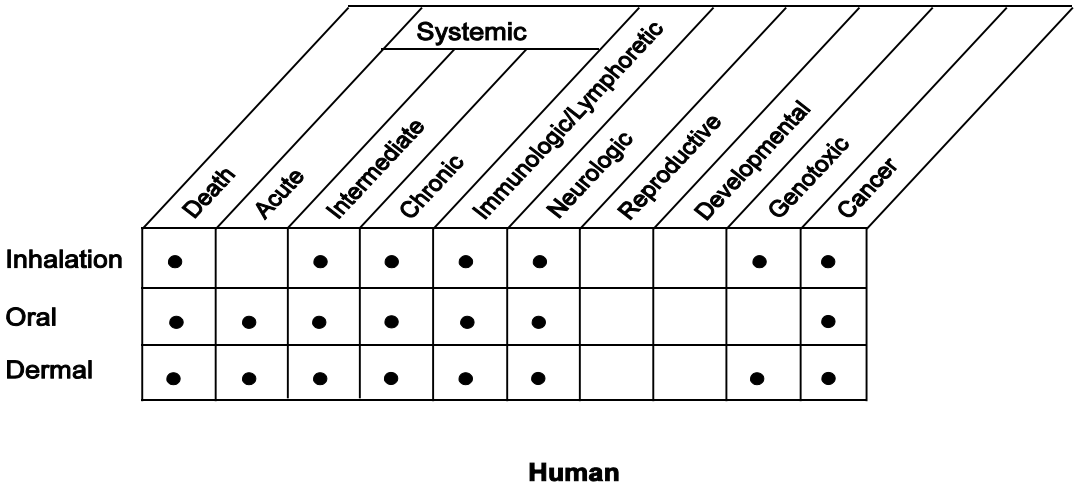
3.12.1 Existing Information on Health Effects of Aldrin

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to aldrin/dieldrin are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of aldrin. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure 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* (Agency for Toxic Substances and Disease Registry 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.

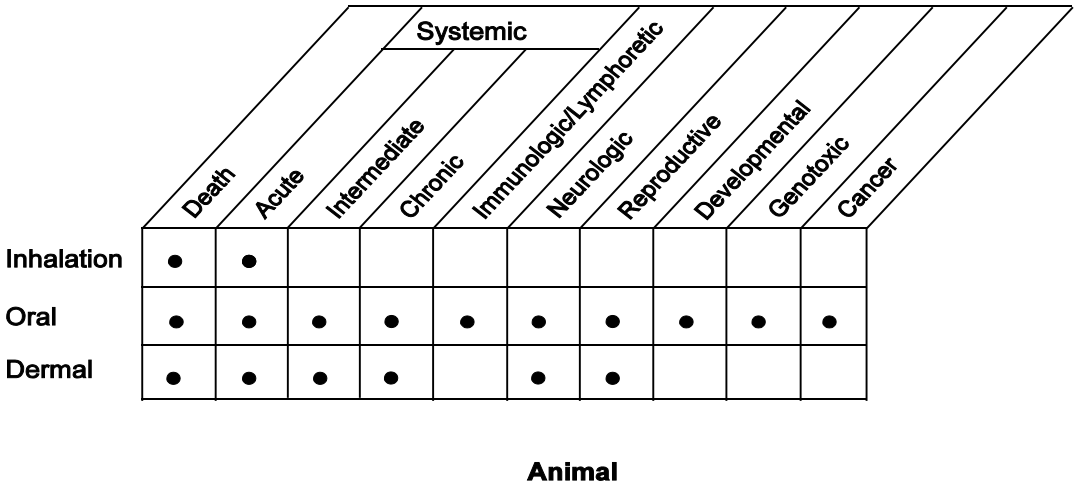
3.12.2 Identification of Data Needs

Acute-Duration Exposure. Populations in areas that contain hazardous waste sites may be exposed to aldrin or dieldrin for brief periods. Exposure would most likely occur by the inhalation or oral routes, but dermal exposure is also possible. There are acute-duration oral exposure data in humans from cases of accidental or intentional poisonings that indicate that the central nervous system is a major target organ of aldrin and dieldrin toxicity by the oral route. Convulsions have been observed following ingestion of very high concentrations of aldrin and dieldrin (Black 1974; Garrettson and Curley 1969; Spiotta 1951). Also, acute oral exposure in humans has been reported to cause renal toxicity (Spiotta 1951). Renal toxicity has not been reported in studies in animals after acute-duration ingestion of high concentrations of aldrin or dieldrin; however, the number of studies examining systemic effects associated with acute-duration exposures is quite limited. Studies in laboratory animals examining the effects of ingestion of aldrin or dieldrin have supported the conclusion that the nervous system is a major target organ of aldrin and dieldrin toxicity (Burt 1975; Carlson and Rosellini 1987; Mehrotra et al. 1989; Treon et al. 1953a; Wagner and Greene 1978; Woolley et al. 1985). In such studies, convulsions as well as impaired responding in operant behavioral paradigms were reported. In addition, immune suppression (Krzystyniak et al. 1985; Loose et al. 1981), developmental toxicity (Al-Hachim 1971; Ottolenghi et al. 1974), and adaptive changes in the liver (Wright et al. 1972) have been observed in acutely exposed animals. Results of these studies indicate that the immune system may be the most sensitive target organ for the effects of brief oral exposures to aldrin or dieldrin. An acute-duration oral MRL was not derived

Figure 3-5. Existing Information on Health Effects of Aldrin/Dieldrin



Human



Animal

● Existing Studies

for dieldrin because the database indicates that the most sensitive target of toxicity is the immune system in rats administered acute doses of dieldrin (Loose et al. 1981) and there are no data to suggest that the immune system may be a target of toxicity in humans following ingestion of dieldrin. An acute-duration oral MRL was derived for aldrin based on a neurological effect (altered electroconvulsive shock threshold) and decreased body weight in offspring of treated mice (Al-Hachim 1971).

No information is available regarding acute-duration inhalation exposure to aldrin or dieldrin in humans, and extremely limited information is available from studies in animals (Treon et al. 1957b). Although the volatility of aldrin and dieldrin is quite low and levels in the atmosphere are expected to be quite low, absorption of these compounds by the lungs occurs to a significant extent (Mehendale and El-Bassiouni 1975). Toxicokinetic data do not indicate that dissimilar target organs would be affected as a result of inhalation exposure to aldrin or dieldrin. Thus, additional studies examining the effects of acute inhalation exposure to saturating concentrations of aldrin or dieldrin would be helpful in determining whether toxic effects would occur as a result of brief inhalation exposure.

Information regarding the acute effects of dermal exposure of aldrin or dieldrin is limited to lethality studies in animals (Gaines 1960; Treon et al. 1953a). Dermal exposure to aldrin and dieldrin is possible in contaminated soil, and toxicokinetic studies indicate that dermally applied aldrin and dieldrin are absorbed (Feldmann and Maibach 1974; Graham et al. 1987; Witherup et al. 1961). Toxicokinetic data do not suggest that dissimilar target organs would be affected as a result of dermal exposure. Thus, studies examining the effects of acute dermal exposure to aldrin or dieldrin would be useful.

Intermediate-Duration Exposure. Few reports were located regarding effects in humans after intermediate-duration exposure to aldrin or dieldrin by any route. In one study, exposure was by the oral route (Gupta 1975). In two other studies, exposure most likely occurred as the result of combined inhalation and dermal (and possibly oral) exposures (Fletcher et al. 1959; Patel and Rao 1958). These studies showed that the nervous system is a major target organ in humans after intermediate-duration exposures. Studies in laboratory animals confirm this observation (Burt 1975; Mehrotra et al. 1988; Smith et al. 1976; Treon et al. 1951b; Wagner and Greene 1978). Other targets identified in intermediate-duration oral studies in animals include the immune system (Loose 1982), the developing neonate (Al-Hachim 1971; Deichmann et al. 1971; Harr et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975), the reproductive system (Treon et al. 1954a; Virgo and Bellward 1975, 1977), the kidney (Ahmed et al. 1986a; Bandyopadhyay et al. 1982b), and the liver (Ahmed et al. 1986a; Shakoori et al. 1982; Treon et al. 1951a, 1951b). An intermediate-duration oral MRL for aldrin was not derived due to lack of

suitable effect levels. Intermediate-duration studies of aldrin are essentially limited to studies that found frank neurotoxic effects (e.g., tremors, convulsions) at the lowest tested doses; LOAELs for serious end points are inappropriate for deriving MRLs. An intermediate-duration oral MRL was developed for dieldrin based on a NOAEL for impaired learning in monkeys (Smith et al. 1976).

No data were located regarding intermediate-duration inhalation exposures in animals, and human exposure levels were not quantified. Therefore, no intermediate-duration inhalation MRL was derived for either aldrin or dieldrin. Also, only limited information was located regarding lethality, neurological effects, and dermal effects after intermediate-duration dermal exposures (Bundren et al. 1952; Treon et al. 1953a). As noted above, absorption occurs by both the inhalation and dermal routes, and toxicokinetic data indicate that similar target organs would be affected following exposure to either route; thus, additional studies examining the effects of aldrin and dieldrin by the inhalation and dermal routes would be helpful.

Chronic-Duration Exposure and Cancer. A number of epidemiological studies have been conducted on workers exposed chronically to aldrin and dieldrin (de Jong 1991; Ditraglia et al. 1981; Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; van Raalte 1977; van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). In these studies, doses are usually not well quantified, and concomitant inhalation, dermal, and possibly oral exposures have occurred. Follow-up and expansion of previously identified worker cohorts could provide additional useful information on chronic effects. It is difficult to recommend new populations for future epidemiological studies of effects caused by chronic-duration inhalation, oral, or dermal exposure because (1) these agents have not been manufactured in the United States since 1974, and (2) workers who have been involved in the use of the remaining stocks of these agents are likely to have been also exposed to a variety of other pesticides. Data from the existing epidemiological studies indicate that the nervous system is a major target organ for chronic inhalation, dermal, and possibly oral exposures in humans (Hoogendam et al. 1962, 1965; Jager 1970; Sandifer et al. 1981). Chronic oral studies in animals also indicate that the nervous system is a major target organ (Fitzhugh et al. 1964; Harr et al. 1970; Kitselman 1953; NCI 1978a, 1978b; Walker et al. 1969), but additionally demonstrate adverse effects of aldrin and dieldrin on the kidney (Deichmann et al. 1967; Fitzhugh et al. 1964; Harr et al. 1970; Treon et al. 1955b) and liver (Fitzhugh et al. 1964; Kitselman 1953; NCI 1978a; Thorpe and Walker 1973; Treon et al. 1955b; Walker et al. 1969). The liver was the most sensitive target of toxicity in chronic-duration studies and hepatic effect levels in rats (Fitzhugh et al. 1964; Walker et al. 1969) were used as the basis of chronic oral MRLs for both aldrin and dieldrin. No chronic animal studies were located for the inhalation

route; only one animal study was located examining the effects of chronic dermal exposure (Witherup et al. 1961). Studies examining the effects caused by low-level chronic exposures by both the inhalation and oral routes would be valuable for determining whether such exposures could cause toxicity in populations exposed to aldrin and dieldrin near hazardous waste sites for extended periods.

Epidemiological studies examining cancer mortality in two series of workers exposed to aldrin and dieldrin provide no conclusive evidence of carcinogenicity in humans (Amoateng-Adjepong et al. 1995; Brown 1992; de Jong 1991; de Jong et al. 1997; Ditraglia et al. 1981; Jager 1970; Ribbens 1985; van Raalte 1977). Possible increases in liver, biliary, and rectal cancer were suggested in some of the later studies, but additional follow-up of these populations is needed to establish the effects. Several studies in mice have shown that oral exposure to aldrin or dieldrin caused an increase in the incidence of malignant liver tumors (Davis and Fitzhugh 1962; Meierhenry et al. 1983; NCI 1978a; Tennekes et al. 1981; Thorpe and Walker 1973; Walker et al. 1972). However, studies in rats (Cabral et al. 1979; Deichmann et al. 1967, 1970; Fitzhugh et al. 1964; NCI 1978b; Walker et al. 1969) have been either equivocal or flawed. Although aldrin and dieldrin are generally regarded as mouse-specific carcinogens, additional studies by the oral route in a species other than the mouse would help to clarify the carcinogenic potential. If species differences in the carcinogenic potential of these chemicals are verified, additional studies related to the mechanism of species specificity would be informative for predicting human susceptibility. Also, studies by routes other than oral would clarify whether inhalation or dermal exposures could also cause cancer. Toxicokinetic data do not indicate that any different response would be expected following exposures by these routes. Accumulating evidence indicates that aldrin and dieldrin are nongenotoxic tumor promoters acting through species-specific susceptibility of the mouse to induction of oxidative stress and inhibition of gap junctional communication (Jone et al. 1985; Klaunig and Ruch 1987; Klaunig et al. 1990, 1995, 1998; Kurata et al. 1982; Ruch and Klaunig 1986; Trosko et al. 1987; van Ravenzwaay and Kunz 1988; Wade et al. 1986; Zhong-Xiang et al. 1986). Additional mechanistic studies would be useful for better understanding the apparent species-specific carcinogenicity of aldrin and dieldrin in animals and relating these findings to humans.

Genotoxicity. There were only two studies on *in vivo* exposure of humans to aldrin or dieldrin. Both were limited due to concomitant exposure to other pesticides and inconclusive route and dose of exposure (Dean et al. 1975; Dulout et al. 1985). Additional genotoxicity assays using tissues from humans exposed *in vivo* would be useful if these were accompanied by adequate quantitative exposure measurements.

Numerous studies investigating the *in vitro* genotoxic effects of aldrin or dieldrin were available in the current literature (Ahmed et al. 1977a, 1977b; Crebelli et al. 1986; Dean et al. 1975; De Flora et al. 1984, 1989; Ennever and Rosenkranz 1986; Galloway et al. 1987; Glatt et al. 1983; Haworth et al. 1983; Klaunig et al. 1984; Majumdar et al. 1976, 1977; Marshall et al. 1976; Probst et al. 1981; Sandhu et al. 1989). They provide no conclusive evidence for genotoxic effects, particularly for direct action on the DNA molecule. The positive studies are primarily from the same research group, and while differences in results could be due to different concentrations used, different strains of test species, or other laboratory protocol differences, it would be useful to have independent confirmation or refutation of these studies using adequate techniques (especially in mammalian systems). Results of such studies would provide useful information on potential genotoxic effects in humans.

Reproductive Toxicity. One study in humans attempted to correlate blood levels of dieldrin with premature labor or spontaneous abortions in pregnant women (Saxena et al. 1980); however, this study failed to establish causality. No other human data regarding reproductive effects of aldrin or dieldrin were located. Studies in laboratory animals exposed orally to aldrin or dieldrin present conflicting data on the ability of these agents to cause decreased fertility (Dean et al. 1975; Epstein et al. 1972; Good and Ware 1969; Harr et al. 1970; Treon et al. 1954a; Virgo and Bellward 1975). Some of these studies are limited. Additional studies examining the effects of oral exposure to aldrin or dieldrin would be helpful for clarifying this issue. No studies in animals were found regarding reproductive effects of exposure by the inhalation or dermal routes. Thus, studies examining effects on reproduction by inhalation or dermal exposure would also be useful. Animal studies performed using intraperitoneal injection of aldrin demonstrate adverse effects on male reproductive capacity (Chatterjee et al. 1988a, 1988b, 1988c). Additional studies examining fertility in animals exposed by the oral, dermal, or inhalation routes would be helpful in determining whether the effects are specific to intraperitoneal injection.

Developmental Toxicity. No human studies are available on developmental effects for any exposure route. Similarly, no studies are available for animals exposed via the inhalation route, and negligible information is available for animals exposed via the dermal route (Glastonbury et al. 1987). Several studies report a decrease in postnatal survival for offspring of dogs, rats, and mice exposed to aldrin or dieldrin by the oral route (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975), although many of these studies are flawed. Additional studies assessing postnatal survival after maternal exposure by all three routes would be helpful. Also, additional studies attempting to clarify the mechanism of the postnatal mortality would be informative. Adverse developmental effects have been observed following maternal oral exposure to aldrin (Al-Hachim 1971),

and an acute-duration oral MRL for aldrin was derived based on the decrease in pup body weight and increased electroconvulsive shock threshold of pups observed in this study. Teratogenic effects have been observed in only a limited number of the studies performed to assess developmental toxicity (Ottolenghi et al. 1974); additional well-conducted studies examining this parameter may help clarify this issue.

Immunotoxicity. Isolated cases of dieldrin-induced immunohemolytic anemia have been reported in humans exposed by the inhalation, oral, and dermal routes (Hamilton et al. 1978; Muirhead et al. 1959). However, in epidemiological studies of workers exposed to these substances, similar effects have not been reported (de Jong 1991; Jager 1970). Thus, this effect may be idiosyncratic in nature. As large populations exposed to aldrin or dieldrin may be difficult to find, this response may be better studied in one of the strains of mice known to have a propensity for developing autoimmune diseases. Studies in animals via the oral (Krzystyniak et al. 1985; Loose 1982; Loose et al. 1981) and intraperitoneal routes (Bernier et al. 1987, 1988; Fournier et al. 1986, 1988; Hugo et al. 1988a, 1988b; Jolicoeur et al. 1988; Krzystyniak et al. 1986, 1987, 1989) indicate that aldrin and dieldrin may be immunosuppressive agents, at least during acute- and short intermediate-duration exposures. These studies have also examined the mechanism for the immune suppression. However, additional studies examining potential longer-term effects on the immune system by all three routes as well as short-term effects by the inhalation and dermal routes would be important for estimating human susceptibility for populations exposed for varying amounts of time at hazardous waste sites.

Neurotoxicity. Numerous human studies across all three routes indicate that the central nervous system is a major target of aldrin and dieldrin toxicity (Black 1974; Garrettson and Curley 1969; Hoogendam et al. 1965; Jager 1970; Kazantzis et al. 1964; Patel and Rao 1958; Spiotta 1951). Studies in animals tend to support these findings, although studies in animals have been primarily by the oral route (Burt 1975; Mehrotra et al. 1989; NCI 1978a, 1978b; Smith et al. 1976; Treon et al. 1951b, 1953a; Wagner and Greene 1978; Walker et al. 1969; Woolley et al. 1985). An intermediate-duration oral MRL was developed for dieldrin based on impaired learning in monkeys (Smith et al. 1976). Both *in vitro* and *in vivo* studies in animals have provided a well-defined mechanism of action for neuroexcitation (Abalis et al. 1986; Bloomquist and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Lawrence and Casida 1984; Matsumura and Ghiasuddin 1983; Obata et al. 1988; Shankland 1982). Reports of human intoxication have provided information regarding blood levels that may be associated with the production of severe neurotoxic symptoms (convulsions, muscle jerks) (Brown et al. 1964; Jager 1970). However, information regarding the mechanism of action suggests that more subtle adverse

effects of neurologic origin may be produced by aldrin and dieldrin. Thus, studies focusing on less severe forms of neurotoxicity (i.e., affective changes) may be informative. Studies in animals using behavioral paradigms designed to detect such changes or studies in persons exposed to aldrin or dieldrin would be useful for further defining these effects and the exposure levels associated with them.

Epidemiological and Human Dosimetry Studies. Human studies on aldrin and dieldrin consist of either case reports of accidental or intentional poisonings (Black 1974; Garrettson and Curley 1969; Hoogendam et al. 1965; Kazantzis et al. 1964; Patel and Rao 1958; Spiotta 1951) or epidemiological studies of workers employed in the manufacture or application of these agents (de Jong 1991; Ditraglia et al. 1981; Hoogendam et al. 1965; Jager 1970; Morgan and Lin 1978; Morgan et al. 1980; Sandifer et al. 1981; van Raalte 1977; van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). Exposures in the case reports are virtually all oral, whereas exposures in the epidemiological studies are mainly inhalation and dermal, with very slight potential for accidental oral intake. Additional follow-up of cohorts from previously conducted epidemiological studies would be the best approach for obtaining additional human data. Locating new populations for future epidemiological studies is likely to be difficult because aldrin and dieldrin have not been manufactured in the United States since 1974 and the use of these agents has been restricted to termite extermination. Also, because aldrin and dieldrin have not been imported into the United States since 1985, use has been limited to the use of remaining pre-1985 stocks. Thus, at the present time, very few persons are likely to be exposed to aldrin or dieldrin. The only subgroups of the population with possible exposure are termite exterminators and persons who have recently had their homes exterminated. If such groups are located, information regarding immunologic, reproductive, and developmental effects and correlation of these effects with blood levels of dieldrin associated with exposure would be useful.

Biomarkers of Exposure and Effect.

Exposure. Exposure to aldrin and dieldrin is currently measured almost exclusively by determining the level of dieldrin in the blood (Jager 1970). This measure is specific for both aldrin and dieldrin. However, because aldrin is rapidly converted to dieldrin in the body (Wong and Terriere 1965), it is impossible to determine which of the two substances caused the blood levels of dieldrin to rise. Because dieldrin has a long half-life of elimination in humans (Hunter and Robinson 1967; Hunter et al. 1969; Jager 1970), measurement of dieldrin levels in the blood does not give any information about whether an acute-, intermediate-, or chronic-term exposure has occurred, whether such exposures have occurred recently, or whether a substantial period of time has elapsed since exposure occurred. The sensitivity of

this biomarker of exposure appears to be sufficient to measure even background levels in the population; thus, no new biomarkers of exposure appear to be needed at this time.

Effect. The central nervous system excitation resulting from aldrin or dieldrin exposure can be monitored, to a great extent, by monitoring EEG changes (Hoogendam et al. 1962, 1965; Jager 1970). Characteristic changes include bilateral synchronous spikes, spike and wave complexes, and slow theta and delta waves (Avar and Czegledi-Janko 1970; Garrettson and Curley 1969; Hoogendam et al. 1962, 1965; Jager 1970; Kazantzis et al. 1964; Spiotta 1951). However, similar changes may be recorded in cases of central nervous system excitation caused by other agents. Thus, this measure is not specific for aldrin- or dieldrin-induced neurotoxicity. Blood levels of dieldrin have been correlated with adverse neurological effects caused by aldrin and dieldrin (Brown et al. 1964; Jager 1970). Such a measurement may also be used to monitor for adverse neurotoxic effects caused by these agents. Also, as understanding of the fundamental mechanism by which aldrin and dieldrin cause central nervous system excitation develops, tests may be developed to specifically monitor for the underlying neurological changes caused by aldrin and dieldrin.

No tests specific for aldrin- or dieldrin-induced toxic effects on the liver or kidney exist; however, standard liver and kidney function tests should be able to identify the hepatic or renal toxicity that is produced. Microsomal enzyme induction may be measured by determining parameters such as urinary levels of D-glucaric acid and the ratio of urinary 6-β-hydroxycortisol to 17-hydroxycorticosteroids. However, these tests are not specific for aldrin or dieldrin. Immune suppression of the type produced by aldrin or dieldrin may be detected by challenge with a T-lymphocyte-dependent antigen; however, this test also is not specific for aldrin or dieldrin.

Absorption, Distribution, Metabolism, and Excretion. Human and animal data are available that show that aldrin and dieldrin are absorbed after exposure via all three routes (Feldmann and Maibach 1974; Graham et al. 1987; Hayes 1974a; Heath and Vandekar 1964; Hunter and Robinson 1967; Hunter et al. 1969; Mehendale and El-Bassiouni 1975; Stacey and Tatum 1985). Quantitative data on the absorption of aldrin and dieldrin in humans and animals following exposure via all routes are limited. Animal studies indicate that aldrin and dieldrin are absorbed rather quickly and that the amount absorbed is proportional to the dose applied for the oral and dermal routes (Graham et al. 1987; Heath and Vandekar 1964; Iatropoulos et al. 1975). However, data concerning absorption rates are needed for all three routes. Because of the limited number of absorption studies for all three routes in general, it would

be helpful to have additional quantitative data in animals that might serve as a basis for estimates of absorption in humans.

No studies were located regarding distribution following inhalation exposure to aldrin or dieldrin in humans or animals. Data on distribution via the dermal route for humans were not located. However, numerous data exist that describe distribution after oral administration of aldrin or dieldrin (Adeshina and Todd 1990; Ahmad et al. 1988; Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974a; Holt et al. 1986; Hunter and Robinson 1967, 1968; Hunter et al. 1969; Iatropoulos et al. 1975). These studies indicate that dieldrin is distributed in the blood to adipose tissue, brain, and liver tissues, and is then redistributed primarily to fat. Concentrations of dieldrin have been shown to increase in a dose-related manner in blood and adipose tissues of humans and eventually reach a steady state (Hunter and Robinson 1967; Hunter et al. 1969). Kinetic studies in rats and dogs support these findings and provide further information on steady state kinetics following repeated dosing (Baron and Walton 1971; Davison 1973; Ludwig et al. 1964; Walker et al. 1969). Because data are sufficient regarding distribution following oral exposure to aldrin or dieldrin, no more studies via this route are needed. However, inhalation and dermal studies investigating distribution would be valuable because the potential exists for exposure to occur in humans via these routes.

No studies were located regarding metabolism of aldrin or dieldrin in humans and animals via the inhalation route. Also, human data on metabolism via the oral and dermal routes were not located. Metabolism has been characterized in animals following oral exposure (Baldwin et al. 1972; Bedford and Hutson 1976; Chipman and Walker 1979; Hutson 1976; Korte and Arent 1965; Matthews and Matsumura 1969; Matthews et al. 1971; Müller et al. 1975; Wolff et al. 1979; Wong and Terriere 1965). Sex-related and species differences have been observed in metabolism in animals (Baldwin et al. 1972; Hutson 1976; Korte and Arent 1965; Matthews and Matsumura 1969; Matthews et al. 1971). Because differences in metabolism may occur with differences in the route of exposure, it would be useful to have more data on inhalation and dermal metabolic studies as a comparison with the available oral studies.

No human or animal data were located regarding excretion following inhalation or dermal exposure to aldrin or dieldrin. There are, however, a number of studies in animals (Baldwin et al. 1972; Hutson 1976; Klein et al. 1968; Klevay 1970; Ludwig et al. 1964; Matthews et al. 1971; Müller et al. 1975) and a limited number of studies in humans (Hunter et al. 1969; Richardson and Robinson 1971; Schecter et al. 1989b) that describe excretion following oral exposure to aldrin or dieldrin. These studies are sufficient to characterize excretion following oral exposure to aldrin or dieldrin. These studies show quantitatively

that the metabolites are excreted primarily in the feces in both humans and animals. Species and sex-related differences in excretion of metabolites have been observed following oral exposure in animals (Baldwin et al. 1972; Hutson 1976; Klein et al. 1968; Klevay 1970; Ludwig et al. 1964; Matthews et al. 1971; Müller et al. 1975). Also, sex-related and species differences have been observed in the rates of excretion. Studies on excretion following inhalation and dermal exposure to aldrin or dieldrin would be useful to determine if excretion patterns vary with different routes.

Comparative Toxicokinetics. Numerous studies using a variety of animal species indicate that the kinetics of aldrin and dieldrin differ across species (Baldwin et al. 1972; Hutson 1976; Klein et al. 1968; Klevay 1970; Ludwig et al. 1964; Matthews et al. 1971; Müller et al. 1975). The differences are primarily quantitative. Although the kinetic data alone do not allow for the identification of target organs common to humans and animals, the distribution data coupled with toxicity data appear to suggest that target organs are similar. Interspecies differences and sex-related differences in rats and mice have been observed for the metabolism and excretion of aldrin and dieldrin. These interspecies differences coupled with a lack of data across different routes indicate that it may be difficult to compare the kinetics of aldrin or dieldrin in animals with that in humans. Further studies across several species and via all three exposure routes would be useful in determining similarities and differences between humans and animals.

Methods for Reducing Toxic Effects. The mechanism by which aldrin and dieldrin are absorbed from the gastrointestinal tract is unknown but is presumed to involve dissolution in the cell membrane. Current methods for reducing absorption from the gastrointestinal tract involve removing these chemicals from the site of absorption (HSDB 2001a, 2001b; Klaassen 1990). Additional studies examining the method of absorption would provide valuable information for developing methods that interfere with gastrointestinal absorption. Numerous studies have examined the distribution of aldrin and dieldrin after gastrointestinal absorption (Adeshina and Todd 1990; Ahmad et al. 1988; Deichmann et al. 1968; DeVlieger et al. 1968; Hayes 1974a; Holt et al. 1986; Hunter and Robinson 1967, 1968; Hunter et al. 1969; Iatropoulos et al. 1975). Additional studies on distribution are not necessary at this time. No established method exists for reducing the body burden of aldrin and dieldrin. However, available information indicates that reducing enterohepatic recirculation or removal from the blood before these chemicals partition to tissue may be effective (Chipman and Walker 1979; Heath and Vandekar 1964; Iatropolous et al. 1975; Richardson and Robinson 1971; Sipes and Gandolfi 1991). Studies examining the effectiveness of repeated doses of activated charcoal, cholestyramine, hemodialysis, and hemoperfusion in reducing body burden would be useful. The neurotoxicity of aldrin and dieldrin is believed to result, at least in part, from interference with GABA function (Abalis et al. 1986; Bloomquist

and Soderlund 1985; Bloomquist et al. 1986; Cole and Casida 1986; Gant et al. 1987; Lawrence and Casida 1984; Obata et al. 1988), and benzodiazepines and barbiturates have been effective in mitigating some of the neurological symptoms of aldrin and dieldrin overexposures (Black 1974; Garrettson and Curley 1969; Spiotta 1951). However, additional studies examining the effectiveness of potentiating the GABAergic function in mitigating aldrin and dieldrin's neurologic effects would be helpful. A decrease in the hepatic and renal effects of dieldrin has been observed when animals received ascorbic acid supplements during dieldrin treatment (Bandyopadhyay et al. 1982b). Further study clarifying this effect and identifying a potential mechanism for the mitigating effects of ascorbic acid would be valuable.

Children's Susceptibility. The information on health effects of aldrin and dieldrin in humans is derived mainly from cases of accidental or intentional exposure of adults to high amounts of the pesticide, and the main adverse effect is neurotoxicity. Limited reports of adverse effects in aldrin- or dieldrin-exposed children (Garrettson and Curley 1969; Gupta 1975) indicate similar signs and symptoms to those in adults. Limited animal data indicate that young animals may respond to aldrin or dieldrin differently than adult animals (Buck and Van Note 1968; Lu et al. 1965), but there is no conclusive evidence to suggest that young animals are more susceptible than older ones. Further studies that evaluate a number of different end points in young as well as older organisms would provide valuable information.

No information was located concerning whether the developmental process is altered in humans exposed to aldrin or dieldrin either prenatally or postnatally. Studies in animals have provided conflicting evidence regarding developmental malformations and anomalies (Chernoff et al. 1975; Dix et al. 1977; Ottolenghi et al. 1974), and further well-conducted research would be helpful to clarify this issue. Although animal studies suggest that aldrin and dieldrin may be disruptive of reproductive hormone levels in males and weakly estrogenic in females, additional well-designed studies are needed to clarify the developmental significance of these findings.

No data were located concerning whether pharmacokinetics of aldrin or dieldrin in children are different from adults. Although dieldrin has been detected in human placenta, amniotic fluid, fetal blood, and breast milk (Polishuk et al. 1977b; Schecter et al. 1989b), additional quantitative studies in animals would provide valuable information. There are no PBPK models for aldrin or dieldrin in either adults or children. There is no information to evaluate whether absorption, distribution, metabolism, or excretion of aldrin or dieldrin in children might be different than in adults.

There are no biomarkers of exposure or effect that have been validated in children. There are no data on interactions of aldrin or dieldrin with other chemicals in children, and extremely limited data in adults which are inadequate to determine whether the same effects will be observed in children. There are no pediatric-specific methods to reduce peak absorption of aldrin or dieldrin following exposure, or to reduce body burden, or to interfere with mechanisms of action for aldrin or dieldrin.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

On-going studies regarding the health effects of aldrin and/or dieldrin were reported in the Federal Research in Progress File (FEDRIP 2001) database. Table 3-7 presents a summary of ongoing studies that address the health effects of aldrin or dieldrin.

Table 3-7. Ongoing Studies on Aldrin and Dieldrin[a]

Investigator	Affiliation	Research description	Sponsor
Ahmed SA	Virginia Polytechnic Institute, College of Veterinarian Medicine, Blacksburg, VA	The effect of environmental estrogens on the lymphocytes: immunologic cell culture	USDA
Bloomquist JR	Virginia Polytechnic Institute, Blacksburg, VA	Insecticide neurotoxicity and Parkinson's diseases	USDA
Dillon G	University of North Texas, Fort Worth, TX	Neurotoxin interactions with ligand-gated ion channels	NIEHS
Freedman J	Duke University, Durham, NC	Mechanism of stress induced developmental abnormalities	NIEHS
Gross T	University of Florida, Gainesville, FL	Organochlorine pesticides and developmental mortality	NIEHS
Lauder J	University of NC at Chapel Hill, Chapel Hill, NC	Organochlorine pesticides and serotonergic development	NIEHS
Narahashi T	Northwestern University, Chicago, IL	Mode of action of insecticides–electrophysiologic	NINDS
Schwartz S	Fred Hutchinson Cancer Research Center, Seattle, WA	Phytoestrogens, organochlorines and fibroid risk	NIEHS

[a] Derived from FEDRIP 2001

NIEHS = National Institute of Environmental Science; NINDS = National Institute of Neurological Disorders and Stroke; USDA = U.S. Department of Agriculture