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Health Effects Support Document for Aldrin/Dieldrin

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Prepared for:

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FOREWORD

The Safe Drinking Water Act (SDWA), as amended in 1996, requires the Administrator of the Environmental Protection Agency to establish a list of contaminants to aid the agency in regulatory priority setting for the drinking water program. In addition, SDWA requires EPA to make regulatory determinations for no fewer than five contaminants by August 2001. The criteria used to determine whether or not to regulate a chemical on the CCL are as follows:

> The contaminant may have an adverse effect on the health of persons.
>
> The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.
>
> In the sole judgment of the administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The Agency's findings for all three statutory criteria are used in order to make a determination to regulate a contaminant. The Agency may determine that there is no need for a regulation when a contaminant fails to meet one of the statutory criteria. A decision not to regulate is considered a final agency action and is subject to judicial review.

This document provides the health effects basis for the regulatory determination for aldrin and dieldrin. In arriving at the regulatory determination for these two contaminants, data on toxicokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. In order to avoid wasteful duplication of effort, information from the following risk assessments by the EPA and other government agencies were used in development of this document.

> ATSDR. 2000. Agency for Toxic Substances and Disease Registry. Draft Toxicological Profile for Aldrin/Dieldrin: Update. Atlanta, GA: U. S. Department of Health and Human Services.
>
> ATSDR. 1993. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Aldrin/Dieldrin. Atlanta, GA: USDepartment of Health and Human Services.
>
> USEPA. 1992. US Environmental Protection Agency. Aldrin Drinking Water Health Advisory. Office of Water.
>
> USEPA. 1988. US Environmental Protection Agency. Dieldrin Drinking Water Health Advisory. Office of Water.
>
> USEPA. 1987a. US Environmental Protection Agency. Integrated Risk Information System (IRIS): Dieldrin. Cincinnati, OH.

USEPA. 1987b. US Environmental Protection Agency. Carcinogenicity assessment of Dieldrin and Aldrin. (CAG).

USEPA. 1986. US Environmental Protection Agency. Integrated Risk Information System (IRIS): Aldrin. Cincinnati, OH.

IARC. 1987. International Agency for Research on Cancer. Evaluation of the carcinogenic risk of chemicals to humans. Overall evaluations of carcinogenicity. Suppl. 7:88-89.

IARC. 1982. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemicals, industry process and industries associated with cancer in humans. IARC Monographs. Vols. 1-29, Supplement 4. Geneva: World Health Organization.

IARC. 1974a. International Agency for Research on Cancer. Evaluation of the carcinogenic risk of chemicals to humans. Aldrin. Lyon, France: IARC Monograph 5:25-38.

IARC. 1974b. International Agency for Research on Cancer. Evaluation of the carcinogenic risk of chemicals to humans. Dieldrin. Lyon, France: IARC Monograph 5:125-156.

In cases where the information in this document originates from one of the references above, a citation to the source document is provided with the bibliographic information in the reference section. Primary references were used for all key studies. Data from the published risk assessments were supplemented with information from literature searches conducted in 2000. Specific emphasis is placed on dose-response information and exposure estimates in making the regulatory determination for aldrin and dieldrin. Dose-reponse conclusions for noncancer effects are reflected in the Reference Dose (RfD).

Generally, a RfD is provided as the assessment of long-term toxic effects other than carcinogenicity. RfD determination assumes that thresholds exist for certain toxic effects, such as cellular necrosis. It is expressed in terms of milligrams per kilogram per day (mg/kg-day). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The carcinogenicity assessment for aldrin and dieldrin includes a formal hazard identification. Hazard identification is a weight-of-evidence judgement of the likelihood that the agent is a human carcinogen via the oral route and the conditions under which the carcinogenic effects may be expressed.

Guidelines that were used in the development of this assessment may include the following: the *Guidelines for Carcinogen Risk Assessment* (USEPA,1986a), *Guidelines for the Health Risk Assessment of Chemical Mixtures* (USEPA, 1986b), *Guidelines for Mutagenicity*

Risk Assessment (USEPA, 1986c), *Guidelines for Developmental Toxicity Risk Assessment* (USEPA, 1991), *Proposed Guidelines for Carcinogen Risk Assessment* (1996a), *Guidelines for Reproductive Toxicity Risk Assessment* (USEPA, 1996b), and *Guidelines for Neurotoxicity Risk Assessment* (USEPA, 1998a); *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (USEPA, 1988); and Health Effects Testing Guidelines (OPPTS series 870, 1996 drafts; USEPA 40 CFR Part 798, 1997; *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (USEPA, 1994c); *Use of the Benchmark Dose Approach in Health Risk Assessment* (USEPA, 1995b); *Science Policy Council Handbook: Peer Review* (USEPA, 1998b, 2000a); Memorandum from EPA Administrator, Carol Browner, dated March 21, 1995, Policy for Risk Characterization; *Science Policy Council Handbook*: *Risk Characterization* (USEPA, 2000b).

The section on aldrin and dieldrin occurrence and exposure through potable water in this document was developed by the Office of Ground Water and Drinking Water. It is based primarily on unregulated contaminant monitoring (UCM) data collected under SDWA. The UCM data are supplemented with ambient water data, as well as information on production, use, and discharge.

ACKNOWLEDGMENTS

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1.0 EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) has prepared this Health Effects Support Document to assist in determining whether to establish a National Primary Drinking Water Regulation (NPDWR) for aldrin and dieldrin. Case study reports of human exposures and laboratory studies with animals demonstrate that oral exposure to both of these compounds can cause various adverse systemic, neurological, reproductive/developmental, immunological, and genotoxic effects. Although multiple bioassays have established aldrin and dieldrin as hepatocarcinogenic in several strains of mice, they are apparently not carcinogenic in rats, and several large epidemiology studies have failed to associate convincingly exposure to them with cancer in humans. While some of these effects occur only at moderate-to-high doses, others have been observed at doses lower than 0.1 mg/kg bw/day. Nonetheless, the relatively infrequent occurrences of aldrin/dieldrin at very low concentrations indicated by monitoring data, coupled with the fact that they are no longer manufactured or used in this country, indicate that aldrin/dieldrin concentrations of concern are unlikely to be found in public water systems. EPA will present a determination and further analysis in the Federal Register Notice covering the Contaminant Candidate List decisions.

Chemical Identities and Properties

Aldrin (CAS Registry Number [RN] 309-00-2) is the most common name for the substance composed of at least 95% of the chemical 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-*exo*-1,4-*endo*-5,8-dimethanonaphthalene. Technical grade aldrin contains at least 90% of this substance (i.e., it has a main ingredient purity of at least 85.5%). Similarly, dieldrin (CAS RN 60-51-1) refers to the substance composed of at least 85% of the chemical 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-*exo*-5,8-dimethanonaphthalene. Technical grade dieldrin contains at least 95% of this substance (i.e., it has a main ingredient purity of at least 80.75%).

Dieldrin, a stereoisomer of endrin, was typically produced by the epoxidation of aldrin with peracetic or perbenzoic acid. In their "pure" formulations, both aldrin and dieldrin are composed of clear-to-white crystals with densities greater than water, and have both low volatilities and aqueous solubilities. Both are relatively stable in the presence of organic and inorganic alkalies and mild acids, slightly corrosive to metals upon storage, and compatible with most fertilizers and pesticides.

Aldrin/Dieldrin Uses, Manufacture, and Environmental Fate

Aldrin and dieldrin are synthetic organochlorine pesticides that act as effective contact and stomach poisons for insects. Originally, they were used as broad-spectrum soil insecticides for the protection of various food crops, as seed dressings, to control infestations of pests like ants and termites, and to control several insect vectors of disease. In 1972, the EPA cancelled all but three specific uses of these compounds (subsurface termite control, dipping of non-food plant roots and tops, and completely contained moth-proofing in manufacturing processes), which by 1987 were voluntarily cancelled by the manufacturer. Use of these compounds peaked in the U.S. during 1966 at 19 million lbs for aldrin and 1 million lbs for dieldrin. These compounds

have not been produced domestically since 1974, and while some importation of aldrin began during that year, this ceased after 1985.

Total releases of aldrin/dieldrin to the environment since 1987 are not known, but hazardous waste treatment facilities in three states (AR, MI, TX) reported releases totaling 25,622 lbs in 1998, most of which was directly to land. Data from the Agency for Toxic Substances and Disease Registry (ATSDR) indicate that these compounds have been detected in site samples from 40 different states; aldrin has been detected at National Priorities List (NPL) hazardous waste sites in 31 states, while dieldrin has been found at NPL sites in 38 states.

Under most environmental conditions, aldrin is largely converted via biological and/or abiotic mechanisms to dieldrin, which is significantly more persistent. Most environmental releases of aldrin and dieldrin are directly to soil. Because of low water solubility and tendency to bind strongly to soils, both compounds migrate downward very slowly through soils or into surface or ground water. Most surface water aldrin/dieldrin has been attributed to particulate surface run-off. Over time, it is possible that significant volatilization of aldrin/dieldrin might occur, with subsequent atmospheric photodegradation and/or rainfall "washout." Collectively, these characteristics will foster low levels of aldrin/dieldrin water contamination over comparatively extended periods of time. Dieldrin's extreme apolarity results in a high affinity for organic matter such as animal fats and plant waxes, which could lead to its bioaccumulation in the food chain.

Exposure to Aldrin/Dieldrin

As neither aldrin nor dieldrin has been used in the U.S. since 1987, new releases to the environment should not occur. Only rare exceptions to this generalization might occur at hazardous waste treatment facilities. Over time, therefore, the frequency and magnitude of population exposure to aldrin/dieldrin can be confidently expected to decline from those experienced to date (2001). Currently available sampling and monitoring data suggest that although potential exposures to aldrin/dieldrin via drinking water could be of similar magnitude to those estimated from the diet, which exposures in turn are likely to be substantially higher than those from breathing air or ingesting soil, they are unlikely to occur at significant frequencies or dose levels.

The data analyzed in this document on the occurrence in drinking water of aldrin/dieldrin were collected beginning in 1993 under "Round 2" of the Safe Drinking Water Act's Unregulated Contaminant Monitoring (UCM) Program. Monitoring ended in January 1999, for small public water systems (PWSs), and in January 2001, for large PWSs. These data, from 34 states and a number of Native American tribal systems, were not collected utilizing a uniform or adequate statistical framework, and were in some cases incomplete and/or biased. To partially address the questionable representativeness of the combined data set, a "national cross-section" of 20 Round 2 states (AK, AR, CO, KY, ME, MD, MA, MI, MN, MS, NH, NM, NC, ND, OH, OK, OR, RI, TX, and WA) was selected. The procedure used to construct this "reasonable representation" of national occurrence evaluated the individual data sets for completeness, quality, bias, pollution potentials from manufacturing/population density and from agricultural activity, and for "geographic coverage" in relation to all states. Because data from MA were

incomplete and considered abnormal for synthetic organic compounds like aldrin/dieldrin (an atypically high percentage of detections in a relatively small number of PWSs), Round 2 cross-section occurrence data for aldrin/dieldrin are discussed primarily in the context of the other 19 states.

The data indicate that each compound is only infrequently detected in PWSs, and then, generally, only at very low concentrations. With respect to the Health Reference Level (HRL, a preliminary estimated health effect level used in these analyses) for these compounds of 0.002 µg/L (based on estimated excess lifetime cancer risks of 10^{-6}), concentrations of aldrin and dieldrin greater than or equal to this level were detected in only 0.016 and 0.093% of the Round 2 cross-section PWSs, respectively. These percentages extrapolate nationally to 11 PWSs serving 38,871 people for aldrin, and 61 PWSs serving 149,827 people for dieldrin. As a consequence of excluding states with positively-biased detect statistics, Round 2 cross-section data underestimate the national occurrence of these compounds in PWSs. It is important to remember that only one positive sample (i.e., taken at a single time point from a single sampling location) was required to classify a PWS as one with aldrin or dieldrin detections—a practice that certainly overestimates population exposures.

Data from all the reporting Round 2 states may be used to derive more conservative, probably over-estimates of the national PWS occurrences of aldrin and dieldrin at levels ≥the HRL. These data yield respective PWS detection rates of 0.212 and 0.211%, which extrapolate nationally to 138 PWSs serving 1,051,989 people and 137 PWSs serving 792,703, respectively. Only five states (AL, MA, NM, PA, TX) and eight states (AL, AR, CT, MA, MD, NC, PA, TX) detected aldrin or dieldrin, respectively, in any PWS.

While the U.S. Geological Survey's National Ambient Water Quality Assessment (NAWQA) Program did not analyze for the presence of aldrin in ambient ground or surface waters, it did analyze for samples of aquatic biota tissue and stream bed sediments taken from 591 sites located in significant watersheds and aquifers from 1992 to 1995. Aldrin was not detected in any of the aquatic biota samples, but was detected above the Method Detection Limit (MDL) of 1 mg/kg at 0.4% of the sites (detections were confined to mixed land use and agricultural sites; there were no urban or forest-rangeland detections). Similarly, dieldrin was detected above the 1 mg/kg MDL at 13.7% of the same sites, as well as above the MDL of 5 mg/kg in 28.6 and 6.4% of whole fish and bivalve samples, respectively. Unlike aldrin, dieldrin was an NAWQA analyte for ambient surface and ground waters from 1991 to 1996. At MDLs of 0.001 and 0.01 mg/L, dieldrin was detected in 4.64 and 2.39%, respectively, of total stream surface water sites, and in 1.42 and 0.93%, respectively, of total ground water sites.

Relative source contribution analyses estimate that ratios of dietary to drinking water intake range from 1.7 to 3.8 for aldrin, and from 0.9 to 8.8 for dieldrin. Ratios were computed for the 70 kg adult and the 10 kg child consuming 2 L/day or 1 L/day, respectively, of drinking water, and utilized either the median or the 99th percentile concentrations of the Round 2 cross-section PWS samples (detections only) for aldrin (0.58 or 0.69 µg/L) and dieldrin (0.16 or 1.36 µg/L), as well as estimated adult and child total dietary intakes of aldrin (3.3 to 6.5 and 13 to 18 $\times 10^{-5}$ mg/kg bw/day, respectively) and dieldrin (3.6 and 14 $\times 10^{-5}$ mg/kg bw/day, respectively), which were based on data from the 1980s to early-to-mid 1990s.

These dietary/drinking water intake ratios would be reduced by factors of approximately 3 to 6 under the very conservative approach of using median and 99th percentile detect concentrations based on monitoring data from all reporting UCM Round 2 states. Thus, drinking water appears capable of potentially providing a significant portion of the total daily dietary intake of aldrin/dieldrin only when analyzed utilizing conservative assumptions, and then only for limited populations under unlikely exposure circumstances.

Even when using 30-year-old air monitoring data that likely substantially overestimate current daily inhalation intakes of aldrin/dieldrin, they are still relatively low (0.013 to 0.24×10^{-5}) compared to dietary estimates and potentially possible (although unlikely) exposures from drinking water. Similarly, data available for dieldrin suggest that ingestion of soil represents only a minor exposure pathway for aldrin/dieldrin.

Toxicokinetics of Aldrin/Dieldrin

Few direct data were found in the literature on the absorption of aldrin/dieldrin, especially in humans. Dose-related increases in blood and adipose tissue levels of dieldrin were reported in volunteers exposed via diet to small amounts for 18 to 24 months, with concentrations in the blood equal to 8.6% of the amount ingested per day under steady-state conditions. Inhalation studies using volunteers suggest that 20 to 50% of inhaled aldrin vapor may be absorbed and retained in the human body. One study in rats estimated that approximately 10% of an orally administered dose of aldrin was absorbed via the gastrointestinal tract. Other studies in rats have demonstrated that dieldrin concentrations in the blood and liver increase during the first 9 days of dietary exposure to 50 parts per million (ppm), then remain fairly constant over the next 6 months; also, that absorption of aldrin and dieldrin is detected within 1 to 5 hours after oral dosing and occurs primarily via the hepatic portal vein instead of the thoracic lymph duct. Additionally, uptake of aldrin in isolated, perfused rabbit lungs was demonstrated to occur in a biphasic process of simple diffusion. Direct absorption of aldrin/dieldrin through intact skin has been reported in rabbits, dogs, monkeys, and humans.

Because of its relatively rapid metabolic conversion to dieldrin, aldrin is infrequently observed in human tissue and there is little information on its distribution in human tissue. As a result of their hydrophobic nature, the highest concentrations of aldrin/dieldrin and their metabolites are typically found in the adipose tissues of both humans and other animals. Based on several studies involving volunteers or human autopsies, the steady-state relative distribution of dieldrin in whole blood, brain grey matter, brain white matter, liver, and adipose tissue is estimated to be 1, 2.8, 4.2, 22.7, and 136, respectively. The leanest individuals appear to have the highest adipose tissue concentration of dieldrin, but both the lowest total body burden of dieldrin and the lowest proportion of total exposure dose is retained in their adipose tissue. Blood levels of dieldrin do not increase during periods of surgical stress or complete fasting, and decline exponentially after termination of exposure, with considerable variation among individuals (mean half-lives of 266 and 369 days were reported in 2 studies). Placental transfer of dieldrin can occur, resulting in fetal blood concentrations higher than those in maternal blood (1.22 vs. 0.53 mg/kg, respectively).

Distribution studies conducted in animals (rats, mice, guinea pigs, dogs, primates, and various domesticated species) generally support the findings from human studies, at least qualitatively. Exposure to aldrin/dieldrin leads to preferential disposition of dieldrin (and metabolites) in adipose tissue, with lesser-to-very small amounts variously reported in liver, kidney, brain, muscle, lung, blood, and certain other tissues. In partial summary, there are some differences in distribution parameters among species and, at least in rodents, between sexes (females reportedly absorb and retain more dieldrin in their adipose tissue and most organs than do males); blood concentrations appear to decline more rapidly upon termination of exposure in animals than in humans; redistribution of dieldrin from the liver to adipose tissue may occur principally via the lymphatic system; transplacental transfer of dieldrin has also been demonstrated in rodents; and the available animal data collectively suggest that distribution patterns of aldrin and dieldrin will be similar for most routes of exposure.

As noted previously, in many organisms the initial and principal biotransformation of aldrin following oral exposure is the relatively rapid, mixed function oxidase-mediated epoxidation to dieldrin. Also referred to as aldrin-epoxidase, these enzymes are prominent in the endoplasmic reticulum of vertebrate hepatocytes. Male rats and mice appear to convert more rapidly and extensively than do females. In some extra-hepatic tissues (e.g., lung) that contain relatively little cytochrome P-450 activity, *in vitro* studies suggest that aldrin may be epoxidized to dieldrin via an alternate, prostaglandin endoperoxide synthase pathway, one which is dependent on arachidonic acid rather than on nicotine adenine dinucleotide phosphate (NADPH). Additionally, several *in vivo* and *in vitro* animal studies have demonstrated the dermal conversion of aldrin to dieldrin. Although data from humans are extremely sparse, one excretion study conducted on workers occupationally exposed to aldrin/dieldrin identified 9-hydroxy dieldrin as a fecal metabolite. Animal studies have collectively demonstrated the following metabolites of dieldrin to be among the most significant: pentachloroketone, 6,7-trans-dihydroxydihydroaldrin and its glucuronide conjugate, 9-hydroxy dieldrin and its glucuronide conjugate, and aldrin dicarboxylic acid. The appearance and proportions of these metabolites can vary by species, strain, and sex, as can the overall rates of aldrin/dieldrin biotransformation.

Limited data from occupational and volunteer studies suggest that in humans, excretion of aldrin/dieldrin and most of their metabolites occurs primarily through the bile and feces, with smaller amounts appearing in the urine. In addition, nursing mothers have been found to excrete dieldrin via lactation. Similar findings are observed in most animals, although in rabbits urinary excretion exceeds fecal excretion. Again, the identity and relative amounts of fecal and urinary excretion products can vary somewhat among species (e.g., pentachloroketone was identified as a significant urinary metabolite in the CFE rat, but was not detected in the CF_1 mouse), as well as between sexes (biliary/fecal and urinary excretion following exposure to radiolabeled dieldrin was found to be higher in male than in female rats).

Adverse Effects from Exposure to Aldrin/Dieldrin

Data from the available literature indicate that oral exposure to aldrin/dieldrin can induce a range of adverse systemic, neurological, reproductive/developmental, immunological, genotoxic, and tumorigenic effects in humans and/or animals. Some of these effects are

manifested only at moderate to relatively high doses, but others have been observed at doses lower than 0.1 mg/kg bw/day.

In humans, acute exposures to high concentrations of aldrin/dieldrin result most notably in toxicity to the central nervous system; effects most commonly reported include hyperirritability, convulsions, and coma, sometimes followed by cardiovascular sequelae such as tachycardia and elevated blood pressure. Persistent headache, nausea and/or vomiting, short-term memory loss, hypothermia, and abnormal electroencephalogram patterns have also been observed. For adult males, the acute oral lethal dose (LD_{50}) for both compounds has been estimated to be 5 g, or about 70 mg/kg bw.

When humans have been exposed for longer periods to lower doses of these compounds, neurotoxic symptoms have included headache, dizziness, general malaise, nausea, vomiting, and muscle twitching or myoclonic jerking. In general, occupational studies indicate that exposure to aldrin/dieldrin does not result in adverse hematological or immunological (e.g., dermal sensitization) effects in humans. However, two cases of immunohemolytic anemia have been linked to dieldrin exposure, as have several instances of aplastic anemia to aldrin/dieldrin exposure. While some of these associations appear fairly suggestive, others are more problematic.

The available literature does not include other significant adverse health effects in humans resulting from longer-term or chronic exposure to aldrin/dieldrin. With the exception of several statistically significant increases in the incidence of rectal or liver/biliary cancer that generally disappeared in follow-up studies, a variety of occupational/epidemiology studies have failed to provide convincing evidence that exposure to aldrin/dieldrin results in elevated risks of either cancerous or noncancerous disease. When standardized mortality ratios of exposed vs. general populations were computed for both specific causes and all causes of death, virtually all were lower than 1.0 in both initial and follow-up reports.

Available animal data (mouse, rat, guinea pig, rabbit, and dog) indicate oral LD_{50} values ranging from 33 to 95 mg/kg bw. Similar to those described in humans, neurotoxic effects observed in animals following acute to chronic exposure to aldrin/dieldrin include increased irritability, salivation, hyperexcitability, tremors followed by convulsions, loss of body weight, depression, prostrations, and death. Convulsions were observed in the rat after exposure to aldrin for 3 days at 10 mg/kg bw/day, as was brain cell histopathology after a 6-month exposure to 2.75 mg/kg bw/day in rats, or a 9-month exposure to 0.89 mg/kg bw/day in dogs. Chronic exposure of rats and mice to 0.45 to 1.5 mg aldrin/kg bw/day has variously resulted in hyperexcitability, tremors, and clonic convulsions.

Single doses of 0.5 to 16.7 mg dieldrin/kg bw were reported to disrupt operant behavior in the rat, and three 2- to 4-month rat studies collectively demonstrated hyperexcitability, tremors, and impaired operant behavior at Lowest-Observed-Adverse-Effect Levels (LOAELs) of 2.5, 0.5, or 0.025 mg dieldrin/kg bw/day, respectively. Various long-term (80 weeks to 29 months) rat studies collectively reported hyperexcitability, irritability, tremors, and/or convulsions at LOAELs of 0.5 to 2.5 mg dieldrin/kg bw/day. In another 2-year study in rats that had several potential limitations, cerebral edema and small degenerative foci were found at doses

as low as 0.0016 mg dieldrin/kg bw/day. In one 2-year study in dogs, convulsions were observed at 0.5 mg dieldrin/kg bw/day, while another reported normal electroencephalograms at 0.05 mg dieldrin/kg bw/day.

In a number of short-to-intermediate term studies in rats and mice, various manifestations of hepatotoxicity (increased relative liver weight, liver enlargement, hepatocyte hypertrophy, and elevated DNA synthesis; induction of mixed function oxidases, increased size and number of focal lesions in the rat, *but not the mouse*, following pretreatment with diethyl nitrosamine) were associated with LOAELs ranging from 0.5 to 1.5 mg dieldrin/kg bw/day, and No-Observed-Adverse-Effect Levels (NOAELs) ranging from 0.15 to 0.5 mg dieldrin/kg bw/day. One 7- to 10-day mouse study reported elevated relative liver weights at doses as low as 0.015 mg dieldrin/kg bw/day (a NOAEL was not determined).

One longer-term (16-month) study in dogs reported increased absolute and relative liver weights and hepatic fatty degeneration at doses of 0.12 to 0.25 mg aldrin/kg bw/day, but not 0.043 to 0.091 mg aldrin/kg bw/day; however, no signs of hepatotoxicity were reported in another 25-month study in dogs at 0.5 mg aldrin/kg bw/day. Liver histopathology was observed in one 2-year rat study at 0.025 mg aldrin/kg bw/day, as were enlarged livers at 2.5 mg aldrin/kg bw/day; nondose-related liver histopathology was also seen at 1 mg aldrin/kg bw/day, and increased relative liver weights at 1.5 mg/kg bw/day, in a second long-term (31-month) study in rats. However, hepatotoxicity was not noted in several other long-term studies in the mouse, rat, or dog. Similarly, while several long-term studies of dieldrin in the rat, mouse, or dog did not report evidence of hepatotoxicity, increased absolute and/or relative liver weights, increased serum alkaline phosphatase activity, and liver histopathology were collectively observed in three other 2-year studies (two rat, one dog) at 0.025 to 0.05 mg aldrin/kg bw/day.

There are limited animal data to suggest that aldrin/dieldrin can induce nephropathy or exacerbate pre-existing nephropathy. One 2-year study in rats reported that nephritis and distended-hemorrhagic urinary bladders were associated with a LOAEL of 2.5 mg aldrin/kg bw/day and a NOAEL of 0.5 mg aldrin/kg bw/day. Exposures to 0.043 to 0.091 mg aldrin/kg bw/day for up to 16 months were reported to cause distal renal tubule vacuolation in female dogs, and in dogs of both sexes at 0.12 to 0.25 mg/kg bw/day. Chronic exposure to 5.0 and 7.5 mg dieldrin/kg bw/day has been reported to result in the development of hemorrhagic and/or distended urinary bladders in male rats, usually accompanied by substantial nephritis.

In general, animal studies have provided only mixed data that moderate-to-relatively high doses of aldrin/dieldrin can result in adverse reproductive or developmental effects. There are some *in vivo* and *in vitro* data to suggest that these compounds may be weak endocrine disruptors, as various effects on male and female hormone levels and/or receptor binding, estrus cycle, endometrial or breast cell proliferation, and male germ cell degeneration and interstitial testicular cell ultrastructure have been reported. A 5-day exposure of male mice to 1 mg aldrin/kg bw/day failed to produce unequivocal evidence of dominant lethality, and a single exposure of male mice to 50 mg dieldrin/kg bw did not produce a significant dominant lethal effect.

Among the effects noted in several studies in rats and dogs at aldrin doses of 0.125 to 0.3 mg/kg bw/day were reduced pup survival during lactation, failure to achieve estrous in some females, impaired mammary development and milk production, and depressed sexual drive in males; initially, reduced fertility was also observed in two 3-generation rat studies at doses of 0.625 to 1.38 mg aldrin/kg bw/day.

Similarly, several studies using rats, mice, or dogs have demonstrated that dieldrin doses of 0.125 to 0.75 mg/kg bw/day can result in reduced pup survival during lactation. Dieldrin doses of 0.125 to 0.275 mg/kg bw/day have also resulted in initially reduced parental generation fertility rates in 3-generation rat studies. Another limited rat study reported various neural lesions in pups born to dams dosed with as little as 0.004 to 0.008 mg dieldrin/kg bw/day. Exposure to dieldrin doses of 4 mg/kg bw/day (gestation day [gd] 15 to postpartum day [ppd] 21) or 6 mg/kg bw/day (gd 7 to 16) did not affect fecundity, stillbirth or terata frequencies, fetotoxicity, or perinatal mortality in two studies in rats. However, teratogenic responses (webbed foot, cleft palate, open eye) were observed in mice and hamsters after dieldrin exposures of 15 mg/kg bw/day (gd 9) or 30 mg/kg bw/day (gd 7 to 9), respectively. Another study in mice noted an increase in supernumerary ribs, but not in major malformations, after a dieldrin exposure of 3 mg/kg bw/day (gd 7 to 16).

With respect to the immunotoxicity of aldrin/dieldrin, several studies in mice suggest that exposure to dieldrin may induce immunosuppression: single oral doses of $\geq$18 mg/kg bw have reportedly decreased the antigenic response to mouse hepatitis virus 3; a 10-week dietary exposure to concentrations as low as 1 ppm (0.15 mg/kg bw/day) increased the lethality of *Plasmodium berghei* or *Leishmania tropica* infections; and 3, 6, or 18 weeks of dietary exposure to concentrations as low as 1 ppm (0.15 mg/kg bw/day) were found to decrease tumor cell killing ability.

Numerous long-term bioassays have convincingly demonstrated that aldrin and dieldrin are hepatocarcinogens in several strains of mice; in one of these studies dieldrin was also judged to have induced lung, lymphoid, and "other" tumors. Increased incidences of hepatocellular carcinoma and/or adenoma in mice have been reported for doses as low as 0.6 to 1.5 mg aldrin/kg bw/day and 0.375 to 1.5 mg dieldrin/kg bw/day. In one dieldrin study, however, dose-related increases in the incidence of hepatocellular carcinoma and combined liver tumors, as well as decreases in tumor latency, began at doses as low as 0.015 mg/kg bw/day. In contrast to these results, all of the available bioassays (some of which are now considered inadequate tests of carcinogenicity) have failed to demonstrate any evidence of liver tumorigenicity in any strain of rats that was tested. Further, only a single rat bioassay of aldrin gave any evidence of tumorigenicity at any site—evidence for increased incidences of thyroid follicular cell adenoma/carcinoma in males and females and adrenal cortex adenoma/carcinoma in females, increases which have been considered equivocal/suggestive by some, and unrelated to treatment by others. As noted previously, aldrin/dieldrin's carcinogenicity has, on balance, not been demonstrated in humans.

Much remains unknown about the modes of action that may underlie the various toxic effects produced by exposure to aldrin/dieldrin. The hyperexcitability associated with aldrin/dieldrin neurotoxicity may arise from enhancement of synaptic activity throughout the

central nervous system (CNS), but it is not clear whether it results from facilitated neurotransmitter release at the nerve terminals or from reducing the activity of inhibitory neurotransmitters within the CNS. One hypothesis suggests that dieldrin may act by inhibiting calcium-dependent brain ATPases, which would inhibit the cellular efflux of calcium and result in higher intracellular calcium levels and subsequent neurotransmitter release. Data from relatively recent studies indicate that aldrin/dieldrin's principal mode of neurotoxic action likely involves their role as antagonists of the membrane receptor for the inhibitory neurotransmitter, gamma aminobutyric acid (GABA), and blocking the influx of chloride ion through the $GABA_A$ receptor-ionophore complex. Further, an *in vitro* study using fetal rat brain cells suggests that dieldrin may have an even greater functional effect on dopaminergic neurons.

From the available studies, the carcinogenic potential of aldrin/dieldrin appears largely confined to the mouse, and it may not rest predominantly on genotoxicity modes of action. This appears most evident in the general failure of aldrin/dieldrin to induce gene point mutations (28 negative assays, 3 positive). However, when considering either direct DNA damage or chromosome-related interactions (aberrations, aneuploidy, SCEs), the assay results are significantly more balanced (15 negative, 2 most likely negative, 11 positive, 4 "questionably" positive).

Aldrin/dieldrin's capacity to inhibit various forms of *in vitro* intercellular communication in both human and animal cells may represent a significant "epigenetic" mode of carcinogenic action with respect to their *in vivo* effects on tumor production. Several recent studies suggest that the mouse-specific hepatocarcinogenic effects of aldrin/dieldrin may result from the induction of intracellular oxidative stress (via the generation of reactive oxygen species that result in oxidative damage to DNA, protein, and lipid macromolecules), as well as increased hepatic DNA synthesis. These effects generally occur after aldrin/dieldrin treatment in mice, but not in rats. After observing the frequency and patterns of *c-Ha-ras* proto-oncogene mutations appearing in the DNA of glucose-6-phosphatase-deficient hepatic lesions found in control mice, or in those treated with dieldrin or phenobarbital, another study concluded that the increase in hepatic lesions (and thus tumors) resulting from dieldrin treatment principally resulted from promotional, rather than initiation, events. It also has been postulated that aldrin/dieldrin induction of hepatic DNA synthesis may result from the modulation of protooncogene expression via various transcription factors.

The available literature included almost no direct evidence for any human subpopulations that would be particularly sensitive to the toxic effects of aldrin/dieldrin, or for which relevant toxicokinetics are known to differ significantly from those for the general population. Speculatively, the fetus and very young children might be at increased risk from exposures to aldrin/dieldrin as a result of immature hepatic detoxification and excretion functions, as well as developing target organ systems. In this regard, a single case study reported that a 3 year-old female child died after ingesting approximately 8.2 mg aldrin/kg bw, which is roughly an order of magnitude below the estimated lethal dose for adult males. Several mechanistic studies that describe the prenatal effects of aldrin/dieldrin on GABA receptor malfunctions and on subsequent behavioral impairment also suggest an increased sensitivity of children. Declining organ and immune functions could potentially render the elderly more susceptible to aldrin/dieldrin toxicity, and it is reasonable to expect that any individuals with compromised

liver, immune, or neurological functions (as a result of disease, genetic predisposition or toxic insult) might be especially sensitive to these compounds.

Dose-Response Assessments

As previously noted, the acute oral lethal dose for aldrin/dieldrin in adult humans has been estimated at 70 mg/kg bw, which is about 3 times the dose reported to have induced convulsions within 20 minutes of ingestion. Oral LD_{50} values in various animal species for the two compounds have been reported to range from 33 to 95 mg/kg bw, and may be affected by age at the time of exposure. In rats, LD_{50} values were reported at 37 mg/kg bw for young adults, 25 mg/kg bw for 2-week-old pups, and 168 mg/kg bw for newborns.

Adequate dose-response relationships have not been characterized in humans for any of the toxic effects of aldrin/dieldrin. In animals, oral exposure has produced a variety of dose-dependent systemic, neurological, immunological, endocrine, reproductive, developmental, genotoxic, and tumorigenic effects over a collective dose range of at least three orders of magnitude (<0.05 to 50 mg/kg bw), depending on endpoint and exposure duration. For noncancer effects, the U.S. EPA has determined oral Reference Doses (RfDs) for both aldrin and dieldrin based on the most sensitive relevant toxic effects (critical effects) reported. For aldrin, the critical effect was liver toxicity observed in one rat study after chronic exposure to approximately 0.025 mg/kg bw/day, the LOAEL and the lowest dose tested. This dose was divided by a composite uncertainty factor of 1,000 (to account for rat-to-human extrapolation, potentially sensitive human subpopulations, and the use of a LOAEL rather than a NOAEL) to yield an oral RfD of 3×10^{-5} mg/kg bw/day. Similarly, for dieldrin a chronic rat NOAEL for liver toxicity of approximately 0.005 mg/kg bw/day was divided by a composite uncertainty factor of 100 (to account for rat-to-human extrapolation and potentially sensitive human subpopulations), yielding an oral RfD of 5×10^{-5} mg/kg bw/day.

Based on long-term mouse bioassays, the EPA has classified both aldrin and dieldrin as Group B2 carcinogens under the 1986 cancer guidelines, that is, as probable human carcinogens with little or no evidence of carcinogenicity in humans, and sufficient evidence in animals. Under the U.S. EPA's proposed 1996/1999 cancer risk assessment guidelines, the weight of evidence indicates that aldrin and dieldrin could be classified as rodent carcinogens that are "*likely to be carcinogenic to humans by the oral route of exposure, but whose carcinogenic potential by the inhalation and dermal routes of exposure cannot be determined because there are inadequate data to perform an assessment*." This characterization must be tempered by the lack of evidence for significant human carcinogenicity from epidemiological studies and by the general lack of corroborative evidence for carcinogenicity in rats. Mechanistic studies suggest that non-genotoxic modes of action may underlie or contribute to aldrin/dieldrin's carcinogenic potential, but their relevance to human carcinogenicity is not fully established, and a role for genotoxic mechanisms cannot confidently be eliminated based on the available data. Based on these considerations, the quantitative cancer risk assessments of aldrin and dieldrin have been conducted conservatively using the linear-default model.

This approach has yielded respective geometric mean cancer potency estimates for aldrin and dieldrin of 17 and 16 $(mg/kg\ bw/day)^{-1}$. These result in drinking water unit risks of $4.9 \times 10^{-}$

^{4} per mg/L and 4.6×10^{-4} per mg/L, respectively. For both compounds, an estimated lifetime excess cancer risk of 10^{-6} results from a drinking water concentration of 0.002 µg/L . This concentration, 0.002 µg/L, was selected as the Health Reference Level (HRL) used elsewhere in this document to put into context the levels of aldrin/dieldrin detected in drinking water.

Risk Characterizations and Regulatory Determinations for Aldrin/Dieldrin

Evaluating the second criterion involves analysis of public water system monitoring data, ambient water concentrations and environmental releases, and the chemical's environmental fate. Since aldrin/dieldrin have not been used in the U.S. since 1987, no new environmental releases are expected (with the possible exception of a very few from hazardous waste treatment plants). Available data indicate that these chemicals are detected very infrequently in drinking water, and then at very low concentrations. Their occurrence in ambient water appears to be of minimal concern, and while environmental fate data suggest that they may continue to be released to water over a long period of time, the concentrations involved will remain quite low.

2.0 IDENTITY: PHYSICAL AND CHEMICAL PROPERTIES

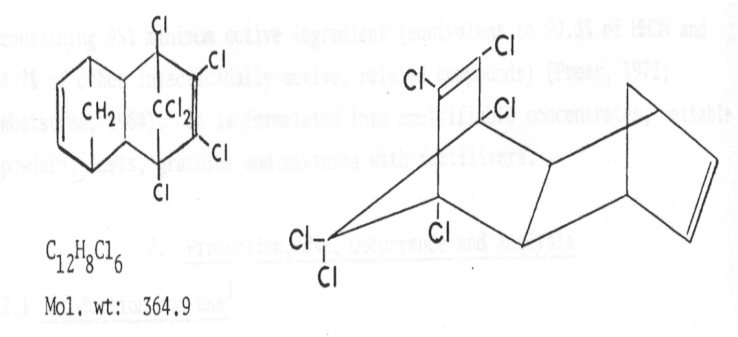

Figure 2-1. Aldrin Chemical Structure

The molecular weight and chemical formula of aldrin (CAS RN 309-00-2) are shown above (Figure 2-1), in conjunction with two representations of its structural formula. Aldrin is the common name approved by the International Standards Organization (except in Canada, Denmark, and the former Soviet Union) for the product that contains at least 95% of the substance identified by one of the following IUPAC chemical names (IARC, 1974a; IPCS, 1989a,b; Lewis, 1993):

1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-*exo*-1,4-*endo*-5,8-dimethanonaphthalene; or
(1R,4S,5S,8R)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene

In Canada, aldrin refers to the pure compound, which in Great Britain is called HHDN. Aldrin has a significant number of chemical synonyms and common trade names (HSDB, 2000a; IARC, 1974a; IPCS, 1989a,b; Sittig, 1991; USEPA, 1992), including:

ALDOCIT
Aldrex
ALDROSOL
Compound 118
Drinox
ENT 15,949
Hexachlorohexahydro-endo-exo-dimethanonaphthalene
HHDN
KORTOFIN
OCTALENE
OMS 194
SEEDRIN

Technical grade aldrin was formulated to contain not less than 90% aldrin (as defined above), i.e., not less than 85.5% of the main ingredient, with not less than 4.5% insecticidal

impurities and not more than 10% other impurities (HSDB, 2000a; IARC, 1974a; IPCS, 1989a,b). Impurities that have been identified include a complex mixture of compounds formed by the polymerization of hexachlorocyclopentadiene (HCCPD) and bicycloheptadiene (BCH) (3.6 to 3.7%), polychlorohexahydrodimethanonaphthalene compounds (isodrin) (3.5%), hexachlorobutadiene (0.5 to 0.6%), chlordane (0.5%), octachlorocyclopentene (0.4 to 0.5%), toluene (0.3 to 0.6%), HCCPD (0.2%), HHDN di-adduct (0.1%), BCH (<0.1%), and hexachloroethane (<0.1%) (IARC, 1974a; IPCS, 1989a,b).

Aldrin has been formulated into seed dressings (75%), dust concentrates (75%), emulsifiable concentrates (24 to 48%), wettable powders (20 to 40%), granules (2 to 25%), low-percentage dusts (2 to 5%), and mixtures with fertilizers (0.4 to 2%) (HSDB, 2000a; IARC, 1974a). Epichlorohydrin, a known carcinogen, was sometimes incorporated into the emulsions to help prevent corrosion by hydrochloric acid, as was urea into wettable powders to prevent dehydrochlorination by certain catalytically-active carriers (HSDB, 2000a).

Aldrin is reported to be stable in the presence of organic and inorganic alkalies, diluted acids, and hydrated metal chlorides (Budavari et al., 1989; IARC, 1974a; Lewis, 1993). While minimally corrosive to steel, brass, monel, copper, nickel, and aluminum, aldrin can be slightly corrosive to metals upon storage as a result of the slow formation of hydrogen chloride (HSDB, 2000a; IPCS, 1989b). Most fertilizers, herbicides, fungicides, and insecticides were reported to be compatible with aldrin (Lewis, 1993), but in general, contact with concentrated mineral acids, acid catalysts, acid oxidizing agents, phenols, or active metals should be avoided (IPCS, 1989a,b; Sittig, 1991).

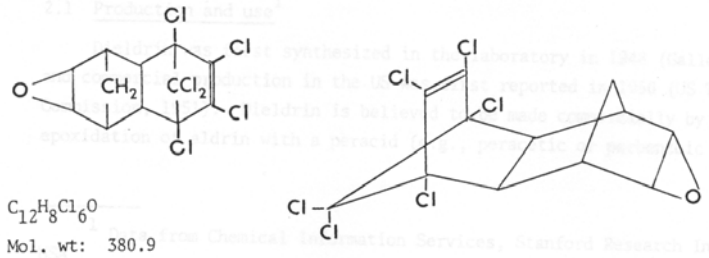

Figure 2-2. Dieldrin Chemical Structure

Dieldrin is formed by the epoxidation of aldrin with peracetic or perbenzoic acid (IARC, 1974a). Some of aldrin's chemical properties are summarized later in Table 2-1.

Table 2-1. Selected Chemical-Physical Properties of Aldrin and Dieldrin[1]

Property	Aldrin	Dieldrin
Chem. Formula (MW)	$C_{12}H_8Cl_6$ (364.93)	$C_{12}H_8Cl_6O$ (380.93)
Physical State	Clear to white crystals; tan to dark brown solid (technical)	Clear to white crystals; buff to light tan flakes (technical)
Melting Point	104–105.5 °C; 49–60 °C (technical)	175–177 °C; > 95 °C (technical)
Boiling Point	145 °C (at 2 mm Hg)	330 °C
Density (at 20 °C)	1.6–1.7 g/cc;1.54 g/cc (technical)	1.75 g/cc;1.62 g/cc (technical)
Solubility (Water)	0.027 mg/L (at 27 °C); also reported as 0.20 mg/L (at 25 °C)	0.1–0.195 mg/L (at 20–29 °C)
Solubility (Organic Solvents)	Moderately to very sol. in most paraf-finic and aromatic hydrocarbons, esters, ketones, and halogenated solvents, less so in alcohols; > 600 g/L in acetone, benzene, and xylene (at 27 °C)	Moderately sol. in common organic solvents, except aliphatic petroleum hydrocarbons, and methanol (in g/L at 20 °C: 400 – benzene, 220 – acetone, 10 – methanol)
Log K_{ow}	3.01 or 6.50; 7.4 (technical)	5.40; 6.2 (technical)
Log K_{oc}	4.96	3.87
Vapor Pressure (20 °C)	2.3–7.5 x 10^{-5} mm Hg	3.1 x 10^{-6} or 1.78 x 10^{-7} mm Hg
Vapor Pressure (25 °C)	1.4 x 10^{-4} mm Hg or 6 x 10^{-6} mm Hg	5.89 x 10^{-6}, 7.78 x 10^{-7}, or 1.8 x 10^{-7} mm Hg
Henry's Law Constant (at 25 °C)	3.2 x 10^{-4} atm-m^3/mol or 1.27 x 10^{-5} atm-m^3/mol (est.)	5.8 x 10^{-5} atm-m^3/mol or 1.51 x 10^{-5} atm-m^3/mol
Odor	Mild chemical odor	Mild chemical odor
Odor Threshold	0.017 mg/L (water) 0.3 mg/m^3 (air)	0.04 mg/L (water) NA (air)
Conversion Factors[2] (at 25 °C, 1 atm)	1 ppm = 14.96 mg/m^3 (at 25 °C, 1 atm)	1 ppm = 15.61 mg/m^3 (at 25 °C, 1 atm)

[1] ATSDR (2000); Budavari et al. (1989); HSDB (2000a,b); IARC (1974a,b); IPCS (1989b); Lewis (1993); Sittig (1991); Verschueren (1983).
[2] ATSDR (2000).

The molecular weight and chemical formula of dieldrin (CAS RN 60-57-1) are shown above (Figure 2-2), in conjunction with two representations of its structural formula. Dieldrin is the common name approved by the International Standards Organization (except in Canada, Denmark, and the former Soviet Union) for the product that contains at least 85% of the substance identified by one of the following IUPAC chemical names (IARC, 1974b; IPCS, 1989a,b; Lewis, 1993):

1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-*exo*-5,8-dimethanonaphthalene; or
(1R,4S,5S,8R)-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene

In Canada, dieldrin refers to the pure compound, which in Great Britain is called HEOD. Dieldrin has a significant number of chemical synonyms and common trade names (HSDB, 2000b; IARC, 1974b; IPCS, 1989a,b; Sittig, 1991; USEPA, 1988), including:

ALVIT
Compound 497
DIELDREX
DIELMOTH
ENT 16,225
HEOD
Hexachloroexpoxyoctahydro-endo-exo-dimethanonaphthalene
Illoxol
Octalux
OMS 18
QUINTOX
Red Shield
TERMITOX

Technical grade dieldrin was formulated to contain not less than 95% dieldrin (as defined above), i.e., not less than 80.75% of the main ingredient; however, it was available in the United States in a formulation containing 100% active ingredient, i.e., not less than 85% HEOD, with not less than 15% related insecticidally-active compounds (HSDB, 2000b; IARC, 1974a; IPCS, 1989a,b; Lewis, 1993). Impurities reportedly found in technical grade dieldrin include aldrin, other polychloroepoxyoctahydrodimethanonaphthalenes (including endrin, 3.5%), free HCl (<0.4%), and water (<0.1%) (HSDB, 2000b; IARC, 1974b; IPCS, 1989a,b).

Dieldrin has been formulated into wettable powders (40 to 75%), oil solutions (18 to 20%), emulsifiable concentrates (15 to 20%), granules (5%), seed dressings, dusts, and mixtures with fertilizers (HSDB, 2000b; IARC, 1974b).

Dieldrin is reported to be stable in the presence of organic and inorganic alkalies, mild acids commonly used in agriculture, and light (Budavari et al., 1989; IARC, 1974b; IPCS, 1989a,b), although it may react with sunlight to produce photodieldrin (IARC, 1974b). As with aldrin, dieldrin can be slightly corrosive to metals upon storage as a result of the slow formation

of hydrogen chloride (HSDB, 2000b; IPCS, 1989b). Most fertilizers, herbicides, fungicides, and insecticides were reported to be compatible with dieldrin (Lewis, 1993), but in general, contact with concentrated mineral acids, acid catalysts, acid oxidizing agents, phenols, or active metals (iron, copper, sodium) should be avoided (Budavari et al., 1989; IPCS, 1989a,b; Sittig, 1991). Dieldrin is formed by the epoxidation of aldrin with peracetic or perbenzoic acid (IARC, 1974a,b), and is a stereoisomer of endrin (Budavari et al., 1989). It reportedly reacts with hydrogen bromide to give the bromohydrin (HSDB, 2000b). Some of dieldrin's chemical properties are summarized in Table 2-1.

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3.0 USES AND ENVIRONMENTAL FATE

This section summarizes information derived from cited secondary references pertaining to the uses, manufacture, and environmental fate of aldrin and dieldrin.

3.1 Uses and Manufacture

These compounds are organochlorine pesticides that act as highly effective contact and stomach poisons for insects (IPCS, 1989a). Aldrin was used as a broad-spectrum soil insecticide (generally at 0.5 to 5 kg/hectare) for the protection of corn, potato, citrus, and other crops against termites, corn rootworms, seed corn beetles and maggots, wireworms, rice water weevil, grasshoppers, Japanese beetles, etc., as well as a seed dressing for rice and to combat ant and termite infestations of wooden structures (ATSDR, 2000; IPCS, 1989a,b; USEPA, 1992). Dieldrin was once used similarly in agriculture, but no longer; it was then used principally to protect wooden structures against ant and termite attack, in industry for protection against termites, wood borers and textile pests, and as a residual spray and larvacide for the control of several insect vectors of disease (ATSDR, 2000; IPCS, 1989a,b; USEPA, 1988).

The US Department of Agriculture banned all uses of aldrin and dieldrin in 1970, but in 1972 under the authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the EPA permitted their use in three cases: subsurface ground insertion for termite control, dipping of non-food plant roots and tops, and mothproofing of woolen textiles and carpets under conditions of no effluent discharge (ATSDR, 2000; USEPA, 1980). The latter two registered uses were abandoned by the manufacturer in 1974, as was the ground-insertion termiticide use in 1987; therefore, all uses of aldrin and dieldrin have been canceled (ATSDR, 2000; USEPA, 1980).

In the United States, the use of aldrin peaked at 19,000,000 lbs in 1966 and had declined to about 10,500,000 lbs by 1970; concurrently, dieldrin use declined from 1,000,000 lbs to about 650,000 lbs (USEPA, 1980). There was some importation of these compounds during the 1970s and early-mid 1980s; the USEPA has reported that no aldrin has been imported since 1985 (ATSDR, 2000). Aldrin was not imported into the United States prior to the 1974 cancellation decision; however, Shell International (Holland) imported the chemical for limited use from 1974 to 1985 (with the exception of 1979 and 1980, when imports were temporarily suspended). An estimated 1 to 1.5 million lbs of aldrin were imported annually from 1981 to 1985, after which time importation ceased. By 1987, all uses of aldrin had been cancelled voluntarily by the manufacturer (ATSDR, 2000). In 1972, USEPA cancelled all but the following three uses of dieldrin: subsurface ground insertion for termite control, the dipping of non-food plant roots and tops, and mothproofing in manufacturing processes using completely closed systems. This cancellation decision was finalized in 1974. By 1987, all uses of dieldrin had been cancelled voluntarily by its manufacturer (the Shell Chemical Company) (ATSDR, 2000).

3.2 Environmental Release and Fate

Aldrin is listed as a Toxic Release Inventory (TRI) chemical. In 1986, the Emergency Planning and Community Right-to-Know Act (EPCRA) established the Toxic Release Inventory

(TRI) of hazardous chemicals. Created under the Superfund Amendments and Reauthorization Act (SARA) of 1986, EPCRA is also sometimes known as SARA Title III. The EPCRA mandates that larger facilities publicly report when TRI chemicals are released into the environment. This public reporting is required for facilities with more than 10 full-time employees that annually manufacture or produce more than 25,000 pounds, or use more than 10,000 pounds, of a TRI chemical (USEPA, 1996/1999; USEPA, 2000a).

Under these conditions, facilities are required to report the pounds per year of aldrin released into the environment both on- and off-site. The production, import, and use of aldrin had been cancelled by the time the TRI was instated; therefore, no release or transfer data were reported. In 1995, Resource Conservation and Recovery Act (RCRA) Subtitle C hazardous waste treatment and disposal facilities were added to the list of those facilities required to present release data to the TRI. This addition became effective for the 1998 reporting year, which is the most recent TRI data currently available. Waste treatment facilities from three states (AR, MI, TX) reported releases of aldrin in 1998, with on- and off-site releases totaling 25,622 pounds. The on-site quantity is subdivided into air emissions, surface water discharges, underground injections, and releases to land. Most of the aldrin released to the environment was released directly to land (22,000 lbs) (USEPA, 2000b).

Although the TRI data can be useful in giving a general idea of release trends, it is far from exhaustive and has significant limitations. For example, only industries that meet TRI criteria (at least 10 full-time employees and the manufacture and processing of quantities exceeding 25,000 lbs/year, or use of more than 10,000 lbs/year) are required to report releases. These reporting criteria do not account for releases from smaller industries. Also, the TRI data is meant to reflect releases and should not be used to estimate general exposure to a chemical (USEPA, 2000c).

Aldrin is included in the Agency for Toxic Substances and Disease Registry's (ATSDR) Hazardous Substance Release and Health Effects Database (HazDat). This database records detections of listed chemicals in site samples; aldrin was detected in 40 states (states without detections are AZ, DE, HI, ME, MS, MT, NV, NM, OR, WY) (ATSDR, 2000). The National Priorities List (NPL) of hazardous waste sites, created in 1980 by the Comprehensive Environmental Response, Compensation & Liability Act (CERCLA), is a listing of some of the most health-threatening waste sites in the United States. Aldrin was detected in NPL hazardous waste sites in 31 states (USEPA, 1999).

Dieldrin is also included in the ATSDR's HazDat. Dieldrin was detected in 40 states (states without detections are AZ, DE, HI, MN, MT, NV, NM, OR, UT, WY) (ATSDR, 2000). Dieldrin was detected in NPL hazardous waste sites in 38 states (USEPA, 1999).

In summary, aldrin and dieldrin have not been produced in the United States since 1974, and all uses of the pesticide were cancelled by 1987. Aldrin had been used mostly on corn and citrus products. Dieldrin had been used mostly on corn, potatoes, tomatoes, and citrus products. Aldrin was imported to the United States from Holland from 1974 to 1985 (with the exception of 1979 and 1980) in quantities of approximately 1 to 1.5 million lbs/year. TRI data from 1998 suggest that aldrin continues to be released into the environment, even though the chemical is no

longer produced or used in the United States. Aldrin's presence and persistence in the environment is evidenced by detections of the compound in hazardous waste sites in at least 31 states (at NPL sites), as well as detections in site samples in at least 40 states (listed in ATSDR's HazDat).

Most aldrin introduced into the environment is relatively rapidly converted through epoxidation to dieldrin, which in turn is notably persistent in the environment due to its very low solubility in water and its extremely low volatility. Because dieldrin is also extremely apolar, it displays a high affinity for fat and is thus retained in animal fats, plant waxes, and other similar organic matter in the environment. This fat solubility can lead to a progressive accumulation of dieldrin in the food chain, which theoretically could eventually produce concentrations in organisms that might exceed lethal limits to predators or consumers (Sittig, 1991; USEPA, 1980).

Environmental Media Transport and Distribution

Given the historical uses of aldrin and dieldrin, their point of entry into the environment has most typically been the soil (IPCS, 1989b). Because of their strong adsorption to soils and their low aqueous solubilities, significant downward leaching of these compounds through the soil profile would not be anticipated (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b). As discussed further below, most aldrin in the soil is gradually converted to dieldrin under most environmental conditions (ATSDR, 2000; HSDB, 2000a; IPCS, 1989b). Field studies of the application of aldrin to the surface layer of various types of soils have demonstrated nearly quantitative adsorption by organic matter and clay minerals, and that even 5 years after application, residual aldrin and dieldrin were still found in the surface layer with very little penetration to lower soil depths (IPCS, 1989b). Water has been found to compete with aldrin for adsorption sites in clay minerals, and thus aldrin binds to a greater extent when the soil is dry; in dry soils, mineral components play the largest role in adsorption, whereas in moist soils, organic materials are predominant; and other factors being equal, adsorption is expected to be the lowest in sandy soils having minimal organic content (IPCS, 1989b).

In one summarized study, aldrin was applied to the upper 5 inches of a silt loam soil (HSDB, 2000a). Combining the results for non-disked soil with those of soil disked for one summer only, the reported distribution of residual aldrin after 10 years by soil depth was as follows: 11 to 13% (0 to 2 inches), 29 to 33% (2 to 4 inches), 29 to 33% (4 to 6 inches), 23 to 29% (6 to 9 inches). In a study by Weisgerber et al. (1974), aldrin was quantified at different soil depths 3 to 6 months after its application at about 3 kg/ha to soils used for growing corn in several countries. Their findings are summarized below in Table 3-1. As is readily apparent, aldrin demonstrated little proclivity to migrate down through the various soil profiles; similar results were observed for soils in England and Germany used to grow wheat (Weisgerber et al.,

Table 3-1. Aldrin Mobility in Soils Used to Grow Corn[1]

Soil Depth (cm)	Residual Aldrin Levels in Soils Used to Grow Corn[2]: ppm (% Total Extractable)			
	Germany	England	Spain	United States
0–10	0.78 (78%)	1.30 (~100%)	0.83 (96.5%)	0.50 (98%)
10–20	0.18 (18%)	<0.01 (<1%)	0.02 (2.3%)	0.01 (1.96%)
20–40	0.03 (3%)	<0.01 (<1%)	0.01 (1.2%)	<0.01 (<1%)
40–60	<0.01 (<1%)	<0.01 (<1%)	<0.01 (<1%)	<0.01 (<1%)

[1] From Weisgerber et al. (1974).
[2] Measured 5, 6, 4, or 3 months (respectively by country) after the application of about 3 kg aldrin/ha.

1974), and for various laboratory studies of soil samples in columns that were eluted with water (HSDB, 2000a; IPCS, 1989b).

In a laboratory test of six types of soil placed in chromatographic columns, the percentage of applied dieldrin that eluted with 1600 ml of water varied from 1% in loam soil, to 65% in soil containing 93% sand (IPCS, 1989b). Little dieldrin leaching was observed in a similar column experiment involving 3 soil types eluted with about 30 L of water over 120 hours (IPCS, 1989b), and even with high temperatures and prolonged leaching, dieldrin has been considered essentially immobile (HSDB, 2000b). Experimentally determined log soil sorption coefficients (K_{oc}) of 2.61 to 4.45 for aldrin and 3.87 for dieldrin further suggest that these compounds are not highly mobile in soils and will not appreciably leach to groundwater (HSDB, 2000a,b). In areas with poorly controlled erosion, surface run-off can carry particle-associated aldrin and dieldrin into surface waters; in the absence of sediment, however, rain water run-off does not appear to be a major transport mechanism (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b). The equilibrium ratio of dieldrin concentration in soil to that in water was shown to be 100 to 500 for mineral soils and likely to be 5 to 6 times higher for aldrin (IPCS, 1989b). Vapor diffusion is, generally, regarded as the principal mechanism whereby aldrin and dieldrin ascend the soil profile. The role of upward mass flow in capillary water through a moisture gradient, though demonstrated in laboratory studies, is now thought to be relatively insignificant in the field (IPCS, 1989b).

Most studies have concluded that the observed, relatively rapid loss of aldrin and dieldrin from soil during the first few months after application is principally attributable to volatilization processes (ATSDR, 2000; IPCS, 1989b). There is substantial evidence for this. Mosquitoes were shown to be killed by vapors emanating from treated soils and it is known that when aldrin is incorporated into soil, it is most readily lost from the surface layer (IPCS, 1989b). Various laboratory studies have reportedly (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b) demonstrated that: volatilization of aldrin is significantly faster than that of dieldrin (about 20-fold, in one

case); chamber rates of volatilization for each chemical decrease with time (about 50% over 6 to 7 hours in one experiment with dieldrin); volatilization of aldrin from sands increases (from trace levels to up to 7.33% after 6 hours) with increased water content in the sands and/or increased humidity in the air passing over the sands; and volatilization rates of aldrin from sand, loam, and humus during the first or second hour after application were 1.08, 0.21, and 0.08, or 0.59, 0.18, and 0.09% per ml evaporated water, respectively.

Actual field studies on volatilization losses from soil are limited in number and appear available only for dieldrin (ATSDR, 2000; IPCS, 1989b). Reported volatilization losses include 2.8% after 18 weeks and 4.5% after 1 year. In one study involving a very high application rate (22 kg/ha or 10 ppm) to soils under three different soil moisture conditions, volatilization losses after 5 months were 18% in a plot kept moist by irrigation, 7% in a non-irrigated plot receiving only natural rainfall, and only 2% in a plot flooded to a depth of 10 cm.

Related studies examining the overall loss (by any mechanism) of aldrin or dieldrin from soil have been reviewed (ATSDR, 2000; HSDB, 2000a; IPCS, 1989b; Verscheuren, 1983). After several years of field application of aldrin at three different rates, residues were shown to be higher in clay loam than in sandy loam soils (half-lives of 79 to 97 vs. 36 to 45 days, respectively), although the rate of conversion to dieldrin was higher in the latter (ATSDR, 1993; HSDB, 2000a). An early study examined various Illinois soils that had been treated with aldrin, demonstrating that aldrin was indeed transformed to dieldrin, and concluding that loss of related residues was a two-stage process—a comparatively rapid phase during the first year after application in which, typically, ~75% of the applied dose was lost. An extended second phase displayed residue half-lives of 2 to 4 years, perhaps due to increased content of the more stable dieldrin in the total residue (IPCS, 1989b). This same qualitative result was observed when aldrin was applied to muck and loam soils, with respective half-lives of 3.75 and 2.40 months during the first half year and then 13.0 and 9.7 months for the following 3 years (HSDB, 2000b).

Following the application of 1.5 kg aldrin/ha to flooded soil, approximately 56, 45, 26, 12, and 0% remained after 30, 90, 120, 240, and 270 days, respectively (HSDB, 2000b). Similarly, 3.5 years after the application of 20 or 200 lbs of aldrin/"6 inch" acre to a Miami silt loam, only 1.12 and 2.55% remained, respectively (HSDB, 2000b). Other reported studies have demonstrated an increase in aldrin loss from soils with increasing temperature, more rapid loss under upland (80% water-saturated) than under flooded conditions, and more rapid loss from the upper layers of most soils (HSDB, 2000b). Although some contrary findings have been reported, aldrin losses from temperate soils often appear more rapid than from tropical soils (IPCS, 1989b). Separate studies carried out with dieldrin suggest residue rate losses that are considerably slower than those observed for aldrin, but the reported range is wide (IPCS, 1989b); one study reported an average time of 8 years for the disappearance of 95% of the dieldrin residues; however, much slower, as well as intermediate, rates can also be found in the literature. Verschueren (1983) indicates a period of 1 to 6 years for the disappearance of 75 to 100% of aldrin from soils; for dieldrin, comparable indicated values were 3 to 25 years for 75 to 100%, and 12.8 years for 95%.

As noted previously, aldrin and dieldrin are highly resistant to being leached from soils, and as a consequence, they have only rarely been observed in ground water samples (ATSDR,

2000; IPCS, 1989b). By contrast, surface waters have frequently been reported to contain small amounts of these pesticides (more frequently dieldrin), probably as a result of surface run-off of rain water in which most of the residues are adsorbed to sediments (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b). The ultimate fate of these small residue amounts is not known with certainty, but adsorption to sediments, volatilization, and bioconcentration have been postulated to play the most significant roles, with certain degradation mechanisms (especially abiotic) also involved to some extent (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b).

While volatilization is considered an important pathway for water residues of these compounds, conflicting data are reported in the literature (e.g., volatilization half-life for dieldrin of hours to months) (HSDB, 2000b). Rates are expected to vary directly with wind and water current velocities, and inversely with the depth of the water body (HSDB, 2000a). Half-lives for the volatilization of aldrin from pure water and from three natural waters were reported to be 0.38 and 0.59 to 0.60 hours, respectively. From a different study, volatilization rates from water during the first and second hours were reported to be 16.3 and 6.03% per ml evaporated water, respectively (HSDB, 2000a). Verschueren (1983) and HSDB (2000a) indicate a derived half-life value of 185 hours (7.7 days) for aldrin in a 1m column of water at 25 °C. Using a water solubility of 0.20 mg/L and a vapor pressure of 6×10^{-6} mm Hg (both measured at 25 °C), an estimated Henry's Law constant of 1.27×10^{-5}, and reasonable assumptions for wind velocity, current velocity and water depth, half-lives for aldrin in streams, rivers, and lakes were calculated as 105.5 hours, 133.9 hours, and 6873.1 hours (286.4 days), respectively (HSDB, 2000a). For dieldrin, Verschueren (1983) and IPCS (1989b) indicate a derived half-life value of 12,940 hours (539.2 days) in a 1 m column of water at 25 °C. A cited experimental volatilization rate for dieldrin in water is 5% of the reaeration rate, which, using typical reaeration rates for ponds, rivers, and lakes, yields estimated evaporation half-lives for dieldrin of 72, 14, and 52 days, respectively; however, values as short as 6 to 9 hours under certain laboratory conditions have been reported (HSDB, 2000b).

From the previous discussion, it is apparent that a substantial portion of the aldrin and dieldrin used in agriculture is, generally, considered to reach the atmosphere (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b). Although there are data to suggest that dieldrin may be transported great distances in the atmosphere, in general, only small amounts have been detected by global atmospheric sampling (ATSDR, 2000; IPCS, 1989b). Washout by rain may play an important role in preventing atmospheric accumulation of these compounds, but the significance of this mechanism is called into question by observations of no detectable levels of aldrin or dieldrin in soils adjacent to treated areas (IPCS, 1989b). As further discussed below, various atmospheric degradation mechanisms may also play a key role in minimizing accumulation.

Environmental Degradation

The principal transformation of aldrin that occurs in all aerobic and biologically active soils is its epoxidation to dieldrin (ATSDR, 2000; HSDB, 2000a; IPCS, 1989b). This reaction has also been observed in plants, but does not occur under anaerobic conditions (IPCS, 1989b). Soil transformation to aldrin dicarboxylic acid has also been well established (ATSDR, 2000;

IPCS, 1989b). Fungi and other soil microbes have been demonstrated to degrade aldrin in culture (ATSDR, 2000; HSDB, 2000a; IPCS, 1989b). Dieldrin is much more resistant to biodegradation than aldrin, and thus microbial degradation is likely only a minor pathway for the loss of dieldrin from soils (ATSDR, 2000; HSDB, 2000b; IPCS, 1989b). This is reflected in the long times (years) that have been reported for dieldrin half-lives or times required for 50 to 100% loss (see previous discussion). There is some evidence that certain microbes can metabolize dieldrin to photodieldrin and that this is more likely to occur under anaerobic conditions. A number of studies have detected low to very low soil concentrations of photodieldrin (ATSDR, 2000; HSDB, 2000b; IPCS, 1989b). Although not biodegraded in standard screening tests, a number of soil microorganisms have been isolated that are capable of degrading dieldrin to limited degrees (ATSDR, 2000; HSDB, 2000b; IPCS, 1989b).

Under aqueous conditions, biodegradation of aldrin is expected to be slow; none was observed through the third subculture with one mixed culture inoculum from sewage, while an activated sludge biodegraded 1.5% of an initial amount of aldrin over an unspecified amount of time (HSDB, 2000a). A water surface film collected off the coast of Hawaii degraded 8.1% of added aldrin to its diol after 30 days; a pure culture of a marine alga degraded 23.3% of the initial aldrin to dieldrin and 5.2% to the diol; and a pure culture of Aerobacter aerogenes was reported to degrade 36 to 46% of an initial amount of aldrin within 24 hours (HSDB, 2000a). Under anaerobic aqueous conditions, aldrin is not epoxidized to dieldrin, but has been reported to be completely degraded to other compounds within 60 days by an anaerobic sewage sludge (ATSDR, 2000; IPCS, 1989b). Although no biodegradation of dieldrin was reported in some studies of river waters, microorganisms isolated from certain lake water and lake-bottom sediments may be able to transform some dieldrin to photodieldrin under anaerobic conditions (ATSDR, 2000).

However, dieldrin was not significantly degraded under anaerobic conditions by an active waste water sludge or by sewage sludge microorganisms in 2 studies and was only degraded by 11% after 48 hours or by 24% after 32 days in 2 other studies (ATSDR, 2000). By comparison, an aerobic activated sludge was able to degrade 55% of the initial level of dieldrin in 9 days, another activated sludge achieved dieldrin degradation of 30 to 60% (time frame not specified in review), and a mixed anaerobic microbial culture degraded 10 μg dieldrin/ml by 50% in 30 days (ATSDR, 2000). Some biodegradation pathways of aldrin and dieldrin are illustrated below in Figure 3-1, taken from Verschueren (1983). Although intended to describe metabolism under oceanic conditions, they are relevant to other soil and fresh water environments as previously discussed.

Various abiotic processes may also contribute to the environmental degradation of aldrin and dieldrin, although their role seems generally to be considered relatively limited (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b). The high reactivity of hydroxyl and other atmospheric free radicals could possibly play a role in the degradation of aldrin and dieldrin occurring as vapors (IPCS, 1989b) and the half-life for vapor phase aldrin reacting with photochemically generated hydroxyl radicals has been estimated at 35 minutes (HSDB, 2000a). As might be expected from its weak absorption to wavelengths above 290 nm, sunlamp photolysis of aldrin vapor has been observed to be rather slow—60% in 1 week, vs. 16% in a dark control (HSDB,

2000a). Both aldrin and dieldrin are susceptible to photochemical reactions following irradiation by sunlight or

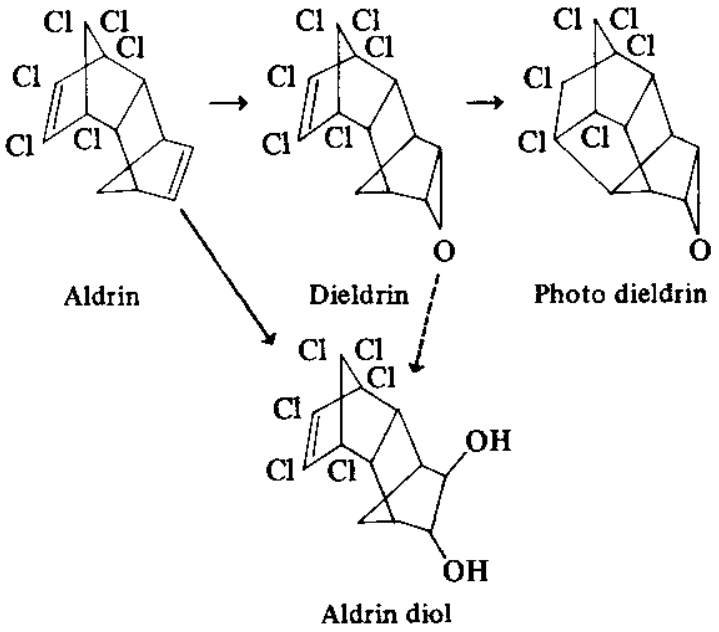

Figure 3-1. Biodegradation Pathways for Aldrin and Dieldrin, With Particular Reference to Oceanic Conditions (Verschueren, 1983)

UV under abiotic laboratory conditions, with epoxidation and isomerization transformations resulting in the formation of photoaldrin and photodieldrin (ATSDR, 2000; HSDB, 2000b; IPCS, 1989b). These reactions are illustrated below in Figure 3-2, taken from Verschueren (1983). Photodieldrin is believed to be a stable photoproduct of aldrin as it no longer contains a chromophore. It has, in fact, proven resistant to further photolysis (ATSDR, 2000).

Other experimental work found that while photoaldrin was produced upon sunlight or ultraviolet light (UV) irradiation of aldrin, the major photoproduct was an unbridged compound that had lost a chlorine atom from the 3 position; the yield of photoaldrin (and photodieldrin from dieldrin) was also found to be substantially enhanced in the presence of benzophenone or other ketones (IPCS, 1989b). Photoproducts arising from the loss of chlorine atoms have also been observed upon the irradiation of photoaldrin and photodieldrin in the presence of triethylamine (ATSDR, 2000). Based on reactions with hydroxyl radicals, the atmospheric half-life of dieldrin has been estimated at approximately 1 day, but could be longer if it is associated with particulate matter (ATSDR, 2000). Again, it should be noted that while small amounts of dieldrin have been found in some atmospheric samples, neither aldrin, photoaldrin, nor photodieldrin has been detected (ATSDR, 2000; IPCS, 1989b). Therefore, if the latter two photoproducts occur to any significant extent in the atmosphere, they do not appear stable enough to accumulate.

When irradiated with UV or natural sunlight in an oxygenated aqueous solution, aldrin underwent little degradation unless amino and humic acids commonly found in natural waters were also present (ATSDR, 2000; IPCS, 1989b). Photolysis half-lives of 4.7 to 11 days for thin

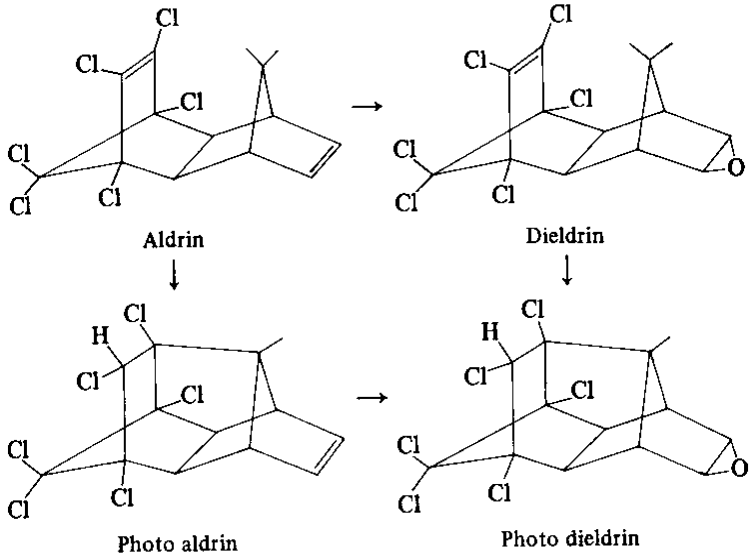

Figure 3-2. Photochemical Transformations (Principally Atmospheric) Reported for Aldrin and Dieldrin (Verschueren, 1983)

films of aldrin irradiated at >300 nm have been reported and exposure of an aldrin film to sunlight for 1 month resulted in a solution containing 2.6% aldrin, 9.6% photoaldrin, 4.1% dieldrin, 24.1% photodieldrin, and 59.7% of an unidentified photoproduct (HSDB, 2000a). The persistence of aldrin in river water was studied in sealed glass jars that were maintained under sunlight and artificial fluorescent light conditions; amounts remaining after 1 hour, 1 week, 2 weeks, 4 weeks, and 8 weeks were 100, 100, 80, 40, and 20%, respectively (Verschueren, 1983; HSDB, 2000a). The conversion was principally to dieldrin (Verschueren, 1983). Irradiation at 238 nm for 48 hours converted 75% of the aldrin in filtered natural field water to dieldrin (ATSDR, 2000).

Hydrolysis is not a significant abiotic degradation mechanism for aqueous dieldrin, as it occurs with a half-life of >4 years; however, aqueous dieldrin will reportedly degrade to photodieldrin in the presence of sunlight with an approximate half-life of 2 to 4 months with the process being accelerated in waters containing photosensitizers (HSDB, 2000b). In somewhat contrary findings, when the persistence of dieldrin was studied in sealed glass jars of river water that were maintained under sunlight and artificial fluorescent light conditions, 100% of the initial dieldrin was reported to be still present after 8 weeks (Verschueren, 1983).

While it is possible that some aldrin and dieldrin may undergo photochemical degradation (as a result of UV irradiation in surface layers), only small amounts of photodieldrin have been observed in soil samples, and the extent to which these may have resulted from microbial action is not certain (ATSDR, 2000; IPCS, 1989b). It appears that photochemical

reactions may be responsible for the epoxidation of some aldrin to dieldrin, and some dieldrin to photodieldrin, that has been observed on the leaf surfaces of various plants (IPCS, 1989b).

With respect to other abiotic mechanisms, dieldrin has been reported to be susceptible to ozone-mediated degradation, and the clay diluents used in dust formulations of aldrin and dieldrin (especially acidic kaolinite and attapulgite) have been reported to contribute to their decomposition (IPCS, 1989b).

Bioaccumulation

As suggested by their relatively high K_{ow}s, both aldrin and dieldrin have moderate to high potentials for bioaccumulation (ATSDR, 2000; HSDB, 2000a,b; IPCS, 1989b). Aldrin and dieldrin uptake by plants has been reported to be substantially higher in root crops than in grain crops; root crops (e.g., carrots, radishes, and turnips) are much more likely to take up residues from treated soils, whereas it is rare in grain crops for residues to reach detectable levels in the grain (IPCS, 1989b). In one model ecosystem study, corn was planted in vermiculite soil to which 2.09 ppm radiolabeled aldrin had been applied; after 14 days, the corn contained 2.83 ppm radiolabeled residue, of which 0.762 ppm was aldrin and 1.538 ppm dieldrin (ATSDR, 2000). About 78% of the residues were found in the roots, with the remainder in the shoots. The mechanism of uptake into plants for these compounds is not clear. It may vary considerably with species and the nature of the soils in which they are grown, and apparently involves both absorption through roots and absorption of vapors through leaves (ATSDR, 2000; IPCS, 1989b). A vole was introduced into this same model ecosystem on day 15, and after 5 days was found to have aldrin and dieldrin concentrations of 0.08 and 3.56 ppm, respectively (ATSDR, 2000).

The bioaccumulation and biomagnification of aldrin occur mostly through its conversion products (IPCS, 1989b). Biotransfer factors (BTFs) for beef and milk, defined as the ratio of a compound in beef or milk (mg/kg) to its daily intake by the animal (mg/day), have been estimated for aldrin to be 0.085 and 0.023, respectively (ATSDR, 2000). In vegetables, a bioconcentration factor (BCF, the ratio of a compound's concentration in above ground plant parts to that in soil) of 0.021 has been calculated for aldrin (ATSDR, 2000). Similarly, BTFs for beef and milk and a vegetable BCF have been estimated for dieldrin, these being 0.008, 0.011, and 0.098, respectively (ATSDR, 2000). BCFs for these compounds in various aquatic organisms (fish, molluscs, algae, waterflea, etc.) have been reported to be in the range of 100 to 15,000, while in various amphibian, avian, earthworm, and mammalian species values have been of the order of 2 to 400 BCFs (HSDB, 2000a,b; IPCS, 1989b; Verschueren, 1983).

Environmental Fate Summary

In summary, aldrin that is applied to soil can be expected to largely be converted to dieldrin through both biological and abiotic mechanisms. Dieldrin is much more persistent and both compounds will strongly adsorb to sediment or dust particles. Potential for leaching into ground water is low, but soil run-off of rain water may carry particle-adsorbed residues into surface waters. Substantial volatilization of both compounds to the atmosphere is thought to occur, where significant levels of photochemical epoxidation, isomerization, and reaction with free radicals (hydroxyl radical) may take place. Washout of atomospheric aldrin and dieldrin

may also be significant. Monitoring data suggest that dieldrin is widely dispersed in the atmosphere. However, while the ultimate fate of it and its related photoproducts remains unclear, it appears they do not accumulate in the atmosphere. Biodegradation of aldrin is generally slow and along with hydrolysis, is thought to be an unimportant fate process for dieldrin. Bioconcentration and bioaccumulation of these compounds and their residues are significant and, in addition to their being continuing contaminants of soil, water, and air, they are often found in aquatic organisms, wildlife, foods, and humans (HSDB, 2000a,b; IPCS, 1989b; USEPA, 1980).

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4.0 EXPOSURE FROM DRINKING WATER

4.1 Aldrin

4.1.1 Ambient Occurrence

To understand the presence of a chemical in the environment, an examination of ambient occurrence is useful. In a drinking water context, ambient water is source water existing in surface waters and aquifers before treatment. The most comprehensive and nationally representative data describing ambient water quality in the United States are being produced through the United States Geological Survey's (USGS) National Water Quality Assessment (NAWQA) program. (NAWQA, however, is a relatively young program and complete national data are not yet available from their entire array of sites across the nation.)

Data Sources and Methods

The USGS instituted the NAWQA program in 1991 to examine water quality status and trends in the United States. NAWQA is designed and implemented in such a manner as to allow consistency and comparison between representative study basins located around the country, facilitating interpretation of natural and anthropogenic factors affecting water quality (Leahy and Thompson, 1994).

The NAWQA program consists of 59 significant watersheds and aquifers referred to as "study units." The study units represent approximately two-thirds of the overall water usage in the United States and a similar proportion of the population served by public water systems. Approximately one-half of the nation's land area is represented (Leahy and Thompson, 1994).

To facilitate management and make the program cost effective, approximately one-third of the study units at a time engage in intensive assessment for a period of 3 to 5 years. This is followed by a period of less intensive research and monitoring that lasts between 5 and 7 years. This way all 59 study units rotate through intensive assessment over a 10-year period (Leahy and Thompson, 1994). The first round of intensive monitoring (1991 to 1996) targeted 20 watersheds. This first group was more heavily slanted toward agricultural basins. A national synthesis of results from these study units focusing on pesticides and nutrients has been compiled and analyzed (Kolpin et al., 1998; Larson et al., 1999; USGS, 1999a).

Aldrin was not an analyte for either the ground water or the surface water NAWQA studies included in the pesticide and nutrient national synthesis (Kolpin et al., 1998; Larson et al., 1999; USGS, 1999b). Because of analytical and budget constraints the NAWQA program targets certain pesticides, many of which have high use and/or have potential environmental significance (Larson et al., 1999; USGS, 1999a). Aldrin may have been excluded because it has not been used in agriculture since the early 1970s and all of its uses were discontinued in the mid-1980s (USGS, 1999a). Also, aldrin breaks down in the environment to dieldrin (among other degradates), a compound that was analyzed in the NAWQA studies (USGS, 1999b). Finally, aldrin persisting in the environment is more likely to be found in sediments or biotic tissues because of its strong hydrophobicity and sorption potential (ATSDR, 1993; Nowell,

1999; USGS, 2000). Consequently, NAWQA investigators focused their aldrin occurrence studies on bed sediments and aquatic biota tissue (Nowell, 1999).

Aldrin is an organochlorine insecticide. As a group, organochlorines are hydrophobic and resist degradation. Hydrophobic ("water hating") compounds have low water solubilities and strong tendencies to sorb to organic material in sediments and accumulate in the tissue of aquatic biota, where they can persist for long periods of time (ATSDR, 1993; USGS, 2000). Organochlorines may be present in bed sediments and tissues of aquatic systems even when they are undetectable in the water column using conventional methods (Nowell, 1999).

To determine their presence in hydrologic systems of the United States, the NAWQA program has investigated organochlorine pesticide detections in bed sediments and biotic tissue, focusing on the organochlorine insecticides that were used heavily in the past (Nowell, 1999). The occurrence of aldrin, one of the top three insecticides used for agriculture in the 1960s and widely used to kill termites in structures until the mid 1980s, was investigated in this study (Nowell, 1999; USGS, 1999a). Sampling was conducted at 591 sites from 1992 to 1995 in the 20 NAWQA study units where the first round of intensive assessment took place. Two of these basins, the Central Nebraska Basins and the White River Basin in Indiana, are located in the corn belt where aldrin use was heavy during the 1960s. Details regarding sampling techniques and analytical methods are described by Nowell (1999).

Results

Aldrin was not detected in aquatic biota tissue samples. However, it was detected in stream bed sediment samples. The occurrence frequencies above the Method Detection Limit (MDL) of 1 µg/kg and basic summary statistics indicate that occurrence in sediments is very low (Table 4-1). Both the median and 95th percentile concentrations were reported as non-detections (< MDL) across all land use categories.

Aldrin was detected in stream bed sediments only at agricultural or mixed land use sites, perhaps reflecting the heavy agricultural use in the late 1960s and early 1970s. Interesting, in light of the more recent termiticide use, no urban detections were reported. This may be partly a function of the NAWQA sampling design that targeted basins more representative of agricultural and mixed land use conditions for the first round of intensive monitoring from which these sediment data were produced (see Section 4.1.1.1). Data from later rounds are not yet available. The occurrence of a toxic compound in stream sediments is pertinent to drinking water concerns because some desorption of the compound from sediments into water will occur through equilibrium reactions, although in very low concentrations. The occurrence of aldrin in sediments is also quite low (see Table 4-1).

Table 4-1. Aldrin Detections in Stream Bed Sediments[1]

	Detection Frequency (% Samples > MDL of 1 µg/kg)	Concentration Percentiles (All Samples; µg/kg Dry Weight)		
		Median	95th	Maximum
urban	0.0%	nd[2]	nd	nd
mixed	0.5%	nd	nd	3
agricultural	0.6%	nd	nd	2.2
forest-rangeland	0.0%	nd	nd	nd
all sites	0.4%	nd	nd	3

[1] Nowell, 1999.

[2] Not detected in concentration greater than MDL.

4.1.2 Drinking Water Occurrence

The Safe Drinking Water Act (SDWA), as amended in 1986, required Public Water Systems (PWSs) to monitor for specified "unregulated" contaminants, on a 5-year cycle, and to report the monitoring results to the states. Unregulated contaminants do not have an established or proposed National Primary Drinking Water Regulation (NPDWR); however, they are contaminants that were formally listed and required for monitoring under federal regulations. The intent was to gather scientific information on the occurrence of these contaminants to enable a decision as to whether or not regulations were needed. All non-purchased community water systems (CWSs) and non-purchased non-transient non-community water systems (NTNCWSs), with greater than 150 service connections, were required to conduct this unregulated contaminant monitoring. Smaller systems were not required to conduct this monitoring under federal regulations, but were required to be available to monitor if the state decided such monitoring was necessary. Many states collected data from smaller systems. Additional contaminants were added to the Unregulated Contaminant Monitoring (UCM) program in 1991 (USEPA, 1991) for required monitoring that began in 1993 (USEPA, 1992).

Aldrin has been monitored under the SDWA Unregulated Contaminant Monitoring (UCM) program since 1993 (USEPA, 1992). Monitoring ceased for small public water systems (PWSs) under a direct final rule published January 8, 1999 (USEPA, 1999a), and ended for large PWSs with promulgation of the new Unregulated Contaminant Monitoring Regulation (UCMR) issued September 17, 1999 (USEPA, 1999b) and effective January 1, 2001. At the time the UCMR lists were developed, the Agency concluded there were adequate monitoring data for a regulatory determination. This obviated the need for continued monitoring under the new UCMR list.

Data Sources, Data Quality, and Analytical Methods

Currently, there is no complete national record of unregulated or regulated contaminants in drinking water from PWSs collected under SDWA. Many states have submitted unregulated contaminant PWS monitoring data to EPA databases, but there are issues of data quality, completeness, and representativeness. Nonetheless, a significant amount of state data are available for UCM contaminants that can provide estimates of national occurrence.

The National Contaminant Occurrence Database (NCOD) is an interface to the actual occurrence data stored in the Safe Drinking Water Information System (Federal version; SDWIS/FED) and can be queried to provide a summary of the data in SDWIS/FED for a particular contaminant. The drinking water occurrence data for aldrin presented here were derived from monitoring data available in the SDWIS/FED database.

The data in this report have been reviewed, edited, and filtered to meet various data quality objectives for the purposes of this analysis. Hence, not all data from a particular source were used, only data meeting the quality objectives described below were included. The sources of these data, their quality and national aggregation, and the analytical methods used to estimate a given contaminant's national occurrence (from these data) are discussed in this section (for further details see USEPA, 2001a,b).

UCM Rounds 1 and 2

The 1987 UCM contaminants include 34 volatile organic compounds (VOCs) (USEPA, 1987). Aldrin, a synthetic organic compound (SOC), was *not* among these contaminants. The UCM (1987) contaminants were first monitored coincident with the Phase I regulated contaminants, during the 1988 to 1992 period. This period is often referred to as "Round 1" monitoring. The monitoring data collected by the PWSs were reported to the states (as primacy agents), but there was no protocol in place to report these data to EPA. These data from Round 1 were collected by EPA from many states over time and put into a database called the Unregulated Contaminant Information System, or URCIS.

The 1993 UCM contaminants include 13 SOCs and 1 inorganic contaminant (IOC) (USEPA, 1991). Monitoring for the UCM (1993) contaminants began coincident with the Phase II/V regulated contaminants in 1993 through 1998. This is often referred to as "Round 2" monitoring. The UCM (1987) contaminants were also included in the Round 2 monitoring. As with other monitoring data, PWSs reported these results to the states. EPA, during the past several years, has requested that all states submit these historic data to EPA and they are now stored in the SDWIS/FED database.

Monitoring and data collection for aldrin, a UCM (1993) contaminant, began in Round 2. Therefore, the following discussion regarding data quality screening, data management, and analytical methods focuses on SDWIS/FED. Discussion of the URCIS database is included where relevant, but it is worth noting that the various quality screening, data management, and analytical processes were nearly identical for the two databases. For further details on the two monitoring periods as well as the databases see USEPA (2001a,b).

Developing a Nationally Representative Perspective

The Round 2 data contain contaminant occurrence data from a total of 35 primacy entities (including 34 states and data for some tribal systems). However, data from some states are incomplete and biased. Furthermore, the national representativeness of the data is problematic because the data were not collected in a systematic or random statistical framework. These state data could be heavily skewed to low-occurrence or high-occurrence settings. Hence, the state data were evaluated based on pollution-potential indicators and the spatial/hydrologic diversity of the nation. This evaluation enabled the construction of a cross-section from the available state data sets that provides a reasonable representation of national occurrence.

A national cross-section from these state Round 2 contaminant databases was established using the approach developed for the EPA report *A Review of Contaminant Occurrence in Public Water Systems* (USEPA, 1999c). This approach was developed to support occurrence analyses for EPA's Chemical Monitoring Reform (CMR) evaluation. It was supported by peer reviewers and stakeholders. The approach cannot provide a "statistically representative" sample because the original monitoring data were not collected or reported in an appropriate fashion. However, the resultant "national cross-section" of states should provide a clear indication of the central tendency of the national data. The remainder of this section provides a summary description of how the national cross-section for the SDWIS/FED (Round 2) database was developed. The details of the approach are presented in other documents (USEPA, 2001a; USEPA, 2001b); readers are referred to these for more specific information.

Cross-Section Development

As a first step in developing the cross-section, the state data contained in the SDWIS/FED database (that contains the Round 2 monitoring results) were evaluated for completeness and quality. Some state data in SDWIS/FED were unusable for a variety of reasons. Some states reported only detections, or their data had incorrect units. Datasets only including detections are obviously biased. Other problems included substantially incomplete data sets without all PWSs reporting (USEPA, 2001a Sections II and III).

The balance of the states remaining after the data quality screening were then examined to establish a national cross-section. This step was based on evaluating the states' pollution potential and geographic coverage in relation to all states. Pollution potential is considered to ensure a selection of states that represent the range of likely contaminant occurrence and a balance with regard to likely high and low occurrence. Geographic consideration is included so that the wide range of climatic and hydrogeologic conditions across the United States are represented, again balancing the varied conditions that affect transport and fate of contaminants, as well as conditions that affect naturally occurring contaminants (USEPA, 2001b Sections III.A. and III.B.).

The cross-section states were selected to represent a variety of pollution potential conditions. Two primary pollution potential indicators were used. The first factor selected indicates pollution potential from manufacturing/population density and serves as an indicator of the potential for VOC contamination within a state. Agriculture was selected as the second

pollution potential indicator because the majority of SOCs of concern are pesticides (USEPA, 2001b Section III.A.). The 50 individual states were ranked from highest to lowest based on the pollution potential indicator data. For example, the state with the highest ranking for pollution potential from manufacturing received a ranking of 1 for this factor and the state with the lowest value was ranked as number 50. States were ranked for their agricultural chemical use status in a similar fashion.

The states' pollution potential rankings for each factor were subdivided into four quartiles (from highest to lowest pollution potential). The cross-section states were chosen from all quartiles for both pollution potential factors to ensure representation, for example, from the following: states with high agrichemical pollution potential rankings and high manufacturing pollution potential rankings; states with high agrichemical pollution potential rankings and low manufacturing pollution potential rankings; states with low agrichemical pollution potential rankings and high manufacturing pollution potential rankings; and states with low agrichemical pollution potential rankings and low manufacturing pollution potential rankings (USEPA, 2001b Section III.B.). In addition, some secondary pollution potential indicators were considered to further ensure that the cross-section states included the spectrum of pollution potential conditions (high to low). The cross-section was then reviewed for geographic coverage throughout all sectors of the United States.

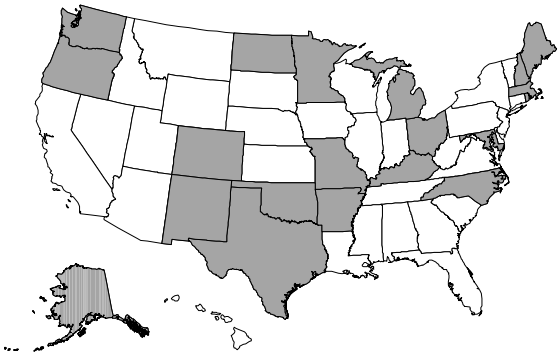
The data quality screening, pollution potential rankings, and geographic coverage analysis established a national cross-section of 20 Round 2 (SDWIS/FED) states. The cross-section states provide a good representation of the nation's varied climatic and hydrogeologic regimes and the breadth of pollution potential for the contaminant groups (Figure 4-1).

Cross-Section Evaluation

To evaluate and validate the method for creating the national cross-sections, the method was used to create smaller state subsets from the 24-state, Round 1 (URCIS) cross-section and aggregations. Again, states were chosen to achieve a balance from the quartiles describing pollution potential, and a balanced geographic distribution, to incrementally build subset cross-sections of various sizes. For example, the Round 1 cross-section was tested with subsets of 4, 8 (the first 4 state subset plus 4 more states), and 13 (8 state subset plus 5) states. Two additional cross-sections were included in the analysis for comparison: a cross-section composed of 16 biased states eliminated from the 24 state cross-section for data quality reasons and a cross-section composed of all 40 Round 1 states (USEPA, 2001b Section III.B.1).

Figure 4-1. Geographic Distribution of Cross-Section States for Round 2 (SDWIS/FED)

Round 2 (SDWIS/FED)	
Alaska	New Hampshire
Arkansas	New Mexico
Colorado	North Carolina
Kentucky	North Dakota
Maine	Ohio
Maryland	Oklahoma
Massachusetts	Oregon
Michigan	Rhode Island
Minnesota	Texas
Missouri	Washington



These Round 1 incremental cross-sections were then used to evaluate occurrence for an array of both high and low occurrence contaminants. The comparative results illustrate several points. The results are quite stable and consistent for the 8, 13, and 24 state cross-sections. They are much less for the 4 state, 16 state (biased), and 40 state (all Round 1 states) cross-sections. The 4 state cross-section is apparently too small to provide balance both geographically and with pollution potential, a finding that concurs with past work (USEPA, 1999c). The CMR analysis suggested that a minimum of six to seven states was needed to provide balance both geographically and with pollution potential. The CMR report used eight states out of the available data for its nationally representative cross-section (USEPA, 1999c). The 16 state and 40 state cross-sections, both including biased states, provided occurrence results that were unstable and inconsistent for a variety of reasons associated with their data quality problems (USEPA, 2001b Section III.B.1).

The 8, 13, and 24 state cross-sections provide very comparable results, are consistent, and are usable as national cross-sections to provide estimates of contaminant occurrence. Including greater data from more states improves the national representation and the confidence in the results, as long as the states are balanced related to pollution potential and spatial coverage. The 20 state cross-section provides the best, nationally representative cross-section for the Round 2 data.

Data Management and Analysis

The cross-section analyses focused on occurrence at the water system level; i.e., the summary data presented discuss the percentage of public water *systems* with detections, not the percentage of *samples* with detections. By normalizing the analytical data to the system level, skewness inherent in the sample data is avoided. System level analysis was used since a PWS with a known contaminant problem usually has to sample more frequently than a PWS that has

never detected the contaminant. Obviously, the results of a simple computation of the percentage of samples with detections (or other statistics) can be skewed by the more frequent sampling results reported by the contaminated site. This level of analysis is conservative. For example, a system need only have a single sample with an analytical result greater than the Minimum Reporting Limit (MRL), i.e., a detection, to be counted as a system with a result "greater than the MRL."

Also, the data used in the analyses were limited to only those data with confirmed water source and sampling type information. Only standard SDWA compliance samples were used; "special" samples, or "investigation" samples (investigating a contaminant problem that would bias results), or samples of unknown type were not used in the analyses. Various quality control and review checks were made of the results, including follow-up questions to the states providing the data. Many of the most intractable data quality problems encountered occurred with older data. These problematic data were, in some cases, simply eliminated from the analysis. For example, when the number of data with problems were insignificant relative to the total number of observations they were dropped from the analysis (for further details see Cadmus, 2000).

As indicated above, Massachusetts is included in the 20-state, Round 2 national cross-section. Noteworthy for SOCs like aldrin, however, Massachusetts SOC data were problematic. Massachusetts reported Round 2 sample results for SOCs from only 56 PWSs, while reporting VOC results from over 400 different PWSs. Massachusetts SOC data also contained an atypically high percentage of systems with analytical detections when compared to all other states. Through communications with Massachusetts data management staff, it was learned that the state's SOC data were incomplete and that the SDWIS/FED record for Massachusetts SOC data were also incomplete. For instance, the SDWIS/FED Round 2 data for Massachusetts indicates 18% of systems reported detections of aldrin. The average percent of systems with detections for all other states was 0.2%. In contrast, Massachusetts data characteristics and quantities for IOCs and VOCs were reasonable and comparable with other states' results. Therefore, Massachusetts was included in the group of 20 SDWIS/FED Round 2 cross-section states with usable data for IOCs and VOCs, but its aldrin (SOC) data were omitted from the Round 2 cross-section occurrence analyses and summaries presented in this report.

Occurrence Analysis

To evaluate national contaminant occurrence, a two-stage analytical approach has been developed. The first stage of analysis provides a straightforward, conservative, broad evaluation of occurrence of the CCL preliminary regulatory determination priority contaminants as described above. These descriptive statistics are summarized here. Based on the findings of the Stage 1 Analysis, EPA will determine whether more intensive statistical evaluations, the Stage 2 Analysis, may be warranted to generate national probability estimates of contaminant occurrence and exposure for priority contaminants. (For details on this two-stage analytical approach see Cadmus, 2000.)

The summary descriptive statistics presented in Table 4-2 for aldrin are a result of the Stage 1 analysis and include data from Round 2 (SDWIS/FED, 1993 to 1997) cross-section

states (excluding Massachusetts). Included are the total number of samples, the percent samples with detections, the 99th percentile concentration of all samples, the 99th percentile concentration of samples with detections, and the median concentration of samples with detections. The percentages of PWSs and population served indicate the proportion of PWSs whose analytical results showed a detection(s) of the contaminant (simple detection, > MRL) at any time during the monitoring period; or a detection(s) greater than half the Health Reference Level (HRL); or a detection(s) greater than the HRL. The HRL, 0.002 µg/L, is a preliminary estimated health effect level used for this analysis.

Aldrin is classified by EPA as a linear carcinogen and would, if regulated, have a MCLG of zero. The value used as the HRL when for the occurrence evaluation was the concentration equivalent to a one-in-a-million risk based on the EPA cancer slope factor.

The 99th percentile concentration is used here as a summary statistic to indicate the upper bound of occurrence values because maximum values can be extreme values (outliers) that sometimes result from sampling or reporting error. The 99th percentile concentration is presented for both the samples with only detections and all of the samples because the value for the 99th percentile concentration of all samples is below the Minimum Reporting Level (MRL) (denoted by "<" in Table 4-2). For the same reason, summary statistics such as the 95th percentile concentration of all samples or the median (or mean) concentration of all samples are omitted because these also are all "<" values. This is the case because only 0.006% of *all* samples recorded detections of aldrin in Round 2.

As a simplifying assumption, a value of half the MRL is often used as an estimate of the concentration of a contaminant in samples/systems whose results are less than the MRL. For a contaminant with relatively low occurrence, such as aldrin in drinking water occurrence databases, the median or mean value of the occurrence using this assumption would be half of the MRL (0.5 * MRL). However, for these occurrence data this is not straightforward. For Round 2, states have reported a wide range of values for the MRLs. This is in part related to state data management differences, as well as real differences in analytical methods, laboratories, and other factors.

The situation can cause confusion when examining descriptive statistics for occurrence. For example, most Round 2 states reported non-detections simply as zeros resulting in a modal MRL value of zero. By definition the MRL cannot be zero. This is an artifact of state data management systems. Because a simple meaningful summary statistic is not available to describe the various reported MRLs, and to avoid confusion, MRLs are not reported in the summary table (Table 4-2).

In Table 4-2, national occurrence is estimated by extrapolating the summary statistics for the 20 state cross-section (excluding Massachusetts) to national numbers for systems, and population served by systems, from the *Water Industry Baseline Handbook, Second Edition* (USEPA, 2000). From the handbook, the total number of community water systems (CWSs) plus non-transient, non-community water systems (NTNCWSs) is 65,030, and the total population served by CWSs plus NTNCWSs is 213,008,182 persons (see Table 4-2). To arrive at the national occurrence estimate for a particular cross-section, the national estimate for PWSs

(or population served by PWSs) is simply multiplied by the percentage for the given summary statistic (i.e., the national estimate for the total number of PWSs with detections [11] is the product of the percentage of PWSs with detections [0.016%] and the national estimate for the total number of PWSs [65,030]).

Included in Table 4-2 in addition to the cross-section data results are results and national extrapolations from all Round 2 reporting states. The data from the biased states are included because of aldrin's very low occurrence in drinking water samples in all states. For contaminants with very low occurrence, such as aldrin where very few states have detections, any occurrence becomes more important, relatively. For such contaminants, the cross-section process can easily miss a state with occurrence that becomes more important. This is the case with aldrin.

Extrapolating only from the cross-section states, aldrin's very low occurrence clearly underestimates national occurrence. For example, while data from biased states like Alabama (reporting 100% detections >HRL, >½ HRL, and >MRL; see Appendix A) exaggerate occurrence because only systems with detections reported results, their detections are real and need to be accounted for because extrapolations from the cross-section states do not predict enough detections in the biased states. Therefore, results from all reporting Round 2 states, including the biased states, are also used here to extrapolate to a national estimate. Using the biased states' data should provide conservative estimates, likely overestimates, of national occurrence for aldrin.

As exemplified by the cross-section extrapolations for aldrin and dieldrin, national extrapolations of these Stage 1 analytical results can be problematic, especially for contaminants with very low occurrence, because the State data used for the cross-section are not a strict statistical sample. For this reason, the nationally extrapolated estimates of occurrence based on Stage 1 results are not presented in the CCL Federal Register Notice. The presentation in the Federal Register Notice of only the actual results of the cross-section analysis maintains a straight-forward presentation, and the integrity of the data, for stakeholder review. The nationally extrapolated Stage 1 occurrence values are presented here, however, to provide additional perspective. A more rigorous statistical modeling effort, the Stage 2 analysis, could be conducted on the cross-section data (Cadmus, 2001). The Stage 2 results would be more statistically robust and more suitable to national extrapolation. This approach would provide a probability estimate and would also allow for better quantification of estimation error.

Additional Drinking Water Data from the Corn Belt

To augment the SDWA drinking water data analysis described above, and to provide additional coverage of the corn belt states where aldrin use as an agricultural insecticide was historically high, independent analyses of SDWA drinking water data from the states of Iowa, Illinois, and Indiana are reviewed below. The Iowa analysis examined SDWA compliance monitoring data from surface and ground water PWSs for the years 1988 to 1995 (Hallberg et al., 1996). Illinois and Indiana compliance monitoring data for surface and ground water PWSs were evaluated mostly for the years after 1993, though some earlier data were also included (USEPA, 1999c). The raw water data from Illinois were collected from rural, private supply

wells (Goetsch *et al.*, 1992). Data sources, data quality, and analytical methods for these analyses are described in the respective reports; they were all treated similarly to the data quality reviews for this analysis.

Results

Occurrence Estimates

The percentages of PWSs with detections are very low (Table 4-2). The cross-section shows only approximately 0.02% of PWSs (approximately 11 PWSs nationally) experienced detections at any concentration level (> MRL, > ½ HRL, and > HRL), affecting about 0.02% of the population served (approximately 40,000 to 50,000 people nationally) (see also Figure 4-2). All of the detections were in systems using ground water. The percentage of PWSs (or population served) in a given source category (i.e., ground water) with detections > MRL, > ½ HRL, or > HRL is the same because the estimated HRL is so low that it is lower than the MRL. Hence, any detection reported is also greater than the HRL. While concentrations are low—for the detections the median concentration is 0.58 µg/L, and the 99th percentile concentration is 0.69 µg/L—these values are greater than the HRL.

As noted above, because of the very low occurrence, the cross-section states yield an underestimate. Hence, all data are used, even the biased data, to present a conservative upper bound estimate. Conservative estimates of aldrin occurrence using all of the Round 2 reporting states still show relatively low detection frequencies (Table 4-2). Approximately 0.2% of PWSs (estimated at 138 PWSs nationally) experienced detections at any concentration level (> MRL, > ½ HRL, and > HRL), affecting about 0.5% of the population served (1,052,000 people nationally). The proportion of surface water PWSs with detections was greater than ground water systems. Again the percentages of PWSs (or populations served) with detections > MRL, > ½ HRL, or > HRL are the same because of the low HRL. The median concentration of detections is 0.18 µg/L, and the 99th percentile concentration is 4.4 µg/L.

The Round 2 reporting states and the Round 2 national cross-section show a proportionate balance in PWS source waters compared to the national inventory. Nationally, 91% of PWSs use ground water (and 9% surface waters). Round 2 reporting states and the Round 2 national cross-section show 87% use ground water (and 13% surface waters). The relative populations served are not as comparable. Nationally, about 40% of the population is served by PWSs using ground water (and 60% by surface water). For the Round 2 cross-section, 29% of the cross-section population is served by ground water PWSs (and 71% by surface water). For all Round 2 reporting states, 31% of the population is served by ground water PWSs (and 69% by surface water). The resultant national extrapolations are not additive as a consequence of these disproportions.

Drinking water data from the corn belt states of Iowa, Indiana, and Illinois also show very low occurrence of aldrin. There were no detections of the pesticide in the Iowa or Indiana SDWA aldrin as well. Only 0.3% of all sampled wells had detections at a reporting limit of 0.004 µg/L (Goetsch *et al.*, 1992).

Table 4-2. Summary Occurrence Statistics for Aldrin

Frequency Factors	20 State Cross-Section[1]	All Reporting States[2]	National System & Population Numbers[3]	
Total Number of Samples	31,083	41,565	--	
Percent of Samples with Detections	0.006%	0.132%	--	
99th Percentile Concentration (all samples)	< (Non-detect)	< (Non-detect)	--	
Health Reference Level	0.002 µg/L	0.002 µg/L	--	
Minimum Reporting Level (MRL)	Variable[4]	Variable[4]	--	
99th Percentile Concentration of Detections	0.69 µg/L	4.40 µg/L	--	
Median Concentration of Detections	0.58 µg/L	0.18 µg/L	--	
Total Number of PWSs	12,165	15,123	65,030	
Number of GW PWSs	10,540	13,195	59,440	
Number of SW PWSs	1,625	1,928	5,590	
Total Population	47,708,156	58,979,361	213,008,182	
Population of GW PWSs	14,043,051	18,279,343	85,681,696	
Population of SW PWSs	33,665,105	40,700,018	127,326,486	
Occurrence by System			**National Extrapolation[5]**	
PWSs with detections (> MRL)	0.016%	0.212%	11	138
Range of Cross-Section States	0 - 0.23%	0 - 100%	N/A	N/A
GW PWSs with detections	0.019%	0.167%	11	99
SW PWSs with detections	0.000%	0.519%	0	29
PWSs > 1/2 Health Reference Level (HRL)	0.016%	0.212%	11	138
Range of Cross-Section States	0 - 0.23%	0 - 100%	N/A	N/A
GW PWSs > 1/2 Health Reference Level	0.019%	0.167%	11	99
SW PWSs > 1/2 Health Reference Level	0.000%	0.519%	0	29
PWSs > Health Reference Level	0.016%	0.212%	11	138
Range of Cross-Section States	0 - 0.23%	0 - 100%	N/A	N/A
GW PWSs > Health Reference Level	0.019%	0.167%	11	99
SW PWSs > Health Reference Level	0.000%	0.519%	0	29
Occurrence by Population Served				
PWS Population Served with detections	0.018%	0.494%	39,000	1,052,000
Range of Cross-Section States	0 - 0.35%	0 - 100%	N/A	N/A
GW PWS Population with detections	0.062%	0.414%	53,000	355,000
SW PWS Population with detections	0.000%	0.530%	0	674,000
PWS Population Served > 1/2 Health Reference Level	0.018%	0.494%	39,000	1,052,000
Range of Cross-Section States	0 - 0.35%	0 - 100%	N/A	N/A
GW PWS Population > 1/2 Health Reference Level	0.062%	0.414%	53,000	355,000
SW PWS Population > 1/2 Health Reference Level	0.000%	0.530%	0	674,000
PWS Population Served > Health Reference Level	0.018%	0.494%	39,000	1,052,000
Range of Cross-Section States	0 - 0.35%	0 - 100%	N/A	N/A
GW PWS Population > Health Reference Level	0.062%	0.414%	53,000	355,000
SW PWS Population > Health Reference Level	0.000%	0.530%	0	674,000

1. Summary Results based on data from 20-State Cross-Section (minus Massachusetts), from SDWIS/FED, UCM (1993) Round 2.
2. Summary Results based on data from all reporting states from SDWIS/FED, UCM (1993) Round 2.
3. Total PWS and population numbers are from EPA March 2000 Water Industry Baseline Handbook.
4. See text for discussion.
5. National extrapolations are from the 20-State data using the Baseline Handbook system and population numbers.

- PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; MRL = Minimum Reporting Level (for laboratory analyses); Health Reference Level = Health Reference Level, an estimated health effect level used for preliminary assessment for this review; N/A = Not Applicable."
- The Health Reference Level (HRL) used for aldrin is 0.002 µg/L. This is a draft value for working review only.
- Total Number of Samples = the total number of analytical records for aldrin.
- 99th Percentile Concentration = the concentration value of the 99th percentile of either all analytical results or just the detections (in µg/L).
- Median Concentration of Detections = the median analytical value of all the detections (analytical results greater than the MRL) (in µg/L).
- Total Number of PWSs = the total number of public water systems with records for aldrin.
- Total Population Served = the total population served by public water systems with records for aldrin.
- % PWS with detections, % PWS > ½ Health Reference Level, % PWS > Health Reference Level = percent of the total number of public water systems with at least one analytical result that exceeded the MRL, ½ Health Reference Level, Health Reference Level, respectively.
- % PWS Population Served with detections, % PWS Population Served >½ Health Reference Level, % PWS Population Served > Health Reference Level = percent of the total population served by PWSs with at least one analytical result exceeding the MRL, ½ Health Reference Level, or the Health Reference Level, respectively.

Regional Patterns

Occurrence results are displayed graphically by state in Figures 4-2 and 4-3 to assess whether any distinct regional patterns of occurrence are present. Thirty-four states reported Round 2 data but seven of those states have no data for aldrin (Figure 4-2). Another 22 states did not detect aldrin. The remaining five states have detected aldrin in drinking water and are generally located either in the southern United States or the Northeast (Figure 4-2). In contrast to the summary statistical data presented in the previous section, this simple spatial analysis includes the biased Massachusetts data.

The simple spatial analysis presented in Figures 4-2 and 4-3 suggests that special regional analyses are not warranted. The State of Alabama does, however, stand out as having relatively high occurrence for reasons that are unclear. While there is a weak geographic clustering of drinking water detections in a few southern and northeastern states (including the State of Massachusetts' biased data), this is partly the result of so few states with any detections. Further, use and environmental release information described in Chapter 3 of this report indicates that aldrin detections are more widespread than the drinking water data suggest. Two out of the three TRI states (Arkansas and Michigan) that reported releases of aldrin into the environment did not report detections of the chemical in PWS sampling. Furthermore, aldrin's widespread presence in the environment is evidenced by detections of the compound in hazardous waste sites in at least 31 states (at NPL sites), as well as detections in site samples in at least 40 states (listed in ATSDR's HazDat [ATSDR, 2000]).

4.1.3 Conclusion

Aldrin is an insecticide that was discontinued for all uses in 1987. It combats insects by contact or ingestion, and was used primarily on corn and citrus products, as well as for general crops and timber preservation. In addition, aldrin was used for termite-proofing plywood, building boards, and the plastic and rubber coverings of electrical and telecommunication cables (ATSDR, 1993). In 1972, USEPA cancelled all uses of aldrin except subsurface ground insertion for termite control, dipping of non-food plant roots and tops, and moth-proofing in closed-system manufacturing processes. This cancellation decision was finalized in 1974, and in 1987, the manufacturer voluntarily cancelled all uses (ATSDR, 1993).

Figure 4-2. States With PWSs With Detections of Aldrin for All States With Data in SDWIS/FED (Round 2)

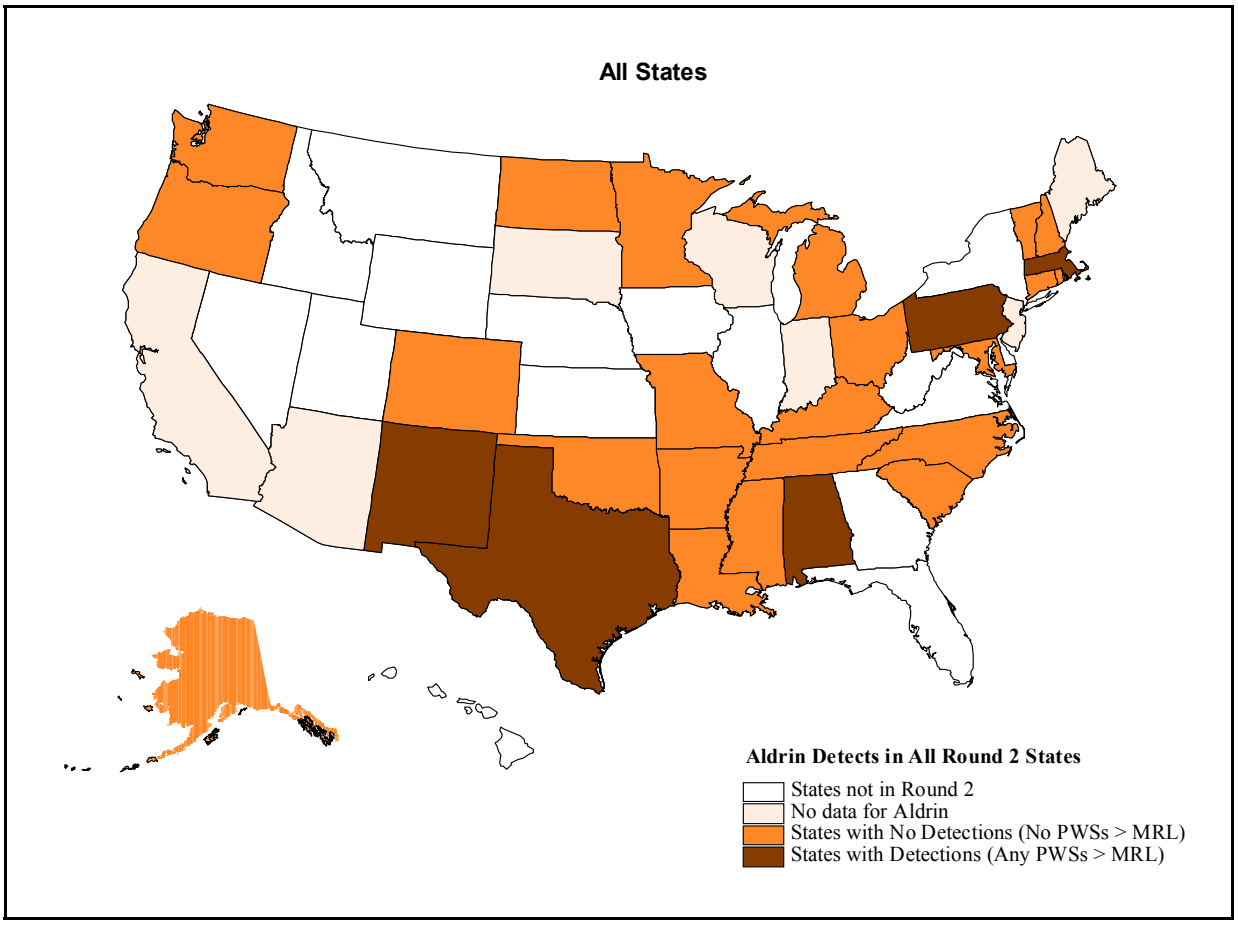
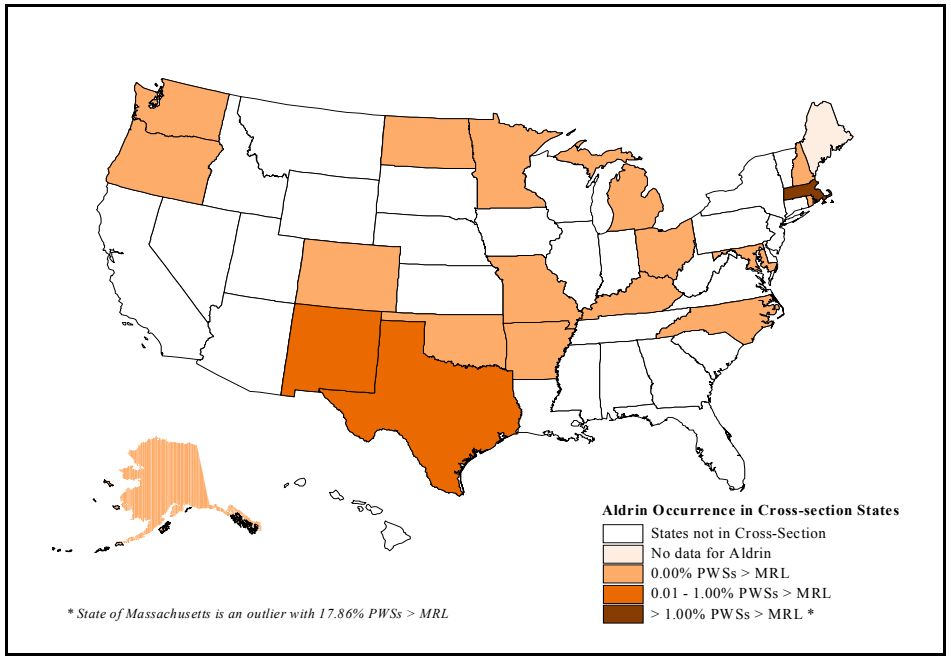
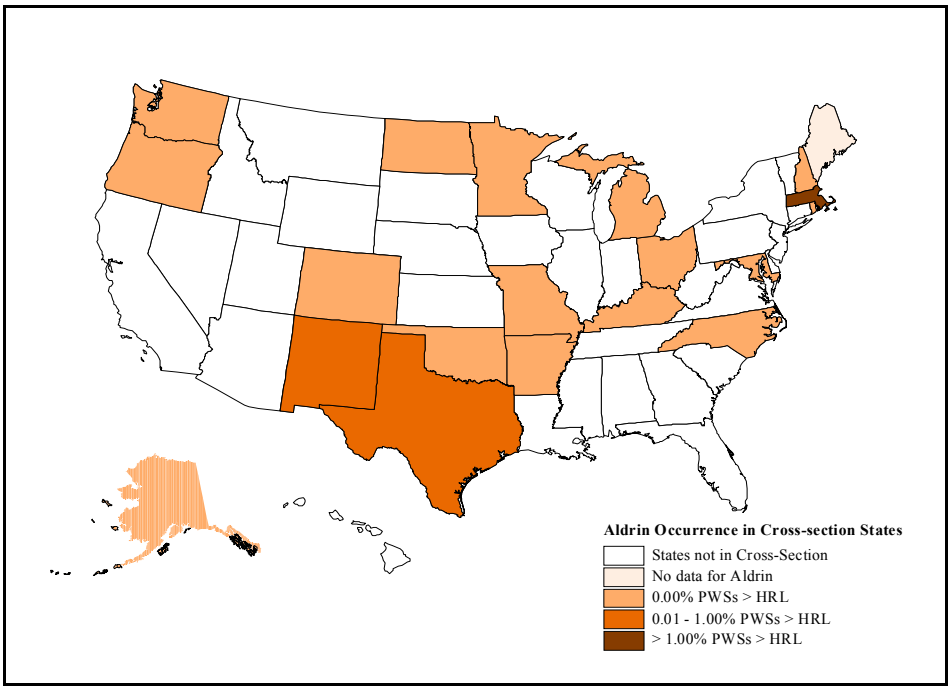


Figure 4-3. Round 2 Cross-Section States With PWSs With Detections of Aldrin (Any PWSs With Results Greater than the Minimum Reporting Level [MRL]; Above) and Concentrations Greater than the Health Reference Level (HRL; Below)





Aldrin has been detected at very low frequencies and concentrations in bed sediments sampled during the first round of the USGS NAWQA studies and in ground water in Illinois. It has also been found at ATSDR HazDat and CERCLA NPL sites across the country. Furthermore, releases have been reported through the Toxic Release Inventory (TRI).

Aldrin has also been detected in PWS samples collected under the Safe Drinking Water Act (SDWA). Occurrence estimates are very low with only 0.006% of all cross-section samples showing detections. Significantly, the values for the 99th percentile and median concentrations of all cross-section samples are less than the Minimum Reporting Level (MRL). For Round 2 cross-section samples with detections, the median concentration is 0.58 µg/L and the 99th percentile concentration is 0.69 µg/L. Systems with detections constitute only 0.02% of Round 2 cross-section systems (an estimate of 11 systems nationally). National estimates for the population served by PWSs with detections are also very low (40,000 to 50,000), and are the same for all categories (> MRL, > ½ HRL, > HRL). These estimates constitute less than 0.02% of the national population. Using more conservative estimates of occurrence from all states reporting SDWA Round 2 monitoring data, including states with biased data, 0.2% of the nations PWSs (approximately 138 systems) and 0.5% of the PWS population served (1,052,000 people) may be estimated to have detections > MRL, > ½ HRL, and > HRL.

Additional SDWA compliance data from the corn belt states of Iowa, Indiana, and Illinois examined through independent analyses support the drinking water data analyzed in this report. There were no detections in either surface or ground water PWSs in the states of Iowa and Indiana. Illinois reported detections only from surface water PWSs with 1.8% of surface water systems, and 0.1% of samples, showing detections. The 99th percentile concentration of all samples was below the reporting level and the maximum concentration was 2.4 µg/L. Furthermore, in a survey of Illinois rural, private water supply wells aldrin and dealdrin were detected in only 0.3% of all sampled wells.

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4.2 Dieldrin

4.2.1 Ambient Occurrence

To understand the presence of a chemical in the environment, an examination of ambient occurrence is useful. In a drinking water context, ambient water is source water existing in surface waters and aquifers before treatment. The most comprehensive and nationally representative data describing ambient water quality in the United States are being produced through the United States Geological Survey's (USGS) National Water Quality Assessment (NAWQA) program. (NAWQA, however, is a relatively young program and complete national data are not yet available from their entire array of sites across the nation.)

Data Sources and Methods

The USGS instituted the NAWQA program in 1991 to examine water quality status and trends in the United States. NAWQA is designed and implemented in such a manner to enable consistency and comparison between representative study basins located around the country, facilitating interpretation of natural and anthropogenic factors affecting water quality (Leahy and Thompson, 1994).

The NAWQA program consists of 59 significant watersheds and aquifers referred to as "study units." The study units represent approximately two-thirds of the overall water usage in the United States and a similar proportion of the population served by public water systems. Approximately one-half of the nation's land area is represented (Leahy and Thompson, 1994).

To facilitate management and make the program cost-effective, approximately one-third of the study units at a time engage in intensive assessment for a period of 3 to 5 years. This is followed by a period of less intensive research and monitoring that lasts between 5 and 7 years. This way all 59 study units rotate through intensive assessment over a 10-year period (Leahy and Thompson, 1994). The first round of intensive monitoring (1991 to 1996) targeted 20 watersheds. This first group was more heavily slanted toward agricultural basins. A national synthesis of results from these study units focusing on pesticides and nutrients has been compiled and analyzed (Kolpin et al., 1998; Larson et al., 1999; USGS, 1999).

Dieldrin is an analyte for both surface and ground water NAWQA studies. Two of the first 20 study basins analyzed in the pesticide and nutrient national synthesis reports, the Central Nebraska Basins and the White River Basin in Indiana, are located in the corn belt where dieldrin use was heavy during the 1960s. The method detection limit (MDL) for dieldrin is 0.001 µg/L (Kolpin et al., 1998), substantively lower than most drinking water monitoring. Additional information on analytical methods used in the NAWQA study units, including method detection limits, are described by Gilliom and others (in press).

Dieldrin is an organochlorine insecticide. As a group, organochlorines are hydrophobic and resist degradation. Hydrophobic ("water hating") compounds have low water solubilities and strong tendencies to sorb to organic material in sediments and accumulate in the tissue of aquatic biota, where they can persist for long periods of time (ATSDR, 1993; USGS, 2000).

Organochlorines may be present in bed sediments and tissues of aquatic systems even when they are undetectable in the water column using conventional methods (Nowell, 1999).

To determine their presence in hydrologic systems of the United States, the NAWQA program has investigated organochlorine pesticide detections in bed sediments and biotic tissue, focusing on the organochlorine insecticides that were used heavily in the past (Nowell, 1999). In addition to its own commercial production and use, dieldrin is a degradation product of aldrin, one of the top three insecticides used for agriculture in the 1960s and widely used to kill termites in structures until the mid 1980s. Given this history, dieldrin was investigated in this study (Nowell, 1999; USGS, 1999). Sampling was conducted at 591 sites from 1992 to 1995 in the 20 NAWQA study units first intensively assessed. Details regarding sampling techniques and analytical methods are described by Nowell (1999).

Data are also available for dieldrin occurrence in surface water in the Mississippi River and six major tributaries draining corn belt states (Goolsby and Battaglin, 1993). These data are the result of a USGS regional water quality investigation and details regarding sampling and analytical methods are described in the report.

Results

NAWQA National Synthesis

Detection frequencies and concentrations of dieldrin in ambient surface and ground water are low, especially in ground water, which is the case for insecticides in general (Table 4-3) (Kolpin et al., 1998; Miller and Wilber, 1999). However, using a common reporting limit of 0.01 µg/L, dieldrin is the most commonly detected insecticide in ground water in these USGS studies. This possibly reflects the historically heavy use of aldrin and dieldrin and clearly indicates dieldrin's environmental persistence (Kolpin et al., 1998; Miller, 2000). Also, though relatively immobile in water when compared to newer pesticides, dieldrin is one of the most mobile of the older organochlorine pesticides (USGS, 1999).

Dieldrin detection frequencies are considerably higher in shallow ground water in urban areas when compared to shallow ground water in agricultural areas (Table 4-3), a likely consequence of the more recent use of aldrin and dieldrin as a termiticide and industrial moth-proofing agent until the mid-1980s. Agricultural uses were discontinued in the 1970s. Major aquifers, generally deep, have very low detection frequencies and concentrations of dieldrin. Hydrophobic compounds have high sorption potential and are not very mobile in ground water, making their occurrence in deep aquifers unlikely.

In streams, detection frequencies are higher compared to ground water (Table 4-3). Dieldrin's chemical characteristics, chiefly its hydrophobicity, make it less likely to be transported to the subsurface with ground water recharge. Instead, dieldrin sorbs easily to sediments and biotic tissues and may persist in surface water environments for many years after applications have ceased. Differences in detection frequencies and concentrations between urban and agricultural settings are less pronounced for streams than for ground water, but frequencies and concentrations are greater for streams in agricultural settings.

The concentrations and detection frequencies of dieldrin in bed sediments and biotic tissues are considerably higher than water, although the median concentration of all samples is still below the MDL (Table 4-4). Occurrence of dieldrin is highest in whole fish, highlighting the potential for it to bioaccumulate (Kolpin et al., 1998). The trend of higher concentrations and detection frequencies in urban environments is again apparent when examining dieldrin

Table 4-3. Dieldrin Detections and Concentrations in Streams and Ground Water[1]

	Detection Frequency (% Samples ≥ MDL[2])		Concentration Percentiles (All Samples; µg/L)		
	% ≥ 0.001 µg/L	% ≥ 0.01 µg/L	Median	95th	Maximum
Streams					
urban	3.67%	1.83%	nd[3]	nd	0.016
integrator	3.27%	1.63%	nd	nd	0.015
agricultural	6.90%	3.90%	nd	0.007	0.027
all sites	4.64%	2.39%	nd	nd	0.19
Ground water					
shallow urban	5.65%	3.32%	nd	0.005	0.068
shallow agricultural	0.97%	0.65%	nd	nd	0.057
major aquifers	0.43%	0.21%	nd	nd	0.03
all sites	1.42%	0.93%	nd	nd	0.068

[1] USGS, 1998.

[2] MDL for dieldrin in water studies:0.001 µg/L.

[3] Not detected in concentration greater than MDL.

Table 4-4. Dieldrin Detections and Concentrations in Sediments, Whole Fish, and Bivalves (All Sites)[1]

	Detection Frequency (% Samples > MDL[2])	Concentration Percentiles (All Samples; µg/kg Dry Weight)		
		Medium	95th	Maximum
sediments	13.7%	nd[3]	2.7	18
whole fish	28.6%	nd	31.9	260
bivalves	6.4%	nd	6.4	20

[1] Nowell, 1999.

[2] MDL for dieldrin in sediments: 1 µg/kg; dieldrin in whole fish and bivalves: 5 µg/kg.

[3] Not detected in concentration greater than MDL.

occurrence across various land use settings for sediments and biotic tissues. Urban areas have the highest detections and concentrations. Occurrence in agricultural and mixed land use settings is lower and approximately equivalent. Forest and rangeland show very low occurrence. The occurrence of a toxic compound in stream sediments is pertinent to drinking water concerns because some desorption of the compound from sediments into water will occur through equilibrium reactions, although in very low concentrations.

While concentrations in water are generally low, a risk-specific dose (RSD) criteria of 0.02 µg/L, a concentration associated with a cancer risk level of 1 in 100,000 people, was exceeded at least at 1 site in both surface and ground water (Kolpin et al., 1998; Larson et al., 1999; USGS, 1998).

Water Quality Investigations from the Corn Belt

A USGS regional water quality investigation provides additional information on the occurrence of dieldrin in the corn belt. For surface water sampling from April 1991 to March 1992 from the Mississippi River and six tributaries draining the corn belt, 8% of all samples and 71% of sites had detections greater than the reporting limit of 0.02 µg/L. The maximum concentration was approximately 0.03 µg/L (Goolsby and Battaglin, 1993).

4.2.2 Drinking Water Occurrence

The Safe Drinking Water Act (SDWA), as amended in 1986, required Public Water Systems (PWSs) to monitor for specified "unregulated" contaminants, conduct monitoring on a 5-year cycle, and report the monitoring results to the states. Unregulated contaminants do not have an established or proposed National Primary Drinking Water Regulation (NPDWR), but they are contaminants that were formally listed and required for monitoring under federal regulations. The intent was to gather scientific information on the occurrence of these

contaminants to enable a decision as to whether or not regulations were needed. All non-purchased community water systems (CWSs) and non-purchased non-transient non-community water systems (NTNCWSs), with greater than 150 service connections, were required to conduct this unregulated contaminant monitoring. Smaller systems were not required to conduct this monitoring under federal regulations, but were required to be available to monitor if the state decided such monitoring was necessary. Many states collected data from smaller systems. Additional contaminants were added to the Unregulated Contaminant Monitoring (UCM) program in 1991 (USEPA, 1991) for required monitoring that began in 1993 (USEPA, 1992).

Dieldrin has been monitored under the SDWA Unregulated Contaminant Monitoring (UCM) program since 1993 (USEPA, 1992). Monitoring ceased for small public water systems (PWSs) under a direct final rule published January 8, 1999 (USEPA, 1999a), and ended for large PWSs with promulgation of the new Unregulated Contaminant Monitoring Regulation (UCMR) issued September 17, 1999 (USEPA, 1999b) and effective January 1, 2001. At the time the UCMR lists were developed, the Agency concluded there were adequate monitoring data for a regulatory determination. This obviated the need for continued monitoring under the new UCMR list.

Data Sources, Data Quality, and Analytical Methods

Currently, there is no complete national record of unregulated or regulated contaminants in drinking water from PWSs collected under SDWA. Many states have submitted unregulated contaminant PWS monitoring data to EPA databases, but there are issues of data quality, completeness, and representativeness. Nonetheless, a significant amount of state data are available for UCM contaminants that can provide estimates of national occurrence.

The National Contaminant Occurrence Database (NCOD) is an interface to the actual occurrence data stored in the Safe Drinking Water Information System (Federal version; SDWIS/FED) and can be queried to provide a summary of the data in SDWIS/FED for a particular contaminant. The drinking water occurrence data for dieldrin presented here were derived from monitoring data available in the SDWIS/FED database.

The data in this report have been reviewed, edited, and filtered to meet various data quality objectives for the purposes of this analysis. Hence, not all data from a particular source were used, only data meeting the quality objectives described below were included. The sources of these data, their quality and national aggregation, and the analytical methods used to estimate a given contaminant's national occurrence (from these data) are discussed in this section (for further details see USEPA [2001a,b]).

UCM Rounds 1 and 2

The 1987 UCM contaminants include 34 volatile organic compounds (VOCs) (USEPA, 1987). Dieldrin, a synthetic organic compound (SOC), was *not* among these contaminants. The UCM (1987) contaminants were first monitored coincident with the Phase I regulated contaminants, during the 1988 to 1992 period. This period is often referred to as "Round 1" monitoring. The monitoring data collected by the PWSs were reported to the states (as primacy

agents), but there was no protocol in place to report these data to EPA. These data from Round 1 were collected by EPA from many states over time and put into a database called the Unregulated Contaminant Information System, or URCIS.

The 1993 UCM contaminants include 13 SOCs and 1 inorganic contaminant (IOC) (USEPA, 1991). Monitoring for the UCM (1993) contaminants began coincident with the Phase II/V regulated contaminants in 1993 through 1998. This is often referred to as "Round 2" monitoring. The UCM (1987) contaminants were also included in the Round 2 monitoring. As with other monitoring data, PWSs reported these results to the states. EPA, during the past several years, requested that the states submit these historic data to EPA, and they are now stored in the SDWIS/FED database.

Monitoring and data collection for dieldrin, a UCM (1993) contaminant, began in Round 2. Therefore, the following discussion regarding data quality screening, data management, and analytical methods focuses on SDWIS/FED. Discussion of the URCIS database is included where relevant, but it is worth noting that the various quality screening, data management, and analytical processes were nearly identical for the two databases. For further details on the two monitoring periods as well as the databases see USEPA (2000a,b).

Developing a Nationally Representative Perspective

The Round 2 data contain contaminant occurrence data from a total of 35 primacy entities (including 34 states and data for some tribal systems). However, data from some states are incomplete and biased. Furthermore, the national representativeness of the data is problematic because the data were not collected in a systematic or random statistical framework. These state data could be heavily skewed to low-occurrence or high-occurrence settings. Hence, the state data were evaluated based on pollution-potential indicators and the spatial/hydrologic diversity of the nation. This evaluation enabled the construction of a cross-section from the available state data sets that provides a reasonable representation of national occurrence.

A national cross-section from these state Round 2 contaminant databases was established using the approach developed for the EPA report *A Review of Contaminant Occurrence in Public Water Systems* (USEPA, 1999c). This approach was developed to support occurrence analyses for EPA's Chemical Monitoring Reform (CMR) evaluation. It was supported by peer reviewers and stakeholders. The approach cannot provide a "statistically representative" sample because the original monitoring data were not collected or reported in an appropriate fashion. However, the resultant "national cross-section" of states should provide a clear indication of the central tendency of the national data. The remainder of this section provides a summary description of how the national cross-section for the SDWIS/FED (Round 2) database was developed. The details of the approach are presented in other documents (USEPA, 2001a; USEPA 2001b).

Cross-Section Development

As a first step in developing the cross-section, the state data contained in the SDWIS/FED database (that contains the Round 2 monitoring results) were evaluated for completeness and quality. Some state data in SDWIS/FED were unusable for a variety of

reasons. Some states reported only detections, or their data had incorrect units. Datasets only including detections are obviously biased. Other problems included substantially incomplete data sets without all PWSs reporting (USEPA, 2001a Sections II and III).

The balance of the states remaining after the data quality screening were then examined to establish a national cross-section. This step was based on evaluating the states' pollution potential and geographic coverage in relation to all states. Pollution potential is considered to ensure a selection of states that represent the range of likely contaminant occurrence and a balance with regard to likely high and low occurrence. Geographic consideration is included so that the wide range of climatic and hydrogeologic conditions across the United States are represented, again balancing the varied conditions that affect transport and fate of contaminants, as well as conditions that affect naturally occurring contaminants (USEPA, 2001b Sections III.A. and III.B.).

The cross-section states were selected to represent a variety of pollution potential conditions. Two primary pollution potential indicators were used. The first factor selected indicates pollution potential from manufacturing/population density and serves as an indicator of the potential for VOC contamination within a state. Agriculture was selected as the second pollution potential indicator because the majority of SOCs of concern are pesticides (USEPA, 2001b Section III.A.). The 50 individual states were ranked from highest to lowest based on the pollution potential indicator data. For example, the state with the highest ranking for pollution potential from manufacturing received a ranking of 1 for this factor and the state with the lowest value was ranked as number 50. States were ranked for their agricultural chemical use status in a similar fashion.

The states' pollution potential rankings for each factor were subdivided into four quartiles (from highest to lowest pollution potential). The cross-section states were chosen from all quartiles for both pollution potential factors to ensure representation, for example, from the following: states with high agrichemical pollution potential rankings and high manufacturing pollution potential rankings; states with high agrichemical pollution potential rankings and low manufacturing pollution potential rankings; states with low agrichemical pollution potential rankings and high manufacturing pollution potential rankings; and states with low agrichemical pollution potential rankings and low manufacturing pollution potential rankings (USEPA, 2001b Section III.B.). In addition, some secondary pollution potential indicators were considered to further ensure that the cross-section states included the spectrum of pollution potential conditions (high to low). The cross-section was then reviewed for geographic coverage throughout all sectors of the United States.

The data quality screening, pollution potential rankings, and geographic coverage analysis established a national cross-section of 20 Round 2 (SDWIS/FED) states. The cross-section states provide good representation of the nation's varied climatic and hydrogeologic regimes and the breadth of pollution potential for the contaminant groups (Figure 4-4).

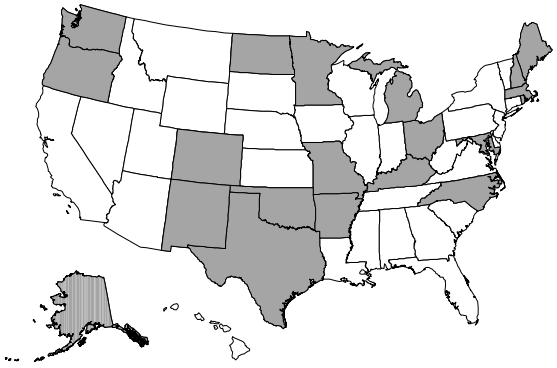
Cross-Section Evaluation

To evaluate and validate the method for creating the national cross-sections, the method was used to create smaller state subsets from the 24-state, Round 1 (URCIS) cross-section and aggregations. Again, states were chosen to achieve a balance from the quartiles describing pollution potential, and a balanced geographic distribution, to incrementally build subset cross-sections of various sizes. For example, the Round 1 cross-section was tested with subsets of 4, 8 (the first 4 state subset plus 4 more states), and 13 (8 state subset plus 5) states. Two additional cross-sections were included in the analysis for comparison: a cross-section composed of 16 biased states eliminated from the 24 state cross-section for data quality reasons and a cross-section composed of all 40 Round 1 states (USEPA, 2001b Section III.B.1).

These Round 1 incremental cross-sections were then used to evaluate occurrence for an array of both high and low occurrence contaminants. The comparative results illustrate several points. The results are quite stable and consistent for the 8, 13, and 24 state cross-sections. They are much less so for the 4 state, 16 state (biased), and 40 state (all Round 1 states) cross-sections. The 4 state cross-section is apparently too small to provide balance both geographically and

Figure 4-4. Geographic Distribution of Cross-Section States for Round 2 (SDWIS/FED)

Round 2 (SDWIS/FED)	
Alaska	New Hampshire
Arkansas	New Mexico
Colorado	North Carolina
Kentucky	North Dakota
Maine	Ohio
Maryland	Oklahoma
Massachusetts	Oregon
Michigan	Rhode Island
Minnesota	Texas
Missouri	Washington



with pollution potential, a finding that concurs with past work (USEPA, 1999c). The CMR analysis suggested that a minimum of 6 to 7 states were needed to provide balance both geographically and with pollution potential. The CMR report used 8 states out of the available data for its nationally representative cross-section (USEPA, 1999c). The 16 state and 40 state cross-sections, both including biased states, provided occurrence results that were unstable and inconsistent for a variety of reasons associated with their data quality problems (USEPA, 2001b Section III.B.1).

The 8, 13, and 24 state cross-sections provide very comparable results, are consistent, and are usable as national cross-sections to provide estimates of contaminant occurrence. Including greater data from more states improves the national representation and the confidence in the results, as long as the states are balanced related to pollution potential and spatial coverage. The 20 state cross-section provides the best, nationally representative cross-section for the Round 2 data.

Data Management and Analysis

The cross-section analyses focused on occurrence at the water system level; i.e., the summary data presented discuss the percentage of public water *systems* with detections, not the percentage of *samples* with detections. By normalizing the analytical data to the system level, skewness inherent in the sample data is avoided. System level analysis was used since a PWS with a known contaminant problem usually has to sample more frequently than a PWS that has never detected the contaminant. Obviously, the results of a simple computation of the percentage of samples with detections (or other statistics) can be skewed by the more frequent sampling results reported by the contaminated site. This level of analysis is conservative. For example, a system need only have a single sample with an analytical result greater than the Minimum Reporting Limit (MRL), i.e., a detection, to be counted as a system with a result "greater than the MRL."

Also, the data used in the analyses were limited to only those data with confirmed water source and sampling type information. Only standard SDWA compliance samples were used; "special" samples, or "investigation" samples (investigating a contaminant problem that would bias results), or samples of unknown type were not used in the analyses. Various quality control and review checks were made of the results, including follow-up questions to the states providing the data. Many of the most intractable data quality problems encountered occurred with older data. These problematic data were, in some cases, simply eliminated from the analysis. For example, when the number of data with problems were insignificant relative to the total number of observations they were dropped from the analysis (for further details see Cadmus [2000]).

As indicated above, Massachusetts is included in the 20-state, Round 2 national cross-section (Figure 4-4). However, problematic Massachusetts data for SOCs like dieldrin is noteworthy. Massachusetts reported Round 2 sample results for SOCs from only 56 PWSs, while VOC results were reported from over 400 different PWSs. Massachusetts SOC data also contained an atypically high percentage of systems with analytical detections when compared to all other states. Through communications with Massachusetts data management staff, it was

learned that the state's SOC data and the SDWIS/FED record for Massachusetts SOC data were incomplete. For instance, the SDWIS/FED Round 2 data for Massachusetts indicates 18% of systems reported detections of dieldrin while the average for all other states was 0.4%. In contrast, Massachusetts data characteristics and quantities for IOCs and VOCs were reasonable and comparable with other states' results. Therefore, Massachusetts was included in the group of 20 SDWIS/FED Round 2 cross-section states with usable data for IOCs and VOCs, but its dieldrin (SOC) data were omitted from Round 2 cross-section occurrence analyses and summaries presented in this report.

Occurrence Analysis

To evaluate national contaminant occurrence, a two-stage analytical approach has been developed. The first stage of analysis provides a straightforward, conservative, broad evaluation of occurrence of the CCL regulatory determination priority contaminants as described above. These descriptive statistics are summarized here. Based on the findings of the Stage 1 Analysis, EPA will determine whether more intensive statistical evaluations, the Stage 2 Analysis, may be warranted to generate national probability estimates of contaminant occurrence and exposure for priority contaminants. (For details on this two stage analytical approach see Cadmus [2000].)

The summary descriptive statistics presented in Table 4-5 for dieldrin are a result of the Stage 1 analysis and include data from Round 2 (SDWIS/FED, 1993 to 1997) cross-section states (minus Massachusetts). Included are the total number of samples, the percent samples with detections, the 99th percentile concentration of all samples, the 99th percentile concentration of samples with detections, and the median concentration of samples with detections. The percentages of PWSs and population served indicate the proportion of PWSs whose analytical results showed a detection(s) of the contaminant (simple detection, > MRL) at any time during the monitoring period; or a detection(s) greater than half the HRL; or a detection(s) greater than the HRL. The HRL, 0.002 µg/L, is a preliminary estimated health effect level used for this analysis.

Dieldrin is classified by EPA as a linear carcinogen and would, if regulated, have a MCLG of zero. The value used as the HRL when for the occurrence evaluation was the concentration equivalent to a one-in-a-million risk based on the EPA cancer slope factor.

The 99th percentile concentration is used here as a summary statistic to indicate the upper bound of occurrence values because maximum values can be extreme values (outliers) that sometimes result from sampling or reporting error. The 99th percentile concentration is presented for both the samples with only detections and all of the samples because the value for the 99th percentile concentration of all samples is below the Minimum Reporting Level (MRL) (denoted by "<" in Table 4-5). For the same reason, summary statistics such as the 95th percentile concentration of all samples or the median (or mean) concentration of all samples are omitted because these also are all "<" values. This is the case because only 0.064% of *all* samples recorded detections of dieldrin in Round 2.

As a simplifying assumption, a value of half the MRL is often used as an estimate of the concentration of a contaminant in samples/systems whose results are less than the MRL. With a

relatively low occurrence contaminant such as dieldrin in drinking water occurrence databases, the median or mean value of occurrence using this assumption would be half the MRL (0.5 * MRL). However, for these occurrence data this is not straightforward. For Round 2, states have reported a wide range of values for the MRLs. This is in part related to state data management differences, as well as real differences in analytical methods, laboratories, and other factors.

The situation can cause confusion when examining descriptive statistics for occurrence. For example, most Round 2 states reported non-detections simply as zeros resulting in a modal MRL value of zero. By definition the MRL cannot be zero. This is an artifact of state data management systems. Because a simple meaningful summary statistic is not available to describe the various reported MRLs, and to avoid confusion, MRLs are not reported in the summary table (Table 4-5).

In Table 4-5, national occurrence is estimated by extrapolating the summary statistics for the 20 state cross-section (minus Massachusetts) to national numbers for systems, and population served by systems, from the *Water Industry Baseline Handbook, Second Edition* (USEPA, 2000). From the handbook, the total number of community water systems (CWSs) plus non-transient, non-community water systems (NTNCWSs) is 65,030 and the total population served by CWSs plus NTNCWSs is 213,008,182 persons (Table 4-5). To arrive at the national occurrence estimate for the cross-section, the national estimate for PWSs (or population served by PWSs) is simply multiplied by the percentage for the given summary statistic (i.e., the national estimate for the total number of PWSs with detections, 61, is the product of the percentage of PWSs with detections, 0.093%, and the national estimate for the total number of PWSs, 65,030).

Included in Table 4-5 in addition to the cross-section data results are results and national extrapolations from all Round 2 reporting states. The data from the biased states are included because for contaminants with very low occurrence, such as dieldrin where few states have detections, any occurrence becomes more important, relatively. For such contaminants, the cross-section process can easily miss a state with occurrence that becomes more important. This is the case with dieldrin.

Extrapolating only from the cross-section states, dieldrin's very low occurrence probably underestimates national occurrence. For example, while data from biased states like Alabama (reporting 100% detections >HRL, >½ HRL, and >MRL; see Appendix B) exaggerate occurrence because only systems with detections reported results, their detections are real and need to be accounted for because extrapolations from the cross-section states do not predict enough detections in the biased states. Therefore, results from all reporting Round 2 states, including the biased states, are also used here to extrapolate a national estimate. Using the biased states' data should provide conservative estimates, likely overestimates, of national occurrence for dieldrin.

Additional Drinking Water Data from the Corn Belt

To augment the SDWA drinking water data analysis described above and to provide additional coverage of the corn belt states where dieldrin use as an agricultural insecticide was historically high, independent analyses of SDWA drinking water data from the states of Iowa, Illinois, and Indiana were reviewed. Raw water monitoring data are also included from Illinois community water supply wells.

The Iowa analysis examined SDWA compliance monitoring data from surface and ground water PWSs for the years 1988 to 1995 (Hallberg et al., 1996). Illinois and Indiana compliance monitoring data for surface and ground water PWSs were evaluated mostly for the years after 1993, though some earlier data were also included (USEPA, 1999c). The raw water data from Illinois were collected from rural, private supply wells (Goetsch *et al.*, 1992). Data sources, data quality, and analytical methods for these analyses are described in the respective reports; they were all treated similarly to the data quality reviews for this analysis.

Results

Occurrence Estimates

The percentages of PWSs with detections are very low (Table 4-5). The cross-section shows approximately 0.1% of PWSs (about 61 PWSs nationally) experienced detections at any concentration level (> MRL, > ½ HRL, and > HRL), affecting less than 0.1% of the population served (150,000 people nationally, see Figure 4-5). The percentage of PWSs (or population served) in a given source category (i.e., ground water) with detections > MRL, > ½ HRL, and > HRL is the same because the estimated HRL is so low that it is less than the MRL. Hence, any detection reported is greater than the HRL. Detection frequencies are marginally higher for surface water systems when compared to ground water systems. While concentrations are also low—for samples with detections the median concentration is 0.16 µg/L and the 99th percentile concentration is 1.36 µg/L—these values are greater than the HRL.

As noted above, because of the very low occurrence, the cross-section states yield an underestimate. Hence, all data are used, even the biased data, to present a conservative upper bound estimate. Conservative estimates of dieldrin occurrence using all of the Round 2 reporting states still show relatively low detection frequencies (Table 4-5). Approximately 0.2% of PWSs (estimated at 137 PWSs nationally) experienced detections at any concentration level (> MRL, > ½ HRL, and > HRL), affecting about 0.4% of the population served (793,000 people nationally). The proportion of surface water PWSs with detections was greater than ground water systems. Again the percentages of PWSs (or populations served) with detections > MRL, > ½ HRL, or > HRL are the same because of the low HRL. The median concentration of detections is 0.42 µg/L and the 99th percentile concentration is 4.4 µg/L.

The Round 2 reporting states and the Round 2 national cross-section show a proportionate balance in PWS source waters compared to the national inventory. Nationally, 91% of PWSs use ground water (and 9% surface waters). Round 2 reporting states and the Round 2 national cross-section show 88% use ground water (and 12% surface waters). The

relative populations served are not as comparable. Nationally, about 40% of the population is served by PWSs using ground water (and 60% by surface water). For the Round 2 cross-section, 30% of the cross-section population is served by ground water PWSs (and 70% by surface water). For all Round 2 reporting states, 32% of the population is served by ground water PWSs (and 68% by surface water). The resultant national extrapolations are not additive as a consequence of these disproportions.

Drinking water data from the corn belt states of Iowa, Indiana, and Illinois also show very low occurrence of dieldrin. There were no detections of the pesticide in the Iowa SDWA compliance monitoring data for surface or ground water PWSs (Hallberg et al., 1996). While Illinois and Indiana also had no detections of the compound in ground water PWSs, it was detected in surface water PWSs in those states (USEPA, 1999c). Occurrence was low in both states: 1.8% of surface water systems (0.1% of samples) showed detections in Illinois; and 2.1% of surface water systems (0.3% of samples) showed detections in Indiana. For Illinois and Indiana surface water PWSs, the 99th percentile concentrations of all samples were below the reporting level and the maximum concentrations were 0.1 µg/L and 0.04 µg/L, respectively (USEPA, 1999c). Furthermore, in a survey of Illinois rural, private water supply wells only 1.6% of all sampled wells had detections of dieldrin (Goetsch et al., 1992).

Regional Patterns

Occurrence results are displayed graphically by state in Figures 4-5 and 4-6 to assess whether any distinct regional patterns of occurrence are present. Thirty-four states reported Round 2 data but seven of those states have no data for dieldrin (Figure 4-5). Another 19 states did not detect dieldrin. The remaining eight states detected dieldrin in drinking water and are generally located either in the southern United States or the Northeast (Figure 4-5). In contrast to the summary statistical data presented in the previous section, this simple spatial analysis includes the biased Massachusetts data.

The simple spatial analysis presented in Figures 4-5 and 4-6 suggests that special regional analyses are not warranted. Alabama does, however, stand out as having relatively high occurrence for reasons that are unclear. While there is a weak geographic clustering of drinking water detections in a few southern and northeastern states (including Massachusetts' biased data), this is partly the result of so few states with any detections. Further, use and environmental release information (Section 3) and ambient water quality data (Section 4.2.1.2) indicate that dieldrin detections are more widespread than the drinking water data suggest. Detections of the compound in hazardous waste sites in at least 38 states (at NPL sites), site samples in at least 40 states (listed in ATSDR's HazDat [ATSDR, 2000]), and water, sediment, and biotic tissue quality data from the NAWQA program provide evidence for nationwide occurrence.

Table 4-5. Summary Occurrence Statistics for Dieldrin

Frequency Factors	20 State Cross-Section[1]	All Reporting States[2]	National System & Population Numbers[3]	
Total Number of Samples	29,603	40,055	--	
Percent of Samples with Detections	0.064%	0.135%	--	
99th Percentile Concentration (all samples)	< (Non-detect)	< (Non-detect)	--	
Health Reference Level	0.002 µg/L	0.002 µg/L	--	
Minimum Reporting Level (MRL)	Variable[4]	Variable[4]	--	
99th Percentile Concentration of Detections	1.36 µg/L	4.40 µg/L	--	
Median Concentration of Detections	0.16 µg/L	0.42 µg/L	--	
Total Number of PWSs	11,788	14,725	65,030	
Number of GW PWSs	10,329	12,968	59,440	
Number of SW PWSs	1,459	1,757	5,590	
Total Population	45,784,187	56,909,027	213,008,182	
Population of GW PWSs	13,831,864	18,044,000	85,681,696	
Population of SW PWSs	31,952,323	38,865,027	127,326,486	
Occurrence by System			**National Extrapolation[5]**	
PWSs with detections (> MRL)	0.093%	0.211%	61	137
Range of Cross-Section States	0 - 0.97%	0 - 100%	N/A	N/A
GW PWSs with detections	0.087%	0.177%	52	105
SW PWSs with detections	0.137%	0.455%	8	25
PWSs > 1/2 Health Reference Level (HRL)	0.093%	0.211%	61	137
Range of Cross-Section States	0 - 0.97%	0 - 100%	N/A	N/A
GW PWSs > 1/2 Health Reference Level	0.087%	0.177%	52	105
SW PWSs > 1/2 Health Reference Level	0.137%	0.455%	8	25
PWSs > Health Reference Level	0.093%	0.211%	61	137
Range of Cross-Section States	0 - 0.97%	0 - 100%	N/A	N/A
GW PWSs > Health Reference Level	0.087%	0.177%	52	105
SW PWSs > Health Reference Level	0.137%	0.455%	8	25
Occurrence by Population Served				
PWS Population Served with detections	0.070%	0.372%	150,000	793,000
Range of Cross-Section States	0 - 2.00%	0 - 100%	N/A	N/A
GW PWS Population with detections	0.146%	0.371%	125,000	318,000
SW PWS Population with detections	0.038%	0.372%	48,000	474,000
PWS Population Served > 1/2 Health Reference Level	0.070%	0.372%	150,000	793,000
Range of Cross-Section States	0 - 2.00%	0 - 100%	N/A	N/A
GW PWS Population > 1/2 Health Reference Level	0.146%	0.371%	125,000	318,000
SW PWS Population > 1/2 Health Reference Level	0.038%	0.372%	48,000	474,000
PWS Population Served > Health Reference Level	0.070%	0.372%	150,000	793,000
Range of Cross-Section States	0 - 2.00%	0 - 100%	N/A	N/A
GW PWS Population > Health Reference Level	0.146%	0.371%	125,000	318,000
SW PWS Population > Health Reference Level	0.038%	0.372%	48,000	474,000

1. Summary Results based on data from 20-State Cross-Section (minus Massachusetts), from SDWIS/FED, UCM (1993) Round 2.
2. Summary Results based on data from all reporting states from SDWIS/FED, UCM (1993) Round 2; see text for further discussion.
3. Total PWS and population numbers are from EPA March 2000 Water Industry Baseline Handbook.
4. See text for discussion.
5. National extrapolations are from the 20-State data using the Baseline Handbook system and population numbers.

- "PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; MRL = Minimum Reporting Level (for laboratory analyses); Health Reference Level = Health Reference Level, an estimated health effect level used for preliminary assessment for this review; N/A = Not Applicable."
- The Health Reference Level (HRL) used for dieldrin is 0.002 µg/L. This is a draft value for working review only.
- Total Number of Samples = the total number of analytical records for dieldrin.
- 99th Percentile Concentration = the concentration value of the 99th percentile of either all analytical results or just the detections (in µg/L).
- Median Concentration of Detections = the median analytical value of all the detections (analytical results greater than the MRL) (in µg/L).
- Total Number of PWSs = the total number of public water systems with records for dieldrin.
- Total Population Served = the total population served by public water systems with records for dieldrin.
- % PWS with detections, % PWS > ½ Health Reference Level, % PWS > Health Reference Level = percent of the total number of public water systems with at least one analytical result that exceeded the MRL, ½ Health Reference Level, Health Reference Level, respectively.
- % PWS Population Served with detections, % PWS Population Served >½ Health Reference Level, % PWS Population Served > Health Reference Level = percent of the total population served by PWSs with at least one analytical result exceeding the MRL, ½ Health Reference Level, or the Health Reference Level, respectively.

Figure 4-5. States With PWSs With Detections of Dieldrin for All States With Data in SDWIS/FED (Round 2)

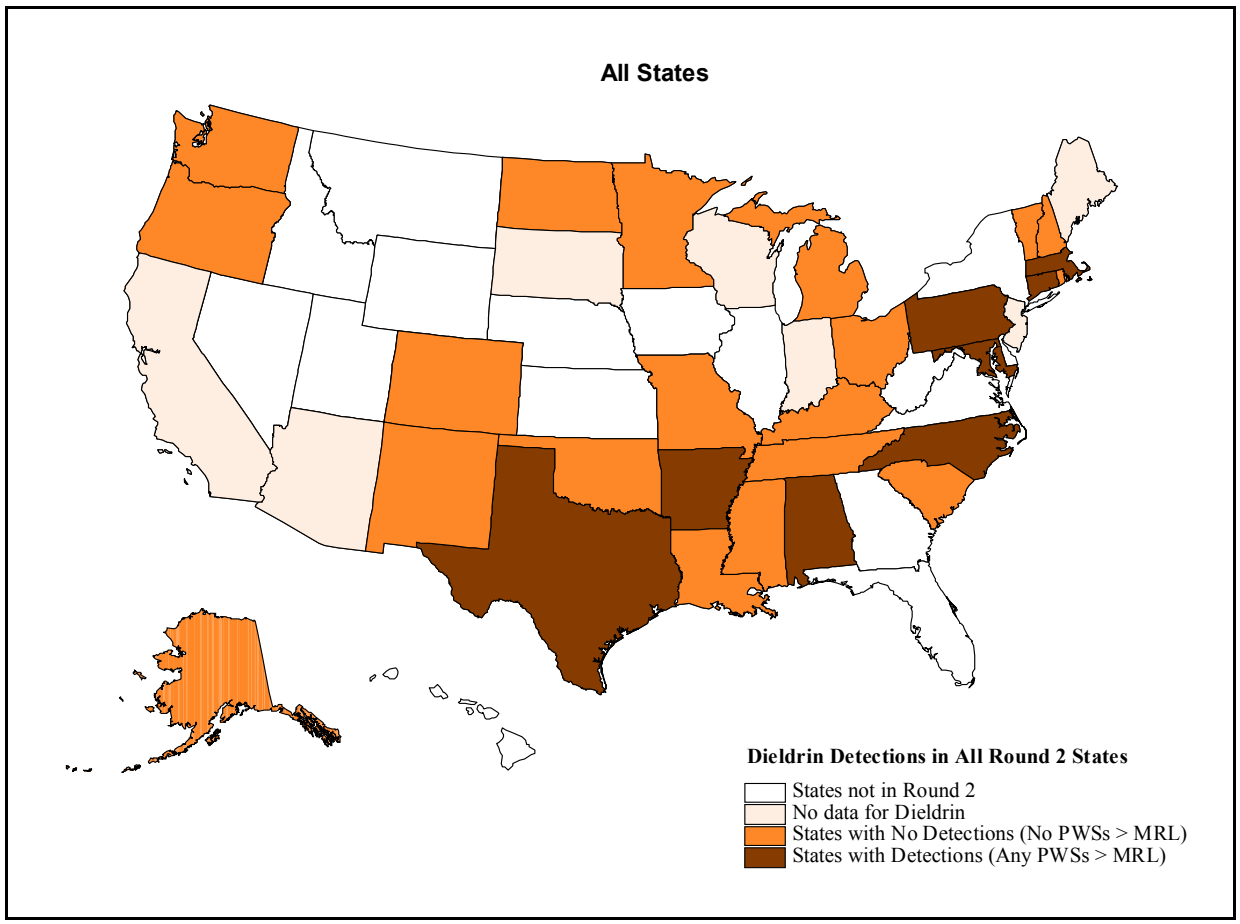
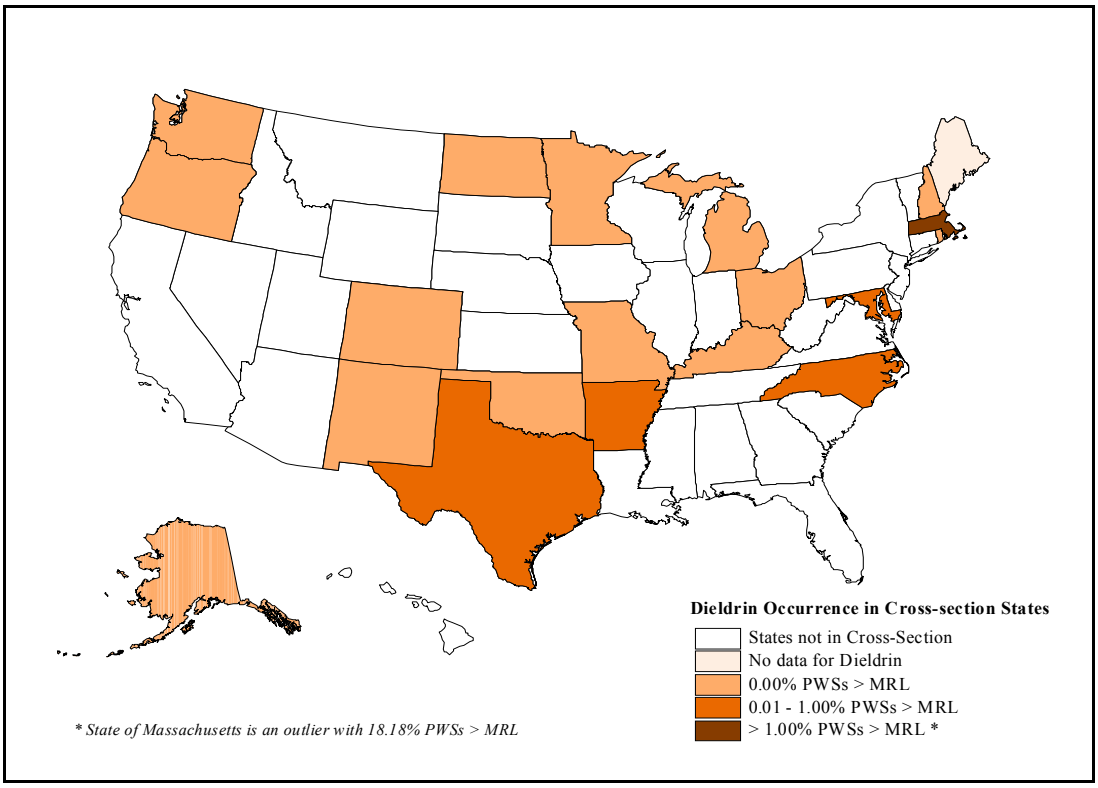
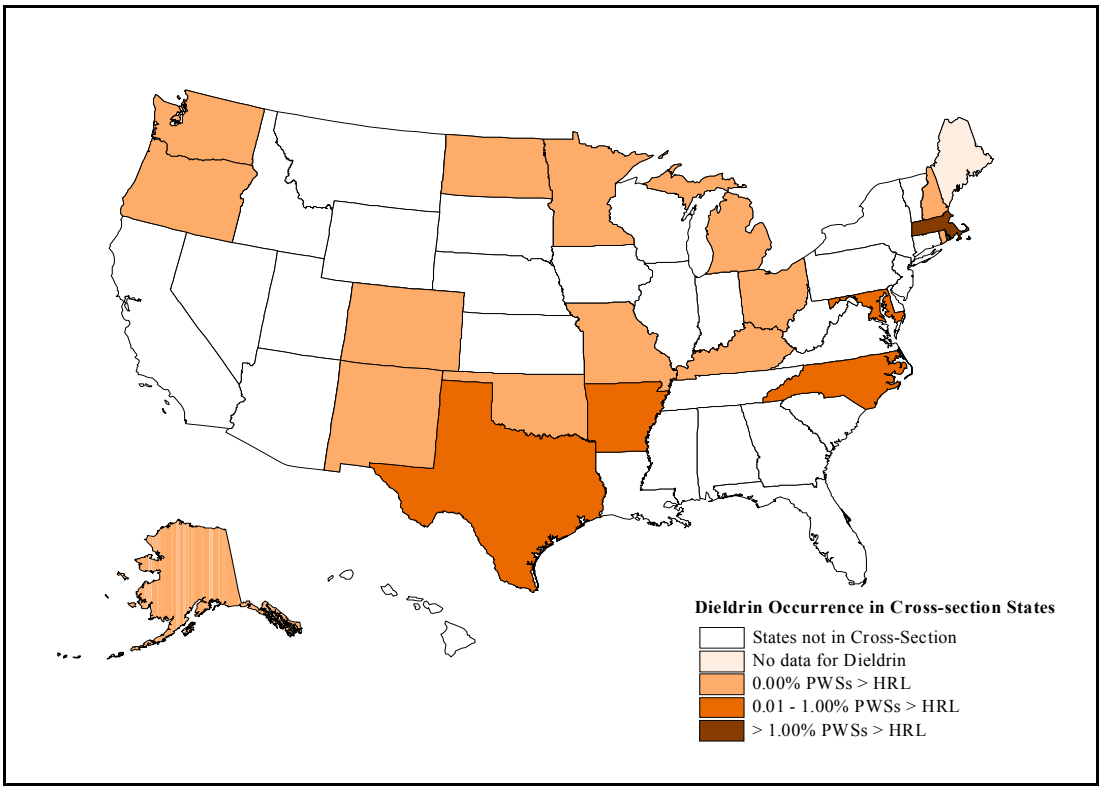


Figure 4-6. Round 2 Cross-Section States With PWSs With Detections of Dieldrin (Any PWS With Results Greater than the Minimum Reporting Level [MRL]; Above) and Concentrations Greater than the Health Reference Level (HRL; Below)





4.2.3 Conclusion

Dieldrin is an insecticide that was discontinued for all uses in 1987. It combats insects by contact or ingestion, and was used primarily on corn and citrus products, as well as for general crops and timber preservation. In addition, dieldrin was used for termite-proofing plywood, building boards, and the plastic and rubber coverings of electrical and telecommunication cables (ATSDR, 1993). In 1972, USEPA cancelled all uses of dieldrin except subsurface ground insertion for termite control, dipping of non-food plant roots and tops, and moth-proofing in closed-system manufacturing processes. This cancellation decision was finalized in 1974 and in 1987 the manufacturer voluntarily cancelled all uses (ATSDR, 1993). Dieldrin is also produced by the environmental degradation of aldrin, an insecticide with similar uses and regulatory history.

Dieldrin has been detected at low frequencies and concentrations in ground and surface water sampled during the first round of the USGS NAWQA studies, and at similar frequencies and concentrations in surface waters of the Mississippi River and major tributaries. Its occurrence is greater in stream bed sediments and biotic tissue. Dieldrin has also been found at ATSDR HazDat and CERCLA NPL sites across the country.

Dieldrin has been detected in PWS samples collected under the SDWA. Occurrence estimates are very low with only 0.06% of all samples showing detections. Significantly, the values for the 99th percentile and median concentrations of all samples are less than the MRL. For Round 2 samples with detections, the median concentration is 0.16 µg/L and the 99th percentile concentration is 1.36 µg/L. Systems with detections constitute approximately 0.1% of Round 2 systems. National estimates for the population served by PWSs with detections are also low (150,000), and are the same for all categories (> MRL, > ½ HRL, > HRL). These estimates are less than 0.1% of the national population. Using more conservative estimates of occurrence from all states reporting SDWA Round 2 monitoring data, including states with biased data, 0.2% of the nations PWSs (approximately 137 systems) and 0.4% of the PWS population served (793,000 people) may be estimated to have detections > MRL, > ½ HRL, and > HRL.

Additional SDWA compliance data from the corn belt states of Iowa, Indiana, and Illinois examined through independent analyses support the drinking water data analyzed in this report. There were no detections in either surface or ground water PWSs in the state of Iowa. Illinois and Indiana reported detections only from surface water PWSs with 1.8% of Illinois' surface water systems (0.1% of samples) and 2.1% of Indiana's surface water systems (0.3% of samples) showing detections. For Illinois and Indiana surface water PWSs, the 99th percentile concentrations of all samples were below the reporting level and the maximum concentrations were 0.1 µg/L and 0.04 µg/L, respectively (USEPA, 1999c). Moreover, in a survey of Illinois rural, private water supply wells dieldrin was detected in only 1.6% of all sampled wells.

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5.0 EXPOSURE FROM ENVIRONMENTAL MEDIA OTHER THAN WATER

This section summarizes human population exposures to aldrin and dieldrin from food, air, and soil. The primary purpose is to estimate average daily intakes of aldrin and dieldrin by members of the general public. When exposure data on subpopulations were located, such as occupationally exposed persons, these data were summarized and included in this section.

5.1 Exposure from Food

Aldrin and dieldrin have been used for pest control on crops such as corn, and citrus products. Aldrin is readily converted to dieldrin, which is persistent in the environment. Although the use of aldrin and dieldrin on crops was cancelled in 1974, soil residues from past uses persist, and may be taken up by crops. Dieldrin additionally bioconcentrates and biomagnifies through terrestrial and aquatic food chains. Thus, the general population may be exposed to aldrin or dieldrin through diet (ATSDR, 2000).

5.1.1 Exposures of the General Population

Concentrations in Non-Fish Food Items

Aldrin

During 1981 through 1992, the U.S. Food and Drug Administration (FDA) conducted a Market Basket Study to evaluate concentrations of pesticides in 234 different food items. Table 5-1 summarizes aldrin concentrations detected in these foods. Aldrin was detected in 5 food items at concentrations ranging from 0.0009 to 0.002 mg/kg food. The mean concentration for all positive samples was 0.0016 mg/kg (KAN-DO Office and Pesticides Team, 1995).

Agriculture and Agri-Food Canada (Neidert and Saschenbrecker, 1996) analyzed 21,982 randomly sampled domestic and imported food and vegetable commodities for pesticide residues between 1992 and 1994. Aldrin was not detected in any domestically produced fruits or vegetables, but was detected in one sample of imported tomatoes at <0.05 mg/kg. Aldrin was not detected in any food items during the 1985 survey (Davies, 1988).

Kannan et al. (1994) reviewed data on aldrin and dieldrin residues in food in South and Southeast Asia and in the South Pacific Islands. Aldrin was detected in several food items collected throughout India during the period of 1975 through 1989. Vegetables, oils, and food grains contained <0.01 to 0.04 mg/kg, 0.01 to 1.1 mg/kg, and 0.05 to 0.1 mg/kg aldrin, respectively.

In 1990, Kannan et al. (1994) analyzed food items collected from various metropolitan locations in Australia for organochlorine pesticides. The highest aldrin concentrations were detected in pulses and dairy products at levels of 2.8×10^{-3} and 8.9×10^{-4} mg/kg wet weight, respectively. Aldrin was also detected in cereals (3×10^{-5} mg/kg), oils (1.5×10^{-4} mg/kg), vegetables (0.01 mg/kg), fruits (<0.01 mg/kg), and meat (3.0×10^{-4} mg/kg).

Table 5-1. Aldrin and Dieldrin in Domestic Food Items 1981 to 1992[1]

Type of Food	Mean Dieldrin Concentrations (mg/kg food) and Number of Positive Samples (N)	Mean Aldrin Concentrations (mg/kg food) and Number of Positive Samples (N)
Condiments, Fats, and Sweetners	0.0011-0.005 (55)	--
Dairy	0.0003-0.0061 (163)	--
Desserts	0.0004-0.0048 (96)	0.0009 (1)
Fruits	0.0005-0.004 (21)	--
Grains	0.0003-0.002 (2)	0.002 (1)
Infant Food (strained junior foods in jars)	0.0003-0.0051 (36)	--
Meat, Poultry, Fish and Eggs	0.0005-0.002 (195)	0.002 (1)
Mixed Foods	0.0006-0.002 (49)	--
Soup	0.0004-0.0008 (9)	0.001 (1)
Vegetables and Vegetable Products	0.0002-0.0108 (210)	0.002 (1)

[1] Source: KAN-DO Office and Pesticides Team, 1995.

Milk samples collected during 1990 through 1991 from 63 metropolitan locations throughout the United States did not contain aldrin residues above the detection limit of 0.0005 ppm (Trotter and Dickerson, 1993).

During FDA Regulatory Monitoring 1985-1991 (Yess et al., 1993) of adult foods eaten by infants, 1 of 735 imported orange samples analyzed contained trace levels of aldrin. However, aldrin was not detected in domestic samples of adult food items eaten by infants analyzed in the same FDA Regulatory Monitoring Survey 1985-1991. Infant foods analyzed during FDA Total Diet Study 1985-1991 (Yess et al., 1993) and Market Basket Survey 1981-1991 (KAN-DO Office and Pesticides Team, 1995) sampling did not contain detectable levels of aldrin.

Dieldrin

Table 5-1 summarizes dieldrin concentrations in various food items analyzed during 1981 through 1992 as part of the FDA's Market Basket Study (KAN-DO Office and Pesticides Team, 1995). Dieldrin was detected in 117 of 234 different food items at concentrations ranging from 0.0002 to 0.0087 mg/kg. The mean dieldrin concentration for all positive samples was 0.0015 mg/kg. The highest dieldrin concentrations were detected in squash (0.0087 mg/kg) and butter (0.0061 mg/kg) samples. Cauliflower (0.0002 mg/kg), soup, canned beets, and red beans (0.0004 mg/kg) had the lowest dieldrin concentrations.

In 1992 and 1994, dieldrin was detected in both domestic and imported food and vegetable commodities analyzed by Agriculture and Agri-Food Canada (Neidert and Saschenbrecker, 1996). Six of the 5,784 domestically produced fruits and vegetables had dieldrin residues ranging from <0.05 to 0.10 mg/kg. Of the 16,198 imported fruits and vegetables sampled, 7 had dieldrin levels ranging from <0.05 to 0.10 mg/kg. One of the 1,858 imported oranges contained 0.50 mg/kg dieldrin. A 1985 Canadian study reported higher levels of dieldrin residues in fruits and vegetables, which ranged from 0.11 to 23.0 μg/kg (Davies, 1988).

Dieldrin has been detected in various meats. Beef, chicken, lamb, and pork samples bought from butcher shops in Australia during 1990 contained a mean dieldrin concentration of 5.1×10^{-3} mg/kg wet weight (Kannan et al., 1994). Levengood et al. (1999) analyzed 44 samples of Canadian goose meat collected in northeastern Illinois during 1994 for pesticide residues. Dieldrin was detected in 16% of the baked skinless samples at concentrations ranging from 0.004 to 0.011 mg/kg, and in 7% of the samples baked with the skin and overlying adipose tissue at concentrations of 0.005 to 0.010 mg/kg. Dieldrin residue levels reported in this study were below FDA residue limits of 0.30 mg/kg (Dey and Manzoor, 1997).

Milk and milk products are additional sources of dieldrin in the diet. During 1990 and 1991, milk samples were collected from 63 metropolitan locations throughout the United States, as part of the EPA's Pasteurized Milk Program. Dieldrin was detected in 21.1% of 806 composited milk samples at concentrations ranging from 0.0005 mg/kg (detection limit) to 0.002 mg/kg (Trotter and Dickerson, 1993). FDA Total Diet Study results from 1985 through 1991 reported mean dieldrin concentrations in whole milk, 2% milk, evaporated canned milk, and chocolate milk samples of 0.0003 mg/kg, 0.0003 mg/kg, 0.0008 mg/kg, and 0.0014 mg/kg, respectively (KAN-DO Office and Pesticides Team, 1995). Maximum dieldrin concentrations detected in vitamin D milk and plain milk samples as part of the FDA Regulatory Monitoring were 0.03 mg/kg and 1 mg/kg, respectively. The maximum residue found in whole milk (1 mg/kg) was above the EPA milk tolerance of 0.30 ppm (0.30 mg/kg) (Yess et al., 1993).

Dingle et al. (1989) found dieldrin to persist in milk butterfat, with a half-life in butter of approximately 9 weeks. Ultra-pasteurized heavy cream and cow milk samples purchased in Binghamton, New York, in 1986 had dieldrin levels of 0.006 mg/kg and 0.003 mg/kg, respectively (Schecter et al., 1989).

Infant foods analyzed during the FDA's Market Basket Survey from 1981 through 1992 contained mean dieldrin residues ranging from 0.003 to 0.0051 mg/kg (KAN-DO Office and Pesticides Team, 1995). Maximum dieldrin concentrations detected in infant foods sampled during the 1985 to 1991 sampling period as part of the FDA's Total Diet Study were 0.002 mg/kg. Adult foods eaten by infants and children also analyzed as part of the FDA Total Diet Study and Regulatory Monitoring programs (from 1985 through 1991) detected dieldrin in creamy peanut butter, pears, and one imported orange at maximum concentrations of 0.003, 0.0005, and 0.01 mg/kg, respectively (Yess et al., 1993).

Because many infants receive human breast milk, their dieldrin intakes may be closely related to its concentration in human breast milk. Current data regarding the levels of dieldrin in human breast milk in the United States were not located. However, data from several older studies are available. Dieldrin was found in the breast milk of 80.8% of 1,436 nursing women sampled in 1980, with a mean fat-adjusted residue level of 0.164 mg/kg (Savage et al., 1981). Additional studies of nursing mothers in Hawaii (Takei et al., 1983) and in Mississippi and Arkansas (Strassman and Kutz, 1977) found dieldrin residues in breast milk at mean concentrations of 1.3 ppb (0.0013 mg/kg) and 4 ppb (0.004 mg/kg), respectively. Breast milk collected from Canadian provinces during 1986 contained an average dieldrin concentration of 4.6×10^{-5} ppm (4.6×10^{-5} mg/kg) (Mes et al., 1993).

Intake from Non-Fish Food Items

Aldrin

The mean aldrin concentration detected in domestic food items during 1981 to 1992 was 0.0016 mg/kg (KAN-DO Office and Pesticides Team, 1995). Based on this concentration, a 70 kg adult with a food intake rate of 1.305 kg/day (USEPA, 1988) would have an average daily aldrin intake of 3.0×10^{-5} mg/kg-day. At the same concentration, the average daily aldrin intake for a 10 kg child would be 1.3×10^{-4} mg/kg-day, assuming a food intake rate of 0.84 kg/day (USEPA, 1988). These intakes are based on the mean aldrin concentrations of positive samples. Food samples where aldrin was not detected are not included in the average. Thus these estimated daily intakes of aldrin from food overestimate the true mean for the general population. ATSDR (2000) reports average aldrin intakes to be approximately <0.001 µg/kg/day ($<1.0 \times 10^{-6}$ mg/kg-day).

Dieldrin

Dieldrin was detected more frequently in food items than aldrin. The mean dieldrin concentration in food items analyzed during FDA Market Basket Study 1981-1992 (KAN-DO Office and Pesticides Team, 1995) was 0.0015 µg/g. Based on this average concentration, a 70 kg adult with a food intake rate of 1.305 kg/day (USEPA, 1988) would have an average daily dieldrin intake of 2.8×10^{-5} mg/kg-day. A 10 kg child, with a food intake rate of 0.84 kg/day (USEPA, 1988) would have a daily dieldrin intake rate of 1.3×10^{-4} mg/kg-day. These estimates are based on the mean of dieldrin concentrations in positive samples and does not incorporate food samples without detectable levels of dieldrin into the average. Thus, these estimates will overestimate the typical dieldrin intakes experienced by the general population. Additional

studies have estimated dietary intakes of dieldrin. MacIntosh et al. (1996) estimated daily dieldrin dietary intakes for adults to range from 2×10^{-5} to 4×10^{-3} mg/day, with a mean of approximately 5×10^{-4} mg/day. These estimates are based on mean dieldrin concentrations reported for 234 ready-to-eat food items from the FDA's Total Diet Study during 1986 through 1991 and approximately 117,000 food consumption surveys from the Nurses' Health Study and the Health Professionals/Follow-up Study. Gunderson (1988) estimated daily dieldrin intakes for adults to be 7×10^{-6} to 8×10^{-6} mg/kg-day during 1982 to 1984.

Rogan and Ragan (1994) estimated a high-end average daily intake (90^{th} percentile) of dieldrin for infants through breast milk in the United States to be 3.6×10^{-6} mg/kg-day. This estimate is based on dieldrin concentrations in breast milk of 0.10 ppm fat (Savage et al., 1984), and daily intakes of 700 g of breast milk (2.5% fat) per day for 9 months.

Concentrations in Fish and Shellfish

Aldrin

Two studies were located that reported aldrin concentrations in fish and shellfish. Murray and Beck (1990) analyzed shrimp (*Penaeus setiferus* and *Penaeus aztecus*) collected from 30 stations along the Calcasieu River Basin in an industrial area of Louisiana during 1985 to 1986. Aldrin was detected in shrimp samples from 7 of the 30 stations, at concentrations ranging from 0.01 to 0.12 μg/g (0.01 to 0.12 mg/kg).

In another study, Kannan et al. (1994) reported aldrin concentrations for fish and shellfish samples collected from various metropolitan locations in Australia, Papua New Guinea, and the Solomon Islands during 1990. Mean aldrin concentrations were 2.1×10^{-3}, 4.5×10^{-4}, and 7.7×10^{-4} mg/kg (wet weight) for oyster, mudcrab, and fish samples, respectively.

Dieldrin

Several studies have reported dieldrin residues in fish and shellfish. Bottom feeding and game fish sampled from 400 sites throughout the United States between 1986 and 1989 as part of the National Study of Chemical Residues in Fish Survey contained mean dieldrin concentrations of 28.1 ng/g (0.0281 mg/kg). Of the 119 total fish species sampled, the 5 most frequently sampled fish species and their respective dieldrin concentrations were as follows: Carp (0.0448 mg/kg), White Sucker (0.0228 mg/kg) and Channel Catfish (0.0154 mg/kg), Largemouth Bass (0.005 mg/kg), Smallmouth Bass (0.00234 mg/kg), and Walleye (0.00373 mg/kg) (Kuehl et al., 1994).

Dieldrin concentrations analyzed in 11 species of fish in the Great Lakes ranged from 0.24 to 41.2 ng/g wet weight (0.00024 to 0.041 mg/kg wet weight). The highest dieldrin concentrations were detected in carp (0.040 mg/kg), trout (0.041 mg/kg), and eel (0.031 mg/kg). Bullhead (0.00024 mg/kg) and perch (0.00098 mg/kg) contained the lowest dieldrin concentrations (Newsome and Andrews, 1993). Walleye and white bass samples (skin on) contained mean dieldrin concentrations ranging from 0.006 to 0.009 mg/kg wet weight and 0.011 mg/kg wet weight, respectively, in raw samples collected from the Great Lakes during April and

July 1991. Pan frying white bass samples (skin removed) reduced dieldrin concentrations on average by 34.8%. Dieldrin loss from deep fat frying (skin and muscle) walleye samples was 26.4% (Zabik et al., 1995).

Fairey et al. (1997) measured pesticide concentrations in fish species commonly caught by anglers from 16 areas throughout the San Francisco Bay during 1994. Dieldrin was detected in six of the seven species of fish analyzed. As listed in Table 5-2, dieldrin concentrations in the seven fish species ranged from non-detectable to 4.2 ng/g (0.0042 mg/kg) wet weight. Concentrations were proportional to fish lipid content. White croaker fish samples had the highest dieldrin levels, and also the highest lipid content. Fish species with lower lipid contents (sharks and halibut) had the lowest dieldrin concentrations.

Blynn et al. (1994) analyzed two composited filet samples from three stations in Pennekamp Coral Reef State Park and Key Largo National Marine Sanctuary for pesticide residues during September 1992. None of the filet samples contained dieldrin concentrations above the detection limit of 0.001 mg/kg.

Shrimp (*Penaeus setiferus* and *Penaeus aztecus*) samples collected from 21 of 30 stations along the Calcasieu River Basin in an industrial area of Louisiana during 1985 to 1986 contained mean dieldrin concentrations of 1.57 µg/g (1.57 mg/kg). Dieldrin concentrations ranged from 0.05 to 9.47 µg/g (0.05 to 9.47 mg/kg) (Murray and Beck, 1990).

Kannan et al. (1994) reported dieldrin levels in fish and shellfish samples collected from various metropolitan locations in Australia, Papua New Guinea, and the Solomon Islands during 1990. Mean dieldrin concentrations were 7.3×10^{-4}, 3.2×10^{-4}, and 9.5×10^{-3} mg/kg (wet weight) for oyster, mudcrab, and fish samples, respectively.

Table 5-2. Aldrin Concentrations in San Francisco Bay Area Fish in 1994[1]

Fish Species	Dieldrin Concentration	Number of Fish Sampled
White Croaker	1.1×10^{-3} to 4.2×10^{-3}	125
Striped Bass	1.1×10^{-3} to 3.0×10^{-3}	16
Shiner Surf Perch	ND[2] to 2.59×10^{-3}	160
Leopard Shark	ND to 6.1×10^{-4}	14
Brown Smoothhound Shark	ND-0.000341	21
Sturgeon	3.1×10^{-3}	3
Halibut	ND	3

[1] Source: Fairley et al. (1997).

[2] ND: Not Detected (detection limit not reported).

Intake from Fish and Shellfish

Aldrin

Only one study was located that reported aldrin concentrations in fish and shellfish (Murray and Beck, 1990). Shrimp samples collected from an industrial area of Louisiana contained aldrin concentrations ranging from 0.01 to 0.12 mg/kg. Based on these concentrations, and an average daily intake of 20.1 g/day (USEPA, 1997), a 70 kg adult would have an average daily intake of 2.9×10^{-6} to 3.5×10^{-5} mg/kg-day. A 10 kg child with a daily intake rate of 4.0 g/day (USEPA, 1997) would have a daily aldrin intake of 4.0×10^{-6} to 4.8×10^{-5} mg/kg-day. These intakes are based on aldrin concentrations in fish from an industrial area, which may be higher than typical aldrin levels in fish. Thus, these estimated aldrin intakes may not be representative of general population exposures to aldrin in fish.

Dieldrin

Assuming an average concentration of dieldrin in fish of 0.0281 mg/kg (Kuehl et al., 1994), and a daily in take of 20.1 g/day (USEPA, 1997), a 70 kg adult would have an average dieldrin daily intake of 8.0×10^{-6} mg/kg-day. A 10 kg child exposed to the same concentrations would have a daily dieldrin intake of 1.1×10^{-5}, based on a daily intakes of 4.0 g/day (USEPA, 1997). Ahmed et al. (1993) estimated dietary exposures to dieldrin from American finfish to be 4.9×10^{-7} mg/kg-day, based on FDA surveillance data collected from 1984 to 1988.

5.1.2 Exposures of Subpopulations

Persons working with or living in areas utilizing aldrin and dieldrin may potentially have higher concentrations of these pesticides in their diets (Melnyk et al., 1997).

Concentrations in Food Items

Aldrin

Additional information on concentrations of aldrin in non-fish food items and fish/shellfish or on intakes of aldrin by subpopulations were not obtained in the available literature.

Dieldrin

One study was located that analyzed dieldrin concentrations in the diets of farmers (Melnyk et al., 1997). Food samples from six farms in Iowa and North Carolina were analyzed during both a pesticide application and non-application period as part of a pilot study to evaluate pesticide exposures of farmers and their families. Food and beverage samples at one of the six farms had dieldrin concentrations ranging from 11 to 28 ppb (0.011 to 0.028 mg/kg). Food samples collected during the non-application period had higher dieldrin concentrations than those collected during the application period of 28 ppb (0.028 mg/kg) and 15 ppb (0.015 mg/kg), respectively. Dieldrin was not detected in beverages collected during application periods,

whereas beverages sampled during the non-application period contained 11 ppb (0.011 mg/kg) dieldrin. Previous aldrin use at the farm, the presence of dieldrin in milk (0.008 to 0.015 mg/kg) from area dairy farms (Bond et al., 1993), and the general persistence of dieldrin in the Midwest (MacMonegle et al., 1984) may all contribute to the high dieldrin concentrations detected in food items at this farm. Dieldrin was not detected in food and beverage samples from the other five farms in the pilot study. Details on the types of foods (e.g., fish and non-fish food items) analyzed in the pilot study were not provided.

Intake from Food Items

Aldrin

Additional information on concentrations of aldrin in non-fish food items and fish/shell fish or on intakes of aldrin by subpopulations were not obtained in the available literature. Thus, intakes of aldrin by subpopulations were not calculated.

Dieldrin

Melnyk et al. (1997) detected dieldrin in food and beverages in the diets of farmers during a pilot study of farms in Iowa and North Carolina. Dieldrin was detected in food items at one of the six farms with a history of aldrin usage analyzed in the study. Mean dieldrin concentrations in food items were 28 ppb (0.028 mg/kg) and 15 ppb (0.015 mg/kg) for non-application and application periods, respectively. Based on these concentrations (0.015 to 0.028 mg/kg) and an intake of 1.305 kg/day (USEPA, 1988), a 70 kg adult worker would have an average daily dieldrin intake ranging from 2.8×10^{-4} to 5.2×10^{-4} mg/kg-day.

5.2 Exposure from Air

Aldrin and dieldrin have both been used for pest control in agriculture and as termiticides. Agricultural uses of aldrin and dieldrin were cancelled in 1974 and their use as a termiticide cancelled in 1987. Aldrin and dieldrin may enter the atmosphere through mechanisms such as spray drift during application, water evaporation, and dispersion and suspension of particulates or soils to which the compounds are absorbed (ATSDR, 2000).

5.2.1 Exposures of the General Population

Concentrations in Air

Aldrin

Current data on ambient concentrations of aldrin in air were not located in the available literature. However, from 1970 to 1972 Kutz et al. (1976) analyzed 2,479 air samples from 16 states. Aldrin was detected in 13.5% of the samples with a mean of 3×10^{-5} ppb (4×10^{-7} mg/m^3). Ambient concentrations reported by this study are likely higher than current ambient aldrin levels, as it was conducted prior to the cancellation of all uses of adrin and dieldrin.

Several studies have measured indoor air concentrations of aldrin, as the potential for higher exposure rates may occur for segments of the population residing in homes using this chemical for termite control (Dobbs and Williams, 1983).

A pilot study of non-occupational exposures to pesticides for the general population from ambient air inside and outside the home was conducted in nine homes during 1985. Indoor and outdoor air, as well as personal air monitors, were sampled over 24-hour periods. Aldrin was detected in indoor air at six of the nine households; outdoors at four of the nine households; and in three of the nine personal monitors. In one designated high-pesticide-use household, aldrin was detected in the indoor air at average concentrations of 0.004 ppb (5.8×10^{-5} mg/m^3). Neither compound was detected in the outdoor air immediately adjacent to the home and concentrations detected with personal air monitors were half of the concentrations reported for indoor air samples (Lewis et al., 1988).

Indoor air concentrations of aldrin were monitored on each level of a two-story home in Bloomington, Indiana, (Wallace et al., 1996) identified in a previous study (Anderson and Hites, 1988) as having elevated concentrations of these chemicals. Aldrin had been poured into the void spaces of the foundation blocks during its construction in 1985 for termite control. Between September 1987 and April 1995, aldrin concentrations had decreased from 5,000 ng/m^3 to 12 ng/m^3 (5×10^{-3} to 1.2×10^{-5} mg/m^3) in the basement, and from 300 ng/m^3 to 2 ng/m^3 (3×10^{-4} to 2×10^{-6} mg/m^3) in the living area.

Dieldrin

Several studies have measured dieldrin in ambient air. Kutz et al. (1976) analyzed 2,479 air samples from 16 states from 1970 to 1972. Dieldrin was detected in 94% of samples with a mean of 1 x 10^{-4} ppb (1.6×10^{-6} mg/m^3).

In another study, dieldrin was detected at an average concentration of 5.1×10^{-6} ppb (8.0×10^{-8} mg/m^3) in ambient air over College Station, Texas, during 1979 through 1980 (Atlas and Giam, 1988).

Several studies have measured indoor air concentrations of dieldrin. One study reported dieldrin concentrations in indoor air for homes 1 to 10 years after the termiticide treatment ranging from 0.002 to 0.17 ppb (3.16×10^{-5} to 1.98×10^{-3} mg/m^3) in roof voids, and from 0.0006 to 0.03 ppb (9.49×10^{-6} to 4.75×10^{-4} mg/m^3) in living rooms, bedrooms, and all interior areas (Dobbs and Williams, 1983).

A pilot study of non-occupational exposures to pesticides for the general population from ambient air inside and outside the home was conducted in nine homes during 1985. Indoor and outdoor air, as well as personal air monitors, were sampled over 24-hour periods. Dieldrin was detected in indoor air at five of the nine households; outdoors at four of the nine households; and by personal monitors for five out of nine individuals. In one designated high-pesticide-use household, dieldrin was detected in the indoor air at average concentrations of 0.002 ppb (3.8×10^{-5} mg/m^3). Neither compound was detected in the outdoor air immediately adjacent to

the home and concentrations detected with personal air monitors were one-third the concentrations for ambient indoor air (Lewis et al., 1988).

Indoor air concentrations of dieldrin were monitored on each level of a two-story home in Bloomington, Indiana, identified in a previous study (Anderson and Hites, 1988) as having elevated concentrations of these chemicals. Aldrin had been poured into the void spaces of the foundation blocks during its construction in 1985 for termite control. Between September 1987 and April 1995, dieldrin concentrations fell from 28 ng/m^3 to 20 ng/m^3 (2.8×10^{-5} to 2.0×10^{-5} mg/m^3) in the basement, and from 7 ng/m^3 to 3 ng/m^3 (7×10^{-6} to 3×10^{-6} mg/m^3) in the living area (Wallace et al., 1996).

Indoor air samples were collected as part of a pilot study in Raleigh, North Carolina, to characterize pesticide exposures of children. Samples were collected at 2 different heights (12.5 cm and 75 cm) from the living rooms of 8 homes, over a 24-hour period. Dieldrin was detected in indoor air samples at four of the eight homes, at a mean concentration of 0.01 μg/m^3 (1×10^{-5} mg/m^3), and at a maximum concentration of 0.02 μg/m^3 (2×10^{-5} mg/m^3) (Lewis et al., 1994).

Intake from Air

Aldrin

Intake of aldrin from air was estimated based on the mean ambient air concentration reported by Kutz et al. (1976) from 1970 to 1972 of 4×10^{-7} mg/m^3. Assuming an inhalation rate of 20 m^3/day (USEPA, 1988), the average estimated daily intake of aldrin for a 70 kg adult would be 1.1×10^{-7} mg/kg-day. The estimated average daily intake of aldrin for a 10 kg child is 6.0×10^{-7} mg/kg-day, based on an inhalation rate of 15 m^3/day (USEPA, 1988). This ambient concentration of aldrin was measured prior to the cancellation of all uses of aldrin and dieldrin. Thus, these estimated daily intakes of aldrin from air will overestimate general population exposures from air.

Dieldrin

The mean dieldrin concentration reported for ambient air from 1970 to 1972 is 1.6×10^{-6} mg/m^3 (Kutz et al., 1976). Assuming an inhalation rate of 20 m^3/day (USEPA, 1988), the average estimated daily intake dieldrin for a 70 kg adult would be 4.6×10^{-7} mg/kg-day. The estimated average daily intake of dieldrin in air for a 10 kg child is 2.4×10^{-6} mg/kg-day, based on an inhalation rate of 15 m^3/day (USEPA, 1988). These estimated daily intakes will overestimate general population exposures to dieldrin from air, as they are based on ambient air concentrations reported prior to the cancellation of all uses of aldrin and dieldrin.

Higher intakes of aldrin and dieldrin may be expected for populations living in homes using these chemicals for termite control (ATSDR, 2000).

5.2.2 Exposures of Subpopulations

Persons involved in the manufacturing or application of aldrin or dieldrin may potentially be exposed to these chemicals in air. However, data on workplace or post-application concentrations of aldrin or dieldrin in air, or intakes of these chemicals by workers were not available from the retrieved literature.

5.3 Exposure from Soil

Aldrin and dieldrin were used as pesticides, until their registrations were cancelled in 1974. Although aldrin was applied more frequently to soils, dieldrin is found more often and in higher concentrations than aldrin residues (ATSDR, 2000).

5.3.1 Exposures of the General Population

Concentrations in Soil

Aldrin

Data on aldrin in residential soils were not located in the available literature. Based on the rapid conversion of aldrin to dieldrin in soils (ATSDR, 2000), the general population is more likely to be exposed to dieldrin than aldrin from soil.

Dieldrin

The National Soils Monitoring Program (Kutz et al., 1976) detected dieldrin in soils throughout 24 states at mean concentrations ranging from 1 to 49 ppb (0.001 to 0.049 mg/kg).

Pesticides may accumulate in carpets from indoor treatment and the tracking in of outdoor soils, thus contributing to residential exposures (Lewis et al., 1994). A composite sample of the dust from four Seattle homes collected during 1988 to 1989 contained 1.1 mg/kg dieldrin, although none of the homeowners could remember using the pesticide (Roberts and Camann, 1989).

Lewis et al. (1994) analyzed house dust and soil samples from nine homes in North Carolina, varying in pesticide use, as part of a pilot study to evaluate monitoring methods used to assess exposures to children. House dust samples were collected by taking 40 passes over a 3800 cm^2 carpet areas of the homes with a HVS3 vacuum system. The mean dieldrin concentration was 0.29 mg/kg (0.12 $\mu g/m^2$), with a maximum concentration of 1.0 mg/kg (0.38 $\mu g/m^2$). Entryway soil samples, collected from outside the doorway most frequently used, had mean dieldrin concentrations of 0.07 mg/kg, and a maximum of 0.19 mg/kg at four of the nine homes sampled. Soils (up to 0.5 mm in depth) collected from childrens' play areas contained mean dieldrin concentrations of 0.03 mg/kg and a maximum concentration of 0.09 mg/kg. Higher dieldrin levels were found in soils from primary walkways of 0.26 mg/kg (mean) and a maximum concentration of 0.54 mg/kg (Lewis et al., 1994).

Intake from Soil

Aldrin

Data on aldrin levels in residential soils were not located in the available literature. Thus, average daily intakes of aldrin by the general population from soil could not be estimated. The use of aldrin as a pesticide was cancelled in 1974. Based on its cancellation and its rapid conversion to dieldrin in the environment (ATSDR, 2000), it is assumed that the general population is more likely to be exposed to dieldrin than aldrin in soils.

Dieldrin

Dieldrin has been detected in both residential soils (Lewis et al., 1994) and house dust (Roberts and Camann, 1989) samples. Mean dieldrin concentrations ranged from 0.03 to 1.1 mg/kg. Based on this range of concentrations, and a daily intake of 50 mg/day (USEPA, 1997) for a 70 kg adult, the total daily intake of dieldrin through soil ranges from 2.1×10^{-8} mg/kg-day to 7.9×10^{-7} mg/kg-day. For a 10 kg child exposed to the same soil concentrations, at an intake rate of 100 mg/day (USEPA, 1997), the total daily dieldrin intake would be 3.0×10^{-7} mg/kg-day to 1.1×10^{-5} mg/kg-day.

5.3.2 Exposures of Subpopulations

Persons involved in the manufacture, handling, or application of aldrin and dieldrin may potentially have higher exposures to these chemicals from soil through incidental ingestion.

Concentrations in Soil

Aldrin

Data on aldrin concentrations in agricultural soils in the Unites States were not located in the available literature. However, one study reported aldrin in soil samples collected from agricultural fields in Farrukhabad, India from 1991 to 1992. Surface soil samples (0 to 15 cm) contained aldrin concentrations ranging from 0.001 to 0.010 mg/kg, with means ranging from 0.001 to 0.004 mg/kg. Subsurface (15 to 30 cm) concentrations ranged from 0.001 to 0.014 mg/kg, with means of 0.001 to 0.006 mg/kg (Agnihotri et al., 1996).

Dieldrin

Several studies have evaluated dieldrin residues in agricultural soils. Aigner et al. (1998) sampled 38 agricultural soils from Ohio, Pennsylvania, Indiana, and Illinois during 1995 and 1996 for pesticide residues. Dieldrin was detected in 21 of 38 soils at concentrations ranging from 0.12 to 71 ng/g (0.00012 to 0.071 mg/kg). One soil sample from Ohio had considerably higher dieldrin concentrations than the other soil samples with residues of 4.25 mg/kg. This soil sample contained the highest concentrations of all individual pesticides analyzed. Samples from two garden soils contained 4.39 ng/g (0.0044 mg/kg) and 3.47 ng/g (0.0035 mg/kg) of dieldrin.

Harner et al. (1999) reported dieldrin concentrations ranging from <0.02 to 23.9 ng/g dry weight (<0.00002 to 0.024 mg/kg), and a mean of 0.0049 mg/kg for 36 agricultural soils surveyed throughout Alabama.

The persistence of dieldrin in agricultural fields is demonstrated by a monitoring survey conducted in and around cotton fields in four counties in Alabama between 1972 and 1974. Although aldrin or dieldrin had not been reportedly used by cotton farmers "for several years," dieldrin was found to be present in 50% of the soil samples, at concentrations ranging from 0.007 to 0.040 mg/kg (Elliott, 1975).

Intakes from Soil

Aldrin

Data on aldrin concentrations in agricultural fields in the United States were not located in the available literature. Although one study (Agnihotri et al., 1996) was located that detected aldrin levels in agricultural soils, it reported residues for soils in India. This study is not representative of exposures to aldrin from agricultural soils that may occur in the United States. The uses of aldrin as a pesticide and termiticide have been cancelled since 1974 and 1987, respectively. Based on the cancellations of its uses in the United States and the rapid conversion of aldrin to dieldrin in the environment (ATSDR, 2000), subpopulations are more likely to be exposed to dieldrin than aldrin in soils.

Dieldrin

Several studies have reported dieldrin concentrations in agricultural soils of the United States. These concentrations range from <0.00002 to 0.071 mg/kg (Harner et al., 1999 and Aigner et al., 1998). Based on these concentrations and an intake rate of 480 mg/day (USEPA, 1997), for a contact intensive worker, the average daily intake of dieldrin from soil for a 70 kg adult worker would range from 1.4×10^{-10} to 2.9×10^{-5} mg/kg-day. A high-end estimate of potential subpopulation exposures to dieldrin in agricultural soils can be determined based on the highest concentration reported by Aigner et al. (1998) of 4.25 mg/kg. At this concentration and an intake rate of 480 mg/day (USEPA, 1997), a 70 kg adult, contact intensive worker would have an average daily dieldrin intake of 2.9×10^{-5} mg/kg-day.

5.4 Other Residential Exposures (Not Drinking Water Related)

Aldrin and dieldrin residues have been reported in rainfall and carpet. Dieldrin has additionally been detected in sediments.

Aldrin

Aldrin was detected in rainfall collected from the Great Lakes Basin during 1986, approximately 10 years after aldrin and dieldrin use was restricted. Aldrin was present in wet precipitation at three of four sampling sites located around the basin, in 6.7% of the samples collected at a mean concentrations ranging from 0.01 ng/L (1×10^{-5} ppb) to 0.24 ng/L (2.4×10^{-4}

ppb). The highest aldrin concentrations were found in samples collected at Pelee Island at the western end of Lake Erie at a maximum concentration of 3.4 ng/L (3.4×10^{-3} ppb) (ATSDR, 2000).

Tepper et al. (1995) studied contaminants in carpets with a history of human-health related complaints. Pesticide concentrations in the carpets were determined using Soxhlet-extraction (with 6% diethyl ether/hexane) and GC/MS. Trace amounts of pesticides were detected in both carpet samples. Aldrin concentrations extracted from the first carpet ranged from ND-83 $\mu g/m^2$. In the second carpet, extracts contained 130 to 150 $\mu g/m^2$ aldrin. Estimates of aldrin emissions from each carpet type were not determined in this study.

Dieldrin

Dieldrin was present in rainfall measured at three points in Canada during 1984, at mean concentrations of 0.78 ng/L (7.8×10^{-4} ppb) over Lake Superior, 0.27 ng/L in New Brunswick, and 0.38 ng/L (3.8×10^{-4} ppb) over northern Saskatchewan (Strachan, 1988). Dieldrin was detected in rainfall over College Station, Texas, at average concentrations of 0.80 ng/L (8×10^{-4} ppb), with a washout ratio (concentration in rain/concentration in air) of approximately 8.9 (Atlas and Giam, 1988).

Dieldrin concentrations in rainfall were collected in the Great Lakes Basin in 1986, approximately 10 years after aldrin and dieldrin use was restricted. Dieldrin was detected at all four sites and in more than 60% of the samples at mean concentrations ranging from 0.41 to 1.81 ng/L (4.1×10^{-4} to 1.8×10^{-3} ppb). The highest concentrations of dieldrin were found in samples collected at Pelee Island at the western end of Lake Erie, with a maximum concentration of 5.9 ng/L (5.9×10^{-3} ppb) (ATSDR, 2000).

Tepper et al. (1995) studied contaminants in carpets with a history of human-health related complaints. Pesticide concentrations in the carpets were determined using Soxhlet-extraction (with 6% diethyl ether/hexane) and GC/MS. Trace amounts of pesticides were detected in both carpet samples. Dieldrin concentrations extracted from the first carpet ranged from ND-120 $\mu g/m^2$. In the second carpet, extracts contained 190 to 230 $\mu g/m^2$ dieldrin. Dieldrin emissions from each carpet type were not determined in this study.

Several studies have reported dieldrin residues in sediments. Composite sediment bed samples collected from 24 navigation pools of the upper Mississippi River in 1994 (after the 1993 flooding) were analyzed for organochlorine pesticides. While dieldrin was detected in several of the navigation pools, specific concentrations were not reported (Barber and Writer, 1998).

An analysis of sediment samples taken from Lake Ontario in 1981 showed that dieldrin levels had increased from approximately 0.026 mg/kg in 1970 to 0.048 mg/kg in 1980, although the use of dieldrin was banned in much of the Great Lakes Basin in the early 1970s (Eisenreich et al., 1989).

Eighty-two and 84 sediment samples were collected in 1994 and 1995, respectively, from estuaries along the Carolinian Province (Cape Henry, Virginia, to St. Lucie Inlet, Florida) as part of the EPA and NOAA's Environmental Monitoring and Assessment Program (EMAP). Dieldrin concentrations ranged from 0 to1.4 ng/g (0 to 1.4×10^{-2} mg/kg) in 1994, and from 0 to 38.5 ng/g (0 to 3.9×10^{-1} mg/kg) in 1995 (Hyland et al., 1998).

Bed sediments were collected from 16 sites along the Lauritzen Canal and Richmond Harbor of the San Francisco Bay area during 1994 to study the distribution of contaminants from a pesticide processing facility point source (also a National Priorities List [NPL] site) along the canal into the San Francisco Bay. Dieldrin concentrations in sediments (up to 5 cm depths) ranged from <0.1 to 400 ng/g (1.1×10^{-4} to 0.4 mg/kg) dry weight. Concentrations decreased with distance from the head of the canal, as the three sites with dieldrin concentrations above 11 ng/g (1.1×10^{-2} mg/kg) were located in Lauritzen Canal (Pereira et al., 1996).

Burt and Ebell (1995) analyzed sediment samples from an industrial, commercial, and recreational area off the coast of Perth, Australia, during November 1991 for organic pollutants. Dieldrin was detected at 3 of the 135 sites sampled at concentrations of 0.002 mg/kg dry weight.

5.5 Summary of Exposure to Aldrin/Dieldrin in Media Other Than Water

Concentration and estimated intake values for aldrin and dieldrin in media other than water are summarized in Tables 5-3 to 5-6 below. Most exposure to aldrin and dieldrin for the general population and agricultural worker subpopulation appears to occur through diet.

Table 5-3. Summary of General Population Exposures to Aldrin in Media Other than Water

Parameter	Medium					
	Food		Air		Soil	
	Adult	Child	Adult	Child	Adult	Child
Concentration in Medium	Non-Fish Food (NF): 0.0016 mg/kg Fish and Shellfish (F): 0.01 to 0.12 mg/kg		4.5×10^{-7} mg/m^3		NA[1]	
Estimated Daily Intake (mg/kg-day)	NF: 3.0×10^{-5} F: 2.9×10^{-6} to 3.5×10^{-5}	NF: 1.3×10^{-4} F: 4.0×10^{-6} to 4.8×10^{-5}	1.3×10^{-7}	6.8×10^{-7}	--[2]	--

[1] NA = Not Available.
[2] -- = Unable to estimate from available information.

Table 5-4. Summary of General Population Exposure to Dieldrin in Media Other than Water

Parameter	Medium					
	Food		Air		Soil	
	Adult	Child	Adult	Child	Adult	Child
Concentration in Medium	Non-Fish Food (NF): 0.0015 mg/kg Fish Food (F): 0.028 mg/kg		1.6×10^{-6} mg/m^3		0.03 to 1.1 mg/kg	
Estimated Daily Intake (mg/kg-day)	NF: 2.8×10^{-5} F: 8.0×10^{-6}	NF: 1.3×10^{-4} F: 1.1×10^{-5}	4.6×10^{-7}	2.4×10^{-6}	2.1×10^{-8} to 7.9×10^{-7}	3.0×10^{-7} to 1.1×10^{-5}

Table 5-5. Summary of Subpopulation Exposures to Aldrin in Media Other than Water

Parameter	Medium		
	Food	Air	Soil
	Adult Worker	Adult Worker	Adult Worker
Concentration in Medium	NA[1]	NA	NA
Estimated Daily Intake (mg/kg-day)	--[2]	--	--

[1] NA = Not Available.

[2] -- = Unable to estimate from available information.

Table 5-6. Summary of Subpopulation Exposures to Dieldrin in Media Other than Water

Parameter	Medium		
	Food	**Air**	**Soil**
	Adult Worker	**Adult Worker**	**Adult Worker[1]**
Concentration in Medium	0.015 to 0.028 mg/kg	NA[2]	<2 x10^{-5} to 0.071 mg/kg high end: 4.25 mg/kg
Estimated Daily Intake (mg/kg-day)	2.8 x 10^{-4} to 5.2 x 10^{-4}	--[3]	1.4 x 10^{-10} to 2.9 x 10^{-5} high end: 2.9 x 10^{-5}

[1] Estimates are intensive contact worker.

[2] NA = Not Available.

[3] -- =Unable to estimate from available information.

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6.0 TOXICOKINETICS

6.1 Absorption

Few studies pertaining to the direct measurement of the absorption of aldrin or dieldrin were found in the available literature, with quantitative human data being especially limited. Dose-related increases in the blood and adipose tissue levels of dieldrin were reported for volunteers who had been fed approximately 0.0001, 0.0007, or 0.003 mg/kg-day of dieldrin for 18 to 24 months (Hunter and Robinson, 1967; Hunter et al., 1969). After 18 months, the low, intermediate, and high exposures resulted in blood concentrations of dieldrin that had increased approximately 2-, 4-, and 10-fold (to 3, 5, and 15 µg/L), respectively. The authors determined that under steady-state conditions, the concentration of dieldrin in the blood (µg/L) was equal to approximately 8.6% of the amount ingested (µg/day). In a case of acute poisoning, one of two children who ingested dieldrin died; 3 days later, the blood level of dieldrin in the surviving child was determined to be 0.27 ppm, decreasing to 0.11 ppm within 2 weeks (Garrettson and Curley, 1969). Concentrations of dieldrin in the plasma of small groups of pregnant women were reported to range from 0.0001 to 0.0061 ppm, while those in whole cord blood of newborns ranged from 0.0002 to 0.0015 ppm (Curley and Kimbrough, 1969; Curley et al., 1969).

Beyermann and Eckrich (1973) conducted inhalation studies with aldrin using human volunteers that suggested approximately 50% of inhaled aldrin vapor was absorbed and retained in the human body. However, based on a study of 10 male volunteers who were exposed to measured aldrin vapor concentrations of 1.31 µg/m^3, followed weeks later by a 60-minute exposure to 15.5 µg/m^3, actual retention may have been closer to 20%. In another study, apparently healthy workers who were occupationally exposed to aldrin and dieldrin were reported to have a mean plasma dieldrin concentration of 0.0185 ppm, with a mean of 5.67 ppm stored in adipose tissue (Hayes and Curley, 1968). Although uncertain, exposure was likely to have been by both inhalation and dermal contact. Similarly, in a study discussed more fully below, Mick et al. (1971) demonstrated plasma levels of aldrin and dieldrin (approximately 0.01 to 0.13 and 0.1 to 0.3 ppm, respectively) in six workers who had formulated 2 million lbs of aldrin over a 5-week period. Stacey and Tatum (1985) conducted a survey study of women in pesticide-treated homes that demonstrated a correlation between home treatment and dieldrin levels in the women's breast milk.

Many distribution/metabolism studies have also demonstrated that absorption of aldrin and dieldrin occurs in animals following oral exposure. After a single oral dose of 10 mg aldrin/kg bw was given to neonatal rats, absorption was indicated by the presence of aldrin and/or dieldrin in various tissues over the succeeding 6 days (Farb et al., 1973). When 2 male rats were given 4.3 µg of radiolabeled aldrin/day in corn oil for 90 days by gavage, 3.6% of the administered total dose remained in the carcass 24 hours after the final exposure (Ludwig et al., 1964). These authors estimated that approximately 10% of the administered dose was absorbed by the gastrointestinal (GI) tract.

Similarly, Hayes (1974) demonstrated that a single oral dose of 10 mg/kg bw of dieldrin in corn oil given to male Sprague-Dawley rats produced consistent concentrations of dieldrin in plasma and various other organs and tissues. When rats were fed 50 ppm of dieldrin in their diet,

its concentration in blood and liver increased for the first 9 days before then remaining fairly constant over the next 6 months. Within 1 to 5 hours after orally dosing rats with radiolabeled aldrin or dieldrin, high levels of radioactivity were detected in the blood, liver, stomach, and/or duodenum (Heath and Vandekar, 1964; Iatropoulos et al., 1975). Heath and Vandekar (1964) were also able to demonstrate that absorption occurred primarily via the hepatic portal vein and not the thoracic lymph duct.

In vivo studies on the inhalation exposure of animals to either aldrin or dieldrin were not available, but Mehendale and El-Bassiouni (1975) demonstrated that aldrin (0.2 to 3.0 μM) was taken up by simple diffusion in isolated, perfused rabbit lungs. Uptake of aldrin was biphasic, a slower phase following the initial rapid phase, and was followed by a slower metabolism to dieldrin, which was first detected 3 minutes after initiation of the experiment.

Several studies have demonstrated that aldrin and dieldrin can be absorbed through the intact skin of rabbits, dogs, monkeys, and humans (Shah and Guthrie, 1976; Sundaram et al., 1978a; Fisher et al., 1985; ATSDR, 2000; IPCS, 1989). It appears to occur rapidly in humans, with aldrin and dieldrin being first detected in the urine of six volunteers just 4 hours after a single dermal application (0.004 mg/cm^2) of the radiolabeled compounds to the forearm (Feldmann and Maibach, 1974). They reported that approximately 8% of the dermally applied compounds (in acetone vehicle) were absorbed after 5 days. The accuracy of these observations has been questioned, however, as the dose and the ^{14}C recovery in the urine were small, the major route of excretion was the feces and not the urine, and there was large inter-individual variation.

In female rats, aldrin (0.006, 0.06, and 0.6 mg/cm^2) was rapidly and proportionally absorbed through the skin, with aldrin and dieldrin detectable in the skin after 1 hour at all three dose levels (Graham et al., 1987). *In vitro* exposure of rat skin strips to aldrin showed that absorption was complete after 80 minutes (Graham et al., 1987). In rabbits, dermal absorption was demonstrated from fabric that had been impregnated with up to 0.04% dieldrin (Witherup et al., 1961).

6.2 Distribution

As a result of its relatively rapid conversion to dieldrin (see Section 6.3), aldrin is seldom observed in human tissues, and very little information is available concerning its distribution within the human body following absorption into the circulating blood (ATSDR, 2000; IPCS, 1989; USEPA, 1992). Given their hydrophobic nature and high solubilities in fat, it is not surprising that the largest concentrations of aldrin, dieldrin, and their metabolites are generally found in adipose tissue, both in human and animal studies (ATSDR, 2000; IPCS, 1989; USEPA, 1992, 1988, 1980).

Dale and Quinby (1963) determined the concentrations of chlorinated hydrocarbon pesticides in the body fat of 30 individuals- 28 from the general population, 1 with previous aldrin exposure and 1 with previous DDT exposure. Mean body fat dieldrin concentration (± SE) for the general population was 0.15 ± 0.02 μg/g, while for the aldrin-exposed individual it was 0.36 μg/g. In several other studies of the same era, values for the adipose tissue

concentration of dieldrin in the general population ranged from 0.04 μg/g (India) to 0.31 μg/g (U.S.) (IARC, 1974b). As briefly noted in the section on absorption, Hayes and Curley (1968) examined the aldrin and dieldrin concentrations in 71 workers involved in manufacturing pesticides. In decreasing order, the mean concentrations (± SE) of dieldrin in adipose tissue, urine and plasma were 5.67 ± 1.11, 0.0242 ± 0.0063, and 0.0185 ± 0.0019 μg/g, respectively; these were significantly higher than corresponding values reported for the general population.

In a study conducted on male volunteers, 3 men/group (4 controls) received a daily oral dose of either 0, 10, 50, or 211 μg dieldrin (approximately equivalent to 0, 0.0001, 0.0007, or 0.003 mg/kg-day) for 18 months (Hunter and Robinson, 1967; Hunter et al., 1969). The 50 and 211 μg groups continued to receive these doses for another 6 months, whereas three of four controls and the 10 μg group were switched to the 211 μg dose. After 18 months, concentrations of dieldrin in the blood of the low-, intermediate-, and high-dose groups had increased approximately 2-, 4-, or 10-fold (to approximately 3, 5, or 15 μg/L), respectively. It was noted that the increase in the low-dose group had essentially been achieved by 5 months, with little change occurring thereafter. No significant increase in blood dieldrin concentration during the 18 to 24 month period was noted for the mid-dose group, while the high-dose group experienced a slight increase during months 18 to 21, but nothing significant thereafter. During the final 18- to 24-month period, the control and low-dose subjects, who were then receiving 211 μg dieldrin/day, experienced 3-fold or greater increases in blood concentrations of dieldrin. After 18 months, adipose tissue concentrations of dieldrin in the low-, intermediate-, and high-dose groups had increased approximately 3-, 4-, or 11-fold (to means of 0.4, 0.7, or 2 mg/kg tissue), respectively. An apparent further increase in these values at 24 months may have been at least partly related to sampling techniques (IPCS, 1989). Using empirically derived relationships between the amounts of dieldrin ingested and those found in the blood or adipose tissue, the authors calculated an adipose tissue to blood distribution ratio under steady state conditions (among intake, storage, and elimination) of 136.

In examining tissue samples from a number of routine autopsies, De Vlieger et al. (1968) determined the mean dieldrin concentrations in adipose tissue, liver tissue, white matter of the brain, and gray matter of the brain to be 0.17, 0.03, 0.0061, and 0.0047, respectively. Figure 6-1, taken from IPCS (1989), represents the tentative tissue distribution scheme for dieldrin initially proposed by De Vlieger et al. (1968), as subsequently recalculated by Jager (1970) to incorporate the empirical formulas of Hunter et al. (1969).

Hunter and Robinson (1968) demonstrated that the leanest subjects had both the highest adipose tissue concentrations of dieldrin, as well as the smallest total body burdens; however, the subjects with the greatest total body fat retained the highest proportion of the total exposure dose in their adipose tissue. As no increase in blood levels of dieldrin were observed during surgical stress or periods of complete fasting, these authors concluded that the general population was not in danger of intoxication as a result of tissue catabolism during periods of illness or weight loss. It should also be noted that when Hunter et al. (1969) followed their subjects for a period of 8 months after the 2-year exposure, the concentration of dieldrin in the blood was observed to

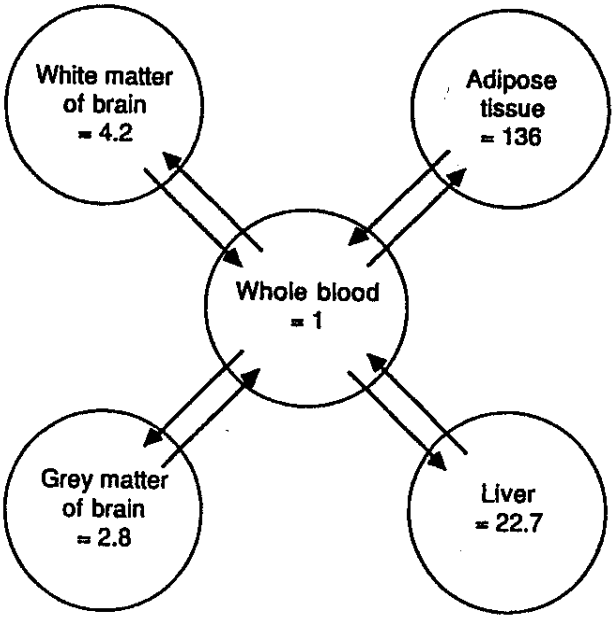

Figure 6-1. Distribution Scheme for Dieldrin Among Blood and Various Tissues in Humans [De Vlieger et al. (1968) as Modified by Jager (1970); From IPCS (1989)]

decline exponentially with an approximate half-life of 369 days. There were, however, significant differences among individuals in the rates of decline. This value compares with a mean half-life of 266 days, which was estimated for dieldrin in the blood of 15 occupationally exposed workers during a 3-year period following termination of their exposure (Jager, 1970). In the Garettson and Curley (1969) study of aldrin poisoning in children that was noted in Section 6.2, 47 ppm dieldrin was measured in a fat specimen taken 3 days after the exposure; 6 months later this value had declined to 15 ppm, where it remained after 8 months.

A study of women and their offspring during labor demonstrated that placental transfer of dieldrin can occur (Polishuk at al., 1977). Higher concentrations of dieldrin were observed in fetal blood (1.22 mg/kg) than in maternal blood (0.53 mg/kg), and in the placenta (0.8 mg/kg) than in the uterus (0.54 mg/kg).

In the previously discussed (Section 6.2) study of six workers occupationally exposed for 5 weeks via inhalation and dermal contact to aldrin, Mick et al. (1971) examined the distribution of aldrin and dieldrin among erythrocytes, plasma, and the alpha- and beta-lipoprotein fractions of blood. The epoxidation of aldrin to dieldrin led to higher plasma concentrations of dieldrin (approximately 0.1 to 0.3 ppm) than aldrin (approximately 0.01 to 0.13 ppm). Average dieldrin residues were approximately four times higher in plasma than in erythrocytes and this ratio tended to increase with increasing concentrations of dieldrin in the blood. Typically, higher dieldrin levels were associated with the beta-lipoprotein fraction than with the alpha-lipoprotein fraction. The *in vitro* study of human blood fractions by Skalsky and Guthrie (1978) also demonstrated that dieldrin could bind to albumin and beta-lipoprotein.

Distribution of aldrin and dieldrin has been studied in a number of animal species (ATSDR, 2000; IARC, 1974a,b; IPCS, 1989; USEPA, 1992, 1988, 1980). Exposure of mammals to aldrin leads to deposition of dieldrin in their adipose tissue (Jager, 1970). Deichmann et al. (1975) fed Swiss-Webster mice diets containing 0, 5, or 10 ppm aldrin (approximately equivalent to 0, 0.75, and 1.5 mg/kg bw, based on Leyman [1959]) over the course of 7 generations (from weaning to age 260 days for each generation, except F_4; see below). After 4 generations of aldrin feeding, metabolic conversion to dieldrin and subsequent retention led to significantly increased levels of dieldrin in abdominal fat and carcass total lipids. Significantly increased retention of dieldrin in the whole carcass was observed for the F_1 generation, with smaller and not statistically significant increases observed for the F_2 and F_3 generations. Dieldrin concentration in F_0 carcass total lipids was 60 mg/kg, whereas the $F_1 + F_2 + F_3$ grouped means for males and females were 100 and 132 mg/kg, respectively. Female mice thus retained higher residue levels in their body fat than male mice. From weaning through day 260, the F_4 generation was fed only the aldrin-free control diet, and the pesticide residues that it absorbed *in utero* and through lactation were found to have been completely excreted by the time of sacrifice. Dieldrin concentrations in F_5 pups were <1 mg/kg; aldrin-containing diets were resumed upon the weaning of these pups, with the findings from the F_4 through F_6 generations largely paralleling those from the F_0 through F_2 generations.

Two male Wistar rats were given daily doses of 4.3 µg ^{14}C-aldrin by gavage for 3 months, and then sacrificed 24 hours after the final dose (Ludwig et al., 1964). Relative to the total administered amount of radiolabel, the amounts recovered in the carcass, abdominal fat, and other tissues were 3.60, 1.77, and 1.83%, respectively. A steady state among intake, storage, and excretion was reportedly achieved after 53 days. Ratios of dieldrin to aldrin found in the carcass and the abdominal fat were approximately 15:1 and 18:1, respectively. In neonatal Sprague-Dawley rats given a single dose of 10 mg aldrin/kg bw, aldrin was detectable up to 6 days later in the stomach and small intestine, but only for 3 days in the kidneys (Farb et al., 1973). Aldrin concentrations in the liver increased during the first 6 hours to a maximum of 13% of the administered dose, then declined to <0.1% by 72 hours. The only metabolite identified in the liver was dieldrin, which was detectable as early as 2 hours post-treatment and which reached a maximum 31% of the administered radiolabeled dose after 24 hours.

Deichmann et al. (1969) administered 0.6 mg aldrin/kg bw/day in corn oil to 6 male beagle dogs for 10 months. Dieldrin concentrations in body fat and the liver were observed to progressively increase to 70 and 20 ppm, respectively, and then decline over the 12 months post-exposure to 25 and 6 ppm, respectively. In a related study, aldrin was administered by capsule to 3 male beagles (0.3 mg/kg bw) and 4 female beagles (0.15 or 0.3 mg/kg bw), 5 days/week for 14 months (Deichmann et al., 1969, 1971). During the last 10 months of exposure, dieldrin concentrations in the blood and subcutaneous fat for the high-dose animals were 0.042 to 0.183 and 37 to 208 mg/L, respectively; those for the low-dose females were 0.040 to 0.130 and 12 to 67 mg/kg, respectively. The apparent subcutaneous fat to blood partition ratio was thus approximately 1000.

An extensive comparative study of the distribution and metabolism of dieldrin and its metabolites in male CFE rats and male CF_1 and LACG mice was conducted by Hutson (1976). ^{14}C-dieldrin was administered as a single oral dose to animals, either with or without a 4-week

pretreatment of dieldrin (20 mg/kg diet for rats, 10 mg/kg diet for mice), and the animals were sacrificed 8 days later. Concentrations of dieldrin were much higher in the fat than in the liver or kidneys of all animals, and were higher in the fat and liver of mice (11.6 and 0.94 mg/kg) than of rats (5.6 and 0.11 mg/kg). Tissue levels of a number of dieldrin metabolites (see Section 6.3) were also assessed, including the 6,7-dihydroxy (diol) derivative that was found to be below the level of detection (< 0.02 mg/kg) in the fat, liver, and kidneys of all animals. Concentrations of the 9-hydroxy metabolite were very low (<0.03 mg/kg) in the fat and kidneys, but small amounts were found in the livers of both mouse strains. The pentachloroketone metabolite was found in rat liver in small amounts and in much larger amounts in the kidneys of rats, with or without pretreatment; small concentrations were also found in the fat of both groups. In both strains of mice, this metabolite was undetectable or present in only very small amounts in the fat, liver, and kidneys in the absence of pretreatment; with pretreatment, higher concentrations were observed (e.g., ~ 1.3 mg/kg in fat).

At 1 to 2 hours after dosing rats with radiolabeled dieldrin, Heath and Vandekar (1964) observed the highest concentration of dieldrin in adipose tissue; high levels were also seen in the liver and kidneys, with moderate concentrations found in the brain. It was also recoverable from the stomach, small and large intestines, and the feces after 1 hour. Following dietary exposure to radiolabeled dieldrin for 8 hours, high levels of radioactivity were detected in the kidneys of treated rats (Matthews et al., 1971). While somewhat more radioactivity was found in the kidneys, lungs, stomachs, and intestines of males, in general, for the other organs and tissues, females had 3 to 4 times the radioactivity as did males. Similar results were observed in a 9-week (5 day/week) feeding study with Osborne-Mendel rats (Dailey et al., 1970). Adipose tissue was again shown to be the principal storage depot for dieldrin, with significant levels also found in the kidneys, liver, lungs, and adrenals; lowest levels were seen in the spleen, brain, and heart. With the exception of the kidneys, more radioactivity was retained in the tissues of females than males. In a single oral dose rat study by Iatropoulos et al. (1975), radiolabeled dieldrin was rapidly taken up by the liver during the first 3 hours, then redistributed in a biphasic manner to adipose tissue (the majority), kidneys, lymph nodes, etc. The lymphatic system appeared to be the principal redistribution pathway and parallel dieldrin increases in the lymph nodes and adipose tissue suggested an equilibrium between lymph and depot fat.

Female Osborne-Mendel rats were fed a diet containing technical grade dieldrin (87% purity) at a concentration of 50 mg/kg diet (approximately 2.5 mg/kg bw/day) for 6 months (Deichmann et al., 1968). Rats were sacrificed at various times up to 183 days and the retention of dieldrin in blood, liver, and fat was examined. Tissue levels increased rapidly over the first 9 days in the blood and liver, and over the first 16 days in fat; thereafter, concentrations fluctuated some but did not appear to significantly increase further. Over the final 4 months, distribution ratios and mean concentrations were: blood = 1 (0.240 mg/L), liver = 28 (6.8 mg/kg), and fat = 665 (159.5 mg/kg).

Groups of Carworth Farm E rats (25/sex; 45 controls/sex) were fed 0, 0.1, 1.0, or 10 mg dieldrin/kg diet for 2 years (Walker et al., 1969). Animals were sacrificed after 26, 52, 78, and 104 weeks, and tissue levels of dieldrin in the blood, brain, liver, and fat were determined. Approximate plateau levels were reached by week 26; tissue uptake ratios (tissue concentration/diet concentration) of dieldrin for the 3 female exposure groups were 0.056

(blood), 0.19 (brain), 0.35 (liver), and 8.8 (fat), and were significantly higher than the corresponding values for males. Estimated partition ratios (tissue concentration/blood concentration) for male/female animals were 1/1 (blood), 3.3/2.6 (brain), 7.8/5.9 (liver), and 104/137 (fat). After 104 weeks, tissue levels were found to be generally 2 to 10 times higher in females than in males (Table 6-1). Robinson et al. (1969) fed Carworth rats 10 mg dieldrin/kg diet for 8 weeks, then a control, dieldrin-free diet for up to an additional 12 weeks. Again, the concentration of dieldrin was found to be substantially the greatest in adipose tissue, followed in descending order by that in the liver, brain, and blood. Following exposure, the decline of dieldrin concentrations in the tissues was approximately exponential, with half-lives in adipose tissue and brain of 10.3 and 3 days, respectively. Elimination from the liver occurred in a rapid and then a slower phase, with respective half-lives of 1.3 and 10.2 days; similar values were estimated for the blood.

Three groups of Sprague-Dawley rats (2/sex) were fed diets containing 0.04 mg ^{14}C-dieldrin/kg plus 0, 0.16 or 1.96 mg/kg of unlabeled dieldrin (totals of 0.04, 0.2, or 2.0 mg dieldrin/kg diet) for 39 weeks (Davison, 1973). For all three groups upon sacrifice, whole carcass radioactivity as a percentage of administered dose was significantly higher in females than males (means of 6.9 versus 2.1%, respectively).

Table 6-1. Distribution of Dieldrin in Rats after 104 Weeks[1]

Sex	Dieldrin Concentration (mg/kg)				
	Diet	Blood[2]	Fat[2]	Liver[2]	Brain[2]
Male	0.0	0.0009	0.0598	0.0059	0.0020
	0.1	0.0021	0.2594	0.0159	0.0069
	1.0	0.0312	1.493	0.1552	0.1040
	10.0	0.1472	19.72	1.476	0.4319
Female	0.0	0.0015	0.3112	0.0112	0.0077
	0.1	0.0065	0.8974	0.0348	0.0224
	1.0	0.0861	13.90	0.4295	0.2891
	10.0	0.3954	57.81	2.965	1.130

[1] Walker et al. (1969); as modified from USEPA (1980).
[2] Geometric mean values.

Baron and Walton (1971) fed male Osborne-Mendel rats 25 mg dieldrin/kg diet (approximately 1.25 mg/kg bw) for 8 weeks. They reported that an equilibrium level of 50 mg dieldrin/kg had been achieved in adipose tissue by week 8, which upon return to a dieldrin-free diet, rapidly declined with an estimated half-life of 4 to 5 days. Within 15 days after the

cessation of exposure to 75 ppm dieldrin in the diet, levels in the adipose tissue of rats had fallen to half that seen after 12 months of exposure (Robinson and Roberts, 1968). In a study by Hayes (1974), male Sprague-Dawley rats received a single dose of 10 mg/kg bw of technical dieldrin (86% purity). At intervals up to 240 hours post-dosing, animals were sacrificed and tissue levels of dieldrin were determined. In plasma, dieldrin concentrations reached a maximum of ~ 0.5 mg/L after 2 hours, fluctuated from 0.2 to 0.5 mg/L up to 48 hours, then declined to ~ 0.01 mg/L at 240 hours. Maximum levels were reached in the brain after 4 hours (~ 1 mg/kg), remaining more or less constant through 48 hours, then declining to a low level (< 0.2 mg/kg) by 240 hours; similar time courses were reported for muscle, kidneys, and the liver. A slower rise of dieldrin concentration was observed in retroperitoneal fat, with 4 and 24 hours values being ~ 10 and 40 mg/kg, respectively; after 48 hours, a decline similar to those for plasma and the brain was observed. For the 4- and 16-hour data, Hayes (1974) set the dieldrin concentrations in the brain equal to 1.00, then calculated the relative concentrations for the other tissues evaluated (Table 6-2).

Table 6-2. Relative Tissue Levels of Dieldrin in the Rat Following a Single Oral Dose[1]

Hour	Brain	Muscle	Liver	Kidney	Plasma	Fat
4	1.00 ± 0	0.62 ± 0.05	2.30 ± 0.11	1.55 ± 0.22	0.20 ± 0.02	7.20 ± 1.18
16	1.00 ± 0	0.55 ± 0.06	3.17 ± 0.25	2.02 ± 0.56	1.35 ± 1.11	17.96 ± 3.23

[1] Dieldrin dose of 10 mg/kg, in corn oil (Hayes, 1974; as modified from USEPA, 1980).

In vitro studies using rats and rabbits have reportedly examined the partitioning of ^{14}C-dieldrin-related radioactivity among the soluble protein and cellular components of the blood (IPCS, 1989). Radioactivity was principally found in erythrocytes (associated with hemoglobin and an unknown constituent) and the plasma, with much lower levels found in leukocytes, platelets, and erythrocyte membranes. In rat serum, it electrophoresed with pre- and post-albumin, whereas in rabbit serum, it was associated with albumin and α-globulin. Ichinose and Kurihara (1985) demonstrated *in vitro* that transport of dieldrin between rat hepatocytes and the extracellular medium occurs much more rapidly than does intra-hepatocyte metabolic transformation.

Several studies have been conducted on the distribution of dieldrin in dogs (Richardson et al., 1967; Keane and Zavon, 1969; Walker et al., 1969). In three beagles fed 0.1 mg dieldrin/kg bw for 128 days, blood levels of dieldrin increased curvilinearly to an approximate plateau of about 0.130 mg/L by day 93 (Richardson et al., 1967). One week post exposure, measured tissue levels of dieldrin were 0.150 mg/L (blood), 1.090 mg/kg (heart), 4.420 mg/kg (liver), 2.330 mg/kg (kidneys), 14.030 mg/kg (pancreas), 0.710 mg/kg (spleen), 1.227 mg/kg (lungs), 25.333 mg/kg (fat), and 0.566 mg/kg (muscle). There was reported a highly significant linear correlation between the logarithms of exposure duration and blood dieldrin level. Keane

and Zavon (1969) orally dosed 4 male and 2 female mongrel dogs with 1 mg dieldrin/kg bw (in corn oil) for 5 days, then with 0.2 mg/kg bw for the next 54 days. Small but significant increases in dieldrin concentration were observed in the blood of all animals for days 7 to 59 (samples taken twice weekly from day 7 onward). Subcutaneous fat biopsies were taken on days 16 and 50 and the fat to blood partition ratios were 216 and 117, respectively.

In addition to the rat study discussed previously, Walker et al. (1969) orally dosed beagle dogs (5/sex) by gel capsule with 0, 0.005, or 0.05 mg dieldrin/kg bw (equivalent to 0, 0.1, or 1.0 ppm in the diet) for 2 years. Blood dieldrin levels increased during the first 12 to 18 weeks, reaching a plateau during weeks 18 to 76. Thereafter, significant deviations from this apparent asymptotic value were observed; while the reasons for this were not clear, a tendency toward higher dieldrin concentrations was also noted in the control animals. Uptake and partition ratios (previously defined) for males were 0.06 and 1.0 (blood), 0.22 and 3.7 (brain), 4.4 and 10 (liver), and 10.0 and 169 (adipose tissue). In contrast to the rat study, no significant sex differences in uptake were apparent.

Mueller et al. (1975a) administered ^{14}C-dieldrin (2.5 mg/kg bw) to two female rhesus monkeys via intravenous injection, and to two males via a single oral dose of either 0.36 or 0.5 mg/kg bw. Females and males were sacrificed at 75 and 10 days post exposure, respectively. In all animals, the highest radioactivity was observed in the adipose tissue, bone marrow and liver, with only a relatively small amount present in the brain (~ 2% that of adipose tissue). Metabolites, though present in the bile, were not detected in the organs or tissues examined. In another primate study, groups of male rhesus monkeys were fed diets containing 0, 0.01, 0.1, 0.5, or 1.0 ppm of technical grade dieldrin for 70 to 74 months (Wright et al., 1978). Several monkeys were started at a 5.0 ppm dose, but when 1 died at 4 months, the others were reduced to a dose of 2.5 ppm for the next 5 months, then 1.75 ppm for a further 64 months. In one animal from this group, the 1.75 ppm dose was gradually increased back up to 5.0 ppm at month 23, where it remained for another 46 months. This study focused on interactions of dieldrin with the liver, and mean concentrations of dieldrin in the livers of the various groups ranged from 1.2 mg/kg (the 0.01 ppm group) to 23.3 mg/kg (the single 5, 2.5, 1.75→5.0 ppm monkey). When the distribution of dieldrin in the liver's various subcellular fractions was examined, ~ 60% was localized in the microsomal fraction, ~ 12.5% in the soluble fraction, and ~ 9% each in the nuclear, mitochondrial, and lysosomal fractions. It was noted that at dietary intakes of about 0.1 ppm, tissue concentrations of dieldrin in rhesus monkeys and humans were similar. However, when compared to male rats, liver concentrations of dieldrin were 200 times higher in these monkeys at a dose only twice as high, suggesting a relatively slow metabolic clearance and a relatively high liver tolerance to dieldrin in this primate species.

With respect to dermal exposure, most of the dieldrin that is absorbed through the skin of guinea pigs, dogs, and monkeys has been found to accumulate in adipose tissue (Sundaram at al., 1978a,b). In guinea pigs dermally exposed for 6 months to concentrations of 0.0001 to 0.1%, the highest tissue levels were observed in adipose tissue, with lesser concentrations appearing in the liver and brain (Sundaram et al., 1978b). After 52 weeks of exposure to fabric strips containing up to 0.04% dieldrin, rabbits also evidenced a slight accumulation of the compound in omental and renal fat (Witherup et al., 1961).

Distribution of dieldrin residues among the blood, brain, liver, and subcutaneous fat in rats following intraperitoneal injection was not found to be significantly different from that seen after oral exposure, i.e., the highest levels were again observed in adipose tissue (Lay et al., 1982). Transplacental transport of dieldrin has been reported to occur to a significant extent in mice following intramuscular injection (Baeckstroem et al., 1965) and after intravenous injections in rats (Eliason and Posner, 1971) and rabbits (Hathway et al., 1967). In pregnant mice exposed intramuscularly to ^{14}C-dieldrin, the highest radioactivities were observed in the adipose tissue, liver, intestines, and mammary glands, while moderate activities were reported for the ovaries and brain (Baeckstroem et al., 1965). Transfer across the placenta was indicated by the moderate levels that were also found in fetal liver, fat, and intestines. Finally, numerous studies suggest that the toxicokinetics of aldrin and dieldrin in most domesticated animals are at least broadly similar to those seen in laboratory species (IPCS, 1989).

Although apparently not a major transformation product in mammals, photodieldrin is likely a significant photodegradation product and microbial metabolite of dieldrin in the environment (see Chapter 3), and therefore several studies have examined its distribution pattern in mammals. Collectively, subacute and subchronic studies in rats (Dailey et al., 1970; Walker et al., 1971; Walton et al., 1971) and mice (Brown et al., 1967) have demonstrated that females accumulate 2- to 15-fold higher concentrations of photodieldrin than do males in adipose and other tissues with the exception of the kidneys. The estimated half-life of photodieldrin in adipose tissue is also longer in female rats (2.6 days) than in male rats (1.7 days) (Brown et al., 1967). When a single oral dose of photodieldrin was administered to one male and one female dog, tissue levels were again reported to be significantly higher in the female than in the male, with the exception of in the liver (Brown et al., 1967). In contrast, a 3-month feeding study in dogs demonstrated dose-related concentrations in the liver, adipose tissue, and kidneys that were similar in both males and females (Walker et al, 1971); additionally, the kidney levels of photodieldrin and pentachloroketone (PCK; see Figures 6-2 and 6-3, Table 6-3, and associated text in Section 6.3) were approximately 0.1 to 0.2 mg/kg, or about 1 to 3 orders of magnitude lower than those observed in rats.

6.3 Metabolism

Radomski and Davidow (1953) first reported the epoxidation of aldrin to dieldrin. Since that time, many studies in a substantial number of organisms have shown this to be the initial and principal step in the biotransformation of aldrin; the reaction is mediated by mixed-function oxidases, sometimes referred to as aldrin-epoxidase, that are known to be found in substantial quantities in the endoplasmic reticulum of hepatocytes in vertebrates (ATSDR, 2000; IPCS, 1989; USEPA, 1992, 1988). Perhaps understandably, no real metabolism studies of aldrin or dieldrin in humans were located or available, so data on the human metabolism of these compounds is sparse. Excretion data in humans have provided some insight, however, as the 9-hydroxydieldrin metabolite was detected in the feces of workers having occupational exposure to aldrin and dieldrin (Richardson and Robinson, 1971). Some additional excretion data from humans on these compounds and their metabolites are presented in Section 6.4.

A variety of metabolites have been isolated from microorganisms, invertebrates, and vertebrates, and the three-dimensional chemical structures of many of these are presented in

Figure 6-2. Their trivial, or common, names are listed in the companion Table 6-3. Those metabolic transformations thought to be most important in laboratory animals are illustrated in Figure 6-3, which again provides three-dimensional chemical structures, as well as some of the enzymes implicated in these pathways. A discussion of some of the more important underlying animal and *in vitro* studies follows.

Winteringham and Barnes (1955) first demonstrated the epoxidation of aldrin to dieldrin (Figure 6-2, compounds I and II; Figure 6-3) in mice, and were able to show that this conversion occurred more rapidly in males than in females; while other metabolites were not observed, methodological limitations may have hindered the detection of polar compounds. The formation of dieldrin from aldrin was also noted early on in cattle, pigs, sheep, rats, and poultry (Bann et al., 1956), and Soto and Deichmann (1967) reported that subsequent to the intravascular administration of aldrin to dogs, approximately 30% was converted to dieldrin during the first 24 hours post-exposure. Using rabbit lung perfusates, Mehendale and El-Bassiouni (1975) were able to demonstrate dose-dependent, *in vitro* metabolism of aldrin to dieldrin within the endoplasmic reticulum; at low doses, up to 70% conversion occurred during the first hour. Following dermal application of 0.1 to 10 mg/kg to rats, the skin has also been shown capable of converting aldrin to dieldrin (Graham et al., 1987). Dieldrin was detected in the skin as soon as 1 hour after application, and enzyme saturation was suggested because the highest percentage of conversion occurred at the lowest dose. The authors estimated that up to 10% conversion to dieldrin by skin enzymes could result in rats from the percutaneous absorption of aldrin. Graham et al. (1987) were also able to demonstrate the *in vitro* dermal conversion of aldrin to dieldrin in studies employing mouse skin microsomal preparations and whole-skin strips from rats.

Using liver microsome preparations from male and female rats, Wong and Terriere (1965) were able to demonstrate the conversion of aldrin to dieldrin via nicotine adenine dinucleotide phosphate (NADPH)-dependent, heat-labile mixed function oxidases, that the reaction proceeded more rapidly in the microsomes from male rat livers than in those from females, and that it could be inhibited by pesticide synergists, such as sesamex. These observations were largely confirmed by Nakatsugawa et al. (1965) using microsome preparations from male rats and rabbits; they also reported that dieldrin did not undergo further microsomal metabolism, that epoxidase activity in liver preparations was 10-fold higher than in lung preparations, and that no such activity was observed in preparations from the kidney, spleen, pancreas, heart, or brain. Wolff et al. (1979) demonstrated a three-fold increase in dieldrin formation with microsomes taken from phenobarbital-treated rats, whereas amounts were substantially decreased in microsomal preparations made from rats pretreated with 3-methylcholanthrene. These results suggested that aldrin epoxidation involved cytochrome P-450 rather than cytochrome P-448.

Kurihara et al. (1984) have demonstrated that cultures of rat hepatocytes are effective in carrying out the epoxidation of aldrin to dieldrin. In other *in vitro* studies, Lang et al. (1986) investigated the epoxidation of aldrin to dieldrin in hepatic and various extra-hepatic tissues in the rat. Unlike the liver, many organs and tissues contain little cytochrome P-450 activity, prompting these authors to look for the presence of an alternative oxidative pathway mediated by prostaglandin endoperoxide synthase (PES) in liver, lung, seminal vesicle, and subcutaneous

granulation tissues. In a two-step process, PES utilizes cyclooxygenase activity to catalyze the bisdioxygenation of arachidonic acid to prostaglandin G_2 (PGG_2), which is subsequently reduced to prostaglandin H_2 (PGH_2) via hydroperoxidase activity; it is during this latter step that xenobiotics (e.g., aldrin) may be co-oxidized (i.e., epoxidized). In hepatocytes and liver microsomes, aldrin epoxidation was reported to be completely NADPH-dependent, whereas in lung microsomes, two pathways appeared involved (Lang et al., 1986). The NADPH-dependent and arachidonic acid-dependent aldrin epoxidation activities were 1.5 and 0.3%, respectively, of the activities observed in liver preparations. Aldrin epoxidation was stimulated by arachidonic acid and inhibited by the cyclooxygenase-specific inhibitor indomethacin, in microsomal preparations from seminal vesicle and subcutaneous granulation tissues. Therefore, the PES pathway would appear to be an alternative route for aldrin epoxidation in extra-hepatic tissues.

In some early work with rabbits, Korte (1963) was able to identify one of the metabolites of aldrin as aldrin trans-diol (Figure 6-2, compound IV; Table 6-3, Figure 6-3). Heath and Vandekar (1964) reported that the principal route of excretion in rats was the feces, that little dieldrin was excreted unchanged, and that a somewhat polar metabolite could be found in the feces, along with other polar metabolites in both the feces and urine. After feeding ^{14}C-aldrin to rats for 3 months, Ludwig et al. (1964) found aldrin, dieldrin, and unidentified hydrophilic metabolites in the urine; these latter constituted 75 and 95% of the radioactivity excreted in the urine and feces, respectively. Two different metabolites were detected in the feces, with one of them and a third metabolite also detected in the urine. In rabbits dosed orally with ^{14}C-dieldrin for 21 weeks, Korte and Arent (1965) isolated 6 urinary metabolites, the major one (86%) being identified as 6,7-trans-dihydroxydihydroaldrin, or the aforementioned aldrin trans-diol. This enzymatic product of epoxide hydrase, however, appears to be of relatively minor importance in most other species (IPCS, 1989).

Other than in mice and rabbits, aldrin trans-diol has reportedly been found in rhesus monkeys and chimpanzees (Mueller et al., 1975b), and its glucuronide conjugation product was detected in liver microsomal preparations from rats or rabbits incubated in the presence of ^{14}C-dieldrin and uridine diphosphoglucuronic acid (UDPGA) (Matthews and Matsumura, 1969). This water soluble metabolite accounted for approximately 45% of the total radioactivity, while the unconjugated form was also found to be present *in vitro*. Matthews and Matsumura (1969) had additionally fed male rats a diet containing dieldrin for a month, and had noted a minor metabolite present in both the feces and the urine. Comparative thin layer chromatography in conjunction with the *in vitro* results indicated this compound to be the aldrin trans-diol in the conjugated and/or unconjugated forms.

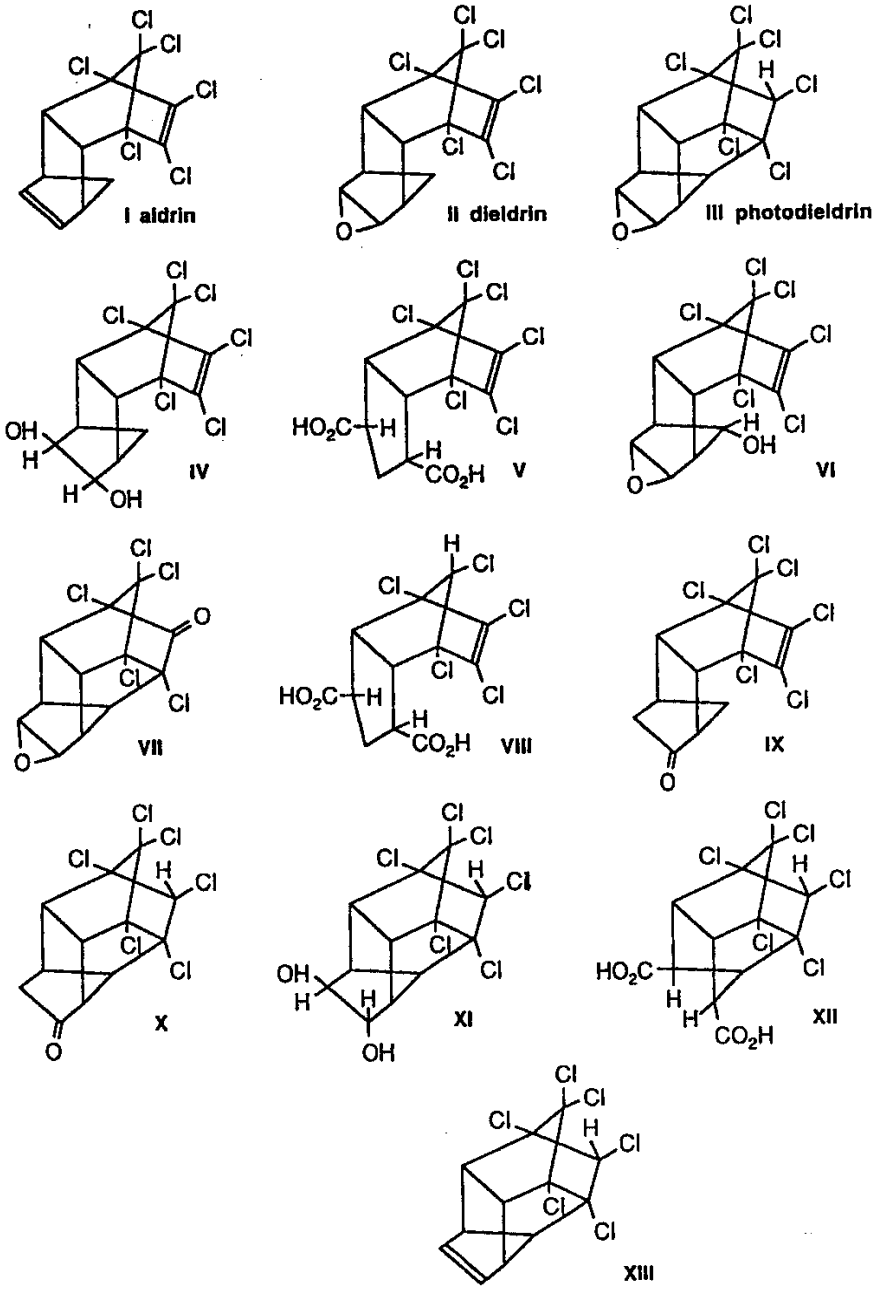

Figure 6-2. Metabolites of Aldrin and Dieldrin (from IPCS, 1989). For the Identity (Trivial Chemical Names) of These Compounds, See Table 6-3

Table 6-3. Trivial Chemical Names of Aldrin, Dieldrin and Their Metabolites (as Identified in Figure 6-2)[1]

ID Code (Fig. 6-2)	Chemical Structure Trivial Names	
	Alternative 1	**Alternative 2**
I	Aldrin	HHDN
II	Dieldrin	HEOD
III	Photodieldrin	
IV	Aldrin trans-diol	6,7-trans-dihydroxydihydroaldrin
V	Aldrin dicarboxylic acid	
VI	9-Hydroxy dieldrin	9-Hydroxydieldrin
VII	(Bridged) Pentachloroketone	PCK (or Klein's metabolite)
VIII	Dechloro-aldrin dicarboxylic acid	
IX	Dieldrin ketone	
X	Photodieldrin ketone	
XI	Photodieldrin trans-diol	Caged aldrin trans-diol
XII	Photoaldrin dicarboxylic acid	Caged aldrin acid
XIII	Photoaldrin	

[1] Taken principally from IPCS (1989) and ATSDR (2000).

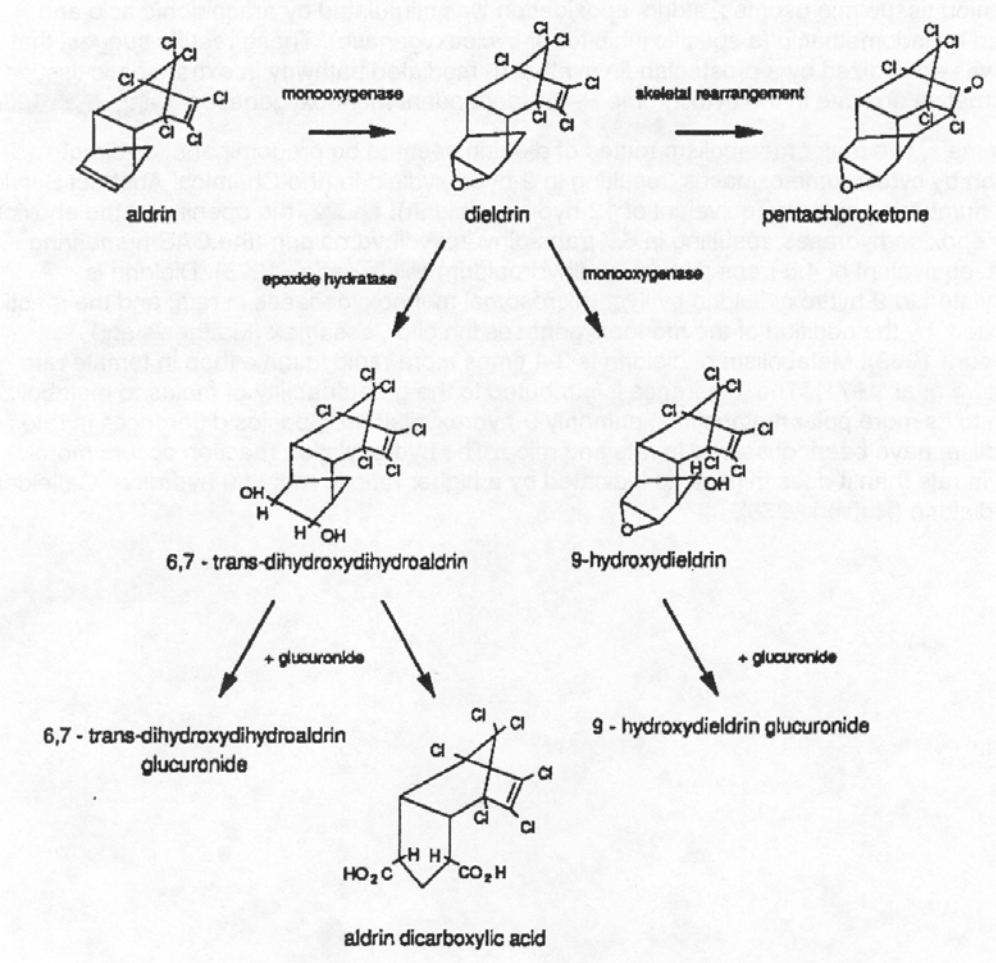

Figure 6-3. Proposed Principal Metabolic Pathways for Aldrin and Dieldrin (from ATSDR, 1993, as Adapted from USEPA, 1987)

The conjugation of aldrin trans-diol with glucuronic acid and/or its further oxidation to aldrin dicarboxylic acid (Figure 6-2, compound XII; Table 6-3, Figure 6-3) have also been reported by Baldwin et al. (1972), Hutson (1976), and Oda and Mueller (1972). Formation of the cis-diol and its epimerization to the trans-diol have been demonstrated to occur in rat microsomes (McKinney et al., 1973).

In two studies involving the feeding of dieldrin to male rats for 7 months (Richardson et al., 1968) or 1 month (Matthews and Matsumura, 1969), two major metabolites were isolated from the urine and feces. The fecal metabolite proved to be 9-hydroxy dieldrin (Figure 6-2, compound VI; Table 6-3, Figure 6-3); this reaction was found to be catalyzed by liver microsomal monooxygenases in rats, and to be inhibited by the monooxygenase inhibitor, sesamex (Matthews and Matsumura, 1969). With the exception of the rabbit, in most of the species studied (i.e., mice, rats, sheep, rhesus monkeys, chimpanzees), this has been the principal

metabolite that has been found (Feil et al., 1970; Mueller et al., 1975b). It has been detected in the feces, and either free or conjugated in the urine. After dosing sheep with ^{14}C-dieldrin, Hedde et al. (1970) isolated six hexane-soluble and two water-soluble urinary metabolites, postulating that one of the latter was the glucuronide conjugate of aldrin trans-diol (Figure 6-3). Two of the hexane-soluble metabolites were subsequently identified as aldrin trans-diol and 9-hydroxy dieldrin (Feil et al., 1970). The glucuronide conjugate of 9-hydroxy dieldrin is formed both *in vivo* and *in vitro* and has been isolated in the bile of rats (Chipman and Walker, 1979); passing through the bile duct into the lower intestines, it is largely converted there into the free 9-hydroxy metabolite before being excreted in the feces (Hutson, 1976). When dieldrin is incubated *in vitro* with rat liver microsomes in the presence of UDPGA, 9-hydroxy dieldrin glucuronide is reported to form rapidly via the consecutive actions of microsomal monooxygenase and uridine diphosphoglucuronyl transferase (Hutson, 1976; Matthews et al., 1971). As evidence of species differences in the rates of metabolism of dieldrin, a higher ratio of 9-hydroxy ^{14}C-dieldrin to ^{14}C-dieldrin has been observed in rats than in mice, indicative of a more rapid hydroxylation reaction in the former (Hutson, 1976).

The second major metabolite (i.e., the one found in the urine) that was reported in the rat studies of Richardson et al. (1968) and Matthews and Matsumura (1969) has been identified as pentachloroketone, or PCK (Figure 6-2, compound VII; Table 6-3, Figure 6-3). Also known as Klein's metabolite, it has been found mainly in the urine and kidneys of male rats, but only in small amounts in female rats, mice, and other species (Baldwin et al., 1972; Damico et al., 1968; Hutson, 1976; Klein et al., 1968; Matthews et al., 1971; Richardson et al., 1968). Male rats have been found to metabolize dieldrin 3 to 4 times more rapidly than females (Matthews et al., 1971), a difference that has been ascribed to males' greater ability to convert dieldrin to its more polar metabolites, including 9-hydroxy dieldrin (ATSDR, 2000) and especially PCK (USEPA, 1980).

Comparative metabolism studies on male CFE rats and male CF_1 and/or LACG mice revealed that much greater quantities of the PCK derivative were produced in the rat than in either mouse strain, smaller amounts of polar urinary metabolites were produced in the mice, and aldrin trans-diol was found in the feces and a dicarboxylic acid derivative in the urine of all animals; both rats and mice produced 9-hydroxy dieldrin (Baldwin et al., 1972; Hutson, 1976). In their study of rats dosed with radiolabeled dieldrin, Matthews et al. (1971) found that the greatest percentage of radioactivity in the feces of both males and females came from 9-hydroxy dieldrin, with aldrin trans-diol and a second, unidentified polar metabolite also present. Significant amounts of PCK was found in the urine of male rats, with initially some aldrin trans-diol and unchanged dieldrin. In female rats, most of the activity in urine was associated with aldrin trans-diol and, initially, up to 20% with dieldrin.

It should also be noted that when photodieldrin (Figure 6-2, compound III; Table 6-3), itself a degradation product of dieldrin, was fed to rats for 13 weeks, it and PCK were isolated from blood, brain, liver, and adipose tissue (Baldwin and Robinson, 1969). When administered orally or intraperitoneally 5 days/week for 12 weeks, PCK and small amounts of other more polar metabolites were found in the urine of rats (Klein et al., 1970). In a female rhesus monkey given daily oral doses of ^{14}C-photodieldrin for 175 days, photodieldrin trans-diol (Figure 6-2, compound XI; Table 6-3) and its glucuronide conjugate were identified in the urine, and possibly

only the diol in the feces (Nohynek et al., 1979). A third metabolite, found both in the urine and feces, was speculated to be a mono-hydroxy derivative of photodieldrin.

Finally, oral administration of dieldrin has been shown capable of inducing hepatic mixed function oxidases (Kohli et al., 1977). Baldwin et al. (1972) have also been able to demonstrate some induction in the CFE male rat (but not in the CF_1 male mouse) by prefeeding low doses of dieldrin for 3 weeks. It is relevant to keep this observation in mind when, for example, comparing the results of long-term versus acute animal studies, or considering the potential effects of aldrin or dieldrin exposure in humans who are chronically exposed to at least low doses of mixed function oxidase inducers (USEPA, 1980).

6.4 Excretion

Much of the available information on the excretion of aldrin and dieldrin has already been introduced in the previous sections describing their absorption, distribution, and metabolism. Some of this information will again be briefly mentioned in this section, along with additional detail in some cases and supplemented with a number of additional studies. These compounds have been found in general to be excreted primarily in the feces, but also to some extent in the urine, in the form of metabolites that are more polar than the parent compounds. When exposure is kept constant, equilibrium levels of aldrin, dieldrin, and their metabolites are generally achieved in most organs and tissues. Body burdens will fluctuate in accordance with increases and decreases in exposure concentration.

Although the data is naturally much less extensive than in animals, excretion in humans following exposure to aldrin or dieldrin appears to occur largely through the bile and feces. In an early study of occupationally exposed workers, Cueto and Hayes (1962) were able to detect the presence of dieldrin and some of its metabolites in their urine. Somewhat later, Cueto and Biros (1967) reported that the mean concentrations of dieldrin found in the urine of five men and five women from the general population were 0.8 ± 0.2 and 1.3 ± 0.1mg/L, respectively. These concentrations were compared with those of male workers (a total of 14) who were deemed to have either low (5 males), medium (4 males), or high (5 males) occupational exposure to dieldrin and other chlorinated insecticides. The respective urinary concentrations of the three worker groups were 5.3, 13.8, and 51.4 mg/L. In another study of workers occupationally exposed to various chlorinated pesticides, the concentrations of aldrin detected in 14 urine samples were all less than 0.2 mg/L, while those for dieldrin ranged from 1.3 to 66.0 mg/L (Hayes and Curley, 1968). Two reports have described detecting 9-hydroxy dieldrin in the feces of seven workers having occupational exposure to aldrin and dieldrin (Richardson, 1971; Richardson and Robinson, 1971). The mean and range of fecal 9-hydroxy dieldrin concentrations measured in the seven workers were 1.74 and 0.95 to 2.80 mg/kg, respectively, while those determined from five males of the general population were 0.058 and 0.033 to 0.12 mg/kg, respectively. Dieldrin at a mean concentration of 0.18 mg/kg was also detected in the feces of the workmen, but it could not be detected in samples from the general population. Examination of the urine for dieldrin and four known metabolites led the authors to conclude that urinary excretion was a minor pathway in human males, although they failed to examine the urine for glucuronide or other conjugates of the potential hydroxy metabolites.

In a study by Hunter et al. (1969), 12 human volunteers ingested various amounts of dieldrin for up to 24 months; dieldrin concentrations in blood and adipose tissue were monitored during this exposure period, as were the blood concentrations for an additional 8 months. For 3 of the volunteers, blood dieldrin concentrations reportedly did not change significantly; for the remaining 9, the mean half-life of dieldrin in the blood was estimated to be 369 days (a range of 141 to 592 days). Though determined with a limited number of samples, this estimate was far longer than the value of less than 10 days that had been reported in animal studies. In an unpublished study by DeJonge, it was reported (Jager, 1970) that in workers who had had previously high exposures to aldrin/dieldrin, and thus high concentrations of the compounds in their blood before being transferred to other areas, the mean half-life of dieldrin in the blood had been calculated to be 0.73 years (or approximately 266 days). This estimate was reportedly based on measurements taken every 6 months for 3 years following cessation of exposure. It agrees reasonably well with that of Hunter et al. (1969), which was derived using limited data.

Feldman and Maibach (1974) demonstrated that 7.7% of a dose of ^{14}C-dieldrin (4 µg/cm^2 in acetone), applied once to the arm of volunteers, was excreted in the urine over a 5-day period; similarly, 3.3% of a single intravenous injection was excreted in the urine over the same period. Finally, dieldrin can be excreted via lactation in nursing mothers, and concentrations ranging from 1 to 29 ppb have been reported in human milk samples taken from women in various countries around the globe (Curley and Kimbrough, 1969; Schecter et al., 1989; IARC, 1974b).

In one of the early animal studies examining the metabolism and excretion of these compounds, Ludwig et al. (1964) gave male Wistar rats daily oral doses of ^{14}C-aldrin (4.3 µg, or about 0.2 mg/kg diet) for up to 3 months. They reported that approximately 9 times as much radioactivity was excreted in the feces as in the urine (urinary excretion increasing from ~ 2% during week 1 to 9 to 10% during week 12). As a percent of administered daily dose, excretion increased from 31% on day 2, to about 80% during week 2, to 100% by weeks 8 to 12, indicating that a steady state, saturation level had been reached in the animals. Once exposure was discontinued, excretion of radiolabeled compounds diminished rapidly; 24 hours, 6 weeks, and 12 weeks after the final dose, 88, 98, and >98% of the total administered dose had been excreted. Urine and fecal extracts were examined by paper chromatography, which indicated that aldrin content in both urine and feces decreased during the exposure period and afterward, while that of dieldrin somewhat increased. Hydrophilic metabolites increased during exposure, constituting after 12 weeks about 75 and 95% of the radioactivity excreted in feces and urine, respectively. Contrary to the predominance of fecal excretion seen in this rat study, it has been reported that male rabbits administered ^{14}C-aldrin excreted more radioactivity in their urine than in their feces (IARC, 1974a). In rabbits orally administered ^{14}C-dieldrin for 21 weeks, Korte and Arent (1965) observed that right after the exposure period (week 22), 42% of the total administered radioactivity had been excreted, with 2 to 3 times as much via the urine as the feces.

In female rats infused for 2.5 to 5 hours with total doses of 8 to 16 mg/kg bw of ^{36}Cl-dieldrin, approximately 70 and 10% of the administered doses were recovered over the ensuing 42 days in the feces and the urine, respectively, indicating that the predominant route of excretion was via the bile (Heath and Vandekar, 1964). The authors also noted that dietary restriction markedly increased the blood dieldrin concentration as fat stores were mobilized. Comparable findings were observed in male rats with/without biliary fistulas that received single

intravenous doses of ^{14}C-dieldrin (0.25 mg/kg bw) (Cole et al., 1970). After 7 days, about 80% of the administered dieldrin dose had been excreted in the feces. At 1,4, and 7 days post-exposure in the rats with biliary fistulas, approximately 30, 60, and >90%, respectively, of the administered dose had been excreted via the bile. In experiments with isolated perfused rat livers, about 20% of the perfused dieldrin dose was collected in the bile during an 8-hour period (Cole et al., 1970), and the rate of biliary excretion in those isolated from males was found to be approximately three times greater than in those from females (Klevay, 1970). Chipman and Walker (1979) reported that in rats receiving dieldrin intraperitoneally, pretreatment with phenobarbital increased the rate of biliary excretion.

Dailey et al. (1970) reported that following exposure to radiolabeled dieldrin, excretion of radioactivity via urine and feces was higher in male rats than in female rats, a finding confirmed in a 39-week study by Davison (1973). The latter study also indicated that the maximal excretion of radioactivity occurred during the 6th week of exposure, regardless of the dieldrin dose, and that a steady state condition existed from weeks 6 through 39. Matthews et al. (1971) found a 10-fold higher level of radioactivity in kidneys isolated from males than from females in rats that had been fed ^{14}C-dieldrin. In male kidneys, most of the radioactivity was associated with PCK, whereas in female kidneys only dieldrin was detected. This greater ability of male rats to convert dieldrin to its more polar metabolites, especially PCK, was thought to underly the three- to four-fold more rapid metabolism of dieldrin that is observed in male versus female rats.

Following the single oral administration of 0.5 mg ^{14}C-dieldrin/kg bw to mice, rats, rabbits, rhesus monkeys, and one chimpanzee, urine and fecal samples were collected for 10 days and analyzed (Mueller et al., 1975b). They reported the main route of excretion to be the feces for all species except the rabbit, accounting for 95, 95, ~ 18, 79, and 79% of the amounts excreted, respectively. The ratios of fecal to urinary excretion are thus approximately 19:1 for rats and mice, 1:5 for rabbits, and 4:1 for rhesus monkeys and the chimpanzee. Ten days after dosing, the total amounts of radioactivity excreted were 37% (mice), 11% (rats), 2% (rabbits), 20% (rhesus monkeys), and 6% (the chimpanzee) of the total administered dose. In all five species, the principal metabolites were 9-hydroxy dieldrin and aldrin trans-diol; unchanged dieldrin, 9-hydroxy dieldrin, and its glucuronide were reported to predominate in rats, rhesus monkeys, and the chimpanzee, whereas mice and rabbits displayed higher amounts of aldrin trans-diol. The glucuronide conjugate of aldrin trans-diol was identified in the urine of the rabbits and rhesus monkeys, and aldrin dicarboxylic acid was noted as a minor metabolite in the feces of rats, rhesus monkeys, and the chimpanzee. As noted previously, Klein et al. (1968) had also detected PCK in the urine of rats fed 1.25 mg aldrin/kg/day.

Baldwin et al. (1972) compared the excretion of dieldrin in the CF_1 mouse and the CFE rat and found the amounts of labeled dieldrin excreted after 7 to 8 days were similar. The feces contained about 10 times the radioactivity found in the urine, and 50 to 70% of the administered dose was excreted during the 1-week collection period. As noted previously, the proportion of various metabolites varied between the two species, a principal difference being that PCK was found in significant amounts in rat urine, but was not detected in mouse urine. Hutson (1976) conducted a similar study on male CFE rats and male CF_1 and LACG mice after a single oral dose, with or without a period of dieldrin pretreatment (see Section 6.3). Dieldrin pretreatment

modestly increased the percentage fecal excretion (of the total administered radiolabeled dose) from 62.4 to 69% in the rats, had no effect in the LACG mice (51.5%), and substantially increased it in CF_1 mice from 27.2 to 48.8%. Urinary excretion in the rats was 5.5 to 6.6%, whereas it was much lower in the mice (0.42 to 2.6%). In the male rats and CF_1 mice, the amount of urinary aldrin dicarboxylic acid was low compared with that of PCK + dieldrin, while in LACD mice it was twice as high. A much higher proportion of an unidentified metabolite was excreted in the urine of both mouse strains than in that of the rat. In rats, the major fecal metabolite was 9-hydroxy dieldrin with or without pretreatment; in both strains of mice, however, it became a major fecal metabolite only after pretreatment.

In a study of sheep dosed with ^{14}C-dieldrin, excretion of radioactivity was higher in the feces than in the urine (Hedde et al., 1970). These authors noted that in two very fat sheep, the ratio of labeled dieldrin in feces to that in urine was >10:1, but in two thin sheep receiving the same dose, it was only slightly greater than 1:1. Only 0.25% of the total dose was exhaled as $^{14}CO_2$, and after 5 to 6 days of collection, less than 50% of the administered dose was recovered.

For more information on the relatively rapid loss of dieldrin and/or its metabolites from various organs and tissues, refer to the relevant studies previously discussed in Section 6.2 (e.g., Robinson et al., 1969; Barron and Walton, 1971). Finally, the excretion of photodieldrin has been explored in rats (Dailey et al., 1970) and monkeys (Nohynek et al., 1979). After 12 weeks of daily dosing with ^{14}C-photodieldrin in the rat, urinary excretion was found to be significantly higher in males than in females, and to gradually increase during the 12-week exposure period. Fecal excretion was initially lower in females, but became greater during the latter part of the study (Dailey et al., 1970). After orally dosing rhesus monkeys for 70 to 76 days with radiolabeled photodieldrin, a steady state between intake and excretion was reported (Nohynek et al., 1979). At the end of exposure, the animals had excreted about 50% of the cumulative dose, and an additional 30% was excreted during the next 100 days. During dosing, photodieldrin was a major fecal metabolite, and 20 to 50% of the radioactivity was excreted in the urine; this amount increased to 60% when the dosing ceased. When one male and one female rhesus monkey were given a single intravenous injection of radiolabeled photodieldrin, excretion remained high during the first 7 days, but then rapidly decreased. By day 21, approximately 45 and 34% of the administered dose had been excreted in the male and female, respectively.

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7.0 HAZARD IDENTIFICATION

The purpose of this section is to characterize the carcinogenic and non-carcinogenic health effects of aldrin and dieldrin, based on an evaluation of information from both human epidemiological and case studies and from animal studies. In addition, mechanistic studies on these compounds from human, animal, and *in vitro* experiments are reviewed, and possible modes of action for some of their various non-carcinogenic and carcinogenic effects are discussed.

7.1 Human Effects

This section briefly highlights the rather limited number of human case and epidemiological studies that have reported acute to chronic effects resulting from exposure to aldrin and/or dieldrin.

7.1.1 Short-Term Studies

The short-term studies summarized below primarily reflect the oral exposure effects of aldrin and dieldrin reported in humans under accidental poisoning scenarios.

General Population

Aldrin

Jager (1970) reported the acute oral lethal dose of aldrin in an adult male to be 5.0 g (approximately 70 mg/kg, assuming a body weight of 70 kg). A somewhat lower ingested dose of aldrin (25.6 mg/kg) has been reported to have caused convulsions in a 23-year old male after 20 minutes (Spiotta, 1951). Although his convulsions ceased after treatment with pentobarbital, he continued to exhibit restlessness, hypothermia, tachycardia, and hypertension for up to 5 days, and electroencephalogram (EEG) abnormalities for up to 6 months.

Severe acute intoxication following aldrin exposure in humans is characterized by a brief period of excitation or drowsiness, followed by convulsions, muscle twitching, and coma. Hypothermia generally accompanies death. The majority of individuals intoxicated with aldrin, however, usually regain consciousness and recover (Hayes, 1982; Jager, 1970).

Dieldrin

Dieldrin has been reported to cause hypersensitivity and muscular fasciculations that may be followed by convulsive seizures and associated changes in the EEG pattern. Acute symptoms of intoxication include hyperirritability, convulsions and/or coma, sometimes accompanied by nausea, vomiting and headache; chronic intoxication may result in fainting, muscle spasms, tremors, and loss of weight. The lethal dose for humans is estimated to be about 5.0 g (ACGIH, 1984).

Black (1974) observed tachycardia, elevated blood pressure, and convulsions in a man who ingested 120 mg/kg dieldrin. These cardiovascular effects were presumed to be due to altered activity in the central nervous system (i.e., increased sympathetic output), as the symptoms were controlled by the administration of β-adrenergic blocking drugs. Persistent headaches, irritability, and short-term memory loss were also reported following the patient's recovery from convulsions.

Sensitive Populations

Children are generally considered at greater risk than adults to the toxic effects of chemicals for reasons that include underdeveloped/developing organ systems or capacities (e.g., nervous system, digestive and reproductive systems, immune systems, metabolic detoxication capacity), increased potential for exposure, increased chemical absorption, etc. One study reported that the ingestion of approximately 120 mg (8.2 mg/kg) of aldrin by a 3-year old female resulted in collapse and convulsions within 5 minutes and death within 12 hours (Hayes, 1982).

Garrettson and Curley (1969) reported convulsions in two children (ages 2 and 4 years) who consumed an unknown amount of a 5% dieldrin solution (also containing solvents and emulsifiers). The children began to salivate heavily, and then developed convulsions within 15 minutes; the younger child died, whereas the older brother had liver dysfunction prior to recovering completely.

7.1.2 Long-Term and Epidemiological Studies

The long-term epidemiological studies were conducted mainly in populations working in pesticide manufacturing plants, although some utilized volunteers. In most cases, some combination of oral, inhalation, and dermal routes of exposure were probably involved.

General Populations

Aldrin

One male, employed 21 years at a chemical plant and reassigned to the handling of aldrin concentrate (period and levels of exposure were not specified), experienced involuntary jerking (rapid flexor movement) of his hands and forearms, vomiting, and chronic irritability, and insomnia (Hodge et al., 1967). His EEG showed alpha-wave irregularities, with discharges of slow and sharp waves. After exposure to aldrin was discontinued, his condition rapidly improved.

Dieldrin (mean = 13 ng/g whole milk) was found in the breast milk of women whose homes were treated annually (or more frequently) with organochlorine pesticides (Stacey and Tatum, 1985). A correlation between dieldrin levels in the milk and aldrin treatment of homes was observed. Dieldrin levels in breast milk rose until the seventh or eighth month after treatment of homes was discontinued. No data were provided on the health effects of children exposed to dieldrin-contaminated breast milk.

Edwards and Priestly (1994) reported elevated plasma dieldrin levels and hepatic enzyme activity (as measured by urinary D-glucaric acid excretion) in 33 workers (29 males and 4 females) from 2 south Australian suburban pesticide treatment businesses; they had worked in the industry ranging from 3 months to 20 years. The plasma dieldrin concentrations in workers applying aldrin ranged from 2.5 to 250 ng/mL, while those for workers not involved with aldrin exposure (office staff) had dieldrin levels ranging from 0.7 to 26 ng/mL. However, there was no correlation between high D-glucaric acid excretion and plasma dieldrin levels.

Dieldrin

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

Aldrin/Dieldrin

No increase in mortality from any cause was reported in workers (n = 233) who had been employed in the manufacture of aldrin, dieldrin, and other pesticides at a facility in the Netherlands for more than 4 years (Van Raalte, 1977; Versteeg and Jager, 1973).

Subsequent studies conducted from the Netherlands included several years of follow up, which may be summarized as follows. De Jong (1991) reported mortality data in a 20-year follow-up study of cohorts exposed to insecticides for at least 1 year between 1954 and 1970 (total cohorts = 570 workers). At the time of the vital status cut-off date (January 1, 1987), of these 570 workers, 445 (78%) were alive; 76 (13.3%) were deceased; 34 (6.0%) emigrated; and 15 (2.6%) were lost to the follow up. Workers on the study represented 14,740 person years of observation. Exposure estimates were made based on the available blood dieldrin data collected from 343 of the workers. The workers were divided into low, medium, and high exposure categories having estimated mean daily aldrin/dieldrin intakes of 90, 419, and 1019 μg, respectively (corresponding mean lifetime intake values were 88, 419, and 1704 mg). The standardized mortality ratios (SMRs) for all causes of death for the workers exposed to aldrin/dieldrin, as compared to Netherlands national mortality rates, were 80.6, 86.8, and 68.9 for low, moderate, and high exposures, respectively.

A more recent study from the Netherlands reported on the mortality of the same cohorts with a latter follow-up date (de Jong et al., 1997). Of the 570 workers, 70.5% (402) were alive; 20.7% were deceased (118); 6.2% (35) emigrated, and 2.6% (15) were lost to the follow-up, at the cut off date of January 1, 1993. The total mortality observed from all causes of death in all the cohorts was lower than the expected number of deaths, calculated from national data according to age, period, and causes of specific mortalities (118 deaths observed versus 156 deaths expected; SMR = 75.6, with a 95% confidence interval of 63 to 91). Similar lower trends were observed for mortality rates from cardiovascular disease and non-malignant respiratory disease. Of all the types of cancers, only two (rectum and liver) had higher frequency than expected, but these results were not dose dependent. Six deaths from rectal cancer were observed in the cohorts, as compared to 1.5 expected (SMR = 390.4, with a 95% confidence interval of 143 to 850). Two deaths due to liver cancer were observed in the cohorts, as

compared to 0.9 expected (SMR = 225, with a 95% confidence interval of 27 to 813). Stratification of the data according to the type of job (operators, maintenance workers, supervisors) showed a significantly ($p < 0.01$) increased mortality rate for rectal cancer only in the operator group (de Jong et al., 1997).

Three follow-up cohort studies were reported on the mortality rates of workers from a pesticide manufacturing plant in Denver, CO (Ditraglia et al., 1981; Brown, 1992; Amaoteng-Adjepong et al., 1995). In the first retrospective cohort study, Ditraglia et al. (1981) reported SMRs for 1,155 workers who had been employed at the plant for at least 6 months prior to 1964 and were exposed to aldrin/dieldrin. Of the 1,155 workers, 75% (870) were alive, 15% (173) deceased, and 10% (112) were of undetermined vital status as of the study cut-off date (December 31, 1976). Workers in the study represented 24,939 person years of observation. They were mainly white males, and the mortality rates of the exposed population were compared to white male cause-specific mortality rates in the U.S. The mortality rate for all causes of death (combination of malignant, circulatory, nonmalignant respiratory, and nervous system diseases) was significantly lower in the exposed group than in the controls (SMR = 84, with a 95% confidence interval of 72 to 98). The SMRs for neoplasms of the liver and the lymphatic/hematopoietic system were not statistically different from 100, the values corresponding to 225 (95% confidence interval of 39 to 1267) and 147 (95% confidence interval of 54 to 319), respectively. However, the authors reported a significant increase in the SMR for nonmalignant respiratory disease at 212, with a 95% confidence interval of 133 to 320.

The study by Brown (1992) extended the observations reported by Ditraglia et al. (1981) having a study cut-off date of December 31, 1987, and 1158 workers. Of these, 803 (70%) were alive, 337 (29%) were deceased, and 13 (10%) were of undetermined vital status. Workers in the study represented 34,479 person years of observation. The mortality rate for all causes of death (combination of malignant, circulatory, nonmalignant respiratory, and cerebrovascular diseases) was lower for the exposed cohort than for controls (SMR = 87, with a 95% confidence interval of 78 to 97). Comparing the cohort mortality rate to national, state, or county statistics did not affect the SMR for all causes of death. However, the SMR for liver/biliary cancer was higher than expected, with values corresponding to 393 (CI = 127 to 920), 510 (CI = 165 to 1,191), or 486 (CI = 157 to 1,136) when compared to U.S., state, or county mortality rates, respectively. Of the five observed cases of liver and biliary cancer, two were also in the dibromochloropropane (DBCP) registry.

Finally, Amaoteng-Adjepong et al. (1995) updated the SMRs of the workers in the Denver pesticide manufacturing plant; the study population is similar to those mentioned in the previous two studies (Ditraglia et al. 1981; Brown, 1992), except that most of the employees worked at the plant between 1952 and 1982, and the race was reported for most (n = 2,384). The unknown race of 262 workers was classified as white. The cohort had the vital status of 1,764 (74%), 496 (21%), and 124 (5.0%) for living, deceased, and unknown categories, at the time of the cut off date of January 1, 1991. Within the cohort, 87% of the workers consisted of white males (n = 2,072); 10% were white females (234); 3% were black males (n = 68); and <1% were black females (n = 10). The analysis of the data suggested no positive relationship between aldrin/dieldrin exposure and mortality due to liver cancer or other causes of death (respiratory, circulatory, or nervous system diseases).

Nair et al. (1992) reported finding aldrin and dieldrin levels in adipose tissue, breast milk, and serum samples collected from Delhi female residents (18 to 24 years old; n = 12) during 1989 through 1990. The subjects were from low socioeconomic status and were residing in parts of Delhi exposed to severe automobile pollution. The average aldrin concentrations were 0.048, 0.003, and 0.004 ppb in adipose tissue, breast milk, and serum, respectively, and the corresponding average dieldrin concentrations were 0.099, 0.06, and 0.002 ppb, suggesting greater concentration of aldrin/dieldrin in adipose tissues. A significant correlation was reported between the levels of aldrin/dieldrin found in adipose tissue and those found in serum ($p<0.01$; $r = 0.503$). The authors also observed that aldrin and dieldrin values were higher in the breast milk of primagravidae (first time deliverers) when compared to women who had undergone their second delivery. They concluded that the aldrin/dieldrin levels in Delhi residents were low when compared to the values found in populations from developed countries.

Conflicting reports exist on the effect of aldrin/dieldin on hematological parameters. A farmer with multiple exposures to insecticides that contained dieldrin died in a hemolytic crisis after developing immunohemolytic anemia (Muirhead et al., 1959). Immunologic testing revealed a strong antigenic response to red blood cells coated with dieldrin. In another study, a worker from an orange grove 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 was considerably more tenuous, being linked only in that the onset of symptoms corresponded with spraying and the condition deteriorated upon subsequent exposure. However, in another study of workers employed in a pesticide manufacturing plant for 4 years, no abnormal values for hemoglobin, white blood cells, or erythrocyte sedimentation rate were found (Jager, 1970). Further, workers, who had been involved in either the manufacture or application of pesticides and who had elevated blood dieldrin levels, had no hematological effects of clinical significance (Warnick and Carter, 1972).

Sensitive Populations

No long-term studies were located that examined the adverse health effects of aldrin or dieldrin exposure in children (who in general are considered to be among the most sensitive populations for exposure to chemicals), or in any other potentially high-risk population (e.g., the aged or those with pre-existing liver or neurological disease).

7.2 Animal Studies

7.2.1 Acute Toxicity (Oral, Inhalation, Dermal)

Oral Exposure

The oral median lethal dose (LD_{50}) values for aldrin in laboratory animals are as follows: mice, 44 mg/kg bw (purity not reported; Borgmann et al., 1952); rats, 39 to 60 mg/kg bw (purity not reported; Gaines, 1969); guinea pigs, 33 mg/kg bw (purity not reported; Borgmann et al., 1952); female rabbits, 50 to 80 mg/kg bw (purity, 95%; Treon and Cleveland, 1955); and dogs, 65 to 95 mg/kg bw (purity not reported; Borgmann et al., 1952).

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

The age of the animals appeared to influence the acute toxicity of a single administration of dieldrin. Two week-old rats had an LD_{50} of 25 mg/kg bw, which is lower, as expected, than the LD_{50} value (37 mg/kg bw) found in young adult rats (Lu et al.,1965). However, newborn rats had a relatively high LD_{50} of 168 mg/kg bw (Lu et al., 1965).

Acute toxicity in animals is characterized by increased irritability, salivation, hyperexcitability, tremors followed by clonic/tonic convulsions, anorexia and loss of body weight, depression, prostration, and eventual death (Borgmann et al., 1952; Hodge et al., 1967).

Inhalation Exposure

Treon et al. (1957) exposed cats, guinea pigs, rats, rabbits, and mice to aldrin vapors and particles generated by sublimating aldrin at 200°C. Aldrin levels of 108 mg/m^3 for 1 hour resulted in the death of 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 one cat and no guinea pigs died following exposure to 215 mg/m^3 for 4 hours. Interpretation of the results of this study is limited in that sublimation may have resulted in the generation of atmospheres containing a higher proportion of volatile contaminants than would be expected in atmospheres typical of most occupational exposures.

Dermal Exposure

In rats, a single dermal application of aldrin in xylene produced an LD_{50} value of 60 mg/kg bw in female rats and 90 mg/kg bw in male rats (Gaines, 1960). 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 bw for both chemicals (Treon et al., 1953).

7.2.2 Short-Term Studies

Oral Exposure

In a short-term study, Treon and Cleveland (1955) observed 100% mortality within 2 weeks in groups of male and female Carworth rats (total number and number/sex not reported) that were fed aldrin (purity 95%) at a concentration of 300 ppm (an approximate dose of 15 mg/kg bw/day, based on Lehman, 1959). No mortality was noted at lower doses. Administration of a diet containing 25 ppm aldrin (purity 95%), an approximate dose of 0.625 mg/kg bw/day, to 2 male and 3 female beagle dogs induced fatalities after periods of feeding ranging from 9 to 15 days (Treon and Cleveland, 1955).

Kolaja et al. (1996a) investigated the short-term effects in male Fisher 344 rats and B6C3F$_1$ mice (5 animals/species/group) after administration of dieldrin at 0 (control), 0.1, 1.0, 3.0, or 10.0 mg/kg bw diet for 7 or 14 days (approximate doses in rats of 0.005, 0.05, 0.15, or 0.5 mg/kg bw/day, and in mice of 0.015, 0.15, 0.45, or 1.5 mg/kg bw/day; based on Lehman, 1959). Relative liver weights (liver weight/body weight) in mice were significantly increased at all doses tested compared to controls. However, in rats, apparent increases in relative liver weights were found only in the 10.0 mg/kg bw diet dieldrin group after 7 days of treatment. Dieldrin was not severely hepatotoxic in either species, as evidenced by no changes in the activities of serum enzymes such as ALT and AST, and no histopathology.

In an another study, Kolaja et al. (1996b) reported selective promotion of hepatic focal lesions in male B6C3F$_1$ mice, but not in male Fisher 344 rats, following administration of dieldrin at 0.1, 1.0, or 10.0 mg/kg bw diet (5 animals/group) for 7 days (approximate doses in rats of 0.005, 0.05, or 0.5, mg/kg bw/day, and in mice of 0.015, 0.15, or 1.5 mg/kg bw/day; based on Lehman, 1959). Study animals including controls were injected intraperitoneally with the hepatic carcinogen, diethyl nitrosamine (150 mg/kg bw/week, 2x for rats; 25 mg/kg bw/week, 8x for mice), prior to dieldrin treatment in order to enhance the formation of hepatic lesions. No significant effects on the number or volume of hepatic focal lesions (total), DNA labeling index, or relative liver weight (liver to body weight ratio) were observed in the rats. However, significant increases ($p < 0.05$) in the number of hepatic focal lesions and in hepatic focal lesion volume, DNA labeling index, and relative liver weight were noted in the mice treated with the high dose of dieldrin. No changes in body weight or in the apoptotic index of the hepatic focal lesions were observed at any of the doses tested, either in rats or mice.

Inhalation Exposure

No studies were obtained that investigated the short-term toxic effects of aldrin or dieldrin in animals after inhalation exposure.

Dermal Exposure

No studies were obtained that investigated the short-term toxic effects of aldrin or dieldrin in animals after dermal exposure.

7.2.3 Subchronic Studies

Oral Exposure

Aldrin

Decreased body weight gain and increased mortality were observed in the high-dose group of Osborne-Mendel rats (5/sex/group) fed aldrin (technical grade, 95% pure) in the diet at concentrations of 0, 40, 80, 160, or 320 ppm aldrin (doses of 0 and approximately 2, 4, 8, or 16 mg/kg bw/day, respectively, based on a food consumption factor of 0.05 from Lehman, 1959) for 42 days then and observed for an additional 14 days (NCI, 1978). The No-Observed-Adverse-Effect Level (NOAEL) for this study was 160 ppm (8 mg/kg bw/day).

This study was a range-finding study for a long-term carcinogenicity study; therefore, a complete toxicology profile was not obtained (e.g., biochemical and hematology assessments were not performed).

In groups of $B6C3F_1$ mice (5/sex/group) fed aldrin (technical grade, 95% pure) at concentrations of 0, 2.5, 5, 10, 20, 40, or 80 ppm (doses of 0 and approximately 0.375, 0.75, 1.5, 3, 6, or 12 mg/kg bw/day, respectively, based on a food consumption factor of 0.15 from Lehman, 1959) in the diet for 42 days, 100% mortality was observed in the 40 and 80 ppm (6 and 12 mg/kg bw/day, respectively) groups. One male and one female died in the 20 ppm (3 mg/kg bw/day) group; 10 and 20 ppm (1.5 and 3 mg/kg bw/day, respectively) were therefore considered the NOAEL and Lowest-Observed-Adverse-Effect Level (LOAEL) values, respectively, for this study (NCI, 1978). This study was a range-finding study for a long-term carcinogenicity study; therefore, a complete toxicology profile was not obtained.

Dieldrin

Kolaja et al. (1996a) reported no statistically significant differences in either body weight gains, food consumption, or water consumption in male $B6C3F_1$ mice or Fisher 344 rats that were administered dieldrin at concentrations of 0.1, 1.0, 3.0, or 10.0 mg/kg bw diet for 21, 28, or 90 days (approximate doses in rats of 0.005, 0.05, 0.15, or 0.5 mg/kg bw/day, respectively, and in mice of 0.015, 0.15, 0.45, or 1.5 mg/kg bw/day, respectively; based on Lehman, 1959). Also, no severe hepatotoxicity was observed in dieldrin-treated animals, as evidenced by no changes in activities of the serum enzymes ALT (alanine aminotransferase) and AST (aspartamine aminotransferase), and no apparent histopathology. However, relative liver weights (liver/body weight ratios) were significantly increased in mice (but not in rats) at the highest dose tested.

In a subsequent report, Kolaja et al. (1996b) reported that dieldrin administered to groups of male $B6C3F_1$ mice or Fisher 344 rats (5/group/species/dose) at concentrations of 0.1, 1.0, or 10.0 mg/kg bw diet for 30 or 60 days (approximate doses in rats of 0.005, 0.05, or 0.5 mg/kg bw/day, respectively, and in mice of 0.015, 0.15 or 1.5 mg/kg bw/day, respectively; based on Lehman, 1959) caused the selective promotion of hepatic focal lesions in the mice but not in the rats. Study animals, including controls, were injected intraperitoneally with the hepatic carcinogen, diethyl nitrosamine (150 mg/kg bw/week, 2x for rats; 25 mg/kg bw/week, 8x for mice), prior to dieldrin treatment in order to enhance the formation of hepatic lesions. No significant effects on the number or volume of hepatic focal lesions (total) were observed for rats at any of the doses tested during the 30 or 60 days after dieldrin treatment. However, significant increases ($p < 0.05$) in the number of hepatic focal lesions and in hepatic focal lesion volume and DNA labeling index were noted in mice treated with the high dose of dieldrin after 30 and 90 days. Dieldrin treatment also caused an inconsistent increase in relative liver weights in both rats and mice. Changes in body weight or in the apoptotic index of hepatic focal lesions were not observed at any dose or duration tested, in either rats or mice.

Stevenson et al. (1995) also reported that dieldrin caused an increase in hepatotoxicity such as liver enlargement, increased DNA synthesis in hepatocytes, hypertrophy of centrilobular hepatocytes, and induction of hepatic ethoxyreosrufin 0-deethylase (microsomal mixed function oxidase) activity at the highest dose in male $B6C3F_1$ mice fed with dieldrin at 1, 3, or 10 mg/kg

diet for 28 days (approximate doses of 0.15, 0.45, or 1.5 mg/kg bw/day; based on Lehman, 1959).

Inhalation Exposure

No studies were obtained that investigated the toxic effects of aldrin or dieldrin in animals after subchronic inhalation exposure.

Dermal Exposure

Aldrin or dieldrin (dry powder) applied to rabbit skin for 2 hours/day, 5 days/week for 10 weeks, was reported to have had no discernible effects (IPCS, 1989).

7.2.4 Neurotoxicity

Oral Exposure

Aldrin

Paul et al. (1992) reported behavioral impairments in Wistar rats (10/group) that were administered 1 mg/kg bw/day aldrin (technical grade, 90% pure) by gavage for up to 90 days. Aldrin inhibited muscle coordination (measured using rota-rod apparatus) beginning on the 15th day in both sexes, with greater motor deterioration occurring in males. Aldrin also inhibited learning ability and the conditioned avoidance response (measured in a pole-climbing apparatus), as the number of animals responding to simultaneous unconditioned and conditioned stimuli was significantly reduced ($p < 0.05$) in aldrin-treated groups when compared to controls.

Neurotoxic signs observed in cattle poisoned with unspecified dietary concentrations of aldrin included tremors, running, hyperirritability, and seizures (Buck and Van Note, 1968). Casteel et al. (1993) reported neurological and muscular symptoms, such as ataxia, tremors, hypersalivation, diarrhea, and disorientation in 6 calves; lateral recumbency and intermittent tonoclonic convulsions in 2 calves; and severe signs such as death in 10 calves, in a group of feedlot cattle (n = 90) exposed to aldrin-contaminated feed in northwest Missouri. The self-feeders in the feedlot contained from 54 to 528 µg aldrin/g of feed. Analysis of aldrin and dieldrin in the rumen content of two dead calves revealed the concentrations of aldrin as 20.6 and 22.4 µg/g of ingesta. The mean dieldrin concentrations in fat samples that were collected 50 days after the withdrawal of contaminated feed from the calves ranged from 9.7 to 18.8 µg/g, and the approximate half-lives of dieldrin in the adipose tissue of calves ranged from 53 to 231 days.

Dieldrin

Convulsions were observed in rats given single doses of dieldrin ranging from 40 to 50 mg/kg (Wagner and Greene, 1978; Woolley et al., 1985). Transient hypothermia and anorexia were also reported following a single dose of 40 mg/kg (Woolley et al., 1985). Tremors were observed in rats receiving a dose of 0.5 mg/kg bw/day for 60 days (Mehrotra et al., 1988), and hyperexcitability was observed with dieldrin at 2.5 mg/kg bw/day in an 8-week study (Wagner

and Greene 1978). Cerebral edema and small foci of degeneration were reported in rats exposed to dieldrin at 0.016 mg/kg bw/day for 2 years (Harr et al., 1970), although the study had various limitations.

Operant behavior was reported to have been disrupted in rats following single doses of dieldrin ranging from 0.5 to 16.7 mg/kg (Burt, 1975; Carlson and Rosellini, 1987). A lower dose of dieldrin (0.025 mg/kg bw/day) for a longer duration (60 to 120 days) was also observed to impair operant behavior in rats (Burt, 1975).

EEGs taken from dogs exposed to dieldrin at 0.05 mg/kg bw/day for 2 years were normal (Walker et al. 1969). However, dogs were reported to develop convulsions when given 0.5 mg/kg bw/day for 25 months (Fitzhugh et al. 1964).

Aldrin/Dieldrin

When aldrin or dieldrin was administered to rats for 3 days, convulsions were observed at a dose of 10 mg/kg bw/day (Mehrotra et al., 1989). Histopathological changes were found in the brain cells of rats that were exposed for 6 months to 2.75 mg/kg bw/day of either aldrin or dieldrin (Treon et al., 1951a).

Irritability, tremors, and convulsions were observed in rats fed aldrin/dieldrin at dietary concentrations ranging from 0.1 to 65 ppm in several 1.5- to 2.5-year studies (Deichmann et al., 1970; NCI, 1978; Walker et al., 1969). Hyperexcitability was observed in Osborne-Mendel rats exposed for 74 to 80 weeks to aldrin in the diet at 30 and 60 ppm (approximate doses of 1.5 and 3.0 mg/kg bw/day, respectively, according to Lehman, 1959) (NCI, 1978), as were tremors and clonic convulsions after 31 months exposure to 20, 30, or 50 ppm (approximate doses of 1.0., 1.5, or 2.5 mg/kg bw/day, respectively) (Deichmann et al., 1970). Similarly, hyperexcitability was observed in Osborne-Mendel rats fed 29 ppm dieldrin for 80 weeks or 65 ppm for 59 weeks (approximate doses of 1.45 and 3.25 mg/kg bw/day, respectively) (NCI, 1978). In a companion study (NCI, 1978), Fischer 344 rats that were fed dieldrin for 2 years at 2, 10, or 50 ppm (approximate doses of 0.1, 0.5, or 2.5 mg/kg bw/day, respectively) showed convulsions, tremors, and nervous behavior at the high dose. CF rats fed 0.1, 1, or 10 ppm dieldrin (approximate doses of 0.005, 0.05, or 0.5 mg/kg bw/day, respectively) for 2 years displayed irritability, tremors, and convulsions (Walker et al., 1969); the latter 2 effects were also noted in Osborne-Mendel rats exposed to 20, 30, or 50 ppm dieldrin (approximate doses of 1, 1.5, or 2.5 mg/kg bw/day, respectively) for 29 months (Deichmann et al., 1970).

B6C3F_1 mice showed slightly greater sensitivity than did the rats in the NCI (1978) 80-week bioassays, with hyperexcitability observed at dietary exposures of aldrin as low as 3 ppm (females) and 4 ppm (males) (approximate doses of 0.45 and 0.60 mg/kg bw/day, respectively, according to Lehman, 1959); and with hyperexcitability, tremors, and hyperactivity observed at dietary exposures of dieldrin as low as 2.5 ppm for both sexes (approximate dose of 0.38 mg/kg bw/day).

Dogs given aldrin at 0.89 to 1.78 mg/kg bw/day, or dieldrin at 0.73 to 1.85 mg/kg bw/day, for up to 9 months experienced neuronal degeneration in the cerebral cortex and

convulsions (Treon et al., 1951b). At these doses, aldrin-treated dogs also displayed hypersensitivity to stimulation, twitching, and tremors, while at higher doses, the basal ganglia and cerebellum were reported to exhibit degenerative changes.

Inhalation Exposure

No studies were obtained that investigated the neurotoxic effects in animals resulting from inhalation exposure to either aldrin or dieldrin.

Dermal Exposure

In a study examining the effects of acute dermal exposure to aldrin or dieldrin, Treon et al. (1953) reported the induction of tremors and convulsions in rabbits. However, the doses associated with these effects were not reported.

Other Routes of Exposure

Castro et al. (1992) reported the effects of prenatal exposure to aldrin on the behavioral development of 90 day-old adult rats. Pregnant female rats (10 to 20/group) were subcutaneously
injected with either aldrin (1.0 mg/kg bw) or its vehicle (0.9% sodium chloride plus Tween 80) from day 1 of pregnancy until delivery. Prenatal exposure to aldrin reportedly produced no changes at 90 days in aldrin or dieldrin levels in serum, or in cellular and structural organization of cerebral cortex neurons, or in the adult animals' behavior as determined by an avoidance learning test. However, prenatal administration of aldrin was found to produce a significant increase ($p < 0.05$) in the locomotor frequency of experimental rats at 21 and 90 days. Also, the performance of adult rats in the hole-board apparatus (total number and duration of head-dips) was significantly higher ($p < 0.05$) in the aldrin-treated groups when compared to that of the control rats.

7.2.5 Developmental/Reproductive Toxicity

Oral Exposure

Aldrin

In a reproduction study reported by Deichmann et al. (1971), groups of beagles were administered 0.15 (4 females) or 0.3 (4 males, 3 females) mg/kg bw/day of aldrin (purity 95%) by capsule, 5 days/week for 14 months. Estrous cycles in the female dogs were delayed by 7 to 12 months, and 2 of the 4 females administered 0.15 mg/kg bw/day failed to achieve estrus during the 8-month period following cessation of aldrin exposure. However, such failure was not observed in dogs given 0.3 mg/kg bw/day. During lactation, the viability of pups from dams receiving either 0.15 or 0.3 mg/kg bw/day was decreased; 84, 75, and 44% of pups from dams ingesting 0, 0.15, and 0.3 mg/kg bw/day, respectively, survived until weaning. The reduced pup survival may have been due to a prenatal effect, or to toxicity associated with dieldrin in the

mothers' milk. Mammary development and milk production also appeared to be severely depressed. Some males reportedly exhibited a depressed sexual drive.

Dieldrin

Coulston et al. (1980) studied the reproductive effects of dieldrin on Long Evans rats. Pregnant rats (18 to 20/dose) were administered 0 or 4 mg/kg bw dieldrin (purity not reported) by gavage, daily from day 15 of gestation through postpartum day 21. The treated group did not differ from the control group when examined for fecundity, number of stillbirths, perinatal mortality, or total litter weights. Pup malformations were not observed in either group.

Harr et al. (1970) fed dieldrin (purity not specified) to 28 day-old OSU-Wistar rats (20/sex/group) until they were mated at 146 days of age; dietary concentrations were 0, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, 20, or 40 mg/kg (0 and approximately 0.004, 0.008, 0.016, 0.032, 0.063, 0.125, 0.25, 0.5, 1, or 2 mg/kg bw/day, respectively, based on Lehman, 1959). Mortality was observed in dams exposed to 1 or 2 mg/kg bw/day, and fertility and litter size were reduced in several groups without demonstrating a clear dose-response relationship. At weaning, no pups survived in the 1 and 2 mg/kg bw/day groups, and the number of survivors was substantially reduced at doses down to 0.125 mg/kg bw/day. At these doses, pups died in convulsions (43%) or starved (57%), the latter occurring because both dams and pups were too hyperesthetic to permit adequate nursing. Neural lesions (e.g., cerebral edema and hydrocephalus) were noted in pups of the 0.004 mg/kg bw/day group (but evidently not in those of higher-dose groups), and hepatic lesions were observed in rats exposed to $\geq$0.016 mg dieldrin/kg bw/day. This study has been considered somewhat limited by the lack of statistical analysis and by the uncertain affect on outcome that may have resulted from the use of a semisynthetic diet (ATSDR, 2000).

Dieldrin (87% pure) was not found to be teratogenic in pregnant CD rats (9 to 25/group) and CD-1 mice (6 to 16/group) that were administered doses in peanut oil of 0, 1.5, 3.0, or 6.0 mg/kg bw/day by gastric intubation on days 7 through 16 of gestation (Chernoff et al., 1975). Fetal toxicity was reported in the mice, as indicated by a significant decrease in the numbers of caudal ossification centers at the 6.0 mg/kg bw/day dose level, and a significant increase in the number of supernumerary ribs in one study group at both the 3.0 and 6.0 mg/kg bw/day doses. In the second study group, the increase was significant only at the 3.0 mg/kg bw/day group. In contrast to these results in mice, exposed rat fetuses evidenced no differences from controls in body weight, mortality, or the occurrence of anomalies. Maternal toxicity in the high-dose rats was indicated by a 4l% mortality and a significant decrease in weight gain; similarly, mice receiving 6.0 mg/kg bw/day showed a significant decrease in maternal weight gain. A significant increase in liver-to-body weight ratio in one group of maternal mice was reported at both the 3.0 and 6.0 mg/kg bw/day doses. Thus, any evidence of dieldrin's potential teratogenicity was accompanied by concomitant maternal toxicity.

CFW Swiss mice (100/sex) fed 5 mg dieldrin/kg diet (purity not reported; approximately equal to 0.75 mg/kg bw/day based on Lehman, 1959) for 30 days prior to mating, and then for 90 days thereafter, experienced no adverse effects on fertility, fecundity, length of gestation period,

size of first litters, or numbers of young produced per day (Good and Ware, 1969). The only adverse reproductive effect observed in this study was a slight decrease (6%) in mean size of all litters combined.

Virgo and Bellward (1975) fed dieldrin (purity not reported) to uniparous female Swiss-Vancouver mice (18 to 19/group) at dietary concentrations of 0, 2.5, 5, 10, 15, 20, or 25 mg/kg (0 and approximately 0.375, 0.75, 1.5, 2.25, 3.0, or 3.75 mg/kg bw/day, respectively, based on Lehman, 1959) for a period extending from 4 weeks prior to their second mating through postpartum day 28. Males were exposed only during the 2-week mating period. Significant pre-parturition mortality was observed in 3.0 and 3.75 mg/kg bw/day females (89 and 56%, respectively), while fertility was decreased in the 1.5 and 2.25 mg/kg bw/day groups. Estrus and gestation period were unaffected by the treatment, but litter size was reduced at 3.75 mg/kg bw/day. Pre-weaning pup mortality was increased from 31% in control animals to 47, 80, or 100% in the 0.375, 0.75, or 1.5 and higher mg/kg bw/day groups, respectively. Hyperactivity was exhibited by dams exposed to 1.5 or more mg/kg bw/day, which was a contributing factor to high pup mortality. Some higher-dose dams violently shook their pups, ultimately killing them, and others neglected their litters. No gross abnormalities were observed in pups from any dose group.

In a subsequent cross-fostering study, Virgo and Bellward (1977) fed primiparous female Swiss-Vancouver mice (number/group not reported in citing references) diets containing dieldrin (purity not reported) at concentrations of 0, 5, 10, or 15 mg/kg (0 and approximately 0.75, 1.5, or 2.25 mg/kg bw/day based on Lehman, 1959) for 4 weeks prior to mating. Nursing was reduced in dams exposed to the two highest doses of dieldrin, although serum progesterone levels, milk production, and the dams' tendencies to build nests or retrieve pups were not adversely affected. When foster dams not exposed to dieldrin nursed pups from the 1.5 mg/kg bw/day group, all died within 4 days; the foster dams' own pups evidenced very low mortality and survived until weaning. Similar results were also reported for pups from the 0.75 mg/kg bw/day group.

Aldrin/Dieldrin

Treon et al. (1954) reported increased mortality during the first 5 days of life in offspring from the first mating of a three-generation reproduction study, in which rats were exposed to 0.275 mg/kg bw/day of either aldrin or dieldrin (purity not reported). Reduced fertility during the
parental generation's first mating was reported at doses of aldrin and dieldrin as low as 1.38 and 0.275 mg/kg bw/day, respectively. Subsequent parental matings did not demonstrate reproductive effects in the aldrin-exposed groups, while fertility effects in the dieldrin-exposed groups failed to exhibit consistent dose-related responses. During matings of the offspring, reductions in fertility were not observed at the 0.275 mg/kg bw/day doses, but could not be adequately assessed at higher doses due to limited numbers of offspring surviving to be mated.

In a three-generation study by Treon and Cleveland (1955), groups of Carworth rats (number/group not reported) were fed aldrin or dieldrin (95% purity) at concentrations of 0, 2.5, 12.5, or 25.0 ppm (doses of 0 and approximately 0.125, 0.625, or 1.25 mg/kg bw/day, respectively, based on Lehman, 1959). Two litters/generation were produced. No reductions in

the numbers of live pups/litter or pup weights were evident in dams fed any dose of either chemical. However, viability of the offspring during lactation was markedly decreased in the 0.625 and 1.25 mg/kg bw/day groups for both chemicals, and slightly-to-moderately decreased in the low-dose groups. Pregnancy rates were reportedly initially reduced at the mid and high doses of aldrin, and at all three doses of dieldrin; this effect, however, gradually disappeared over successive generations.

In a study that examined two litters/generation over six generations, Keplinger et al. (1970) fed Swiss white mice (4M to 14F/group) diets containing aldrin (purity not reported) at concentrations of 0, 3, 5, 10, or 25 mg/kg (0 and approximately 0.45, 0.75, 1.5, or 3.75 mg/kg bw/day, respectively, according to Lehman, 1959). The 3.75 mg/kg bw/day group was discontinued due to excessive litter mortality in the few dams reaching gestation. Otherwise, the most pronounced effect reported was a reduction in suckling pup survival at 1.5 mg/kg bw/day, and to a lesser degree at 0.75 mg/kg bw/day. Similarly, groups of mice were fed diets containing dieldrin at concentrations of 0, 3, 10, or 25 mg/kg (0 and approximately 0.45, 1.5, or 3.75 mg/kg bw/day). As with aldrin, the high dieldrin dose was soon discontinued for reasons of excessive litter toxicity, and the 1.5 mg/kg bw/day dose was discontinued after the first generation because of low pup survival. At the remaining 0.45 mg/kg bw/day dose, no effects on fertility, viability, or gestation were noted. Although a decrease in suckling pup survival was observed in the F_{2b} litters, a similar decrease also occurred in one of the six control groups.

Ottolenghi et al. (1974) exposed pregnant CD-1 mice (10/group) and Syrian golden hamsters (41 to 43/group) to high (one half the oral LD_{50}), single oral doses of either aldrin or dieldrin (>99% purity) in corn oil. Negative control groups consisted of untreated and corn oil-dosed animals. Mice were exposed on gestation day 9 to aldrin at 25 mg/kg bw or dieldrin at 15 mg/kg bw; hamsters on either gestation day 7, 8, or 9 to aldrin at 50 mg/kg bw, or dieldrin at 30 mg/kg bw. In mice, the aldrin treatment did not affect fetal survival or weight, but significantly increased the incidence of abnormalities such as webbed feet, cleft palate, and open eyes (33% of the live fetuses had malformations). In hamsters, aldrin treatment did cause a reduction in fetal survival and weight, as well as a significant increase in the incidence of the same types of abnormalities that were observed in mice; these effects were less pronounced when treatment was on gestation day 9, rather than on days 7 or 8. In mice, dieldrin produced the same types of abnormalities (in 17% of the live fetuses) as seen with aldrin and the effects in hamsters were also similar to those described for aldrin with respect to fetal toxicity, malformation types, and degree of severity according to day of treatment.

No apparent effects on the fertility or pregnancy rates were evident in groups of mongrel dogs (2/group, at least 1/each sex) receiving 0, 0.2, 0.6, or 2.0 mg/kg bw/day of either aldrin or dieldrin (purity 99%) in medicated meatballs for 1 year (Kitselman, 1953). However, the majority of apparently healthy pups that were delivered from dams in all dose groups of aldrin, and from the mid- and high-dose groups of dieldrin, died within 3 days postpartum and evidenced degenerative liver and renal tubule changes upon histopathological examination. It should be noted that this study had several limitations with respect to size and design parameters.

In dominant lethal studies, Epstein et al. (1972) and Dean et al. (1975) reported no unequivocal adverse effects on reproduction subsequent to acute exposure of male mice to aldrin at doses up to 1 mg/kg bw/day for a period of 5 days, or to single oral doses of dieldrin ranging from 12.5 to 50 mg/kg bw.

Inhalation Exposure

No studies were obtained that investigated the developmental or reproductive effects of aldrin or dieldrin in animals following inhalation exposure.

Dermal Exposure

No studies were obtained that investigated the developmental or reproductive effects of aldrin or dieldrin in animals following dermal exposure.

Other Routes of Exposure

Castro et al. (1992) reported the effects of prenatal exposure to aldrin on the physical and behavioral developments of rats (1 to 21 day-old and 90 day-old groups). Pregnant female rats (10 to 20/group) were subcutaneously injected with either aldrin (1.0 mg/kg bw) or its vehicle (0.9% sodium chloride plus Tween 80), from day 1 of pregnancy until delivery. Pups from the aldrin group evidenced a decreased median effective time (TE_{50}) for incisor teeth eruption, and an increased TE_{50} for testes descent; other parameters indicative of physical development, such as pinna detachment, development of fur and ears, and eye opening, were not altered. No changes in body weight were observed between control and aldrin treated rats on the day of birth, at weaning, or at 90 days. Prenatal exposure to aldrin produced no changes in aldrin or dieldrin levels in serum, or in cellular and structural organization of cerebral cortex neurons, when tested at 90 days.

Johns et al. (1998) reported no significant differences in birth weight, sex ratio, day of eye opening, or weight gain between the pups of control and dieldrin-treated female rats, which had been intraperitoneally injected daily from E12 to E16 (embryonic days 12 to 16) with 0, 5, or 10 mg/kg bw of dieldrin.

7.2.6 Chronic Toxicity

Oral Exposure

Aldrin

Treon and Cleveland (1955) administered aldrin in the diet to 40 Carworth rats/sex at concentrations of 2.5, 12.5, or 25 ppm (approximate doses of 0.125, 0.65, or 1.25 mg/kg bw/day, respectively, based on Lehman, 1959) for a period of 2 years. Forty animals/sex served as controls. Mortality of the treated rats was greater than that of controls, with 50% surviving in the 2.5 and 12.5 ppm groups and 40% surviving in the 25 ppm group at the end of the experiment.

Fitzhugh et al. (1964) fed groups (12/sex/group) of Osborne-Mendel rats aldrin (purity 99%) in the diet at concentrations of 0.5, 2, 10, 50, 100, or 150 ppm (approximated doses of 0.025, 0.1, 0.5, 2.5, 5.0, and 7.5 mg/kg bw/day, respectively, based on Lehman, 1959) for 2 years. A dose-related increase in mortality was observed at dietary levels of 50 ppm or greater. In addition, significant ($p \leq 0.05$) dose-related increases in relative liver weights were observed. Histopathological changes observed in the livers of aldrin-treated rats were referred to as primarily the characteristic "chlorinated insecticide" lesions that occur only in rodents. These lesions consist of enlarged centrilobular hepatic cells, with increased cytoplasmic oxyphilia, and peripheral migration of basophilic granules. The incidence and severity of these nonneoplastic histologic changes increased with increasing dietary aldrin level. In rats ingesting amounts of aldrin at 50 ppm or higher, distended and hemorrhagic urinary bladders, enlarged livers, and increased incidences of nephritis were reported. The apparent LOAEL for this study was 0.5 ppm (0.025 mg/kg bw/day), while a NOAEL was not established.

Deichmann et al. (1970) fed groups of Osborne-Mendel rats (50/sex/dose) aldrin (technical grade, 95% pure) for 31 months at concentrations of either 20, 30, or 50 ppm (1, 1.5, or 2.5 mg/kg bw/day, respectively, based on Lehman, 1959). Groups of 100 rats/sex served as controls. Survival and body weight gains were comparable between the treated and the control groups, but treated animals exhibited tremors and clonic convulsions. Liver-to-body weight ratios were increased in males fed 30 or 50 ppm aldrin. Moderate increases (not dose-related) in the incidences of hepatic centrilobular cloudy swelling and necrosis were observed in all aldrin-treated male and female rats, but not in the controls. A LOAEL of 20 ppm (1 mg/kg bw/day) was established by this study, but a NOAEL was not determined.

Groups of Osborne-Mendel rats (50/sex/group) were exposed to 30 or 60 ppm of aldrin (95% purity) in the diet (approximate doses of 1.5 or 3.0 mg/kg bw/day, based on Lehman, 1959) for 74/80 weeks (M/F), followed by 32 to 38 weeks of observation (NCI, 1978). Pooled controls (58M/60F from similar bioassays, plus 10M/10F concurrent controls) were used for statistical evaluations. While no significant effects of aldrin exposure on mortality were observed, mean body weight gains during the second year were lower than control values. Signs typical of organochlorine intoxication (hyperexcitability, tremors, convulsions), with frequency and severity increasing, especially during the second year. Routine gross and/or microscopic evaluation revealed no adverse, non-neoplastic respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, or ocular effects resulting from exposure to aldrin.

Aldrin (technical grade, 95% pure) was administered in the diet for 80 weeks (followed by 10 to 13 weeks of observation) at concentrations of 4 or 8 ppm (approximate doses of 0.6 or 1.2 mg/kg bw/day, respectively, based on Lehman, 1959) to groups of 50 male mice, and at concentrations of 3 or 6 ppm (approximate doses of 0.45 or 0.90 mg/kg bw/day, respectively, based on Lehman, 1959) to groups of 50 female mice (NCI, 1978). Pooled controls (92M/79F from similar bioassays, plus 20M/10F concurrent controls) were used for statistical evaluations. In a trend test, a significant ($p = 0.037$), dose-dependent increase in mortality was observed in females; a similar effect was not observed in males. Hyperexcitability was observed in all exposed groups, with frequency and severity increasing during the second year. Mean body weight was unaffected during the first year, but somewhat lower than control values during the

second year. Routine gross and/or microscopic evaluation revealed no adverse, non-neoplastic respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, or ocular effects resulting from exposure to aldrin. A NOAEL was not established because of toxicity at 3 ppm (0.45 mg/kg bw/day), the lowest dose tested.

Kitselman and Borgmann (1952) fed groups of 7 mongrel dogs of both sexes (number/sex not specified) either 0.2, 0.6, or 2 mg/kg bw/day of aldrin in medicated meatballs, for up to 228 days. The test material was reported to have been 99% pure. Dogs that were administered the 2 mg/kg bw/day dose exhibited marked body weight loss, and they all died between days 60 and 90. No treatment-related effects were observed in dogs receiving the 0.2 mg/kg bw/day dose for 190 days, or in those administered the 0.6 mg/kg bw/day dose for 228 days. Based on body weight loss, 0.6 mg/kg bw/day and 2 mg/kg bw/day were considered to be the NOAEL and LOAEL, respectively, for this study.

In a long-term feeding study by Treon and Cleveland (1955), beagles (2/sex/dose) fed diets containing aldrin (purity 95%) at concentrations of 1 or 3 ppm (approximate doses of 0.043 to 0.091 or 0.12 to 0.25 mg/kg bw/day, respectively, as reported by the authors) for 15.6 months, gained weight at rates similar to control dogs. However, at 3 ppm, significant ($p < 0.05$) increases in absolute and relative liver weights were noted. Histopathologic changes, such as fatty degeneration of the liver and vacuolation of renal tubular cells, were also observed in both sexes at the 3 ppm level. At the 1 ppm level, females exhibited vacuolation of the distal renal tubules. The LOAEL for this study was 1 ppm (0.043 to 0.091 mg/kg bw/day), while a NOAEL was not established.

Fitzhugh et al. (1964) administered 0.2, 0.5, 1, 2, or 5 mg/kg bw/day aldrin (purity 99%) to 12 mongrel dogs (sexes combined), 6 days/week, for periods of up to 25 months. Each group consisted of one dog/sex except for the 0.5 mg/kg bw/day group, which had one male and three female dogs. All dogs receiving 1, 2, or 5 mg/kg bw/day died within 49 weeks; the first death occurred on day 22 in a female administered 5 mg/kg bw/day. Prior to death, the animals exhibited body weight loss, dehydration, and convulsions. Slight to moderate fatty degeneration was noted in hepatic and renal tubular cells and reduced numbers of mature erythroid cells were found in the bone marrow. In animals receiving 0.5 mg/kg bw/day, clinical signs of toxicity were limited to convulsions in one male dog during the 24th month. Dogs in the 0.2 mg/kg bw/day group exhibited no adverse effects. The NOAEL in this study thus appears to be 0.2 mg/kg bw/day, based on the absence of clinical signs of toxicity, body weight loss, and histopathological changes. However, the adequacy of this study for establishing a reliable NOAEL is limited by the small number of dogs used.

Dieldrin

Groups of Osborne-Mendel rats, 12/sex/dose, were fed 0, 0.5, 2, 10, 50, 100, or 150 ppm dieldrin (recrystallized, 100% active ingredient) in their diet for 2 years (Fitzhugh et al., 1964). These concentrations correspond to doses of 0 and approximately 0.025, 0.1, 0.5, 2.5, 5.0, or 7.5 mg/kg bw/day, respectively, based on Lehman (1959). Survival was markedly decreased at levels of 50 ppm and above. Liver-to-body weight ratios were significantly increased at all treatment levels, with females showing the effect beginning at 0.5 ppm, and males at $\geq$10 ppm.

Microscopic lesions were described as being characteristic of chlorinated hydrocarbon exposure. These changes were minimal at the 0.5 ppm level. Male rats, at the two highest dose levels (100 and 150 ppm), developed hemorrhagic and/or distended urinary bladders, usually associated with considerable nephritis. A LOAEL of 0.025 mg/kg bw/day, the lowest dose tested, was identified in this study.

Groups of Carworth Farm "E" strain rats (25/sex/dose level) were fed dieldrin (>99% purity) in the diet at concentrations of 0, 0.1, 1.0, or 10.0 ppm for 2 years. These doses correspond to doses of 0 and approximately 0.005, 0.05, or 0.5 mg/kg bw/day, respectively, based on Lehman (1959). At 7 months, the 1 ppm intake level was equivalent to approximately 0.05 and 0.06 mg/kg bw/day for males and females, respectively. No effects on mortality, body weight, food intake, hematology or blood, and urine chemistries were reported. At the 10 ppm level, all animals became irritable after 8 to 13 weeks of treatment and developed tremors and occasional convulsions. Liver weights and liver-to-body weight ratios were significantly increased in females receiving both 1.0 and 10 ppm. Pathological findings, described as organochlorine-insecticide changes of the liver, were found in one male and six females at the 10 ppm level. No evidence of tumorigenesis was found (Walker et.al., 1969). Based on the significantly increased liver weight and relative liver weight reported for female rats, this study establishes a NOAEL and a LOAEL of 0.005 and 0.05 mg/kg bw/day, respectively.

Walker et al. (1972) administered dieldrin (>99% pure) to groups of CF1 mice (30/sex/dose) in the diet for 128 weeks at concentrations of 1.25, 2.5, 5, 10, or 20 ppm (approximate doses of 0.19, 0.38, 0.75, 1.5, or 3 mg/kg bw/day, respectively, based on Lehman, 1959). At the 20 ppm dose level, approximately 25% of the males and nearly 50% of the females died during the first 3 months of the experiment. Palpable intra-abdominal masses were detected after 40, 75, or 100 weeks in the 10, 5, and 2.5 ppm-treated groups, respectively. At 1.25 ppm, liver enlargement was not palpable and morbidity was similar to that of controls. A NOAEL cannot confidently be established from this study because clinical chemistry parameters were not determined.

Groups of Osborne-Mendel rats (50/sex/group) were exposed to 29 or 65 ppm of dieldrin (95% purity) in the diet (approximate doses of 1.45 or 3.25 mg/kg bw/day, respectively, based on Lehman, 1959) for 80 weeks followed by 30 to 31 weeks of observation for the low dose, or for 59 weeks followed by 51 to 52 weeks of observation for the high dose (NCI, 1978). Pooled controls (58M/60F from similar bioassays, plus 10M/10F concurrent controls) were used for statistical evaluations. While no statistically significant end-result effects of dieldrin exposure on mortality were observed, it was perhaps accelerated in treated animals, and mean body weight gains during the second year were lower than control values. Signs typical of organochlorine intoxication (hyperexcitability, tremors, convulsions) were evident, with frequency and severity increasing, especially during the second year and in high-dose animals. Routine gross and/or microscopic evaluation revealed no adverse, non-neoplastic respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, or ocular effects resulting from exposure to dieldrin.

In a related study, groups of Fischer 344 rats (24/sex/group) were exposed to 2, 10, or 50 ppm of dieldrin ("purified technical grade") in the diet (approximate doses of 0.1, 0.5, or

2.5 mg/kg bw/day, respectively, based on Lehman, 1959) for 104 to 105 weeks (NCI, 1978). Body weight and mortality were not significantly affected by dieldrin exposure, but signs typical of organochlorine intoxication (hyperexcitability, tremors, convulsions) were noted in both sexes at the high dose after 80 weeks. As in the previously discussed study, no other significant adverse systemic effects were observed.

Dieldrin (95% pure) was administered in the diet for 80 weeks (followed by 10 to 13 weeks of observation) at concentrations of 2.5 or 5 ppm (approximate doses of 0.375 or 0.75 mg/kg bw/day, respectively, based on Lehman, 1959) to groups of $B6C3F_1$ mice (50/sex/group) (NCI, 1978). Pooled controls (92M/79F from similar bioassays, plus 20M/10F concurrent controls) were used for statistical evaluations. Treatment had no appreciable effect on survival, while weight gains were non-significantly lower than control values during the second year. Hyperexcitability, hyperactivity, fighting, and tremors were found to be treatment-related, and were first observed in males, then later in females. Routine gross and/or microscopic evaluation revealed no adverse, non-neoplastic respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, or ocular effects resulting from exposure to aldrin.

Mongrel dogs, 1/sex/dose (2/sex at 0.5 mg/kg bw/day), that were fed dieldrin (recrystallized, 100% active ingredient) at dose levels of 0.2 to 10 mg/kg bw/day, 6 days/week for up to 25 months, showed various toxic effects, including weight loss and convulsions at dosages of 0.5 mg/kg bw/day or more. Survival was inversely proportional to dose level. No toxic effects, gross or microscopic, were seen at a dose level of 0.2 mg/kg bw/day (Fitzhugh et. al., 1964). A NOAEL of 0.2 mg/kg bw/day appears to have been established for this study, but its reliability is substantially limited because of the low number of animals studied.

Groups of beagle dogs (5/sex/dose) were treated daily by capsule with dieldrin (>99% purity) at 0.0, 0.005, or 0.05 mg/kg in olive oil for 2 years. No treatment-related effects were seen in general health, behavior, body weight, or urine chemistry. A significant increase in plasma alkaline phosphatase activity in both sexes and a significant decrease in serum protein concentration in males receiving the high dose were not associated with any clinical or pathological change. Liver weight and liver-to-body weight ratios were significantly increased in females receiving the high dose, 0.05 mg/kg bw/day, but no gross or microscopic lesions were found. There was no evidence of tumorigenic activity (Walker et al., 1969).

Inhalation Exposure

No studies were obtained that examined the chronic effects of aldrin or dieldrin in animals after chronic inhalation exposure.

Dermal Exposure

There is one available study, which was conducted in rabbits, that examined the chronic effects of dermal exposure to dieldrin. Witherup et al. (1961) reported no effects on lung weight or pathology, heart weight or pathology, liver weight, serum proteins, thymol turbidity, serum alkaline phosphatase, or pathology in a chronic study in which rabbits were wrapped with

material containing up to 0.04% dieldrin for up to 52 weeks. However, this study is limited in that some animals were treated with a variety of drugs to control "extraneous" diseases.

7.2.7 Carcinogenicity

Oral Exposure

Aldrin

In a Food and Drug Administration (FDA) long-term carcinogenesis bioassay, Davis and Fitzhugh (1962) exposed a group of 215 C3HeB/Fe mice (numbers/sex were not provided, but the group was reportedly divided approximately equally by sex) for up to 2 years to a diet containing aldrin (purity not specified) at 10 ppm, constituting a dose of approximately 1.5 mg/kg bw/day using the conversion factor of Lehman (1959). The average long-term survival rate of the treated group was approximately 2 months less than that of the controls, although these rates may have been affected by intercurrent diseases, pneumonia and intestinal parasitism. Results, reported for the combined sexes, indicated a significant ($p < 0.001$) increase in the number of treated mice with hepatic cell adenomas (35/215 or 23%) when compared to that for the control group (9/217 or 7%). These hepatic cell adenomas were described as "expanding nodules of hepatic parenchymal tissue, usually with altered lobular architecture, and morphologically ranging from very benign lesions to borderline carcinomas." As reported by Epstein (1975a), an independent reevaluation of these lesions by other pathologists concluded that most were liver carcinomas. Despite the short-comings of poor survival rate, lack of detailed pathology, loss of a large number of animals to the study, and failure to report the results separately by sex, the study provided evidence for aldrin's hepatocarcinogenicity to this strain of mouse.

In an FDA follow-up to the previous study, aldrin of unspecified purity was fed to groups of C3H mice (100/sex) at concentrations of 0 or 10 ppm (approximately 1.5 mg/kg bw/day using the conversion factor of Lehman, 1959) for up to 2 years (Davis, 1965). The incidences (for both sexes combined) of hepatic hyperplasia and benign hepatomas in the treated group were reported to be approximately double those of the controls, whereas the incidence of hepatic carcinomas was judged to be about the same. This study suffered some of the deficiencies of its predecessor, and again an independent review concluded that most of the hepatomas were actually hepatocellular carcinomas (Epstein, 1975a). This reevaluation provided incidences of hepatocellular carcinomas in the treated vs. control group of 82% vs. 30% for males, and 85% vs. 4% for females, both significant increases at $p < 0.05$.

Song and Harville (1964) fed a total of 55 C3H and CBA mice 15 ppm of aldrin (unspecified purity) for an unspecified amount of time; 10 mice served as controls. In a companion study, mice were similarly fed dieldrin. Seven mice treated with aldrin or dieldrin were reported to have developed liver tumors by 330 to 375 days; however, as no further details were described, this report provides little useful information.

In a somewhat more recent carcinogenicity bioassay, technical grade aldrin (95% pure) was administered in the diet for 80 weeks to $B6C3F_1$ mice (50/sex) at time-weighted averages of

4 or 8 ppm for males, and at 3 or 6 ppm for females (NCI, 1978). Based on Lehman (1959), these concentrations approximate doses of 0.6 and 1.2 mg/kg bw/day (males), and 0.45 and 0.90 mg/kg bw/day (females). The animals were observed for an additional 10 to 13 weeks. A significant ($p \leq 0.001$) dose-related increase in the incidence of hepatocellular carcinomas was observed in male, but not female, mice when compared to matched or pooled controls. Tumor incidences were 3/20, 17/92, 16/49, and 25/45 for the matched control, pooled control, low-dose male, and high-dose male groups, respectively.

When compared with control animals, NCI (1978) also reported increased incidences for combined follicular cell adenoma and carcinoma of the thyroid in both male and female Osborne-Mendel rats. Treated animals (50/sex) were fed technical grade aldrin (95% pure) at concentrations of 30 or 60 ppm (1.5 and 3 mg/kg bw/day, respectively, based on Lehman, 1959) for 74 or 80 weeks (males or females, respectively), then observed for an additional 37 to 38 or 32 to 33 weeks (males or females, respectively). The combined incidences from the pooled control, low-dose, and high-dose groups were respectively 4/48, 14/38, and 8/38 for males, and 3/52, 10/39, and 7/46 for females. Differences were significant ($p = 0.001$) for the low-dose groups, but not for the high-dose groups. A significant ($p = 0.001$) increase in the incidence of cortical adenomas of the adrenal gland were also observed in the low-dose females, but this was not considered to be compound related by the authors. Aldrin produced no significant effect on the mortality of rats of either sex. Overall, the authors concluded that none of the observed tumors were associated with treatment, a view that has been echoed elsewhere (USEPA, 1993a). However, other evaluations of the report have concluded that the occurrence of the thyroid and adrenal cortex tumors should be considered suggestive or equivocal evidence of aldrin's potential carcinogenicity in the rat (Griesemer and Cueto, 1980; Haseman et al., 1987; USEPA, 1987).

A number of other carcinogenicity bioassays utilizing Carworth rats (Treon and Cleveland, 1955), Holtzman rats (Song and Harville, 1964), or Osborne-Mendel rats (Deichmann et al., 1967, 1970; Deichmann, 1974) failed to find evidence of aldrin-induced tumors, but all suffered from substantial experimental and/or reporting deficiencies that resulted in their being judged inadequate as tests of aldrin's possible carcinogenicity (USEPA, 1987, 1993a).

Dieldrin

In an FDA long-term carcinogenicity bioassay, Davis and Fitzhugh (1962) exposed groups of approximately 218 C3HeB/Fe mice (numbers/sex not specified, other than that they were approximately equal) for up to 2 years to dieldrin of unspecified purity at concentrations in the diet of either 0 or 10 ppm (the latter corresponding to a dose of approximately 1.5 mg/kg bw/day, Lehman, 1959). Although compromised by poor survival rates, loss of a large percentage of the animals to the study and failure to treat the data separately by sex, the study did demonstrate a significantly increased incidence of hepatomas in the treated group when compared with the controls (36/148 or 24% vs. 9/134 or 7%). In a subsequent follow-up study by FDA, groups of C3H mice (100/sex) were fed either 0 or 10 ppm (0 or approximately 1.5 mg/kg bw/day) of dieldrin (purity not specified) for up to 2 years (Davis, 1965). This study suffered much the same limitations as its predecessor, but again demonstrated a significant increase in the incidence of benign hepatomas (and in the combined incidence of benign

hepatomas plus hepatocellular carcinomas) in the dieldrin group relative to controls. As for the companion aldrin studies discussed previously, a subsequent pathology reevaluation of both of these studies concluded that most of the hepatomas were in fact malignant hepatocellular carcinomas (Epstein, 1975a,b).

As noted previously, Song and Harville (1964) fed a total of 55 C3H and CBA mice 15 ppm of dieldrin (unspecified purity) for an unspecified amount of time; 10 mice served as controls. In a companion study, mice were similarly fed aldrin. Seven mice treated with aldrin or dieldrin were reported to have developed liver tumors by 330 to 375 days; however, as no further details were described, this report provides little useful information.

Epstein (1975a) reviewed and provided reevaluations of an unpublished study by MacDonald et al. (1972), in which "technical grade" dieldrin was fed for an uncertain period of time to groups of Swiss-Webster mice (100/sex/group) at dietary concentrations of either 0, 3, or 10 ppm (corresponding to approximate doses of 0, 0.45, or 1.5 mg/kg bw/day, respectively, Lehman, 1959). The authors concluded that dieldrin was not carcinogenic, but that it induced various nonneoplastic lesions of the liver, including a dose-dependent increase in the incidence of hepatic nodules (0, 2.5, and 48% at 0, 3, and 10 ppm, respectively). However, a reevaluation of some of the histopathological data by independent pathologists (as well as by one of the original authors) demonstrated that more than half of the reexamined livers from high-dose mice contained hepatocellular carcinoma, thus confirming dieldrin's carcinogenicity to mice.

Walker et al. (1972) conducted a number of studies in which they exposed groups of CF_1 mice (29 to 200/sex/dose; 29 to 300 controls/sex/study) for 2 to 132 weeks to dietary concentrations of dieldrin (>99% pure) ranging from 0.1 to 20 ppm (approximating doses of 0.015 to 3.0 mg/kg bw/day, Lehman, 1959). Significant dose-related increases in the incidences of benign and total liver tumors were observed beginning at concentrations as low as 2.5 ppm, while the incidence of malignant liver tumors was significantly increased at concentrations of 5, 10, and 20 ppm. Liver tumors were also demonstrated to occur much earlier in treated than in control mice. In one of the studies, dieldrin also induced significant increases ($p < 0.05$) in the incidences of lung, lymphoid, and "other" tumors in female mice.

In another study using CF_1 mice (Thorpe and Walker, 1973), groups (30/sex; 45 controls/sex) were fed dieldrin (>99% pure) in the diet for up to 110 weeks at concentrations of 0 or 10 ppm (an approximate dose of 1.5 mg/kg bw/day, Lehman, 1959). Again, a statistically significant ($p < 0.01$) increase in malignant liver tumors (many of which metastasized to the lung) and a shortened latency period were induced by dieldrin.

In an NCI (1978) study, $B6C3F_1$ mice (50/sex/dose) were fed technical grade dieldrin (>96% purity) for 80 weeks (with an additional 10 to 13 weeks of observation) at time-weighted average concentrations of 2.5 or 5 ppm (equivalent to 0.375 or 0.75 mg/kg bw/day, respectively, based on Lehman, 1959). Matched (20 male, 10 female) and pooled (92 male, 91 female) controls received no dieldrin (or other test chemical) in their feed. This assay was considered an acceptable test for carcinogenicity based on achieving a maximum tolerated dose without excess toxicity or mortality (USEPA, 1987). When compared with pooled controls, male mice

evidenced a significant ($p = 0.02$) dose-related increase in the incidence of hepatocellular carcinomas, as well as a significant ($p = 0.025$) increase in such tumors at the high dose.

In a study by Tennekes et al. (1981, 1979), groups of 19 to 82 male CF_1 mice were fed dieldrin (>99% pure) at concentrations of 0 or 10 ppm (an approximate dose of 1.5 mg/kg bw/day, Lehman, 1959) for up to 110 weeks. Two types of diet and two types of bedding were examined as part of the study. Dieldrin treatment was reported to have shortened the liver tumor latency period, increased the incidence of combined liver tumors from 10 to 81%, and significantly ($p < 0.01$) increased the incidences of hepatocellular carcinoma (from 1 to 39%) and lung metastases (from 0 to 14%).

In a large study intended to investigate dieldrin's enhancing affect on liver tumor formation (Tennekes et al., 1982), a total of 1,800 CF_1 mice (17 to 297/sex/dose) were fed dieldrin (>99.9% purity) over the course of their lifetimes at concentrations of 0, 0.1, 1, 2.5, 5, 10, or 20 ppm (doses of 0 and approximately 0.015, 0.15, 0.375, 0.75, 1.5, or 3.0 mg/kg bw/day, respectively, based on Lehman, 1959). In both sexes, treatment appeared to result in dose-related increases in the incidences of both combined (benign plus malignant) and malignant liver tumors up to 10 ppm; somewhat lower incidences at 20 ppm were speculated to result from significant toxicity/lethality at that concentration. Dieldrin also induced a dose-dependent reduction in tumor latency periods; the lowest doses associated with a significant ($p < 0.05$) reduction in median time-to-tumor formation were 0.1 and 1.0 ppm for females and males, respectively. The lack of a linear relationship between daily exposure level and median time-to-tumor formation or median total dose led the authors to speculate that dieldrin may affect tumor promotion rather than initiation.

Meierhenry et al. (1983) exposed groups of male C3H/He, $B6C3F_1$, and $C_{57}BL/6J$ mice (50 to 71/strain; 50 to 76 controls/strain) for 85 weeks (followed by 47 weeks of observation) to dieldrin (>99% purity) at a dietary concentration of 10 ppm (an approximate dose of 1.5 mg/kg bw/day, based on Lehman, 1959). Dieldrin induced significant ($p < 0.05$) increases in the incidences of hepatocellular carcinomas relative to controls in all three strains of mice.

Osborne-Mendel rats treated with dieldrin (>96% purity) at time-weighted average concentrations of 29 or 65 ppm in the diet (approximate doses of 1.45 or 3.25 mg/kg bw/day, respectively, based on Lehman, 1959) for 80 weeks, and then observed for an additional 30 to 31 weeks, did not show any treatment-related increase in tumors (NCI, 1978). A second NCI (1978) study that exposed groups (24/sex) of Fischer rats to dieldrin (technical grade, purified) for 104 to 105 weeks at dietary concentrations of 0, 2, 10, or 50 ppm (doses of 0 and approximately 0.1, 0.5, or 2.5 mg/kg bw/day, respectively, based on Lehman, 1959) produced similarly negative tumorigenic results. Both of these bioassays were judged to be adequate tests for carcinogenicity (USEPA, 1987).

As evaluated by USEPA (1987), one other minimally acceptable study (Deichmann et al., 1970) and four inadequate studies (Treon and Cleveland, 1955; Fitzhugh et al., 1964; Song and Harville, 1964; Walker et al., 1969, which was reevaluated by Stevenson et al., 1976) collectively exposed several strains of rats (Carworth, Osborne-Mendel, or Holtzman) to dietary concentrations of dieldrin (varying purities) ranging from 0.1 to 285 ppm (approximate doses of

0.005 to 14.25 mg/kg bw/day, respectively, based on Lehman, 1959) for periods of 1 to 2 years. Although all of these studies failed to demonstrate any evidence for dieldrin's potential carcinogenicity, all suffered from one or more serious deficiencies (e.g., too few animals, excessive mortality, inadequate duration, data missing or inadequately reported, etc.). Additionally, several dieldrin bioassays involving dogs or monkeys were evaluated by the USEPA (1987) as being inadequate or unacceptable tests of potential carcinogenicity due to serious limitations.

Inhalation Exposure

No studies were obtained that examined the carcinogenicity of either aldrin or dieldrin in animals after inhalation exposure.

Dermal Exposure

No studies were obtained that examined the carcinogenicity of either aldrin or dieldrin in animals after dermal exposure.

7.3 Other Key Data

7.3.1 Mutagenicity/Genotoxicity Effects

Aldrin

In bacterial reverse mutation assays that were conducted by several investigators, aldrin was not mutagenic to *Salmonella typhimurium* (Simmon and Kauhanen, 1978; Cotruvo et al. 1977; Simmon et al., 1977; Probst et al., 1981; Nishimura et al., 1982) or *E. coli* (Ashwood-Smith et al., 1972; Probst et al., 1981), nor was it found to induce plasmid DNA breakage in *E. coli*, although it was tested only in the absence of S9 metabolic activation (Griffin and Hill, 1978).

Simmon and Kauhanen (1978) reported that aldrin, at concentrations of 10 to 5,000 µg/plate, did not cause gene conversion in *Saccharomyces cerevisiae*, either in the presence or absence of exogenous metabolic activation provided by Aroclor-induced rat liver microsomes. It has, however, been reported to induce reverse mutation in the same organism (Guerzoni et al., 1976).

Several doses of aldrin were tested in a mouse dominant lethal assay conducted by Epstein et al. (1972), and although some reductions in the level of implantation were demonstrated, they were judged to be statistically nonsignificant. Negative results have also been reported for its induction of sex-linked recessive lethal mutation in *Drosophila melanogaster* (Benes and Sram, 1969).

Georgian (1975) reported that aldrin induced chromosome aberrations in human lymphocytes *in vitro* and in rat and mouse bone marrow cells *in vivo*. However, the evidence for an *in vivo* clastogenic response is somewhat equivocal because the observed chromosomal

aberration frequencies increased only at cytotoxic levels. Additionally, chromosome and chromatid gaps, which historically have been considered unreliable indicators of significant damage to genetic material, were included in the aberration totals. Therefore, the extent of the more meaningful, non-gap, chromosomal damage cannot be ascertained. Negative results have also been reported for the *in vivo* induction of micronuclei in mice at an aldrin dose of 13 mg/kg bw (Rani et al., 1980).

Dulout et al. (1985) studied the incidences of sister chromatid exchanges (SCEs) and chromosome aberrations in a population of floriculturists who were exposed to several pesticides, including aldrin. For those floriculturists who exhibited clinical symptoms of pesticide exposure, there were statistically significant increases in SCEs when compared with asymptomatic floriculturists, and in exchange-type chromosome aberrations when compared with nonfloriculturists. However, interpretation of the role of aldrin in these findings is confounded by the concomitant exposure to other organophosphorous, carbamate, and organochlorine pesticides. Edwards and Priestly (1994) reported that occupational exposure to aldrin did not alter SCE frequencies in lymphocytes derived from workers (n = 33) recruited from two south Australian suburban pesticide application companies.

Unscheduled DNA synthesis (UDS) was not induced when primary rat hepatocytes were exposed to aldrin at concentrations ranging from 0.5 to 1,000 nmol/mL for 5 to 20 hours (Probst et al., 1981), and most likely not when human lymphocytes were exposed to concentrations of up to 100 µg/mL (Rocchi et al., 1980). However, Ahmed et al. (1977a) reported the induction of UDS in transformed human cells at aldrin concentrations as low as 0.4 µg/mL, and Sina et al. (1983) observed DNA strand breaks in the alkaline elution/rat hepatocyte assay at an aldrin concentration of 110 µg/mL.

Dieldrin

Dieldrin was not mutagenic in the *Salmonella*/microsome test (Ames test), either with or without S-9 mix as a source of exogenous metabolic activation (McCann et al., 1975). Similarly, nine other studies have collectively reported negative responses for dieldrin in at least eight different Ames tester strains of *S. typhimurium*, both with and without exogenous metabolic activation (Anderson and Styles, 1978; Bidwell et al., 1975; Glatt et al., 1983; Haworth et al., 1983; Marshall et al., 1976; Nishimura et al., 1982; Probst et al., 1981; Shirasu et al., 1976; Wade et al., 1979). Negative responses have also been reported for dieldrin in *E. coli* using both a reverse mutation assay (Ashwood-Smith et al., 1972; Probst et al., 1981) and two forward mutation assay systems (Gal Rz2 and streptomycin resistance) (Fahrig, 1974). Additionally, Dean et al. (1975) reported negative findings in a host-mediated assay (microbial cells in animal hosts). However, in one contrary study, Majumdar et al. (1977) reported that dieldrin was mutagenic for *S. typhimurium*, both with and without exogenous metabolic activation.

Dieldrin produced negative responses in assays for forward mutation and aneuploidy induction in *Aspergillus nidulans* (although it was not tested with exogenous metabolic activation) (Crebelli et al., 1986), gene conversion in *S. cerevisiae,* and reverse-mutation in *S. marcesans* (Fahrig, 1974), *in vitro* DNA strand breaks in *E. coli* plasmids or in animal cell alkaline elution assays (Swenberg et al., 1976; Swenberg, 1981), UDS in rat primary hepatocytes

(Probst et al., 1981), and most probably for UDS in human lymphocytes (Rocchi et al., 1980). Dieldrin also failed to induce cell transformation in Syrian hamster embryo cells (Mikalsen and Sanner, 1993). However, it was reported to induce forward mutation in Chinese hamster V79 cells (Ahmed et al., 1977b), as well as UDS in transformed human cells (Ahmed et al., 1977a).

In a dominant lethal study that orally exposed male CF_1 mice to dieldrin, mean implantation levels (versus controls) were significantly reduced in females mated with males receiving 12.5 mg/kg bw. However, in a subsequent experiment, mean implantations were not reduced, or even significantly increased, in females mated with males receiving 25 or 50 mg/kg bw (Dean et al., 1975). In another mouse dominant lethal assay, several doses of dieldrin up to 26 mg/kg bw were found to be without mutagenic effect (Epstein et al., 1972). Dieldrin also reportedly did not induce sex-linked recessive mutation in *D. melanogaster* (Benes and Sram, 1969).

Studies have demonstrated that dieldrin can cause chromosomal aberrations in mouse bone marrow cells following *in vivo* exposure (Markaryan, 1966; Dean et al., 1975; Majumdar et al., 1976) in human lymphoblastoid cells (Trepanier et al., 1977) and human WI-38 embryonic lung cells (Majumdar et al., 1976) after *in vitro* exposure. In the latter case, the cytogenetic effects were accompanied by significant cytotoxicity, as there was evidence of cell degeneration.

Dean et al. (1975) failed to find evidence of elevated frequencies of chromosomal aberrations in human lymphocytes after *in vivo* exposure to undetermined amounts of dieldrin. SCEs, but not chromosome aberrations, were induced by dieldrin in CHO cells, both in the presence and absence of S9 exogenous metabolic activation (Galloway et al., 1987). Aneuploidy and/or nuclear polyploidization were reportedly induced in the liver of CF_1 mice treated with dieldrin at 0.6 mg/kg bw/day (van Ravenzwaay and Kunz, 1988). In a human occupational exposure study, Dean et al. (1975) compared the frequencies of both chromatid- and chromosome-type aberrations in lymphocytes that were isolated from workers exposed to dieldrin in a manufacturing facility with those from unexposed control subjects. No statistically significant differences in the frequencies were observed.

With respect to *in vivo* exposure, currently available data do not indicate unequivocally that either aldrin or dieldrin directly interacts with DNA to cause mutations in either the germ cells or the somatic cells of mammals.

7.3.2 Immunotoxicity

No studies were obtained that examined the immunological effects of aldrin in either humans or animals, and only limited information was located regarding these types of effects in humans following exposure to 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 response for antibodies to dieldrin-coated red blood cells (RBCs). Another case of immunohemolytic anemia was reported in a man who had had multiple exposures to dieldrin, heptachlor, and toxaphene while spraying cotton fields (Muirhead et al., 1959); the individual's serum was found to contain antibodies to RBCs coated with either dieldrin or heptachlor. In contrast, volunteers who were

re-exposed to fabric that contained up to 0.5% dieldrin 2 weeks after an initial 4-day exposure did not reveal any evidence of sensitization (Suskind, 1959).

Immunosuppression by dieldrin has been reported in a number of studies in mice. A decrease in the antigenic response to the mouse hepatitis virus 3 (with a corresponding increase in its lethality) was observed in mice given a single oral dose of dieldrin (≥18 mg/kg) (Krzystyniak et al., 1985). Similarly, an increase in the lethality of infections with the malaria parasite, *Plasmodium berghei*, or with *Leishmania tropica* was produced in mice by treatment with dieldrin in the diet at concentrations as low as 1 ppm (approximately equivalent to 0.15 mg/kg bw/day based on Lehman, 1959 for 10 weeks [Loose, 1982]). In addition, decreased tumor cell killing ability was observed in mice after dieldrin treatment with concentrations as low as 1 ppm (approximately equivalent to 0.15 mg/kg bw/day based on Lehman, 1959) for 3, 6, or 18 weeks (Loose et al., 1981).

Loose et al. (1981) also observed a decrease in antigen processing by alveolar macrophages in mice following administration of dieldrin at concentrations as low as 0.5 ppm (approximately equivalent to 0.075 mg/kg bw/day based on Lehman, 1959) for 2 weeks. This occurred in the absence of observable effects on macrophage respiration, phagocytic activity or capacity, or microbial activity. In addition, macrophages from mice exposed for 10 weeks to dieldrin in the diet at 5 ppm (approximately 0.75 mg/kg bw/day based on Lehman, 1959) were found to produce a soluble factor that induced T-lymphocyte suppressor cells, suggesting suppressed immune system function (Loose, 1982). In another limited study, lymphocyte proliferation appeared inhibited in a mixed lymphocyte reaction test in which splenic cells taken from mice treated twice with 16.6 mg/kg bw of dieldrin were combined with stimulator cells taken from control animals (Fournier et al., 1988).

7.3.3 Hormonal Disruption

Wade et al. (1997) examined hormone levels in the serum and uterine tissues of young female Spargue-Dawley rats after intraperitoneal exposure to 3 mg/kg-day dieldrin from days 18 to 21 after birth. As compared to the vehicle treated controls, this acute exposure to dieldrin produced no significant effects in serum thyroxine levels, or in uterine tissue levels of follicle stimulating hormone (FSH), lutenizing hormone (LH), thyroid stimulating hormone, prolactin, or growth hormone. Pituitary weight was also reported to be unaltered by dieldrin treatment.

In an *in vitro* study, Brown (1998) reported that very low dose of dieldrin decreased fetal testicular hormone output. Tissue samples from 6 human male fetuses, terminated after 12 to 19 weeks of gestation, were cultured and tested for the production of testosterone and inhibin after exposure to dieldrin, either in the presence or absence of a combination of FSH and LH (10 nM). Diledrin treatment alone did not reduce hormone secretions, but coadministration of FSH+LH and dieldrin (10^{-12} M) significantly reduced ($p<0.03$) testosterone and inhibin B levels when compared to control levels.

7.3.4 Physiological or Mechanistic Studies

One mechanism considered as a possible explanation for the aldrin/dieldrin-induced convulsions and tremors observed in animals and humans involves the effects of these insecticides on the GABA (gamma-aminobutyric acid) receptor. Several lines of evidence suggest that organochlorine insecticides, such as aldrin and dieldrin, can act as $GABA_A$ receptor antagonists, blocking the chloride ion channel in the central nervous system. Such inhibition of the chloride ion channel could be a significant contributing factor to convulsions and tremors (Klaassen, 1996).

Using whole cell and single-channel patch clamp techniques Nagata and Narahashi (1995) examined dorsal root ganglion (DRG) neurons, isolated from the lumbo-dorsal region of newborn rats, that had been treated with dieldrin (0.0001 to 10 μM). They reported that dieldrin exposure suppressed the $GABA_A$ receptor-induced chloride currents (both sensitive and less-sensitive types) in a time- and dose-dependent manner. The IC_{50} values were estimated as being 3.7 nM and 98 nM for the sensitive and the less-sensitive currents, respectively. Dieldrin-induced suppression of chloride currents were directly dependent on GABA concentration (up to 1000 μM) and appeared irreversible as the current did not recover after a 30-minute wash-out with dieldrin-free solution. This suppression of chloride currents *in vitro* may explain the *in vivo* hyperactivity that has been noted in animals exposed to dieldrin.

Nagata and Narahashi (1994) observed that dieldrin (1 μM) exhibited dual effects on chloride currents in primary cultures of DRG; i.e., initial transient enhancement followed by suppression after repeated co-applications. The dieldrin-caused desensitization and suppression of chloride current occurred at an EC_{50} of 92 nM, but the enhancement of chloride current needed a higher EC_{50} of 754 nM. These authors also reported that the dieldrin-induced suppression of the GABA-mediated chloride current was non-competitive and irreversible, as recovery was not observed after prolonged washing of the neurons with dieldrin-free solution.

Nagata et al. (1994) speculated that dieldrin may cause differential effects on the GABA-induced chloride currents in human embryonic kidney cells, depending upon the subunit combinations of the $GABA_A$-receptor-chloride channel complex. The current molecular biological evidence indicates this complex to normally be a pentameric protein comprised of five subunits (α, β, γ, δ, ρ) in various combinations. Using the whole cell variation of the patch clamp technique, the EC_{50} values for GABA induction of chloride current were estimated as 9.8 μM for the α1β2 γ2s combination, 2.0 μM for the α1β2 combination, and 3.0 μM for the α6β2 γ2s combination. When co-applied with GABA, dieldrin (1 to 3 μM) produced mixed effects: initial transient enhancement, followed by suppression, was observed for the GABA-induced chloride currents in the α1β2 γ2s and α6β2 γ2s combinations. However, suppression alone was observed in the α1β2 combination, indicating that the γ subunit is necessary for dieldrin enhancing effects. The EC_{50} values for dieldrin's suppression of GABA induced current were estimated as being 2.1 μM for the α1β2 γ2s combination, 2.8 μM for the α1β2 combination, and 1.0 μM for the α6β2 γ2s combination. The authors concluded that dieldrin-induced suppression of chloride current did not require specific subunit combinations, at least among the three combinations tested.

Using the radioligand, t-^{35}S-butyl-bicyclophosphorothionate (^{35}S-TBPS), Brannen et al. (1998) demonstrated that dieldrin could interfere with GABA receptor binding. The authors

observed that injection of dieldrin (10 mg/kg bw/day) to pregnant dams from days E12 through E17 (embryonic days 12 to 17) caused a significant reduction in the amount of γ-^{35}S-TBPS binding to the $GABA_A$ receptor in E17 brainstem when compared to vehicle-injected controls. However, dieldrin treatment caused no significant effect on radioligand binding in the "rest of the brain."

Johns et al. (1998) reported findings that suggest the prenatal binding of dieldrin to GABA receptor might alter the expression of $GABA_A$ subunit mRNAs in adult offspring, and thus might explain the postnatal behavioral changes observed in adult offspring. Pregnant rats were injected intraperitoneally daily during E12 through 16 with 0, 5, or 10 mg/kg bw dieldrin. On postnatal day 56, testing of these adult offsprings in the elevated plus maze suggested that the dieldrin-treated males spent less time in the closed arms of the elevated maze, indicating a lower level of anxiety. Consistent with these behavioral effects, ^{35}STBPS-binding and several $GABA_A$ subunit mRNA levels were elevated in regions of the brain from the adult offspring of dieldrin-treated dams.

In an *in vitro* study, Liu et al. (1997) studied the mechanisms involved in the neurotoxic effect of dieldrin on γ-aminobutyric acid ($GABA_A$) receptors. Using embryonic day 14 (E14) rat brain stem cell cultures, the authors examined the effects of dieldrin on the expression of five GABA receptor mRNA subunits (α1, β3, γ1, γ2L, γ2S). Following a 48-hour treatment of brain stem cells with 10 μM dieldrin, $GABA_A$ receptor subunit mRNA levels were found to be differentially regulated from those of control cultures. Levels of β3 subunits were significantly increased (300%; $p<0.05$) by dieldrin, whereas expression of γ2S and γ2L transcripts were decreased by 50 and 40%, respectively ($p<0.05$). The levels of α1 and γ1 subunits, as well as the ratio of γ2S to γ2L, were not significantly affected by dieldrin treatment. As the evidence in general suggested a correlation between gene expression and receptor function, the altered expression of GABA receptor subunit mRNAs by prenatal dieldrin exposure may affect the functional properties of the $GABA_A$ receptor in the developing brain.

Liu et al. (1998) also studied the effect of prenatal *in vivo* exposure to dieldrin on the expression in the rat fetal brain stem of the five $GABA_A$ receptor subunit mRNAs (α1, β3, γ1, γ2L, γ2S). Pregnant rats, intraperitoneally administered dieldrin at 1 mg/kg bw/day from E12 to E17, evidenced a decrease in the mRNA levels of the α1, β3, and γ1 subunits, but not of those for γ2S or γ2L. Again, it was speculated that altered expression of these subunit mRNAs might impact the functional properties of the $GABA_A$ receptor, and thus GABA-mediated behaviors.

In addition to its effects on GABA-ergic neurons, dieldrin might also perturb or interact with dopaminergic neurons. In an *in vitro* study, Sanchez-Ramos et al. (1998) examined the effects of a 24- or 48-hour treatment with dieldrin (0.01 to 100 μM) on primary cultures of mesencephalic neurons isolated from the fetal brains of Sprague-Dawley rats or C_{57}/BL mice. Toxicities toward dopaminergic and GABA-ergic neurons were assessed by determining the survival of tyrosine hydroxylase-immunoreactive (TH-ir) cells and glutamate decarboxylase (GAD)-ir neurons, respectively. Dieldrin exposure for 24 hours resulted in a dose-dependent decrease in the survival of TH-ir cells from rat mesencephalic cultures, with 50% relative cell survival occurring at 12 μM. The 24-hour dieldrin treatment also produced a dose-dependent decrease in TH-ir cell survival in mouse mesencephalic cultures, with 75% relative cell survival

occurring at 10 μM. In general, the toxic effects of dieldrin were reported to be more severe for TH-ir neurons than for GABA-ergic neurons. Microscopic changes in neurons treated with dieldrin were observed in TH-ir cells, such as diminished numbers and lengths of neurites, and rounded cell bodies, as opposed to the polygonal or spindle form found in control neurons. Consistent with the cell survival effects, dopamine uptake was impaired by lower concentration of dieldrin than was GABA uptake (the EC_{50} for DA uptake was 7.98 μM, compared to 43 μM for GABA uptake) suggesting that dieldrin had a greater functional effect on dopaminergic neurons than on GABA-ergic neurons. Finally, the authors concluded that the greater toxicity of dieldrin on dopaminergic neurons might contribute to the Parkinsonism effects observed in workers exposed to pesticides, such as dieldrin.

Chatterjee et al. (1992) reported a number of estrogenic effects following subcutaneous administration of aldrin (1 mg/kg bw/day) for 3 days to groups (8/group) of young (22-day old) or ovariectomized adult (90-day old) female Wistar rats. Aldrin exposure caused significant increases in both young and old rats, as compared to their respective control groups, for each of the following parameters indicative of positive estrogenic effects: uterine weight, endometrial gland thickness and proliferation, and the staining of periodic acid-Schiff positive substance in the uterus. In ovariectomized adult rats, aldrin exposure also induced a persistent vaginal estrus, as compared to the constant diestrus seen in controls.

Several mechanistic studies have also been conducted to evaluate the estrogenic activity of dieldrin. Wade et al. (1997) examined the possible estrogenic effects of dieldrin *in vivo* by measuring the estrogen binding activity, peroxidase activity, and uterine weight in young female Spargue-Dawley rats, and *in vitro* by measuring the cell proliferation activity in MCF-7 cells (human breast cancer cells). Dieldrin treatment (2 to 10 μM) could competitively inhibit the binding of ^{3}H-17β-estradiol (E_2) to estrogen receptors in the rat uterus, indicating the similarities between the two compounds. The authors observed that the intraperitoneal administration of dieldrin at a dose of 3 mg/kg bw to young female rats during the period of 18 to 21 days after birth, produced no changes in uterotrophic activity (uterine weight, peroxidase activity, estrogen receptor number, and progesterone receptor number). In contrast to the lack of these specific *in vivo* estrogenic effects, dieldrin caused a positive response in the *in vitro* test; treatment of cultured MCF-7 cells with 50 μM dieldrin resulted in a 3.4-fold increase in cell proliferation, as compared to control cells. Wade et al. (1997) also reported that dieldrin lacked any synergistic effects in estrogenic activity when tested with endosulfan in both *in vitro* and *in vivo* assays. The weak *in vivo* estrogenic response of dieldrin is not likely attributable to study design limitations, as the positive control, diethylstilbesterol, produced significant estrogenic effects.

In another study, Soto et al. (1994) examined the estrogenic effects of dieldrin *in vitro* by measuring its proliferative effects on MCF-7 cells. Dieldrin treatment (1.0 pM to 10 μM) of MCF-7 cells produced a significant increase in the proliferation capacity only at the highest concentration. The relative proliferative efficiency for dieldrin at 10 μM was 54.89% that of estradiol, which induced its maximum level of proliferation (i.e., 100% relative proliferation) at a concentration of only 10 pM (1×10^{-6} of the tested dieldrin concentration). This indicates the relatively very weak estrogenic effect of dieldrin.

Ramamoorthy et al. (1997) investigated the possible estrogenic activity of dieldrin using a series of molecular biology assays: estrogen binding activity and estrogen effects in 21-day old $B6C3F_1$ mouse uterus, estrogen-mediated proliferation in MCF-7 cells, and reporter gene assays in yeast cells transformed with mouse or human estrogen receptor genes. They observed that dieldrin did not bind to the estrogen receptor in mouse uterus or MCF-7 cells in a competitive manner; produced no estrogen-dependent effects, such as increase in uterine wet weight or progesterone binding in uterus excised from mice (treated intraperitoneally with 2.5 to 60 μmol/kg bw/day for 3 days); did not induce MCF-7 cell proliferation at concentrations ranging from 10^{-8} to 10^{-5} M; and produced minimal induction of the reporter gene activity at concentrations of up to 2.5×10^{-5} M or 1×10^{-4} M in yeast cells transformed with either mouse estrogen receptor or human estrogen receptor, respectively. The negative findings reported in this study regarding dieldrin's estrogenic effects are not attributable to study design limitations, as the positive controls (17β-estradiol and diethylstilbesterol) had a strong estrogenic effects in these assays. Overall, the authors suggested that dieldrin produced only minimal estrogenic effects when tested alone, and moreover, when examined with toxaphene, exhibited no synergistic effects.

In contrast to the studies of Ramamoorthy and colleagues, Arnold et al. (1996) reported that dieldrin might have estrogenic effects when tested alone, or possess synergistic effects when combined with endosulfan. This was demonstrated by the induced expression of reporter gene activity in yeast or baculovirus (insect) cells that had been transformed with human estrogen receptors.

Using an *in vitro* biomembrane assay, Demetrio et al. (1998) investigated the effects of incubating phosphatidylcholine and dimyristoylphosphatidylcholine (DMPC) with aldrin concentrations of up to 100 μM for 18 to 20 hours, over the temperature range 12 to 40 °C. They reported a decrease in the fluidity of the lipid bilayers, as measured by changes in fluorescence polarization of DPH (1,6-diphenyl-1,3,5-hexatriene) and of its propionic acid derivative DPH-PA, which indicated fluidity changes in the bilayer core and in the outer regions of the bilayer, respectively. Although these membrane fluidity changes may alter membrane functions, it is not known whether they occur *in vivo*.

Wright et al. (1972) reported that within 1 week of exposing rats or mice to 8 or 1.6 mg/kg bw/day of dieldrin, respectively, increases were observed in liver cell cytoplasmic vacuoles, smooth endoplasmic reticulum, microsomal protein, and mixed-function oxidase activity. They also reported similar effects in dogs after 4 weeks of exposure to 2 mg/kg bw/day of dieldrin. Exposure of monkeys to concentrations as high as 0.1 mg/kg bw/day of dieldrin for up to 6 years also produced increased mixed-function oxidase activity and cytochrome P-450 content in liver cells (Wright et al., 1972, 1978).

Finally, *in vitro* studies have indicated that concentrations of aldrin as low as 5.0 to 6.0 μg/ml can inhibit gap-junctional intercellular communication among human teratocarcinoma cells (Zhong-Xiang et al., 1986) and metabolic cooperation among Chinese hamster cells (Kurata et al., 1982). Similarly, dieldrin has also been reported to inhibit intercellular communication/metabolic cooperation among human teratocarcinoma cells (Wade et al., 1986;

Zhong-Xiang et al., 1986), Chinese hamster cells (Kurata et al., 1982), and Syrian hamster embryo cells (Mikalsen and Sanner, 1993).

7.3.5 Structure-Activity Relationship

Four compounds structurally related to aldrin and dieldrin- chlordane, heptachlor, heptachlor epoxide, and chlorendic acid- have induced malignant liver tumors in mice; chlorendic acid has also induced liver tumors in rats (USEPA, 1993a,b).

7.4 Hazard Characterization

7.4.1 Synthesis and Evaluation of Noncancer Effects

Acute exposures to aldrin and/or the metabolic product, dieldrin, could cause neurotoxic effects in humans characterized by hyperirritability, convulsions, and coma (Jager, 1970; Spiotta, 1951; ACGIH, 1984). Cardiovascular effects, such as tachycardia and elevated blood pressure, may occur subsequent to convulsions (Black, 1974).

Evidence suggesting that children would experience the neurotoxic toxic effects upon acute exposure to aldrin and/or dieldrin is limited. In many instances, children may be more sensitive than adults as a result of their developing organ systems (e.g., nervous system) and metabolic detoxication capacities (Hayes, 1982; ATSDR, 2000). Long-term effects of aldrin/dieldrin in children have not been studied.

Occupational studies suggest that workers involved in the manufacture or application of aldrin/dieldrin have increased dieldrin levels in plasma (up to 250 ng/mL). From the plasma, the aldrin and dieldrin could be distributed and stored in adipose tissue (Nair et al., 1992).

Aldrin and dieldrin are quite toxic, as they have low acute toxicity values when tested in animals (LD_{50} values of generally $\leq$100 mg/kg) (Borgmann et al., 1952; Gaines, 1960; Treon et al., 1952; Lu et al., 1965). Common acute or subchronic neurotoxic effects observed in animals are characterized by increased irritability, salivation, hyperexcitability, tremors followed by convulsions, loss of body weight, depression, prostration, and death (Borgmann et al., 1952; Walker et al., 1969; Wagner and Greene, 1978; Wooley et al., 1985; NCI, 1978; Casteel, 1993). These symptoms are similar to those observed in humans exposed to aldrin or dieldrin (Jager, 1970; Spiotta, 1951; ACGIH, 1984; ATSDR, 2000). In addition, cardiovascular effects, such as tachycardia and elevated blood pressure, may occur in humans subsequent to convulsions (Black, 1974).

Evidence suggests that short-term or subchronic oral exposure to aldrin at dietary concentrations of 300 ppm in rats and 80 ppm in mice could result in high mortality rates (Treon and Cleveland, 1955; NCI, 1978).

Subchronic exposure of $B6C3F_1$ mice to dieldrin caused no significant effects in body weight gains, food consumption, or water consumption, but could increase relative liver weights (liver weight to body weight ratios), and promote hepatic lesions induced by the hepatic

carcinogen diethylnitrosamine. These dieldrin-induced hepatic effects may be specific to mice, as they were not observed in rats (Kolaja et al., 1996a,b).

Aldrin/dieldrin exposure has been shown to produce developmental and reproductive toxic effects. In a 3-generation reproduction study conducted in rats, a reduction in the pregnancy rate was reported (Treon and Cleveland, 1955). Prenatal exposure to aldrin also appears to have caused a reduction in pup survival in dogs (Deichmann et al., 1971). An increase in fetal deaths, a decrease in live fetal weight, and increased incidences of webbed foot, cleft palate, and open eye were reported in Syrian golden hamsters and CD1 mice that were exposed to dieldrin prenatally (Ottolenghi et al., 1974). Prenatal exposure to dieldrin may also cause maternal toxic effects, such as the increase in maternal mortality reported in mice (Virgo and Bellward 1975).

However, evidence from several animal studies does not indicate that reproductive effects such as changes in fertility, fecundity, length of gestation, or perinatal mortality would be likely to result from exposure at environmental levels to either aldrin or dieldrin (Kitselman, 1953; Good and Ware, 1969; Harr et al., 1970; Coulston et al., 1980).

Experimental evidence suggesting that dieldrin may be capable of producing estrogenic effects is not consistent (Ramamoorthy et al., 1997; Arnold et al., 1996; Wade et al., 1997). Chatterjee et al. (1992) found that administration of dieldrin to rats increased uterine weight, endometrial gland thickness and proliferation, and the level of staining for periodic acid-Schiff positive substances in the uterus in a fashion similar to that seen for estrogen. Soto et al. (1994) reported weak estrogenic-like effects for dieldrin with respect to its enhancement of the proliferation of human breast cancer cells.

Chronic feeding of aldrin (1 to 10 mg/kg bw/day) to animals has in general produced high mortality effects (Treon and Cleveland, 1955; Fitzhugh et al., 1964; NCI, 1978; Kitselman and Borgmann, 1952). Similar results were also reported for dieldrin exposure in mice (Walker et al., 1972).

Increased liver weights and liver-to-body weight ratios were observed consistently in rats chronically exposed to aldrin (Treon and Cleveland, 1955; Deichmann et al., 1970; Fitzhugh et al., 1964), and in rats, dogs, and mice exposed to dieldrin (Fitzhugh et al., 1964; Walker et al., 1969; Walker et al., 1972).

Neurotoxic effects similar to those seen after acute exposure, such as tremors and convulsions, have also been reported in long-term oral studies of animals exposed to aldrin (Fitzhugh et al., 1964; Deichmann et al., 1970) or dieldrin (Fitzhugh et al., 1964).

Chronic oral exposure of rats to aldrin has also caused some histopathological alterations in the liver, which were characterized by enlarged centrilobular hepatic cells having increased cytoplasmic oxyphilia and peripheral migration of basophilic granules (Fitzhugh et al., 1964).

No studies were obtained that examined the toxic effects of aldrin or dieldrin in animals following inhalation exposure, and only very limited information was found regarding dermal exposure.

7.4.2 Synthesis and Evaluation of Carcinogenic Effects

Long-term follow-up studies suggest that standardized mortality rates for all causes of death in workers employed in pesticide manufacturing plants are significantly lower than the corresponding national mortality rates (de Jong, 1991; de Jong et al., 1997; Ditraglia et al., 1981; Brown, 1992; Amaoteng-Adjepong et al., 1995). Slight increases in the incidence of rectal and liver cancers have been observed in the aldrin/dieldrin exposed groups, but they are not robust or dose-dependent (de Jong et al., 1997; Ditraglia et al., 1981). Most of the results from the various occupational studies on the human health effects of aldrin/dieldrin exposure are complicated to some degree by the simultaneous exposure to other pesticides; most plants were also involved in the manufacture of other pesticides, and the association of adverse human health effects with aldrin/dieldrin contact is weakened by the lack of adequate exposure assessment.

Several lines of evidence suggest that chronic exposure to aldrin/dieldrin selectively increases the incidence of liver cancer in several different strains of mice (Meierhenry et al., 1983; Davis and Fitzhugh, 1962, Davis, 1965; Epstein, 1975a,b; NCI, 1978; Thorpe and Walker, 1973; Walker et al., 1972; Tennekes et al., 1981). These results were not observed in several strains of rats that have also been tested (Treon and Cleveland, 1955; Fitzhugh et al., 1964; Song and Harville, 1964; Walker et al., 1969; Deichmann et al., 1970; NCI, 1978). Evidence from a single rat study (NCI, 1978) suggesting possible increases in the incidences of follicular cell adenoma and carcinoma of the thyroid and of cortical adenoma of the adrenal gland after chronic aldrin exposure has not been supported by other studies. It must be kept in mind, however, that a number of these studies has been deemed inadequate tests for carcinogenicity due to a variety of significant study limitations.

Seven studies that collectively utilized 4 strains of rats, which were fed 0.1 to 285 ppm dieldrin for durations varying from 80 weeks to 31 months, did not produce positive results for carcinogenicity (Treon and Cleveland, 1955; Fitzhugh et al., 1964; Song and Harville, 1964; Walker et al., 1969; Deichmann et al., 1970; NCI, 1978). Three of these studies used Osborne-Mendel rats, two studies used Carworth rats, and one each used Fischer 344 and Holtzman strains. As noted above for aldrin, only three of the seven dieldrin studies were considered adequate in design and conduct (USEPA, 1987, 1993b). The others used too few animals, had unacceptably high levels of mortality, were too short in duration, and/or had inadequate pathology examination or reporting.

The status of aldrin and dieldrin as genotoxins is somewhat equivocal. Summarizing the studies reviewed in this document by certain genotoxicity endpoint categories, the assays performed on one or both of these chemicals have produced the following responses:

bacterial gene mutation:	21 (–)	1 (+)
fungal gene mutation/conversion:	4 (–)	1 (+)
in vitro mammalian cell gene mutation:		1 (+)
mammalian host-mediated bacterial gene mutation:	1 (–)	

in vivo gene mutation - insects:	2 (–)	
in vitro chromosome damage/aneuploidy:	2 (–)	3 (+)
in vivo chromosome damage/aneuploidy:	6 (–)	4 (+), 3 (?+)
in vitro SCE:		1 (+)
in vivo SCE:	1 (–)	1 (?+)
bacterial/plasmid DNA damage:	2 (–)	
in vitro mammalian cell DNA damage:	4 (–), 2 (?–)	3 (+)
in vitro cell transformation:	1 (–)	

While the preponderance of these assay results are negative, some of the *in vitro* assays failed to employ some form of exogenous metabolic activation, such as S9 mix. Based on these data, it is currently difficult to reject at least the possibility that aldrin/dieldrin can interact with chromosomes or induce DNA damage. However, as suggested in the following section, some or all of aldrin/dieldrin's apparent genotoxicity may indirect or reflect epigenetic mechanisms.

7.4.3 Mode of Action and Implications in Cancer Assessment

There have been several mechanistic studies conducted to explain the selective hepatocarcinogenic effects of aldrin and dieldrin in mice. Several studies suggest that these chemicals can induce at least hepatic tumors in mice, but are much less likely to do so, if at all, in rats. Although the mechanisms responsible for this species specificity are not fully understood, accumulating evidence indicates that increased hepatic DNA synthesis and oxidative stress may be involved.

Kolaja et al. (1996a) observed an increased DNA labeling index in the centrilobular region of liver in male B6C3F$_1$ mice, but not in male Fisher 344 rats, as early as 7 or 14 days after exposure to dieldrin at concentrations of 3.0 or 10.0 mg/kg diet. Increases in the liver DNA labeling index in mice, but not in rats, were also reported by Kolaja et al. (1995) for the high-dose groups when animals (5/species/dose) were fed with dieldrin in the diet at 0 (control), 0.1, 1.0, or 10.0 mg dieldrin/kg diet for 7 or 14 days. In a subsequent study, Kolaja et al. (1996b) described a selective promotion of hepatic focal lesions and an increase in DNA labeling at the highest dose in male B6C3F$_1$ mice, but not in male Fisher 344 rats. Groups of animals (5 animals/species/dose) were treated with the hepatic carcinogen, diethylnitrosamine (150 mg/kg bw/week, 2x for rats; 25 mg/kg bw/week, 8x for mice), prior to the administration of dieldrin at 0.1, 1.0, or 10.0 mg/kg diet for 7 days.

In vivo experiments by Bachowski et al. (1997) demonstrated the following in B6C3F$_1$ mice, but not in F344 rats, upon feeding 10.0 mg dieldrin/kg diet for up to 540 days: 1) increased production of 2,3-DHBA (2,3-dihydroxybenzoic acid, a marker used for measuring oxidative stress) in hepatocytes and their microsomes; 2) elevated production of MDA (malondialdehyde, a marker for oxidative damage to lipids) in liver and urine; 3) increased OH8dG (8-hydroxy-2'-deoxyguanosine, a marker for oxidative damage to DNA) levels in urine; and 4) decreased hepatic vitamin E (α-tocopherol) content. The authors concluded that oxidative stress mechanisms may be involved in the mediation of dieldrin-induced hepatic DNA synthesis that is observed in mice, but not in rats.

In a more recent study, Bachowski et al. (1998) also examined the *in vivo* association between dieldrin-induced hepatic DNA synthesis and oxidative damage to lipids (MDA), DNA (OH8dG), or levels of nonenzymatic antioxidants (ascorbic acid, glutathione, vitamin E) in male $B6C3F_1$ mice and F344 rats that were fed dieldrin (0.1, 1.0, or 10 mg/kg diet) for up to 90 days. Consistent with the increase in hepatic DNA synthesis induced by dieldrin treatment, decreases in hepatic and serum vitamin E levels (α-tocopherol), and increases in hepatic MDA and urinary MDA and OH8dG levels, were observed in mice. In contrast, these effects were less dramatic or not observed in rats, which may have been protected by higher basal levels of vitamin E (and vitamin C) in their hepatic tissue.

Stevenson et al. (1995) found indirect evidence for an oxidative stress mechanism when they measured a partial protective effect of vitamin E in ameliorating the dieldrin-induced hepatic DNA synthesis observed in $B6C3F_1$ mice (fed dieldrin at 10 mg/kg diet for 28 days). However, supplementation of the diet with vitamin C (another antioxidant) at up to 400 mg/kg diet resulted in only an inconsistent reduction in dieldrin-induced hepatic DNA labeling.

Kolaja et al. (1998) also reported that supplementation of the diet with vitamin E (450 mg/kg diet) for up to 60 days blocked the dieldrin (10 mg/kg diet) treatment effects of increased hepatic focal lesion volume, focal lesion number, and focal lesion DNA labeling index that were observed in mice pre-treated with the hepatic carcinogen, diethylnitrosamine.

Bauer-Hofmann et al. (1992) analyzed the frequency and pattern of c-Ha-ras proto-oncogene mutations at codon 61 in polymerase chain reaction-amplified DNA taken from glucose-6-phosphatase deficient ($G6P^-$) hepatic lesions in groups of male C3H/He mice; groups had received either 10 ppm dieldrin, 500 ppm phenobarbital (PB), or no treatment in the diet for 52 weeks. The incidence of $G6P^-$ hepatic lesions was reported to increase from 41% (15/37) in the control group to 67% (10/15) and 63% (10/16) in the dieldrin and PB groups, respectively. The corresponding average numbers of focal lesions/mouse were 0.57, 1.5, and 1.0. Upon DNA analysis, c-Ha-ras mutations were observed in 57% (12/21) of the lesions from the control group, but in only 22% (5/23) and 25% (4/16) of those from the dieldrin and PB groups, respectively. As dieldrin (like PB) increased the frequency of c-Ha-ras wild-type, but not mutated, focal hepatic lesions, the authors concluded that the c-Ha-ras mutations had likely occurred spontaneously rather than as a result of dieldrin treatment. Further, no significant differences in the mutation spectra were noticed between control and dieldrin treated mice, the most prominent class of mutation being C→A transversion. These data suggest that the principal role for dieldrin in liver tumor formation may be one of promotion, rather than initiation.

Based on existing studies, Stevenson et al. (1999) have also suggested that aldrin/dieldrin exposure induces hepatocarcinogenesis in mice through non-genotoxic mechanisms such as increased production of reactive oxygen species (ROS) in mouse hepatocytes (possibly by futile cycling of P450 enzymes), increased hepatic DNA synthesis, and augmentation of tumor-promotional effects, rather than by causing point mutations or otherwise directly interacting with DNA. A possible mode of action for aldrin/dieldrin in animals is depicted in Figure 7-l. Although the figure depicts aldrin/dieldrin induction of hepatic DNA synthesis through modulation of proto-oncogene expression (via transcription factors such as Nf-kB, AP-1, etc.),

data directly relating the effects of aldrin/dieldrin exposure to protooncogene expression remain to be established.

In addition to mechanisms that involve oxidative stress and the direct promotion of cellular proliferation, the previously discussed capacity of aldrin and dieldrin to inhibit various forms of *in vitro* intercellular communication in both human and animal cells may be significant with respect to their *in vivo* effects on tumor production (Kurata et al., 1982; Wade et al., 1986; Zhong-Xiang et al., 1986; Mikalsen and Sanner, 1993).

7.4.4 Weight of Evidence Evaluation for Carcinogenicity

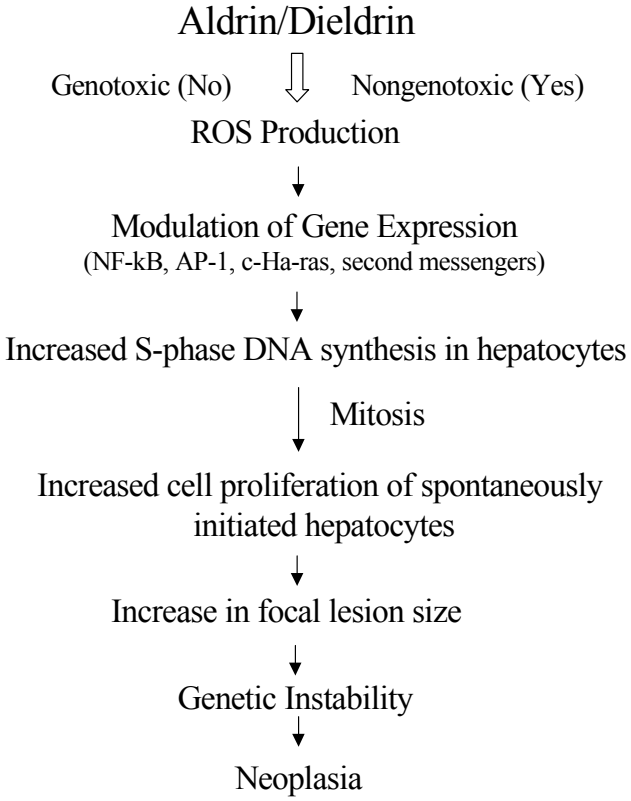
Using current EPA (1986) cancer guidelines, aldrin and dieldrin are classified as B2 carcinogens, i.e. probable human carcinogens with little or no evidence of carcinogenicity in humans and sufficient evidence in animals (different strains of mice). With inadequate data on carcinogenic effects in humans, under the USEPA's cancer risk assessment guidelines (USEPA, 1996/1999), the weight of evidence indicates that aldrin and dieldrin could be classified as rodent carcinogens that are "*likely to be carcinogenic to humans by the oral route of exposure, but whose carcinogenic potential by the inhalation and dermal routes of exposure cannot be determined because there are inadequate data to perform an assessment*." This characterization is based on the tumor effects of aldrin and dieldrin observed in several strains of mice subsequent to oral exposures and must be tempered by the lack of evidence for significant human carcinogenicity from epidemiological studies. It should be noted that the USEPA has quantified the estimated carcinogenic risks from inhalation exposure to aldrin and dieldrin by extrapolating from available oral exposure route data (USEPA, 1993a,b). Mechanistic studies performed in

Figure 7-1. The Possible Mode of Action of Aldrin/Dieldrin on Hepatocarcinogenesis Adapted from Stevenson et al. (1999)

vitro and *in vivo* suggest that one or more non-genotoxic modes of action may underlie or contribute to the carcinogenic potential of aldrin and dieldrin, but these effects are not completely established, or can a role for genotoxic mechanisms confidently be eliminated based on the available data . In the absence of adequate data to fully support a non-linear mechanism(s) of tumor formation, the quantitative cancer risk assessment of aldrin and dieldrin should conservatively be conducted using the linear-default model.

7.4.5 Sensitive Populations

No human studies were obtained that adequately address the effect of aldrin and dieldrin on sensitive populations, such as children. Several mechanistic studies, which describe the



prenatal effects of aldrin/dieldrin on GABA receptor malfunctions and on subsequent behavioral impairment, may suggest that children could be more sensitive to aldrin and dieldrin exposures than the general adult population (Brannen et al., 1998; Liu et al., 1998; Johns et al., 1998; Castro et al., 1992).

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8.0 DOSE-RESPONSE ASSESSMENTS

8.1 Dose-Response for Non-Cancer Effects

8.1.1 Reference Dose Determination

The oral Reference Dose (RfD), formerly termed the Acceptable Daily Intake (ADI), is based on the assumption that thresholds exist for most, if not all, noncancer toxic effects. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is expressed in units of mg/kg bw/day, and has traditionally been derived from the NOAEL (or LOAEL) identified from the data in a chronic (or subchronic) study, divided by an uncertainty factor composed of one or more elements defined by EPA or NAS/OW guidelines.

Aldrin

Choice of Principal Study and Critical Effect

The rat study by Fitzhugh et al. (1964), designed as a carcinogenesis bioassay, has been selected to serve as the basis for the Reference Dose principally because it displayed strength in histopathologic analysis, it examined a wider dose range (0.5 to 150 ppm in the diet) when compared with other available chronic studies, and in the absence of a reliable NOAEL, its data established the lowest available LOAEL. The database is fairly extensive and, generally, supportive of the principal study's findings, but is rated medium because of the lack of NOELs. Other chronic studies in rats (using dietary exposures of 2.5 to 60 ppm) and dogs have also demonstrated aldrin's toxic effects on the liver (Deichmann et al., 1970; Treon and Cleveland, 1955; NCI, 1978; the dog study in Fitzhugh et al., 1964).

In the principal study, groups of 24 rats (12/sex) were fed aldrin in the diet at levels of 0, 0.5, 2, 10, 50, 100, or 150 ppm for 2 years. Liver lesions characteristic of chlorinated insecticide poisoning were observed at all exposure levels of aldrin. These lesions were characterized by enlarged centrilobular hepatic cells, with increased cytoplasmic oxyphilia and peripheral migration of basophilic granules. In addition, a statistically significant increase in liver-to-body weight ratio was observed at all dose levels. Kidney lesions at the highest dose levels were also reported and survival was markedly decreased at dose levels of 50 ppm and greater. The effect and no-effect levels for liver toxicity are similar to those reported in the same study for dogs exposed to aldrin in the diet for 15 months (Fitzhugh et al., 1964). While not permitting the determination of a NOAEL, the study does establish a LOAEL at the lowest aldrin concentration tested, 0.5 ppm.

RfD Derivation

The RfD for aldrin was derived from the critical effect (liver toxicity) that it induced in rats during a 2-year chronic feeding study (Fitzhugh et al., 1964). This principal study reported that various toxic effects occurred in the liver at all aldrin concentrations tested (0.5 to 150 ppm).

The resulting LOAEL dietary concentration of 0.5 ppm can be converted to a dose of 0.025 mg/kg bw/day by using an equivalency factor of 1 ppm in the diet = 0.05 mg/kg bw/day based on the food consumption rate in rats as described by Lehman (1959).

The RfD for aldrin is calculated as follows:

$$\text{RfD} = \frac{0.025 \text{ mg / kg bw / day}}{1000} = 0.000025 \text{ mg/kg bw/day (rounded to 3E-5 mg/kg bw/day)}$$

where:

0.025 mg/kg bw/day = LOAEL, based on liver toxicity in rats exposed to aldrin in the diet for 2 years

1000 = uncertainty factor; this composite uncertainty factor was chosen in accordance with EPA or NAS/OW guidelines in which uncertainty factors of 10 each were applied to extrapolate from rats to humans, to account for uncertainty in the range of human sensitivity (i.e., to protect sensitive human subpopulations), and to account for additional uncertainty because the study identified a LOAEL (but not a NOAEL).

Dieldrin

Choice of Principal Study and Critical Effect

The study by Walker et al. (1969), also designed as a carcinogenesis bioassay, has been selected to serve as the basis for the Reference Dose principally because it was fairly extensively reported, the exposure period was of chronic duration, NOAELs were determined, and it is generally supported by other toxicity studies of dieldrin.

Walker et al. (1969) administered dieldrin (recrystallized, 99% active ingredient) to Carworth Farm "E" rats (25/sex/dose; controls 45/sex) for 2 years at dietary concentrations of 0, 0.1, 1.0, or 10.0 ppm. Based on intake assumptions presented by the authors, these dietary levels are approximately equivalent to 0, 0.005, 0.05, and 0.5 mg dieldrin/kg bw/day, respectively. Body weight, food intake, and general health remained unaffected throughout the 2-year period, although at 10.0 ppm (0.5 mg/kg bw/day) all animals became irritable and exhibited tremors and occasional convulsions. No effects were observed for various hematological and clinical chemistry parameters. At the end of 2 years, females fed 1.0 and 10.0 ppm (0.05 and 0.5 mg/kg bw/day, respectively) had increased liver weights and liver-to-body weight ratios ($p < 0.05$). Histopathological examinations revealed liver parenchymal cell changes, including focal proliferation and focal hyperplasia. These hepatic lesions were considered by the authors to be characteristic of exposure to an organochlorine insecticide. Based on these toxic effects

observed in the liver, the LOAEL was identified as 1.0 ppm (0.005 mg/kg bw/day) and the NOAEL as 0.1 ppm (0.005 mg/kg bw/day).

RfD Derivation

The RfD for dieldrin was derived from the critical effect (altered absolute and relative liver weights that were accompanied by histopathological changes) that it induced in rats during a 2-year chronic feeding study (Walker et al., 1969). Liver toxicity was noticed only at the 1.0 and 10 ppm diet groups in female rats. The NOAEL dietary concentration of 0.1 ppm dieldrin served as the basis for the RfD derivation, after being converted to a dose of 0.005 mg dieldrin/kg bw/day utilizing the authors' assumptions on dietary intake (which also comport with the 1 ppm = 0.05 mg/kg bw/day conversion factor of Lehman [1959] for food consumption in rats).

The RfD for dieldrin is calculated as follows:

$$\text{RfD} = \frac{0.005 \text{ mg / kg bw / day}}{100} = 5\text{E-}5 \text{ mg/kg bw/day}$$

where:

0.005 mg/kg bw/day = NOAEL, based on liver toxicity in rats exposed to dieldrin in the diet for 2 years

100 = uncertainty factor; this composite uncertainty factor was chosen in accordance with EPA or NAS/OW guidelines in which uncertainty factors of 10 each were applied to extrapolate from rats to humans and to account for uncertainty in the range of human sensitivity (i.e., to protect sensitive human subpopulations).

8.1.2 Reference Concentration (RfC) Determination

No human or animal studies were identified that would currently support the derivation of RfC values for either aldrin or dieldrin.

8.2 Dose-Response for Cancer Effects

8.2.1 Choice of Study/Data With Rationale and Justification

Aldrin

Three marginally adequate-to-adequate long-term carcinogenicity bioassays of aldrin have been conducted using B6C3F_1, C3HeB/Fe, and C3H mice. Based on these studies, there is

sufficient evidence that aldrin is carcinogenic for mice. Dietary administration of aldrin induced statistically significant increases in hepatocellular carcinomas in male $B6C3F_1$ mice ($p < 0.001$) (NCI, 1978), hepatomas in combined male plus female C3HeB/Fe mice ($p < 0.001$) (Davis and Fitzhugh, 1962), and hepatomas in the combined sexes of C3H mice ($p < 0.05$) (Davis, 1965). Reevaluation of the hepatomas observed in the latter two studies indicated that most were actually hepatocellular carcinomas (Epstein, 1975).

Dietary administration of aldrin was reported to increase the combined incidences of follicular cell adenomas and carcinomas of the thyroid in both male and female Osborne Mendel rats; however, the increase was not dose-related and was significant ($p = 0.001$) only at the low dose. This increase was not considered to be treatment related. Although the study authors concluded that aldrin was not carcinogenic to rats (NCI, 1978), these data (in conjunction with the adrenal cortex tumors observed in low-dose female rats) have been subsequently considered equivocal or suggestive evidence of carcinogenicity in rats (Griesemer and Cueto, 1980; Haseman et al., 1987; USEPA, 1987).

Based on the available data, IARC (1987) concluded that there was limited evidence for the carcinogenicity of aldrin in animals and inadequate evidence in humans. IARC's conclusion with respect to animal carcinogenicity was based on the occurrence of malignant liver neoplasms in mice, since one study using rats could not clearly associate the occurrence of thyroid tumors with aldrin treatment, three additional studies using rats gave negative results, and another rat study was judged to be inadequate. Consequently, IARC classified aldrin as a Group 3 chemical, a possible human carcinogen.

Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (USEPA, 1986), aldrin may be classified in Group B2: probable human carcinogen. This category includes agents for which there is inadequate evidence of carcinogenicity in human studies and sufficient evidence of carcinogenicity in animal studies. Under the more recent Proposed Guidelines for Carcinogen Risk Assessment (USEPA, 1996/1999), aldrin would probably be categorized as "likely" to produce cancer in humans by the oral route of exposure, while its carcinogenic potential via other routes of exposure would merit a classification of "cannot be determined due to inadequate data."

From the several carcinogenicity studies that have provided evidence that aldrin is carcinogenic in mice, three data sets have been deemed adequate for quantitative risk estimation (USEPA, 1987): those for both male and female C3H mice in the Davis (1965) study, as reevaluated by Reuber and cited in Epstein (1975); and that for male $B6C3F_1$ mice in the NCI (1978) bioassay. Utilizing the linearized multistage model, the USEPA (1987) performed potency estimates for each of these data sets after interspecies dose conversion; they ranged from 12 to 23 $(mg/kg\ bw/day)^{-1}$. Their geometric mean, $(q1^*) = 17\ (mg/kg\ bw/day)^{-1}$, was estimated as the cancer potency of aldrin for the general population.

Using this cancer potency estimate and assuming that a 70-kg human adult consumes 2 liters of water a day over a 70-year lifespan, the linearized multistage model yields a drinking water unit risk of 4.9 E-4 per µg/L. This in turn can be used to estimate that concentrations of

0.2, 0.02, and 0.002 µg/liter of aldrin may result in excess cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively.

The linearized multistage model is only one of several that can be used for estimating carcinogenic risk. From the three aldrin data sets that were identified in the USEPA (1987) report as being suitable for quantitative cancer risk estimation, it was determined that one was also suitable for determining slope estimates using the probit, logit, Weibull, and gamma-multihit models. Each model utilizes a different set of assumptions in order to extrapolate from observed experimental data to predicted cancer risks at the low doses more characteristic of human exposure scenarios. Based on current limitations in the understanding of biological mechanisms relevant to carcinogenesis, as well as in the availability of mechanistic data for most chemicals, the relative accuracy of these models cannot generally be predicted. The drinking water levels of aldrin estimated by each of these models (at the upper 95% confidence limit) to be associated with an excess cancer risk of one per 1,000,000 persons exposed (i.e., an excess risk of 10^{-6}) were 0.00206 µg/L (multistage model), 0.00356 µg/L (probit model), 0.00376 µg/L (logit model), 0.00356 µg/L (Weibull model), and 0.00310 µg/L (multihit model) (USEPA, 1992).

Dieldrin

Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (USEPA, 1986), dieldrin also may be classified in Group B2, probable human carcinogen. Again, under the more recent Proposed Guidelines for Carcinogen Risk Assessment (USEPA, 1996/1999), dieldrin would probably be categorized as "likely" to produce cancer in humans by the oral route of exposure, while its carcinogenic potential via other routes of exposure would merit a classification of "cannot be determined due to inadequate data." IARC (1982) has concluded that there is limited evidence for dieldrin's carcinogenicity in laboratory animals.

Evidence reported in a number of carcinogenicity studies indicates that dieldrin is carcinogenic to several strains of mice (Davis and Fitzhugh, 1962; Davis, 1965; Walker et al., 1972; Thorpe and Walker, 1973; NCI, 1978; Tennekes et al., 1981; Meierhenry et al., 1983). Thirteen sex and strain-specific data sets from these studies were judged adequate for quantitative risk estimation; for each of them, the USEPA generated potency estimates utilizing the linearized multistage model (USEPA, 1987). These estimates ranged from 7 to 55 $(mg/kg\ bw/day)^{-1}$, with the geometric mean of $q_1^* = 16\ (mg/kg\ bw/day)^{-1}$ taken as the estimated potency of dieldrin for the general population.

Using this q_1^* value and assuming that a 70-kg human adult consumes 2 liters of water a day over a 70-year lifespan, the linearized multistage model estimates a drinking water unit risk of 4.6 E-4 per µg/L. Therefore, excess cancer risk levels of 10^{-4} , 10^{-5}, and 10^{-6} would be estimated to result from drinking water concentrations of approximately 0.2, 0.02, and 0.002 µg dieldrin per liter, respectively.

As noted previously, the linearized multistage model is only one of several that can be used for estimating carcinogenic risk. From the 13 dieldrin data sets data that were identified in the USEPA (1987) report as being suitable for quantitative cancer risk estimation, it was

determined that 5 were also suitable for determining slope estimates using the probit, logit, Weibull, and gamma-multihit models. Again, each model utilizes a different set of assumptions in order to extrapolate from observed experimental data to predicted cancer risks at the low doses more characteristic of human exposure scenarios. Based on current limitations in the understanding of biological mechanisms relevant to carcinogenesis, as well as in the availability of mechanistic data for most chemicals, the relative accuracy of these models cannot generally be predicted. The drinking water unit risks (those estimated for a 70 kg human drinking, over a the course of a lifetime, 2 L/day of water containing 1 μg/L of dieldrin) estimated by each of these models (at the upper 95% confidence limit) have been reported as 4.78×10^{-4} (multistage model), 7.7×10^{-12} (probit model), 5.09×10^{-6} (logit model), 1.13×10^{-4} (Weibull model), and 5.68×10^{-4} (multihit model) (USEPA, 1988).

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9.0 REGULATORY DETERMINATION AND CHARACTERIZATION OF RISK FROM DRINKING WATER

9.1 Regulatory Determination for Chemicals on the CCL

The Safe Drinking Water Act (SDWA), as amended in 1996, required the Environmental Protection Agency (EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. EPA published a draft of the first Contaminant Candidate List (CCL) on October 6, 1997 (62 FR 52193, USEPA, 1997). After review of and response to comments, the final CCL was published on March 2, 1998 (63FR 10273, USEPA, 1998). The CCL grouped contaminants into three major categories as follows:

Regulatory Determination Priorities - Chemicals or microbes with adequate data to support a regulatory determination,

Research Priorities - Chemicals or microbes requiring research for health effects, analytical methods, and/or treatment technologies,

Occurrence Priorities - Chemicals or microbes requiring additional data on occurrence in drinking water.

The March 2, 1998, CCL included 1 microbe and 19 chemicals in the regulatory determination priority category. More detailed assessments of the completeness of the health, treatment, occurrence and analytical method data led to a subsequent reduction of the regulatory determination priority chemicals to a list of 12 (1 microbe and 11 chemicals), which was distributed to stakeholders in November 1999.

SDWA requires EPA to make regulatory determinations for no fewer than five contaminants in the regulatory determination priority category by August 2001. In cases where the Agency determines that a regulation is necessary, the regulation should be proposed by August 2003 and promulgated by February 2005. The Agency is given the freedom to also determine that there is no need for a regulation if a chemical on the CCL fails to meet one of three criteria established by SDWA and described in Section 9.1.1.

9.1.1 Criteria for Regulatory Determination

These are the criteria used to determine whether or not to regulate a chemical on the CCL:

The contaminant may have an adverse effect on the health of persons,

The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern,

In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The findings for all criteria are used in making a determination to regulate a contaminant. As required by SDWA, a decision to regulate commits the EPA to publication of a Maximum Contaminant Level Goal (MCLG) and promulgation of a National Primary Drinking Water Regulation (NPDWR) for that contaminant. The Agency may determine that there is no need for a regulation when a contaminant fails to meet one of the criteria. A decision not to regulate a contaminant is considered a final Agency action and is subject to judicial review. The Agency can choose to publish a Health Advisory (a nonregulatory action) or other guidance for any contaminant on the CCL independent of its regulatory determination.

9.1.2 National Drinking Water Advisory Council Recommendations

In March 2000, the EPA convened a Working Group under the National Drinking Water Advisory Council (NDWAC) to help develop an approach for making regulatory determinations. The Working Group developed a protocol for analyzing and presenting the available scientific data and recommended methods to identify and document the rationale supporting a regulatory determination decision. The NDWAC Working Group report was presented to and accepted by the entire NDWAC in July 2000.

Because of the intrinsic differences between microbial and chemical contaminants, the Working Group developed separate but similar protocols for microorganisms and chemicals. The approach for chemicals was based on an assessment of the impact of acute, chronic, and lifetime exposures, as well as a risk assessment that includes evaluation of occurrence, fate, and dose-response. The NDWAC Protocol for chemicals is a semi-quantitative tool for addressing each of the three CCL criteria. The NDWAC requested that the Agency use good judgement in balancing the many factors that need to be considered in making a regulatory determination.

The EPA modified the semi-quantitative NDWAC suggestions for evaluating chemicals against the regulatory determination criteria and applied them in decision making. The quantitative and qualitative factors for aldrin and dieldrin that were considered for each of the three criteria are presented in the sections that follow.

9.2 Health Effects

The first criterion asks if the contaminant may have an adverse effect on the health of persons. Because all chemicals have adverse effects at some level of exposure, the challenge is to define the dose at which adverse health effects are likely to occur, and estimate a dose at which adverse health effects are either not likely to occur (threshold toxicant), or have a low probability for occurrence (non-threshold toxicant). The key elements that must be considered in evaluating the first criterion are the mode(s) of action, the critical effect(s), the dose-response for critical effect(s), the RfD for threshold effects, and the slope factor for non-threshold effects.

A description of the health effects associated with exposures to aldrin or dieldrin is presented in Chapter 7 of this document, and is summarized below in Section 9.2.2. Chapter 8 and Section 9.2.3 present dose-response information.

9.2.1 Health Criterion Conclusions

The data available on aldrin and dieldrin demonstrate the capacity of both chemicals to cause a variety of adverse systemic, neurological, reproductive/developmental, immunological, genotoxic, and/or tumorigenic effects in humans, animals, or both. While some of these noncancer effects are observed only at moderate to relatively high doses, others have been observed to occur at doses below 0.1 mg/kg bw/day. The current oral RfDs for aldrin and dieldrin are 3×10^{-5} and 5×10^{-5} mg/kg bw/day based on hepatic effects.

Both compounds have been convincingly demonstrated to be hepatocarcinogenic in several strains of mice in multiple bioassays, although they are apparently not carcinogenic to rats and have not been convincingly associated with human cancer in any of several large epidemiology studies. Based on the mouse studies and using the linear multistage model, the cancer potency for aldrin is 17 $(mg/kg/day)^{-1}$, and that for dieldrin, 16 $(mg/kg/day)^{-1}$. For both compounds, a drinking water concentration of 0.002 μg/L would lead to an estimated lifetime excess cancer risk of 10^{-6}.

9.2.2 Hazard Characterization and Mode of Action Implications

Following acute exposure to high doses, the primary adverse health effects of aldrin and dieldrin in humans are those resulting from neurotoxicity to the central nervous system, including hyperirritability, convulsions, and coma (Jager, 1970; Spiotta, 1951; ACGIH, 1984). In some cases, these may be followed by cardiovascular effects, such as tachycardia and elevated blood pressure (Black, 1974). Under conditions of longer-term exposure to lower doses of these compounds, neurotoxic symptoms may also include headache, dizziness, general malaise, nausea, vomiting, and muscle twitching or myoclonic jerking (Jager, 1970; ATSDR, 2000a). Dieldrin exposure has been linked to two cases of immunohemolytic anemia (Hamilton et al., 1978; Muirhead et al., 1959), as has aldrin/dieldrin exposure to several instances of aplastic anemia (de Jong, 1991; Pick et al., 1965; ATSDR, 2000a). However, at least some of these associations are problematic, and in any case, hematological or immunological (e.g., dermal sensitization) effects have not generally been found in humans following exposure to either compound.

Common acute or subchronic neurotoxic effects observed in animals are characterized by increased irritability, salivation, hyperexcitability, tremors followed by convulsions, loss of body weight, depression, prostration, and death (Borgmann et al., 1952; Walker et al., 1969; Wagner and Greene, 1978; Woolley et al., 1985; NCI, 1978; Casteel, 1993). These symptoms are similar to those described above for humans exposed to aldrin or dieldrin. Various manifestations of hepatotoxicity (elevated serum enzyme levels, reduced levels of serum proteins, hyperplasia, focal degeneration, necrosis, bile duct proliferation, etc.) have been observed in animals following subchronic-to-chronic exposure to moderate-to-high concentrations of aldrin/dieldrin (ATSDR, 2000a). Relatively low-dose, chronic exposures to either compound have been

associated with histopathological liver changes in rat studies (e.g., Fitzhugh et al., 1964; Walker et al., 1969). There is some evidence from animals that aldrin/dieldrin exposure may either induce renal lesions or exacerbate pre-existing nephropathy (ATSDR, 2000a; Fitzhugh et al., 1964; Harr et al., 1970).

Various *in vivo* and *in vitro* studies have provided evidence that aldrin and dieldrin may be weak endocrine disruptors. Effects on male and female hormone levels and/or receptor binding, male germ cell degeneration and interstitial testicular (Leydig) cell ultrastructure, estrus cycle, and proliferation of endometrial and breast cells have been noted (see Sections 7.3.3 and 7.3.4; ATSDR, 2000a). Oral administration of aldrin/dieldrin to maternal or paternal animals has produced somewhat equivocal evidence of decreased fertility (Dean et al., 1975; Epstein et al., 1972; Good and Ware, 1969; Harr et al., 1970; Virgo and Bellward, 1975), and intraperitoneal injection of aldrin has produced various adverse effects on the male reproductive system (ATSDR, 2000a). In general, animal studies have provided only mixed evidence that exposures to aldrin/dieldrin at moderate-to-high levels can result in adverse reproductive or developmental effects, such as reduced fertility or litter size, reduced pup survival, fetotoxicity, or teratogenicity (Section 7.2.5).

Immunosuppression by dieldrin has been reported in a number of mouse studies: a decrease in the antigenic response to the mouse hepatitis virus 3 after a single oral dose of $\geq$18 mg/kg bw (Krzystyniak et al., 1985); an increase in the lethality of *Plasmodium berghei* or *Leishmania tropica* infections at dietary concentrations as low as 1 ppm (0.15 mg/kg bw/day) for 10 weeks (Loose, 1982); and decreased tumor cell killing ability after dietary concentrations as low as 1 ppm (0.15 mg/kg bw/day) for 3, 6, or 18 weeks (Loose et al., 1981).

A number of long-term bioassay studies have provided evidence that aldrin and dieldrin are hepatocarcinogens in the mouse (Davis and Fitzhugh, 1962; Davis, 1965; Song and Harville, 1964; NCI, 1978; MacDonald et al., 1972; Walker et al., 1972; Thorpe and Walker, 1973; Tennekes et al., 1982, 1981, 1979; Meierhenry et al., 1983). In one mouse study, dieldrin was also found to have induced lung, lymphoid, and "other" tumors (Walker et al., 1972). In contrast, neither compound has been found to induce liver tumors in various strains of rat (Treon and Cleveland, 1955; Song and Harville, 1964; Deichmann et al., 1967, 1970; Deichmann, 1974; NCI, 1978; Fitzhugh et al., 1964; Walker et al., 1969), although a number of these studies suffered from one or more serious deficiencies. The NCI (1978) rat study also yielded some increased incidences of thyroid follicular cell and adrenal cortex adenomas/carcinomas following aldrin exposure, which have been considered either unrelated to treatment (NCI, 1978; USEPA, 1993a), or suggestive of equivocal evidence of aldrin's potential carcinogenicity in the rat (Griesemer and Cueto, 1980; Haseman et al., 1987; USEPA, 1987).

Despite some sporadic statistically significant increases in rectal or liver/biliary cancer, occupational and epidemiology studies have failed to provide any convincing evidence for the carcinogenicity of either aldrin or dieldrin in humans (Van Raalte, 1977; Versteeg and Jager, 1973; de Jong, 1991; de Jong et al., 1997; Ditraglia et al., 1981; Brown, 1992; Amaoteng-Adjepong et al., 1995). In fact, standardized mortality ratios of exposed vs. general populations for both specific causes and all causes of death have generally been less than 1.0.

Not a great deal is known about the modes of action that may underlie the various toxic effects produced by exposure to aldrin or dieldrin. The hyperexcitability associated with these compounds' neurotoxicity has generally been thought to arise from enhancement of synaptic activity throughout the central nervous system; but whether this results from facilitated neurotransmitter release at the nerve terminals, or from reducing the activity of inhibitory neurotransmitters within the central nervous system, has been unclear (ATSDR, 2000a). Mehrota et al. (1988, 1989) have proposed that dieldrin may act by inhibiting calcium-dependent brain ATPases, which would inhibit the cellular efflux of calcium and result in higher intracellular calcium levels that would promote neurotransmitter release. More recent work provides significant evidence that aldrin and dieldrin's principal mode of neurotoxic action likely involves their role as antagonists for the membrane receptor for the inhibitory neurotransmitter, gamma aminobutyric acid (GABA), and blocking the influx of chloride ion through the $GABA_A$ receptor-ionophore complex (Klaassen, 1996; Nagata and Narahashi, 1994, 1995; Nagata et al., 1994; Brannen et al., 1998; Johns et al., 1998; Liu et al., 1997, 1998). Additionally, at least one *in vitro* study using fetal rat brain cells suggests that dieldrin may have an even greater functional effect on dopaminergic neurons (Sanchez-Ramos et al., 1998).

As noted previously, the cumulative evidence to date (2001) suggests that the carcinogenic potential of aldrin and dieldrin may largely be limited to the mouse. The preponderance of evidence from the studies reviewed in this document argues against a predominant role for genotoxicity in the mode of action for these compounds' carcinogenicity (Sections 7.3.1 and 7.4.2). This appears especially true when considering the overwhelmingly negative results for aldrin and dieldrin's ability to induce gene point mutations (28 negative assays, 3 positive assays). However, when considering either direct DNA damage or chromosome-related interactions (aberrations, aneuploidy, SCEs), the assay results are significantly more balanced (15 negative, 2 most likely negative, 11 positive, 4 "questionably" positive).

Considering "epigenetic" modes of carcinogenic action, the capacity of aldrin and dieldrin to inhibit various forms of *in vitro* intercellular communication in both human and animal cells may be significant with respect to their *in vivo* effects on tumor production (Kurata et al., 1982; Wade et al., 1986; Zhong-Xiang et al., 1986; Mikalsen and Sanner, 1993). As discussed in Section 7.4.3, a number of recent studies have provided suggestive evidence that the apparent mouse-specific hepatocarcinogenic effects of aldrin/dieldrin may result from epigenetic modes of action that involve the induction of intracellular oxidative stress (via the generation of reactive oxygen species that result in oxidative damage to DNA, protein, and lipid macromolecules), as well as increased hepatic DNA synthesis (Kolaja et al., 1995, 1996a,b, 1998; Bachowski et al., 1997, 1998; Stevenson et al., 1995, 1999). These effects have been found to occur after aldrin/dieldrin treatment in mice, but not in rats. After observing the frequency and patterns of *c-Ha-ras* protooncogene mutations appearing in the DNA of glucose-6-phosphatase-deficient hepatic lesions found in control mice, or in those treated with dieldrin or phenobarbital, Bauer-Haufmann et al. (1992) were able to conclude that the increase in hepatic lesions (and thus tumors) resulting from dieldrin treatment likely resulted primarily from promotional, rather than initiation, events. It has been postulated that aldrin/dieldrin induction of hepatic DNA synthesis may also result from the modulation of proto-oncogene expression via various transcription factors (Stevenson et al., 1999).

The available literature did not provide direct evidence for any human subpopulations that would be particularly sensitive to the toxic effects of chronic aldrin/dieldrin exposure, or for which relevant toxicokinetics are known to be differ significantly from those for the general population. Speculatively, the fetus and very young children might be at increased risk from exposures to aldrin/dieldrin as a result of immature hepatic detoxification and excretion functions, as well as developing target organ systems. Some support for this is found in a single case study involving acute exposure to aldrin (Hayes, 1982) in which a 3 year-old female child died after ingesting approximately 8.2 mg/kg, or roughly an order of magnitude less than the estimated lethal dose for an adult male. Several mechanistic studies, which describe the prenatal effects of aldrin/dieldrin on GABA receptor malfunctions and on subsequent behavioral impairment, may suggest an increased sensitivity of children (Brannen et al., 1998; Liu et al., 1998; Johns et al., 1998; Castro et al., 1992). Declining organ and immune functions may also render the elderly more susceptible to aldrin/dieldrin toxicity. Additionally, it is reasonable to expect that individuals with compromised liver, immune, or neurological functions (as a result of disease, genetic predisposition, or other toxic insult) might also display increased sensitivity to these compounds.

9.2.3 Dose-Response Characterization and Implications in Risk Assessment

In adult humans, the acute oral lethal dose for aldrin/dieldrin has been estimated at approximately 70 mg/kg bw (Jager, 1970; ATSDR, 2000a), which is about 3 times the dose reported to have induced convulsions within 20 minutes of ingestion (Spiotta, 1951). Oral LD_{50} values in various animal species for the two compounds have been reported to range from 33 to 95 mg/kg bw, and appear to be affected by age at the time of exposure. In rats, LD_{50} values were reported as 37 mg/kg bw for young adults, 25 mg/kg bw for 2-week-old pups, and a somewhat surprisingly high 168 mg/kg bw for newborns (Lu et al., 1965).

Meaningful dose-response relationships have not been adequately characterized in humans for any of the toxic effects of aldrin or dieldrin. In animals, oral exposure to aldrin/dieldrin has produced a variety of dose-dependent systemic, neurological, immunological, endocrine, reproductive, developmental, genotoxic, and tumorigenic effects over a collective dose range of at least three orders of magnitude (<0.05 to 50 mg/kg bw), depending on the specific endpoint and the duration of exposure (Sections 7.2 and 7.3) (ATSDR, 2000a). Dose-response information for some key studies is summarized below in Table 9-1. For noncancer effects, the USEPA has determined oral RfDs for both aldrin and dieldrin (see Sections 8.1.1.1 and 8.1.1.2) based on the most sensitive relevant toxic effects (critical effects) that have been reported. For aldrin, the critical effect was liver toxicity observed in rats after chronic exposure to approximately 0.025 mg/kg bw/day, the LOAEL and lowest dose tested (Fitzhugh et al., 1964). This dose was divided by a composite uncertainty factor of 1,000 (to account for rat-to-human extrapolation, potentially sensitive human subpopulations, and the use of a LOAEL rather than a NOAEL) to yield an oral RfD for aldrin of 3×10^{-5} mg/kg bw/day. Similarly for dieldrin, a chronic rat study NOAEL for liver toxicity of approximately 0.005 mg/kg bw/day (Walker et al., 1969) was divided by a composite uncertainty factor of 100 (to account for rat-to-human extrapolation and potentially sensitive human subpopulations) to yield an oral RfD of 5×10^{-5} mg/kg bw/day.

Based on the long-term mouse bioassays discussed in Sections 7.2.7 and 7.4.2 to 7.4.4, the USEPA has classified both aldrin and dieldrin as group B2 carcinogens under the current cancer guidelines (USEPA, 1986), that is, as probable human carcinogens with little or no evidence of carcinogenicity in humans, and sufficient evidence in animals. Under the USEPA's proposed cancer risk assessment guidelines (USEPA, 1996/1999), the weight of evidence indicates that aldrin and dieldrin could be classified as rodent carcinogens that are "*likely to be carcinogenic to humans by the oral route of exposure, but whose carcinogenic potential by the inhalation and dermal routes of exposure cannot be determined because there are inadequate data to perform an assessment*." This characterization must be tempered by the lack of evidence for significant human carcinogenicity from epidemiological studies and by the general lack of corroborative evidence for carcinogenicity in rats. Mechanistic studies performed *in vitro* and *in vivo* suggest that one or more non-genotoxic modes of action may underlie or contribute to the carcinogenic potential of aldrin and dieldrin, but these effects are not completely established, nor can a role for genotoxic mechanisms confidently be eliminated based on the available data. Based on these considerations, the quantitative cancer risk assessments of aldrin and dieldrin have been conducted conservatively using the linear-default model.

Table 9-1. Dose-Response Information from Key Studies of Aldrin and Dieldrin Toxicity

Study	Species	No./Sex per Group	Doses mg/kg bw/day	Duration	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Effects
Chronic Studies – Aldrin[1]							
Fitzhugh et al. (1964)	Rat Osborne-Mendel	12 M 12 F	0 0.025 0.1 0.5 2.5 5.0 7.5	2 yr	– 0.5	0.025 2.5	Liver histopathology Increased mortality; enlarged livers; nephritis; distended and hemorrhagic urinary bladders
Chronic Studies – Dieldrin[1]							
Walker et al. (1969)	Rat Carworth Farm "E"	25 M 25 F	0 0.005 0.05 0.5	2 yr	0.005 0.05	0.05 0.5	Increased absolute and relative liver weights Irritability, tremors, convulsions; CHIRL[2]
Cancer Bioassay Studies – Aldrin[3]							
Davis (1965)[4]	Mouse C_3H	100 M 100 F	0 1.5	2 yr	–	1.5	Hepatomas and hepatocellular carcinomas (not tabulated by sex)

Table 9-1 (continued)

Study	Species	No./Sex per Group	Doses mg/kg bw/day	Duration	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Effects
NCI (1978)	Mouse $B6C3F_1$	50 M 50 F	0 0.45 (F) 0.6 (M) 0.9 (F) 1.2 (M)	80 wk	–	0.6 (M)	Hepatocellular carcinoma (M); no statistically significant tumor increases were observed in (F)
NCI (1978)[5]	Rat Osborne-Mendel	50 M 50 F	0 1.5 3	74 wk (M) 80 wk (F)	–	1.5 ?	Suggestive/equivocal evidence of thyroid follicular cell adenoma and carcinoma (M/F) and adrenal cortex adenoma (F) at low, but not high, dose
Cancer Bioassay Studies – Dieldrin[3]							
Davis (1965)[4]	Mouse C_3H	100 M 100 F	0 1.5	2 yr	–	1.5	Hepatomas and hepatocellular carcinomas (not tabulated by sex)

Table 9-1 (continued)

Study	Species	No./Sex per Group	Doses mg/kg bw/day	Duration	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Effects
Walker et al. (1972)	Mouse CF_1	125-300 M 125-300 F	0 0.015 0.15 1.5	132 wk	–	0.15	Hepatocellular carcinoma (F), no statistically significant tumor increase was observed at low dose; [hepatocellular carcinoma and hepatoma at high dose (M/F); lung and lymphoid tumors at low and medium doses (F)]
		30 M 30F	0 0.188 0.375 0.75 1.5 3	128 wk	–	0.375	Hepatocellular carcinomas and/or hepatomas (M/F), no statistically significant tumor increases were observed at the low dose
Thorpe and Walker (1973)	Mouse CF_1	30-45 M 30-45 F	0 1.5	110 wk	–	1.5	Hepatocellular carcinomas and hepatomas (M/F)
NCI (1978)	Mouse $B6C3F_1$	50 M 50 F	0 0.375 0.75	80 wk	–	0.75 (M)	Hepatocellular carcinomas (M); no statistically significant tumor increases were observed at the low dose (M) or in (F)
Tennekes et al. (1981)	Mouse CF_1	139 M (total; 252 controls)	0 1.5	110 wk	–	1.5 (M)	Hepatocellular carcinomas and hepatomas (M; 2 experiments with different diets)

Table 9-1 (continued)

Study	Species	No./Sex per Group	Doses mg/kg bw/day	Duration	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Effects
Meierhenry et al. (1983)	Mouse C57BL/6J	69-71 M	0 1.5	85 wk	–	1.5 (M)	Hepatocellular carcinomas (and hepatomas in C57BL/6J and $B6C3F_1$ strains)
	Mouse C3H	50 M	0 1.5	85 wk	–	1.5 (M)	
	Mouse $B6C3F_1$	62-76 M	0 1.5	85 wk	–	1.5 (M)	

[1] Studies serving as the principal basis for oral RfD determinations.
[2] Chlorinated hydrocarbon insecticide rodent liver.
[3] Studies utilized in the derivation of cancer potency estimates.
[4] As reevaluated by Reuber and reported in Epstein (1975).
[5] This study was not used for the derivation of cancer potency estimates, but is the source of the only data that provides any evidence of aldrin/dieldrin's tumorigenic potential in the rat.

This approach has yielded geometric mean cancer potency estimates for aldrin and dieldrin of 17 and 16 $(mg/kg\ bw/day)^{-1}$, respectively (Sections 8.2.1.1 and 8.2.1.2). These result in drinking water unit risks of 4.9×10^{-4} per mg/L and 4.6×10^{-4} per mg/L, respectively. For both compounds, a drinking water concentration of 0.002 µg/L would lead to an estimated lifetime excess cancer risk of 10^{-6}. This concentration, 0.002 µg/L, was selected as the Health Reference Level (HRL) for each chemical, and was used in Chapter 4 to put into context the levels of aldrin/dieldrin detected in drinking water.

9.3 Occurrence in Public Water Systems

The second criterion asks if the contaminant is known to occur, or if there is a substantial likelihood that the contaminant will occur, in public water systems with a frequency and at levels of concern for public health. In order to address this question, the following information was considered:

- Monitoring data from public water systems
- Ambient water concentrations and releases to the environment
- Environmental fate

Data on the occurrence of aldrin and dieldrin in public drinking water systems were the most important determinants in evaluating the second criterion. EPA looked at the total number of systems that reported detections of aldrin/dieldrin, as well those that reported concentrations of aldrin/dieldrin above an estimated drinking water health reference level (HRL). For noncarcinogens, the estimated HRL risk level was calculated from the RfD assuming that 20% of the total exposure would come from drinking water. For carcinogens, the HRL was the 10^{-6} risk level. The HRLs are benchmark values that are used in evaluating the occurrence data while the risk assessments for the contaminants are being developed.

The available monitoring data, including indications of whether or not the contamination is a national or a regional problem, are included in Chapter 4 of this document and are summarized below. Additional information on production, use, and environmental fate are found in Chapters 2 and 3.

9.3.1 Occurrence Criterion Conclusions

Since aldrin and dieldrin have not been used in this country since 1987, there should be no new releases to the overall environment. The analyses presented previously for aldrin and dieldrin indicate that these chemicals are detected very infrequently and at very low concentrations in drinking water. Therefore, it is unlikely that aldrin and dieldrin will occur in public water systems with any significant frequency at levels of concern for public health.

9.3.2 Monitoring Data

Drinking Water

As more fully discussed in Chapter 4, the analyzed drinking water occurrence data for aldrin and dieldrin were collected beginning in 1993 under "Round 2" of the Safe Drinking Water Act's Unregulated Contaminant Monitoring (UCM) Program. Monitoring ended for small public water systems (PWSs) on January 8, 1999, and for large PWSs on January 1, 2001. Round 2 UCM data were collected from 35 "primacy entities," which included 34 states and some Native American tribal systems. However, because the data from some states were incomplete and/or otherwise biased, and because the data were not collected within a systematic or random statistical framework, the national representativeness of the combined data set is considered problematic. In an attempt to at least partially address these concerns, a cross-section of state data sets was constructed that provides a reasonable representation (although not a truly "statistically representative" sample) of national occurrence. This was accomplished by a process of first evaluating the data sets for completeness, quality, and bias; after eliminating unusable state data, the remaining states were reevaluated for their pollution potential (from manufacturing and population density, and from agricultural activity) and their "geographic coverage" in relation to all states. The result of this process established a "national cross-section" of Round 2 states (AK, AR, CO, KY, ME, MD, MA, MI, MN, MS, NH, NM, NC, ND, OH, OK, OR, RI, TX, and WA).

It should be noted that while MA was included in the Round 2 cross-section on the basis of usable and complete data for volatile organic compounds (VOCs) and inorganic compounds (IOCs), it was excluded from the analysis of synthetic organic compounds like aldrin and dieldrin because of incomplete and abnormal data (atypically high percentage of detects in a relatively small number of PWSs). Therefore, the Round 2 cross-section (R2-X) data discussed here exclude that from MA and are based on the other 19 states; selected summary statistics are shown in Table 9-2. For perspective and to provide a conservative "upper bound" analysis of aldrin/dieldrin occurrence in drinking water, certain summary statistics and national extrapolations based on all reporting Round 2 states (i.e., "R2-ARS" data) are presented here and in Chapter 4.

The data indicate that both compounds are only infrequently detected in PWSs and only at very low concentrations. Because the HRL (0.002 µg/L) is below all of the states Minimum Reporting Levels (MRLs), any sample detect is also greater than the HRL and ½ HRL levels; thus, summary occurrence statistics are all the same, whether based on the MRL, HRL, or ½ HRL. Aldrin was detected in 0.016% of the R2-X PWSs at concentrations ≥ the HRL, which yields a national extrapolation of 11 PWSs serving 39,000 people. Although excluded from the Round 2 cross-section, states with positively-biased detect statistics (e.g., AL) nonetheless represent real detections of aldrin in drinking water that are not adequately accounted for by R2-X data extrapolation. As a consequence, R2-X data extrapolation clearly underestimates the national occurrence of aldrin in PWSs. To provide a more conservative estimate, one which is likely an overestimate of national occurrence, R2-ARS data may be used for extrapolation. In this case, an R2-ARS PWS detection rate of 0.212% extrapolates nationally to 138 PWSs having aldrin concentrations ≥the HRL, and serving 1,052,000 people.

Table 9-2. Selected Summary Statistics for Occurrence of Aldrin and Dieldrin in Drinking Water

Parameter	Round 2 Cross-Section (19 States)[1]	Round 2 Reporting States[2]
Aldrin		
Total samples	31,083	41,565
Percent of samples with detections	0.006%	0.132%
Median concentration (all samples)	<(Non-detect)	<(Non-detect)
99th Percentile concentration (all samples)	<(Non-detect)	<(Non-detect)
Median concentration (detections only)	0.58 µg/L	0.18 µg/L
99th Percentile concentration (detections only)	0.69 µg/L	4.40 µg/L
Minimum Reporting Level (MRL)	variable	variable
Draft Health Reference Level (HRL)	0.002 µg/L	0.002 µg/L
Percent of PWSs with detections >MRL	0.016%	0.212%
Percent of PWSs with detections >(1/2 HRL)	0.016%	0.212%
Percent of PWSs with detections > HRL	0.016%	0.212%
Dieldrin		
Total samples	29,603	40,055
Percent of samples with detections	0.064%	0.135%
Median concentration (all samples)	<(Non-detect)	<(Non-detect)
99th Percentile concentration (all samples)	<(Non-detect)	<(Non-detect)
Median concentration (detections only)	0.16 µg/L	0.42 µg/L
99th Percentile concentration (detections only)	1.36 µg/L	4.40 µg/L
Minimum Reporting Level (MRL)	variable	variable
Draft Health Reference Level (HRL)	0.002 µg/L	0.002 µg/L
Percent of PWSs with detections >MRL	0.093%	0.211%
Percent of PWSs with detections >(1/2 HRL)	0.093%	0.211%
Percent of PWSs with detections > HRL	0.093%	0.211%

[1]Based on data from the 20-State Cross Section, minus MA (SDWIS/FED, UCM Round 2, 1993).
[2]Based on data from all reporting states (SDWIS/FED, UCM Round 2, 1993).
Source: Data taken from Tables 4-2 and 4-5 in Section 4.0 of this document.
Abbreviations: HRL = Health Reference Level; MRL = Minimum Reporting Level; PWS = Public Water System.

Although only five states (AL, MA, NM, PA, TX) reported detecting aldrin in any of their PWSs, their distribution is sufficiently broad to categorize aldrin's drinking water occurrence as national in scope, rather than just regional or local. This conclusion is further supported by the observations that aldrin has been detected at NPL sites in at least 31 states, and at least in 40 states at sites listed in ATSDR's HazDat database. Independent analysis of data from the corn belt states of Iowa, Indiana, and Illinois revealed that aldrin was not detected in any surface or ground water PWS in Iowa or Indiana, or in any ground water PWS in Illinois. It was, however, detected in 1.8% of Illinois' surface water PWSs.

Similarly, dieldrin was detected in 0.093% of the R2-X PWSs at concentrations ≥ the HRL, which yields a national extrapolation of 61 PWSs serving 150,000 people. As with aldrin, a more conservative estimate (a likely overestimate) of national dieldrin occurrence in drinking water may be derived using R2-ARS data for extrapolation. In this case, an R2-ARS PWS detection rate of 0.211% extrapolates nationally to 137 PWSs with dieldrin concentrations ≥ the HRL, serving 793,000 people.

Again, although only eight states (AL, AR, CT, MA, MD, NC, PA, TX) reported detecting dieldrin in any of their PWSs, their distribution is sufficiently broad to categorize dieldrin's drinking water occurrence as national in scope, rather than just regional or local. This conclusion is further supported by the observation that dieldrin has been detected at NPL sites in at least 31 states and at least in 40 states at sites listed in ATSDR's HazDat (ATSDR, 2000b) database. Independent analysis of data from the corn belt states of Iowa, Indiana, and Illinois revealed that dieldrin was not detected in any surface or ground water PWS in Iowa, or in any ground water PWS in Illinois or Indiana. It was, however, detected in 1.8% of Illinois' and 2.1% of Indiana's surface water PWSs.

Ambient Water

In the context of drinking water, "ambient water" may be defined as source water that exists in surface waters and aquifers before treatment (Chapter 4). The U.S. Geological Survey's (USGS's) National Ambient Water Quality Assessment (NAWQA) Program, which began in 1991, provides the most comprehensive and nationally representative data available that describe ambient water quality. Unfortunately, aldrin was not selected as an analyte for either the NAWQA's ground water or surface water studies. However, the NAWQA did analyze for aldrin in aquatic biota tissue and stream bed sediments at 591 sites from 20 of its 59 "study units" (i.e., significant watersheds and aquifers) during the period from 1992 to 1995. While aldrin was not detected in any aquatic biota tissue samples, it was detected above the Method Detection Limit (MDL) of 1 mg/kg in 0.4% of all sites (urban = 0.0%, mixed land use = 0.5%, agricultural = 0.6%, forest-rangeland = 0.0%). Additionally, a mid-1980s survey of community water supply wells in Illinois detected aldrin in only 0.3% of the wells, using an MRL of 0.004 mg/L.

In contrast to aldrin, dieldrin was selected as an NAWQA analyte for both surface and ground water studies during the first round of intensive monitoring (1991 to 1996), which targeted 20 study unit watersheds. Dieldrin detection frequencies at two MDLs (0.001 mg/L; 0.01 mg/L) were as follows for stream surface waters: urban (3.67%; 1.83%), integrator (3.27%;

1.63%), agricultural (6.90%; 3.90%), and total sites (4.64%; 2.39%). For ground water sources, the comparable data were: shallow urban (5.65%; 3.32%), shallow agricultural (0.97%; 0.65%), major aquifers (0.43%; 0.21%), and total sites (1.42%; 0.93%). As with aldrin, the NAWQA program also analyzed for dieldrin in aquatic biota tissue and stream bed sediments at 591 sites from 20 of its 59 "study units" during the period from 1992 to 1995. It was detected at levels above the MDL of 1 mg/kg in 13.7% of the sediments from all sites, and at levels above the MDL of 5 mg/kg in 28.6% of whole fish samples and in 6.4% of bivalve samples. Additionally, a 1991 to 1992 survey of surface waters from the Mississippi River and six of its tributaries that drain the corn belt reported 8% of all samples and 71% of all sites registered detections above the MRL of 0.02 mg/L.

9.3.3 Use and Fate Data

Both aldrin and dieldrin are SOC pesticides that were at one time extensively used in a wide variety of agricultural and residential/urban pest-control applications (Chapters 2 and 4). They were manufactured and distributed in the United States by the Shell Chemical Company until 1974. From 1974 through 1985 (except 1979 to 1980), Shell International (Holland) imported lesser amounts (e.g., 1 to 1.5 million lb/year from 1981 to 1985). Importation information for dieldrin was not available. In 1972, the USEPA cancelled all but three specific uses of these compounds (subsurface ground insertion for termite control, dipping of non-food plant roots and tops, and moth-proofing in manufacturing processes using completely closed systems). This decision was finalized in 1974, and by 1987 these remaining uses were voluntarily cancelled by the manufacturer.

Use of aldrin in the U.S. peaked at 19,000,000 lbs in 1966, decreasing to 10,500,000 lbs by 1970; during the same period, dieldrin use declined from 1,000,000 to 670,000 lbs (ATSDR, 2000a). By the time the Toxic Release Inventory (TRI) was mandated in 1986 by the Emergency Planning and Community Right-to-Know Act (EPCRA) and then subsequently implemented, the manufacture, import, and use of aldrin/dieldrin had been cancelled. The EPCRA mandates that facilities with more than 10 full-time employees that manufacture/import more than 25,000 lbs, or use more than 10,000 lbs, of a TRI chemical are required to report the lb/year of the chemical that were released to the environment, both on-site and off-site. It was not until 1995 that hazardous waste treatment and disposal facilities were added to the list of those required to report TRI data. In 1998, the first year for which this requirement became effective, hazardous waste facilities in three states (AR, MI, TX) reported releases of aldrin totaling 25,622 lbs. No such releases of dieldrin were reported.

The environmental fate of aldrin and dieldrin is extensively summarized in Chapter 3. Briefly, under most environmental conditions, aldrin is largely converted biologically or abiotically to dieldrin, which is significantly more environmentally stable. Most of these compounds are released to the environment via the soil, where relatively high log K_{ow} and K_{oc} are indicative of their low water solubility and strong affinity for adsorption to soil. Over time, significant quantities may volatilize to the atmosphere or be carried aloft by wind-born particles, where they are subject to certain photodegradation processes and/or subsequent "washout" in rainfall. Because of their low water solubilities and strong soil adsorption tendencies, aldrin and dieldrin slowly migrate downward through the soil or enter surface or ground water. Most

aldrin/dieldrin found in surface water is thought to result from particulate surface run-off (the compounds being bound to soil particles). In summary, these characteristics will tend to maintain relatively low levels of water contamination over relatively prolonged periods of time.

Obviously, neither compound is used as a drinking water treatment chemical, nor is either likely to be a leachate from drinking water contact surfaces. However, it is not unreasonable to expect that they may co-occur in drinking water with each other, as well as with certain other persistent pesticides; in such cases, additive or synergistic toxic effects may be possible.

9.4 Risk Reduction

The third criterion asks if, in the sole judgment of the Administrator, regulation presents a meaningful opportunity for health risk reduction for persons served by public water systems. In evaluating this criterion, EPA looked at the total exposed population, as well as the population exposed above the estimated HRL. Estimates of the populations exposed and the levels to which they are exposed were derived from the monitoring results. These estimates are included in Chapter 4 of this document and are summarized in Section 9.4.2.

In order to evaluate risk from exposure through drinking water, EPA considered the net environmental exposure in comparison to the exposure through drinking water. For example, if exposure to a contaminant occurs primarily through ambient air, regulation of emissions to air provides a more meaningful opportunity for EPA to reduce risk than regulation of the contaminant in drinking water. In making the regulatory determination, the available information on exposure through drinking water (Chapter 4) and information on exposure through other media (Chapter 5) were used to estimate the fraction that drinking water contributes to the total exposure. The EPA findings are discussed in Section 9.4.3.

In making its regulatory determination, EPA also evaluated effects on potential sensitive populations, including the fetus, infants, and children. The sensitive population considerations are included in Section 9.4.4.

9.4.1 Risk Criterion Conclusions

The data discussed in this section and Section 9.3.3 indicate that there is not a substantial likelihood that aldrin and dieldrin will occur in public water systems with frequencies and at levels of concern for public health.

9.4.2 Exposed Population Estimates

As noted previously, because the HRL of 0.002 mg/L for these compounds is below the MRL, any recorded detection will be above all three reference levels (MRL, HRL, ½ HRL). Therefore, estimates of the national population exposed to concentrations greater than any of these levels will be equivalent. Summary data for exposed population estimates are provided below in Table 9-3.

It must be remembered that the complete R2-ARS-based estimates are very conservative in nature, in that they are derived from a collective database that includes incomplete and biased state data sets, and because only a single detection is sufficient to classify a PWS as "positive" – these factors will tend to significantly overestimate the true sizes of the exposed populations. On the other hand, using data only from the Round 2 cross-section (from 19 states, the R2-X-based estimates), which have been screened to remove incomplete, biased, and otherwise unusable data and then selected to geographically represent the entire nation, is less likely to overestimate and may even underestimate to some extent the potentially exposed national populations.

For aldrin, the median and 99th percentile concentrations of detections based on all Round 2 UCM data were 0.18 and 4.40 µg/L, respectively. Based only on the 19-state Round 2 cross-section data, the corresponding values are 0.58 and 0.69 µg/L. The respective two sets of values for dieldrin are 0.42 and 4.40 µg/L, and 0.16 and 1.36 µg/L. While these values are above the HRL of 0.002 µg/L, it must also be kept in mind that the corresponding values for all samples were below the detection limit, and that the HRL itself is likely a very conservative estimate of any human risk resulting from exposure to these chemicals.

Table 9-3. National Population Estimates for Aldrin and Dieldrin Exposure via Drinking Water

Population of Concern	Round 2 Cross-Section (19 States)[1]	Round 2 Reporting States[2]
Aldrin		
Served by PWS with detections	38,871	1,051,989
Served by PWSs with detections > (1/2 HRL)	38,871	1,051,989
Served by PWSs with detections > HRL	38,871	1,051,989
Dieldrin		
Served by PWS with detections	149,827	792,703
Served by PWSs with detections > (1/2 HRL)	149,827	792,703
Served by PWSs with detections > HRL	149,827	792,703

[1]Based on data from the 20-State Cross Section, minus MA (SDWIS/FED, UCM Round 2, 1993).
[2]Based on data from all reporting states (SDWIS/FED, UCM Round 2, 1993).
Source: Data taken from Tables 4-2 and 4-5 in Section 4.0 of this document.
Abbreviations: HRL = Health Reference Level; PWS = Public Water System.

9.4.3 Relative Source Contribution

Analysis of relative source contribution compares the magnitude of exposures (i.e., intakes) expected via consumption of drinking water with those estimated for other relevant media such as food, air, and soil. The data summarized in Chapter 4.0 provide the basis for estimating the amounts of aldrin and dieldrin ingested via drinking water in exposed populations. For this exercise, the non-conservative approach was taken by utilizing the median and 99th percentile detect concentrations derived from only UCM Round 2 cross-section data (realizing that this will certainly underestimate to some degree the true contribution of drinking water to the exposed population's total intake of aldrin/dieldrin).

For a 70 kg adult consuming 2 L/day of water containing aldrin at either 0.58 μg/L (median detect concentration) or 0.69 μg/L (99th percentile detect concentration), the corresponding aldrin intake values from drinking water are 1.7×10^{-5} and 2.0×10^{-5} mg/kg bw/day, respectively. For a 10 kg child consuming 1 L/day of water, the comparable values are 5.8×10^{-5} and 6.9×10^{-5} mg/kg bw/day.

Similarly, for median and 99th percentile detect concentrations of dieldrin (0.16 and 1.36 μg/L, respectively), the corresponding adult drinking water intake values of dieldrin are 0.46×10^{-5} and 3.9×10^{-5} mg/kg bw/day, respectively. Dieldrin drinking water intake values for the 10 kg child are 1.6×10^{-5} and 14×10^{-5} mg/kg bw/day.

Chapter 5 presents data on the estimated daily dietary intake of aldrin and dieldrin (see Tables 5-3 and 5-4). Combining estimates for non-fish food with those for fish and shellfish, adult and child dietary intakes of aldrin are estimated at 3.3 to 6.5×10^{-5} and 13 to 18×10^{-5} mg/kg bw/day, respectively. For dieldrin, the comparable adult and child dietary intakes are 3.6×10^{-5} and 14×10^{-5} mg/kg bw/day.

Comparing these derived estimates for intakes via drinking water and diet, the ratios of dietary intake to drinking water intake for aldrin range from 1.7 to 3.8 across all combinations of age and drinking water concentration level. For dieldrin, the food/water intake ratios for adults and children are 0.9 and 1.0 using the 99th percentile water concentration, and 7.8 and 8.8 using the median water concentration. Applying the more "conservative" aldrin/dieldrin water concentrations based on the monitoring data of all reporting UCM Round 2 states would reduce all of these food/water ratios by a factor of approximately 3 to 6. Thus, when conservatively analyzed relative to the diet, drinking water could potentially be responsible for a significant portion of total daily intake of aldrin/dieldrin, but only for limited populations under exposure circumstances that are considered unlikely.

Referring again to Tables 5-3 and 5-4, it can be seen that the estimated daily intakes of aldrin and dieldrin from air for adults and children range from 0.013×10^{-5} to 0.24×10^{-5} mg/kg bw/day. Despite the fact that these values are likely significant overestimates since they are based on data that is 30 years old, they are still small relative to drinking water and dietary intakes. Although soil data were not available for aldrin, those for dieldrin indicate that ingestion of soil represents only a minor exposure pathway for these compounds.

9.4.4 Sensitive Populations

The issue of sensitive populations has already been addressed to the extent currently possible. While there is some reasonable basis to suspect that fetuses, young children, the elderly, and those having compromised liver, immune, or even neurological function may be at increased risk for one or more of the toxic effects of aldrin/dieldrin, such susceptibility has not yet been convincingly demonstrated or adequately quantified in the scientific literature.

9.5 Regulatory Determination Summary

While there is evidence that aldrin/dieldrin may have adverse health effects, including the probability to cause cancer in humans,.neither contaminant has been used in the US since 1987. Furthermore, monitoring data indicate that the contaminants' concentrations have been declining since the cancellation of their registrations as pesticides. Their occurrences in public water systems have also been very limited and at very low concentrations. For these reasons, regulation of aldrin and dieldrin may not present a meaningful opportunity for health risk reduction for persons served by public water systems. Therefore, EPA may not propose to regulate aldrin/dieldrin with NPDWRs. All final determinations and future analysis will be presented in the Federal Register Notice covering CCL proposals.

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Abbreviations and Acronyms

ACGIH	- American Conference of Governmental Industrial Hygienists
ADI	- Acceptable Daily Intake
AI	- active ingredient
ATSDR	- Agency for Toxic Substances and Disease Registry
BCF	- bioconcentration factor
BCH	- bicycloheptadiene
BTFs	- biotransfer factors
CASRN	- Chemical Abstract Service Registry Number
CCL	- Contaminant Candidate List
CERCLA	- Comprehensive Environmental Response, Compensation & Liability Act
CI	- Confidence Interval
CMR	- Chemical Monitoring Reform
CNS	- central nervous system
CWSs	- community water systems
DBCP	- dibromochloropropane
2,3-DHBA	- 2,3-dihydroxybenzoic acid
DMPC	- dimyristoylphosphatidylcholine
DNA	- deoxyribonucleic acid
DPH	- 1,6-diphenyl-1,3,5-hexatriene
DPH-PA	- propionic acid deriative of DPH
DRG	- dorsal root ganglion
EEG	- electroencephalogram
EMAP	- Environmental Monitoring Assessment Program
EPA	- Environmental Protection Agency
EPCRA	- Emergency Planning and Community Right-to-Know Act
F	- female
FDA	- Food and Drug Administration
FIFRA	- Federal Insecticide, Fungicide, and Rodenticide Act
FSH	- follicle stimulating hormone
GABA	- gamma aminobutyric acid
GAD-ir	- glutamate decarboxylase immunoreactive
GC/MS	- gas chromotography/ mass spectometry
gd	- gestation day
GI	- gastrointestinal tract
$G6P^-$	- glucose-6-phosphatase deficient
GW	- ground water
HazDat	- Hazardous Substance Release and Health Effects Database

HCCPD	- hexachlorocyclopentadiene
HRL	- Health Reference Level
HSDB	- Hazardous Substances Data Bank
IARC	- International Agency for Research on Cancer
IC_{50}	-
IOC	- inorganic contaminant
IPCS	- International Programme on Chemical Safety
IRIS	- Integrated Risk Information System
IUPAC	- International Union of Pure and Applied Chemistry
LD_{50}	- lethal dose
LH	- Lutenizing hormone
LOAEL	- lowest-observed-adverse-effect level
M	- male
MCLG	- Maximum Contaminant Level Goal
MDA	- malondialdehyde
MDL	- Method Detection Limit
MMT	- methylcyclopentadienyl manganese tricarbonyl
MRL	- Minimum Reporting Level
mRNA	- messenger ribonucleic acid
MW	- molecular weight
NADPH	- nicotine adenine dinucleotide phosphate
NAS/OW	- National Academy of Sciences/Office of Water
NAWQA	- National Water Quality Assessment Program
NCOD	- National Drinking Water Contaminant Occurrence Database
NDWAC	- National Drinking Water Advisory Council
NOAA	- National Oceanic and Atmospheric Administration
NOAEL	- no-observed-adverse-effect level
NPDWR	- National Primary Drinking Water Regulation
NPL	- National Priorities List
NTNCWSs	- non-purchased non-transient non-community water systems
OH8dG	- 8-hydroxy-2'-deoxyguanosine
PB	- phenobarbital
PES	- prostaglandin endoperoxide synthase
PGG_2	- prostaglandin G_2
PHG_2	- prostaglandin H_2
ppd	- postpartum day
ppm	- part per million
PWS	- Public Water System

q1*	- geometric mean
R2-ARS	- Round 2 states
RBCs	- red blood cells
RCRA	- Resource Conservation and Recovery Act
RfD	- Reference Dose
ROS	- reactive oxygen species
RSD	- risk-specific dose
R2-X	- Round 2 cross-section
SARA Title III	- Superfund Amendments and Reauthorization Act
SCE	- sister chromatid exchanges
SDWA	- Safe Drinking Water Act
SDWIS/FED	- Safe Drinking Water Information System (Federal version)
SMRs	- standardized mortality ratios
SOC	- synthetic organic compound
^{35}S-TBPS	- t-^{35}S butyl-bicyclophosphorothionate
SW	- surface water
TE_{50}	- median effective time
TH-ir	- tyrosine hydroxylase-immunoreactive
TRI	- Toxic Release Inventory
UCM	- Unregulated Contaminant Monitoring
UCMR	- Unregulated Contaminant Monitoring Regulation/Rule
UDPGA	- uridine diphosphoglucuronic acid
UDS	- unscheduled DNA synthesis
URCIS	- Unregulated Contaminant Monitoring Information System
USDA	- United States Department of Agriculture
USEPA	- United States Environmental Protection Agency
USGS	- United States Geological Survey
UV	- ultraviolet
VOC	- volatile organic compound
atm	- atmospheres
atm-m^3/mol	- atmospheres cubic meter per mole
^oC	- degrees Celsius
cm	- centimeters
cm^2	- square centimeters
g	- grams
g/cc	- grams per cubic centimeter
kg	- kilograms
kg/day	- kilograms per day
kg/ha	- kilograms per hectare
L/day	- liters per day

lbs	- pounds
M	- molar
m	- meter
mg/cm^2	- milligrams per square centimeter
mg/day	- milligrams per day
mg/kg	- milligrams per kilogram
mg/kg bw	- milligrams per kilogram per body weight
mg/kg bw/day	- milligrams per kilogram per body weight per day
mg/kg bw/week	- miiligrams per kilogram per body weight per week
mg/L	- milligrams per liter
mg/m^3	- milligrams per cubic meter
mL	- milliliter
mm Hg	- millimeters of mercury
ng/g	- nanograms per gram
ng/L	- nanograms per liter
ng/m^3	- nanograms per cubic meter
ng/mL	- nanograms per milliliter
nM	- nanomolar
nm	- nanometers
nmol/mL	- nanomole per milliliter
pM	- pico molar
ppb	- parts per billion
µg	- micrograms
$µg/cm^2$	- micrograms per square centimeter
µg/g	- micrograms per gram
µg/L	- micrograms per liter
$µg/m^2$	- micrograms per square meter
$µg/m^3$	- micrograms per cubic meter
µM	- micro molar

APPENDIX A: Round 2 Aldrin Occurrence

Aldrin Occurrence in Public Water Systems in Round 2, UCM (1993) results

STATE	TOTAL UNIQUE PWS	# GW PWS	# SW PWS	% PWS with detections	% GW PWS with	% SW PWS with detections	% PWS > HRL	% GW PWS > HRL	% SW PWS > HRL	99% VALUE (µg/L)
Tribes (06)	26	25	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.50
AK	34	24	10	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
AL	16	11	5	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	0.68
AR	536	431	105	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
AZ										
CA										
CO	750	538	212	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
CT	70	35	35	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
IN										
KY	366	184	182	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 2.00
LA	1,363	1,295	68	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.01
MA	56	29	27	17.86%	17.24%	18.52%	17.86%	17.24%	18.52%	4.40
MD	726	669	57	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 1.00
ME										
MI	2,650	2,570	80	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
MN	1,264	1,234	30	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
MO	378	280	98	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.10
MS	12	11	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
NC	536	490	46	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
ND	296	258	38	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.01
NH	593	560	33	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
NJ										
NM	720	691	29	0.14%	0.14%	0.00%	0.14%	0.14%	0.00%	< 1.00
OH	1,029	882	147	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 30.00
OK	98	76	22	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
OR	1,152	999	153	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
PA	68	57	11	5.88%	7.02%	0.00%	5.88%	7.02%	0.00%	0.10
RI	24	15	9	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.20
SC	939	841	98	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
SD										
TN	7	2	5	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
TX	427	122	305	0.23%	0.82%	0.00%	0.23%	0.82%	0.00%	< 0.20
VT	401	349	52	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
WA	586	517	69	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	< 0.00
WI										
TOTAL	15,123	13,195	1,928	0.21%	0.17%	0.52%	0.21%	0.17%	0.52%	< 1.00
20 STATES	12,221	10,569	1,652	0.10%	0.07%	0.30%	0.10%	0.07%	0.30%	< 2.00
19 STATES[1]	12,165	10,540	1,625	0.02%	0.02%	0.00%	0.02%	0.02%	0.00%	< 2.00

1. Massachusetts data not included in "19 States" summary statistics for Aldrin.

PWS= Public Water Systems;GW= Ground Water (PWS Source Water Type); SW= Surface Water (PWS Source Water Type); MRL= Minimum Reporting Limit (for laboratory analyses).

The Health Reference Level (HRL) is the estimated health effect level as provided by EPA for preliminary assessment for this work assignment.

"% > HRL" indicates the proportion of systems with any analytical results exceeding the concentration value of the HRL.

The Health Reference Level (HRL) used for Aldrin is 0.002 µg/L. This is a draft value for working review only.

The highlighted States are part of the SDWIS/FED 20 State Cross-Section.

APPENDIX B: Round 2 Dieldrin Occurrence

Dieldrin Occurrence in Public Water Systems in Round 2, UCM (1993) results											
STATE	TOTAL UNIQUE PWS	# GW PWS	# SW PWS	% PWS > MRL	% GW PWS > MRL	% SW PWS > MRL	% PWS > HRL	% GW PWS > HRL	% SW PWS > HRL	99% VALUE (µg/L)	
Tribes (06)	25	24	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.10
AK	16	12	4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
AL	4	4	0	100.00%	0.00%	0.00%	100.00%	100.00%	0.00%		0.10
AR	536	431	105	0.19%	0.00%	0.95%	0.19%	0.00%	0.95%	<	0.00
AZ											
CA											
CO	749	537	212	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
CT	70	35	35	1.43%	0.00%	2.86%	1.43%	0.00%	2.86%	<	0.00
IN											
KY	44	20	24	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.21
LA	1,363	1,295	68	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.07
MA	55	28	27	18.18%	17.86%	18.52%	18.18%	17.86%	18.52%		4.40
MD	725	668	57	0.97%	0.90%	1.75%	0.97%	0.90%	1.75%	<	1.00
ME											
MI	2,650	2,570	80	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
MN	1,264	1,234	30	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
MO	378	280	98	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.10
MS	12	11	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
NC	522	475	47	0.38%	0.42%	0.00%	0.38%	0.42%	0.00%	<	0.00
ND	296	258	38	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.01
NH	593	560	33	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
NJ											
NM	716	687	29	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.20
OH	1,029	883	146	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	20.00
OK	98	76	22	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
OR	1,148	995	153	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
PA	67	56	11	7.46%	8.93%	0.00%	7.46%	8.93%	0.00%		0.10
RI	15	6	9	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.30
SC	939	841	98	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
SD											
TN	7	2	5	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
TX	427	122	305	0.23%	0.82%	0.00%	0.23%	0.82%	0.00%	<	0.20
VT	395	343	52	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
WA	582	515	67	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	<	0.00
WI											
TOTAL	14,725	12,968	1,757	0.21%	0.18%	0.46%	0.21%	0.18%	0.46%	<	0.30
20 STATES	11,843	10,357	1,486	0.18%	0.14%	0.47%	0.18%	0.14%	0.47%	<	1.00
19 STATES	11,788	10,329	1,459	0.09%	0.09%	0.14%	0.09%	0.09%	0.14%	<	1.00

1. Massachusetts data not included in "19 States" summary statistics for Dieldrin.

PWS= Public Water Systems; GW= Ground Water (PWS Source Water Type); SW= Surface Water (PWS Source Water Type); MRL= Minimum Reporting Limit (for laboratory analyses).

The Health Reference Level (HRL) is the estimated health effect level as provided by EPA for preliminary assessment for this work assignment.

"% > HRL" indicates the proportion of systems with any analytical results exceeding the concentration value of the HRL.

The Health Reference Level (HRL) used for Dieldrin is 0.002 µg/L. This is a draft value for working review only.
The highlighted States are part of the SDWIS/FED 20 State Cross-Section.