CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Aldrin and dieldrin are readily absorbed from the gastrointestinal tract; limited data indicate that aldrin or dieldrin are also absorbed from the lung and skin.
- Absorbed aldrin is rapidly converted to dieldrin (primarily in the liver); distribution is initially widespread, but quickly redistributed mainly to adipose tissue.
- Dieldrin and its metabolites are mainly excreted in the feces (via bile) and to a lesser extent in the urine.

3.1.1 Absorption

Studies directly measuring absorption of aldrin or dieldrin in humans following inhalation exposure of known amounts of these pesticides were not located. However, measurement of aldrin and dieldrin in human breast milk in general populations indicates that both chemicals are absorbed (Al-Antary et al. 2018; Kao et al. 2019b; Stacey and Tatum 1985). Results from a survey of women in pesticide-treated homes showed a correlation between the treatment and dieldrin levels in human breast milk. 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).

Absorption of orally-administered dieldrin has been demonstrated in volunteers fed dieldrin at concentrations of 0.0001, 0.0007, or 0.003 mg/kg/day for 18–24 months. Dose-related increased levels of dieldrin were observed in blood and adipose tissue (Hunter and Robinson 1967; Hunter et al. 1969).

Although data are limited regarding absorption of aldrin or 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 ^{14}C-labeled aldrin or dieldrin to the forearm of six volunteers. Based on urinary radioactivity, 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, recovery of radioactivity 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.

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).

Aldrin and dieldrin are readily absorbed by the gastrointestinal tract following oral exposure of a variety of experimental animals, including rats, mice, and dogs (Brown et al. 1964; Furusawa 2002; Hayes 1974; Korte and Kochen 1966; Müller et al. 1979). Following oral dosing with radiolabeled aldrin or 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 of dieldrin to rats at 10 mg/kg, approximately 50% of the dose was found in fat (Hayes 1974). Several metabolic studies indicate that dieldrin is absorbed from the gastrointestinal tract and is transported via the hepatic portal vein (Heath and Vandekar 1964).

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). Both aldrin and dieldrin were detected in the skin 1 hour after aldrin application. 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 of dieldrin from fabric that had been impregnated with up to 0.04% dieldrin was also demonstrated in rabbits (Witherup et al. 1961).

Due to the high lipophilic nature of aldrin and dieldrin, they are likely absorbed via passive diffusion.

3.1.2 Distribution

Aldrin is rapidly converted to dieldrin in environmental and biological systems. 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 consistent with 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 relationship between the concentration of dieldrin in the adipose tissue with respect to 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 dieldrin 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 (de Vlieger 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. Aldrin and dieldrin have also been detected in gall bladder tissue and gall stones (Kailani et al. 2020).

Studies measuring cord blood and fetal blood show that placental transfer of aldrin and dieldrin occurs (Cabrera-Rodríguez et al. 2020; Dwivedi et al. 2021; Polishuk et al. 1977a). In cord blood in a population in Spain, the ranges of aldrin and dieldrin cord blood concentrations were 0.002–0.161 and 0.001–0.723 ng/mL, respectively (Cabrera-Rodriguez et al. 2020) 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) (Polishuk et al. 1977a). A study of 88 mother-infant pairs (full-term births) showed that the concentration of dieldrin in maternal blood (0.0016 ng/mL) was higher than in cord blood (00012 ng/mL) (Dwivedi et al. 2021), but the concentrations of aldrin were similar in maternal blood (0.00259 ng/mL) and cord blood (0.00263 ng/mL). Dieldrin levels were also higher in the placenta (0.8 mg/kg) than in the uterus (0.54 mg/kg) (Polishuk et al. 1977a).

Tissue distribution of radioactivity following single-dose oral administration of ^{14}C-dieldrin (0.43 mg/kg) to rats indicated that the initial rapid uptake of radioactivity 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 1974). 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 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 2 and 10 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 or 18–30 weeks, respectively (Walker et al. 1969). In rats receiving 0.002–0.10 mg/kg/day dieldrin from the diet, steady state was reached by 6 weeks (Davison 1973); time to steady state was similar at the tested dose levels. 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).

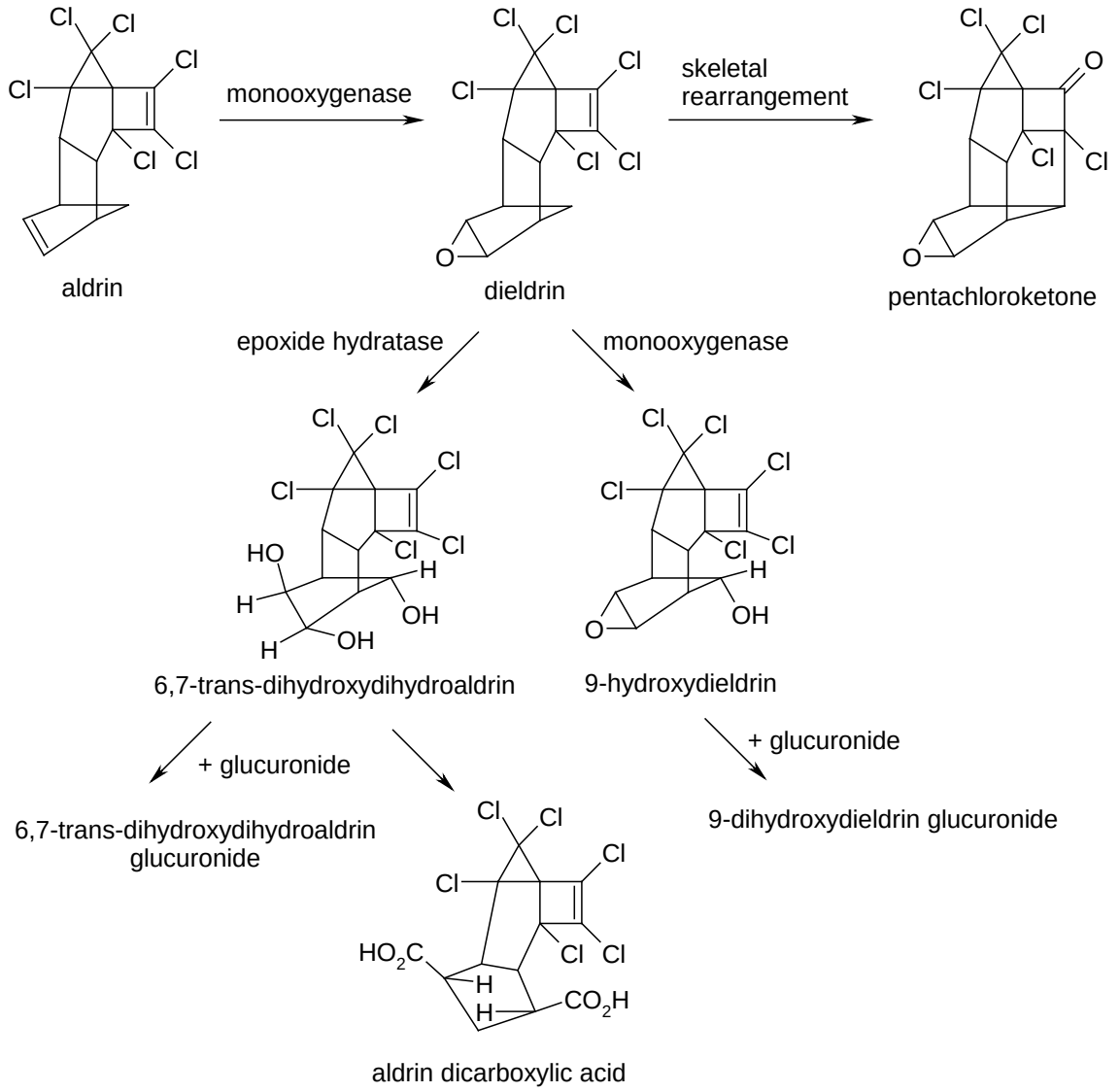
In another study, the steady-state concentration in adipose tissues of rats receiving dietary concentrations of 1.25 mg/kg/day dieldrin for 8 weeks was reported to be 50 mg/kg dieldrin (Baron and Walton 1971). The elimination of dieldrin residues from the adipose tissue of rats subsequently placed on untreated diets was reasonably rapid with an estimated half-life of 4.5 days (Baron and Walton 1971). The estimated half-lives for 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).

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

3.1.3 Metabolism

The initial and major step in the biotransformation of aldrin in experimental animals is the formation of the corresponding epoxide 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 3-1.

Figure 3-1. Proposed Metabolic Pathway for Aldrin and Dieldrin



Source: EPA 1987a

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 3-fold increase in dieldrin formation, whereas 3-methylcholanthrene treatment markedly depressed enzyme activity. Thus, cytochrome P-450 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 bis-dioxygenation of arachidonic acid to prostaglandin G_2 (PGG_2). In a second step, a reduction by hydroperoxidase to prostaglandin H_2 (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 epoxide ring by epoxide hydrases, resulting in 6,7-*trans*-dihydroxydi-hydroaldrin (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 rats 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 hydrolase 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).

Data show that the skin is capable of metabolizing aldrin to the stable epoxide 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).

3.1.4 Excretion

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). A half-life for dieldrin elimination was estimated 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. 1989a). Aldrin and dieldrin have been detected in breast milk in women (n=50) in Saudi Arabia, with mean concentrations of 11.2 and 5.07 ng/g lipid, respectively (El-Saeid et al. 2021). A study of 55 women in Taiwan also detected aldrin and dieldrin in breast milk; the mean aldrin and dieldrin concentrations were 0.366 and 0.422 ng/g lipid, respectively (Kao et al. 2019a).

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 versus 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 dieldrin at 0.5 mg/kg (Müller et al. 1975) and in urine from dieldrin-treated mice (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). Chata et al. (2019) estimated the half-life of dieldrin in rats of 13.0 hours.

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 (Baldwin et al. 1972; Hutson 1976). Excretion was more rapid in the rat than in the mouse. The ratio of 9-hydroxy-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).

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

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 endpoints.

No PBPK models for aldrin or dieldrin were located.

3.1.6 Animal-to-Human Extrapolations

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 (Amoateng-Adjepong et al. 1995; Brown 1992; 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-duration 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; de Vlieger et al. 1968; Hayes 1974; Hunter and Robinson 1967; Hunter et al. 1969; Iatropoulos 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.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. 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. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to aldrin or dieldrin are discussed in Section 5.7, Populations with Potentially High Exposures.

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 (Feldmann 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 that was inadvertently 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 was 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 2.21 (Mechanisms of Action), *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.

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. 1977a). Furthermore, dieldrin is excreted in the breast milk of nursing mothers (Schecter et al. 1989a). 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 ovariectomized 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.

Two studies evaluated polymorphisms and cancer risk. In a study of single nucleotide polymorphisms, Koutros et al. (2013b) found an increased risk of prostate cancer risk among men with aldrin use and two A alleles at rs7679673 in TET2 region. The second study examined mutations in the p53 suppressor gene and breast cancer risk associated with dieldrin exposure (Høyer et al. 2002). Although no significant alterations in breast cancer risk was associated with this polymorphism, women with 'wild-type' p53 had an increased risk of dying.

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 3.1 (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.

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 3.4, Interactions With Other Chemicals) did not suggest that such interactions would be different in children.

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 (Rami 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.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to aldrin or dieldrin are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for aldrin and dieldrin from this report are discussed in Section 5.6, General Population Exposure.

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 effect caused by aldrin or dieldrin are discussed in Section 3.3.2.

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 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

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.

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 is the major inhibitory neurotransmitter in the central nervous system (see Section 2.15). 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.

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.

3.3.2 Biomarkers of Effect

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 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 attempts 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 performed 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.

3.4 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 homeostasis, by upregulating 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. 1997).