2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ALDRIN AND DIELDRIN IN THE UNITED STATES

Aldrin ($C_{12}H_8Cl_6$) and dieldrin ($C_{12}H_8Cl_6O$) are two organochlorine insecticides that were used for agricultural and public health purposes from the early 1950s until 1989, when their manufacture in the United States was discontinued. Aldrin and dieldrin were popular pesticides for corn and cotton crops, and were used as a prophylactic and for treatment of timber against termite infestation. Consistent with their intended use on insects in soil, aldrin and dieldrin are not very water soluble, but readily bind to sediment and are rarely leached into deeper soil layers and groundwater. As they take decades to break down in the environment, past agricultural uses of aldrin and dieldrin have resulted in persisting soil residues and uptake in a wide range of crops. In biological systems of soils, plants, and animals, aldrin converts rapidly to dieldrin by a microsomal oxidation reaction (epoxidation). The half-life of dieldrin in temperate soils is about 5 years, while it disappears more quickly (up to 90% in 1 month) from tropical soils. Organochlorine pesticides, including dieldrin, continue to enter streams in the United States from atmospheric deposition and erosion of soils contaminated from past use. Aldrin and dieldrin may be volatilized from sediment and redistributed by air currents, contaminating areas far from their sources. Nationally, levels of aldrin and dieldrin have declined since their agricultural uses were discontinued. Aldrin bioconcentrates in mollusks and fish, and high levels of dieldrin have been found concentrated in fish, snails, and lake trout. Detectable dieldrin concentrations in fish have shown a strong association with corn production acreage.

Exposure to aldrin or dieldrin at hazardous waste sites is possible via inhalation, oral, or dermal routes. The Henry's law constants of aldrin and dieldrin indicate that volatilization from moist soil surfaces will occur. Both compounds also bind strongly to soil particles and are often associated with dust particles in the atmosphere. Exposure to these pesticides can therefore occur through inhalation and dermal contact with vapor and particulate phase aldrin and dieldrin. Populations residing near hazardous waste disposal sites may be subject to higher levels of aldrin and dieldrin in environmental media (i.e., air, soil) than those experienced by the general population. Aldrin has been identified in at least 207 of the 1,613 hazardous waste sites while dieldrin has been identified in at least 287 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of NPL sites evaluated for aldrin and dieldrin is not known. As more sites are evaluated, the number of sites where aldrin and/or dieldrin has been detected may increase.

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Exposure of the general population to aldrin and dieldrin may occur through ingestion of contaminated food (including fish and shellfish) or water, through inhalation of contaminated air, especially in homes that have been treated with either pesticide, and through dermal contact with contaminated soil or water. The dietary contribution is likely the most significant route of human exposure. Oral exposure may occur through consumption of foods that are contaminated with aldrin or dieldrin. These foods would include those obtained from plants grown on contaminated lands or from animals living in contaminated areas, as well as commercial food products high in animal fat, such as dairy, fish, and meat products. This is the result of previous widespread use, biomagnification, and persistence in the environment. Because of aldrin's rapid conversion to dieldrin, most of the dietary intake is in the form of dieldrin. During the period of 1965–1970, U.S. dietary intake was reported to be #40 ng aldrin/kg/day and #80 ng dieldrin/ kg/day. Since 1970, the use of aldrin and dieldrin on food has been cancelled, and dietary intake has decreased. In 1988, on the basis of total diet analyses, daily intake of dieldrin in adults in the United States was estimated at #5 ng/kg/day; a slightly higher daily intake of #11 ng/kg/day was estimated for infants. High levels of dietary exposures to dieldrin in adults were estimated to be primarily due to frequent consumption of summer and winter squash grown on contaminated lands. Dieldrin was found in Food and Drug Administration (FDA) Total Diet study foods during the period of 1991–1999, with maximum levels in squash. Aldrin currently appears to be below the FDA limit of detection in food. Oral exposure to aldrin or dieldrin could also occur through ingestion of contaminated water. Studies indicate, however, that levels of aldrin and dieldrin in drinking water are extremely low.

Regarding exposure of the general population through inhalation of contaminated air, air samples from several states collected in 1970–1972 revealed mean ambient concentrations of 0.4 ng/m^3 for aldrin and 1.6 ng/m^3 for dieldrin. In 1972, the estimated U.S. average daily intake of aldrin plus dieldrin from the atmosphere was about 0.6 ng/kg body weight. Another source of exposure not related to living near a hazardous waste site is residue from the past use of aldrin or dieldrin for termite extermination. Although use for this application was voluntarily canceled by the manufacturer in 1987, aldrin and dieldrin levels in treated homes have been shown to decline slowly, with detectable levels present as many as 10 years after treatment. Dieldrin has been detected in human placenta, amniotic fluid, fetal blood, and breast milk, and breast milk levels appear to be correlated to dwelling dieldrin treatment for termite control. Dieldrin tends to be stored in high-fat tissues within the body, but can be mobilized during lactation or starvation.

See Chapter 6 for more detailed information regarding concentrations of aldrin and dieldrin in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Data regarding the health effects of aldrin or dieldrin in humans come from either epidemiological reports of occupational exposure or case reports of accidental or intentional poisonings. As precise levels of exposure are not known, these studies are inadequate for quantitative assessment of the health effects of aldrin or dieldrin. The main and best documented effect of acute high-level exposure to aldrin or dieldrin in humans is central nervous system excitation culminating in convulsions. Central nervous system stimulation is the cause of death in acute poisoning. Longer-term exposure of humans in occupational settings has also been associated with central nervous system intoxication, but other toxic effects in workers routinely exposed to these pesticides have not been conclusively established. A few case reports have attributed liver and kidney toxicity and hemolytic anemia to oral exposure to aldrin or dieldrin, but these effects were not observed in larger occupational studies, suggesting that they are likely to be quite rare.

Studies in animals have mainly involved oral exposure. Oral data in animals are consistent with the findings in humans that the central nervous system is an important target of toxicity, but further show that other effects may also be associated with exposure to aldrin or dieldrin, including liver and kidney toxicity, immunosuppression, fetal toxicity and increased postnatal mortality, neurodevelopmental effects, and decreased reproductive function. No studies were located regarding developmental effects in humans and conflicting results exist in animals. Fetuses may be affected through transplacental exposure. The liver is the critical target of chronic toxicity in several species based on available long-term oral studies, although data on other end points known to be sensitive from shorter-duration studies (e.g., immunosuppression, subtle neurological effects) are insufficient. The mechanism for aldrin and dieldrin toxicity is not equally well understood for all target organs.

Aldrin and dieldrin are carcinogenic in animals, but this effect appears to be specific to the mouse liver. The International Agency for Research on Cancer has categorized aldrin and dieldrin as Group 3 (unclassifiable as to human carcinogenic potential) chemicals. Based on the finding of liver tumors in mice, EPA classified both aldrin and dieldrin as B2, probable human carcinogens; however, current mechanistic data suggest that the mouse carcinogenicity data may not be highly relevant to humans. 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).

Limited reports of adverse effects in aldrin- or dieldrin-exposed children (indicate similar signs and symptoms to those in adults. Limited animal data indicate that dose-response may change with age. The principal health effects are discussed in the following sections.

Hepatic Effects. While adverse hepatic effects have not generally been observed in workers employed in the manufacture or application of aldrin or dieldrin, the liver was the most sensitive target of aldrin and dieldrin toxicity in chronic-duration animal studies. Serum liver enzyme activities (alkaline phosphatase, alanine and aspartate aminotransferases) were normal in volunteers who ingested low doses of dieldrin (0.14–3 g/kg/day) for 18 months; however, slight increases in alanine and aspartate aminotransferase activities have been correlated with increased serum levels of dieldrin in pesticide-exposed workers. Liver injury was observed in a child who drank an unknown quantity of a 5% dieldrin solution. However, the dieldrin solution most likely contained a substantial amount of solvent, and it is unclear whether the hepatic toxicity was directly due to the dieldrin or the solvent. The injury appeared to be reversible to some extent; however, the child was not followed for a sufficient period to determine whether the injury was completely reversible. Exposure of animals to $0.025 mg/kg/day of aldrin or dieldrin over intermediate-to-chronic periods has also been reported to cause adverse effects such as elevated serum enzyme levels, decreased serum proteins, hyperplasia, bile duct proliferation, focal degeneration, and areas of necrosis in the liver.

These degenerative effects are distinct from the adaptive changes observed in livers of a number of animal species in response to exposure to aldrin, dieldrin, or other chlorinated hydrocarbon pesticides. Such adaptive changes occur as a result of the induction of microsomal enzymes by aldrin or dieldrin and include increases in liver weight and/or size, liver cell enlargement, cytoplasmic eosinophilia, an increase in the smooth endoplasmic reticulum, an increase in microsomal protein, an increase in cytochrome P-450 content, and/or an increase in microsomal enzyme activity. Studies of workers employed in the manufacture or application of aldrin or dieldrin have not shown evidence of microsomal enzyme induction. Studies have shown, however, that species differences exist with respect to the magnitude of these changes. The most prolific changes have been observed in rats, with dogs, mice, and monkeys experiencing progressively lesser changes. It might be expected, based on the close evolutionary relationship between Rhesus monkeys and humans, that limited enzyme induction might also occur in humans.

Neurological Effects. Central nervous system excitation is the primary adverse effect observed in humans in cases of aldrin or dieldrin intoxication. In cases of acute intoxication, in which a large amount of these pesticides is ingested over a short period of time, convulsions occur within several minutes after ingestion. In cases of longer-term exposures, where a slow rate of elimination from the body results in a gradual buildup of these agents in the blood to toxic levels, convulsions may also be produced . During such longer-term exposures, however, other less-serious symptoms of central nervous system toxicity may also be observed including headaches, dizziness, hyperirritability, general malaise, nausea, vomiting, muscle twitching, or myoclonic jerking.

Both acute- and longer-duration studies in animals support these findings. For example, acute-duration oral exposure to aldrin caused subtle neurological changes as indicated by altered electroconvulsive shock threshold in the offspring of mice exposed during gestation. Operant behavior was disrupted in rats following single doses of dieldrin ranging from 0.5 to 16.7 mg/kg, whereas convulsions resulted at higher doses ranging from 40 to 50 mg/kg. When aldrin or dieldrin was administered to rats for 3 days, convulsions were observed at a dose of 10 mg/kg/day.

In intermediate-duration animal studies, impaired learning was found at 0.1 dieldrin/kg/day, physical signs of neurotoxicity (tremors) occurred at aldrin or dieldrin doses at as low as 0.5 mg/kg/day, and histopathological degenerative changes in the brain were found at doses as low as 0.7 mg/kg/day.

In chronic studies, serious neurological effects including convulsions and/or tremors developed in rats and dogs administered dieldrin at doses as low as 0.5 mg/kg/day and in rats administered 2.1 mg aldrin/kg/day. Central nervous system histopathological changes were noted at lower doses. Slight neuronal degeneration in dogs was reported following 1 year of exposure to aldrin or dieldrin at 0.2 mg/kg/day, and cerebral edema and small foci of degeneration were reported in rats exposed to dieldrin at 0.016 mg/kg/day for 2 years; however, these effects were reported in studies limited by the small number of animals examined.

It is highly unlikely that high enough levels of aldrin or dieldrin could be absorbed acutely by persons living near hazardous waste sites to cause convulsions, although exposure to sufficiently high levels may cause some of the less adverse central nervous system effects.

It is generally believed that the central nervous system excitation observed in animals results from a generalized activation of synaptic activity throughout the central nervous system; however, it has not been

established whether aldrin and dieldrin act at the nerve terminal to facilitate neurotransmitter release or whether these agents cause excitation by depressing activity of inhibitory neurotransmitters within the central nervous system. Experimental evidence appears to indicate a blocking action on the $GABA_A$ receptor-chloride channel complex. Additional information on mechanisms of neurotoxicity of aldrin and dieldrin is included in Section 3.5.

Reproductive Effects. Studies in humans have not addressed whether adverse reproductive effects occur as a result of exposure to aldrin or dieldrin. However, decreased fertility was observed in several (but not all) studies at doses as low as 0.63 mg aldrin/kg/day or 0.125 mg dieldrin/kg/day administered to maternal or paternal animals by the oral route. In additional animal studies of reproductive toxicity following intraperitoneal injection of aldrin, investigators have observed several adverse effects of this agent on the male reproductive system. These findings 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. Also, *in vitro* studies conducted using rat prostate tissue have shown that dieldrin blocks binding of the androgen, 5α-dihydrotestosterone, to a protein fraction of the prostate. These findings may provide clues regarding the mechanism of the decreased fertility in males. Based on the findings reported in these studies, an adverse effect of exposure to sufficiently high levels of aldrin or dieldrin on male fertility cannot be excluded.

Developmental Effects. Studies in humans have not addressed whether adverse developmental effects occur as a result of exposure to aldrin or dieldrin. External malformations have been observed in a study in mice and hamsters at doses of 15 and 30 mg dieldrin/kg/day, respectively, but at doses 10 times lower, conflicting results regarding these types of effects were reported. Decreased postnatal survival following *in utero* exposure to dieldrin has been observed in a number of studies in laboratory animals. This decrease in survival does not appear to be dependent on exposure to this agent postnatally via the mothers' milk or to effects of dieldrin on maternal behavior, although these factors appear to contribute to the postnatal mortality. However, the mechanism for the neonate lethality at present is not known. In addition, subtle changes in neurological function, such as changes in the electroconvulsive shock threshold, have been observed in offspring of mice treated with aldrin during pregnancy.

See Chapter 3 for more detailed information regarding the health effects of aldrin and dieldrin.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

Information regarding inhalation toxicity of aldrin and dieldrin in humans is mainly available from studies of workers involved in the manufacture or use of the chemicals (de Jong 1991; Hunter et al. 1972; Jager 1970; Kazantzis et al. 1964; Morgan and Lin 1978; Morgan and Roan 1974; Morgan et al. 1980; Patel and Rao 1958; Sandifer et al. 1981; van Raalte 1977; van Sittert and de Jong 1987; Versteeg and Jager 1973; Warnick and Carter 1972). Limitations associated with these reports include lack of quantitative exposure data, lack of data on duration of exposure, the possibility of multiple routes of exposure (i.e., dermal as well as inhalation), and concurrent exposure to other chemicals. The human occupational data therefore essentially provide only qualitative data on health effects associated with inhalation exposures to aldrin and dieldrin and are unsuitable for MRL derivation. Extremely limited animal inhalation toxicity data are available for aldrin and dieldrin in several species (Treon et al. 1957b), but limitations of these studies, particularly lack of exposure levels and sublimation of the chemicals that may have generated thermal decomposition products and/or other volatile contaminants, also preclude derivation of inhalation MRLs.

Oral MRLs

Acute-duration Oral MRLs

Aldrin

- An MRL of 0.002 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to aldrin.

The acute-duration oral MRL for aldrin was derived based on observations of 18% decreased body weight and a significantly increased electroconvulsive shock brain seizure threshold in the offspring of mice gavaged with 2 or 4 mg/kg/day for 5–7 days during the third trimester of pregnancy (Al-Hachim 1971). There was no effect on the acquisition of a conditioned avoidance response in the offspring. Another acute-duration oral developmental toxicity study of aldrin showed developmental toxicity at higher doses of aldrin in both mice and hamsters (Ottolenghi et al. 1974). Administration of aldrin by gavage caused an increase in the incidence of webbed feet in mice following 25 mg/kg on gestation day (Gd) 9 and

increased fetal mortality in hamsters following 50 mg/kg/day on Gd 7, 8, or 9. These results support the developmental toxicity of aldrin. Additionally, the neurodevelopmental effect is consistent with evidence showing that the central nervous system is a well-documented target of aldrin and dieldrin toxicity in adult animals. Because the end points measured in the current study may be more sensitive indicators of fetal toxicity than overt neonatal neurological effects and fetal death or malformations, the lowest tested dose is considered to be a lowest-observed-adverse-effect level (LOAEL) for developmental toxicity. The acute-duration MRL of 0.002 mg/kg/day was derived by dividing the 2 mg/kg/day LOAEL by an uncertainty factor of 1,000 (10 for extrapolating from a LOAEL to a NOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

Dieldrin

An acute-duration oral MRL was not derived for dieldrin. Severe signs of neurotoxicity were reported in humans accidently or intentionally ingesting relatively large doses of dieldrin (Black 1974; Garrettson and Curley 1969). Convulsions were observed in rats given dieldrin in single oral doses ranging from 10 to 50 mg/kg (Mehrotra et al. 1989; Wagner and Greene 1978; Woolley et al. 1985). Other studies in rats reported disruption of operant behavior (Burt 1975) and impaired responses in an inescapable foot shock stress paradigm (Carlson and Rosellini 1987) following acute oral administration of dieldrin at doses of 2.5 and 0.5 mg/kg, respectively. Monkeys orally administered 0.1 mg dieldrin/kg/day for 55 days showed signs of impaired learning <15 days after the initiation of treatment (Smith et al. 1976). This study identified a no-observed-adverse-effect level (NOAEL) of 0.01 mg/kg/day for impaired learning in monkeys treated for up to 55 days; the NOAEL was used as the basis for derivation of an intermediate-duration oral MRL for dieldrin. Adverse effects were also observed in the immune system of mice following acute oral exposure to dieldrin levels as low as 0.065 mg/kg (Loose et al. 1981), indicating that the immune system may be the most sensitive target of dieldrin-induced toxicity in animals. However, due to the lack of data to suggest that the immune system may be a target of toxicity in humans following ingestion of dieldrin, an acute-duration oral MRL for dieldrin based on immunotoxicity was not derived.

Intermediate-duration Oral MRLs

Aldrin

An intermediate-duration oral MRL was not derived for aldrin due to lack of appropriate effect levels. In intermediate-duration oral studies, the lowest NOAEL of 0.63 mg/kg/day was identified for decreased body weight in rats consuming aldrin for 27 weeks (Treon et al. 1953b). The associated LOAEL of 1.25 mg/kg/day, which was also a NOAEL for other systemic effects (liver and kidney weight), was within the range of 0.89–1.78 mg/kg/day reported in dogs exposed for 9 months for frank signs of neurotoxicity that included tremors, convulsions, labored respiration, and vomiting (Treon et al. 1951b). NOAELs for these neurotoxic effects were not identified. The neurotoxic effects are considered by ATSDR to be serious effects, and MRLs are not derived using LOAELs for serious end points. An intermediate-duration MRL was not derived based on the NOAEL of 0.63 mg/kg/day for decreased body weight because of its proximity (within a factor of 10) to the LOAELs for serious end points.

Dieldrin

- An MRL of 0.0001 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to dieldrin.

The intermediate-duration oral MRL for dieldrin was derived based on observations of impaired learning of a successive discrimination reversal task in squirrel monkeys fed 0.1 mg dieldrin/kg/day for 55 days, whereas the 0.01 mg/kg/day dose level had no apparent effect on learning (Smith et al. 1976). The study by Burt (1975) provides supporting evidence of neurotoxicity in rats fed dieldrin in the diet for 60–120 days. A concentration of 5 ppm (a calculated dose level of 0.25 mg/kg/day, using reference values from EPA (1986m) resulted in significantly impaired maze training; no adverse effects were seen in rats exposed for 60 days to a concentration resulting in a dose level of 0.025 mg/kg/day. The intermediate-duration oral MRL of 0.0001 mg/kg/day was calculated by dividing the 0.01 mg/kg/day NOAEL by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

Chronic-duration Oral MRLs

Aldrin

- An MRL of 0.00003 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to aldrin.

The liver was the most sensitive target of aldrin toxicity in chronic-duration studies. Rats exposed to aldrin at doses as low as 0.025 mg/kg/day for 2 years had increases in relative liver weight and hepatic histopathological changes similar to those induced by other chlorinated insecticides (Fitzhugh et al. 1964). The hepatic lesions that were seen at 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 proliferations. Liver changes were marked at 2.5 mg/kg/day and included an increase in the severity of hepatic cell vacuolation; this is consistent with evidence for dose-related progression of hepatotoxicity in other studies (Deichmann et al. 1967; Harr et al. 1970; Thorpe and Walker 1973; Treon et al. 1955b).

Several of the liver cell changes that were observed at 0.025 mg/kg/day were considered to be consistent with marked adaptation. Modifications occurring in the mixed function oxidase system consequent to the adaptive response may result in it's functional enhancement or neutralization. This in turn has the consequence of potentiating or inhibiting toxic responses to other exogenous substances. Even though the mechanism of aldrin-mediated hepatotoxicity has not been elucidated, the potential significance of the marked adaptive response in cell injury cannot be dismissed. The extreme magnitiude of cellular adaption that results from aldrin toxicity creates a liver that potentially has a tremendously heightened state of metabolic activity which correspondingly may have a similiarly heightened capacity to toxify or detoxify upon continued exposure to aldrin (or other substance that may be present at NPL sites).

Particularly in considering that the liver is a major target organ for aldrin toxicity, and the marked adaptive response and other histopathologic lesions (cytoplasmic vacuolation and bile duct proliferation) observed in the Fitzhugh et al. study, a chronic-duration oral MRL for aldrin of 0.00003 mg/kg/day was derived by dividing the LOAEL of 0.025 mg/kg/day by 1,000 (10 for extrapolating from a LOAEL to a NOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

Dieldrin

- An MRL of 0.00005 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to dieldrin.

The liver was the most sensitive target of dieldrin toxicity in chronic-duration studies. Rats that were exposed to 0.005, 0.05, or 0.5 mg/kg/day dieldrin in the diet for 2 years had increased relative liver weight at $0.05 mg/kg/day and liver parenchymal cell changes characteristic of organochlorine exposure,

as well as indications of focal hyperplasia, at 0.5 mg/kg/day (Walker et al. 1969). There were no indications of dieldrin-related changes in serum alkaline phosphatase or SGPT, histology of non-liver tissues, or body weight in any of the exposed groups, although signs of dieldrin neurotoxicity (irritability, tremors, and occasional convulsions) occurred at 0.5 mg/kg/day. These behavioral changes usually occurred during handling, did not progress after 3 months of exposure, and did not affect well-being. Based on the 0.005 mg/kg/day NOAEL for liver effects and considering the evidence for dose-related progression of hepatotoxicity, the chronic oral MRL of 0.00005 mg/kg/day was calculated for dieldrin using an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

The main source of general population oral exposure to aldrin and dieldrin is through the diet (see Section 6.5). In an FDA Total Diet study conducted in 1982–1984, mean dietary intake of dieldrin in the United States was 0.5 µg/day (0.007 µg/kg/day assuming a 70-kg body weight) (Gunderson 1988; Lombardo 1986), which is approximately 7 times lower than the dieldrin chronic oral MRL. In the same study, aldrin intake was <0.001 µg/kg/day, which is approximately 30 times lower than the aldrin chronic oral MRL.