DIELDRIN

DRAFT

Health Advisory Office of Drinking Water U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

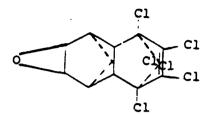
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term > (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived car differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 60-57-1

Structural Formula



Dieldrin: 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene (Windholz, 1983).

Synonyms

HEOD; Alvit; Quintox; Octalox (IPCS, 1987).

Uses

Formerly used for control of soil insects, public health insects, termites and many other pests. These uses have been cancelled and manufacture discontinued in the United States (Meister, 1983).

Properties (NAS, 1977; Weast and Astle, 1982; Windholz, 1983)

Chemical Formula C12H8C160 Molecular Weight 380.93 Physical State Crystals Boiling Point Melting Point 175 to 176°C Density Vapor pressure (20°C) 3.1 x 10-6 mm Hq Water Solubility (25°C) 0.25 mg/L Log Octanol/Water Partition Coefficient Taste Threshold Odor Threshold (water) 0.04 mg/L Conversion Factor

Occurrence

Dieldrin has been found in 9,809 of 52,453 surface water samples analyzed and in 217 of 6,042 ground water samples (STORET, 1987). Samples were collected at 8,831 surface water locations and 4,522 ground water locations, and Dieldrin was found in 48 states, Canada and Puerto Rico. The 85th percentile of all nonzero samples was 0.01 ug/L in surface water and 0.10 ug/L in ground water sources. The maximum concentration found was 301 ug/L in surface water and in 10.08 ug/L in ground water.

Environmental Fate

- · Dieldrin is stable and highly persistent in the environment.
- Dieldrin has the longest half-life of the chlorinated hydrocarbons in water 1-m deep (half-life = 723 days) (MacKay and Wolkoff, 1973).

III. PHARMACOKINETICS

Absorption

A single oral dose of dieldrin at 10 mg/kg body weight (bw) administered in corn oil to male Sprague-Dawley rats produced consistent concentrations of dieldrin in plasma, muscle, brain, kidney and liver for periods up to 48 hours suggesting slow absorption of the substance (Hayes, 1974).

Distribution

• Rats given a single oral dose of dieldrin at 10 mg/kg showed concentrations of dieldrin in fat, muscle, liver, blood, brain and kidney. The highest concentration of dieldrin was in fat. The lowest concentration was in the kidney (Hayes, 1974).

Metabolism

Both the CFE rat and CF1 mouse, following a single oral dose of dieldrin (not less than 85% HEOD) at 3 and 10 mg/kg in olive oil, respectively, metabolized dieldrin to 9-hydroxydieldrin, 6,7-transdihydroaldrindiol and some unidentified metabolites. The rat, but not the mouse, also metabolized dieldrin to pentachloroketone (Baldwin and Robinson, 1972).

Excretion

• Female rats infused with total doses of 8 to 16 mg ³⁶Cl-dieldrin/kg bw excreted approximately 70% of the infused dose in the feces over a period of 42 days, while only about 10% of the dose was recovered in the urine. Excretion was markedly increased by restriction of the diet indicating that the concentration of dieldrin in the blood increased as fat was mobilized (Heath and Vandekar, 1964).

IV. HEALTH EFFECTS

Humans

Dieldrin has been reported to cause hypersensitivity and muscular fasciculations that may be followed by convulsive seizures and respective changes in the EEG pattern. Acute symptoms of intoxication include hyperirritability, convulsions and/or coma sometimes accompanied by nausea, vomiting and headache, while chronic intoxication may result in fainting, muscle spasms, tremors and loss of weight. The lethal dose for humans is estimated to be about 5 g (ACGIH, 1984).

Animals

Short-term Exposure

RTECS (1985) reported the acute oral LD₅₀ values of dieldrin in the rat, mouse, dog, monkey, rabbit, pig, guinea pig and hamster as 38.3, 38, 65, 3, 45, 38, 49 and 60 mg/kg, respectively.

Dermal/Ocular Effects

Aldrin or Dieldrin (dry powder) applied to rabbit skin for 2 h/day,
 5 days/week had no discernible effects (IPCS, 1987).

Long-term Exposure

- Groups of Osborne-Mendel rats, 12/sex/level, were fed 0, 0.5, 2, 10, 50, 100 or 150 ppm dieldrin (recrystallized, 100% active ingredient) in their diet for 2 years. These doses correspond to approximately 0, 0.025, 0.1, 0.5, 2.5, 5.0 or 7.5 mg/kg/day, respectively (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 at 0.5 ppm and males at 10 ppm and greater. 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 (Fitzhugh et al., 1964). A Lowest-Observed-Adverse-Effect-Level (LOAEL) of 0.025 mg/kg/day, the lowest dose tested, was identified in this study.
- Dogs, one/sex/dose level (two/sex at 0.5 mg/kg/day), fed dieldrin (recrystallized, 100% active ingredient) at 0.2 to 10 mg/kg/day, 6 days/week for up to 25 months, showed toxic effects including weight loss and convulsions at dosages of 0.5 mg/kg/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/day (Fitzhugh et al., 1964).
- Groups of Carworth Farm "E" strain rats, 25/sex/dose level, were fed dieldrin (>99% purity) in the diet at 0.0, 0.1, 1.0 or 10.0 ppm for 2 years. These doses correspond to approximately 0, 0.005, 0.05 or 0.5 mg/kg/day, respectively (Lehman, 1959). At 7 months, the 1-ppm intake level was equivalent to approximately 0.05 and 0.06 mg/kg/day for males and females, respectively. No effects on mortality, body weight, food intake, hematology and blood or urine chemistries were seen. At the 10-ppm level, all animals became irritable after 8 to 13 weeks of treatment and developed tremors and occasional convulsions. Liver weight 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).

- Groups of beagle dogs (five/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 phosphate 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/day, but no gross or microscopic lesions were found. There was no evidence of tumorigenic activity (Walker et al., 1969).
- Dieldrin (>99% pure) was administered to CF1 mice of both sexes in the diet for 128 weeks. Dosages were 1.25, 2.5, 5, 10 or 20 ppm dieldrin. These doses are equivalent to 0.19, 0.38, 0.75, 1.5 or 3 mg/kg body weight (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 No-Observed-Adverse-Effect-Level (NOAEL) cannot be established because clinical chemistry parameters were not determined (Walker et al., 1972).

Reproductive Effects

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

Developmental Effects

- Pregnant Syrian golden hamsters given 30 mg/kg bw dieldrin (≥99% pure) in corn oil on days 7, 8 or 9 of gestation manifested an embryocidal and teratogenic response as evidenced by a statistically significant increase in fetal deaths, a decrease in live fetal weight and an increased incidence of webbed foot, cleft palate and open eye (Ottolenghi et al., 1974). Similar anomalies were observed in CD₁ mice administered 15 mg/kg bw dieldrin on day 9 of gestation, but no effect was seen on fetal survival or weight.
- Dieldrin (87% pure) was not found to be teratogenic in the CD rats and CD-1 mice administered doses of 1.5, 3.0 or 6.0 mg/kg/day by gastric intubation on days 7 through 16 of gestation. Fetal toxicity, as indicated by a significant decrease in numbers of caudal ossification centers at the 6.0-mg/kg/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/day dose level, was reported in the experiments in mice. Maternal toxicity in the high-dose rats was indicated by a 41% mortality and a significant decrease in weight gain; similarly, mice

receiving 6.0 mg/kg/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 3.0 and 6.0 mg/kg/day (Chernoff et al., 1975).

Mutagenicity

- Dieldrin was not mutagenic in the <u>Salmonella</u>/microsome test with and without S-9 mix (McCann et al., 1975).
- Dieldrin significantly decreased the mitotic index and increased chromosome abnormalities in STS mice bone marrow cells in an in vivo study. Similar observations were made in human WI-38 embryonic lung cells in an in vitro test that also gave evidence of cytotoxicity, as indicated by degree of cell degeneration (Majumdar et al., 1976).

Carcinogenicity

- A dose-related increase in the incidence of hepatocellular carcinomas was observed in B6C3F₁ mice, with the incidence in the high-dose males being significantly higher when compared to pooled controls (NCI, 1978). Mice were given dieldrin (technical grade, >85% purity) in the diet at concentrations of 2.5 or 5 ppm for 80 weeks. These doses correspond to approximately 0.375 or 0.75 mg/kg/day, respectively (Lehman, 1959).
- Osborne-Mendel rats treated with dieldrin at Time-Weighted Average (TWA) doses of 29 or 65 ppm in the diet (approximately 1.45 or 3.25 mg/kg/day, respectively, based on Lehman, 1959) for 80 weeks, did not elicit treatment-related tumors (NCI, 1978).
- Diets containing 0.1, 1.0 or 10 ppm dieldrin (>99% purity), when given to mice of both sexes for 132 weeks, were associated with an increased incidence of liver tumors at all dose levels tested (Walker et al., 1972). These doses are equivalent to approximately 0.015, 0.15 or 1.5 mg/kg/day, respectively (Lehman, 1959).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{\text{(NOAEL or LOAEL)} \times \text{(BW)}}{\text{(UF)} \times \text{(}} = \frac{\text{mg/L}}{\text{L/day}}$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

- BW = assumed body weight of a child (10-kg) or an adult (70 kg).
- UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.
- L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that was suitable for determination of a One-day HA value for dieldrin. It is, therefore, recommended that the modified DWEL for a 10-kg child (0.0005 mg/L, calculated below) be used as a conservative estimate for the One-day HA value.

Ten-day Health Advisory

No data were found in the available literature that was suitable for determination of a Ten-day HA value for dieldrin. It is, therefore, recommended that the modified DWEL for a 10-kg child (0.0005 mg/L, calculated below) be used as a conservative estimate for the Ten-day HA value.

Longer-term Health Advisory

No data were found in the available literature that was suitable for determination of a Longer-term HA value for dieldrin. It is, therefore, recommended that the modified DWEL for a 10-kg child (0.0005 mg/L, calculated below) be used as a conservative estimate for the Longer-term HA value.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of

carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study of Walker et al. (1969), in which rats were fed dieldrin in the diet at 0.0, 0.1, 1 or 10 ppm for 2 years (approximately 0, 0.005, 0.05 or 0.5 mg/kg/day based on Lehman, 1959), has been selected as the basis for calculating the DWEL. In this study, liver weight and liver-to-body weight ratios were significantly increased in females receiving 1 and 10 ppm, while pathological changes consistent with exposure to organochlorides were evident at the 10-ppm level. This study established a NOAEL of 0.1 ppm (equivalent to 0.005 mg/kg/day).

Using a NOAEL of 0.005 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RFD = \frac{0.005 \text{ mg/kg/day}}{100} = 0.00005 \text{ mg/kg/day}$$

where:

0.005 mg/kg/day = NOAEL, based on the absence of hepatic effects in rats fed dieldrin in the diet.

> 100 = uncertainty factor, chosen in accordance with NAS/ODW quidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent (DWEL)

$$DWEL = \frac{(0.00005 \text{ mg/kg/day})(70 \text{ kg})}{2 \text{ L/day}} = 0.00175 \text{ mg/L} (1.75 \text{ ug/L})$$

where:

0.00005 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Dieldrin may be classified in Group B2: probable human carcinogen. A Lifetime HA is not recommended for dieldrin.

The estimated excess cancer risk associated with lifetime exposure to drinking water containing dieldrin at 1.75 ug/L is approximately 8.05 x 10-4. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group (U.S. EPA, 1987) using the linearized multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's proposed guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dieldrin may be classified in Group B2: probable human carcinogen.
- Evidence has been presented in several carcinogenicity studies showing that dieldrin is carcinogenic to mice. Thirteen data sets from these studies are adequate for quantitative risk estimation. Utilizing the linearized multistage model, the U.S. EPA performed potency estimates for each of these data sets. The geometric mean of the potency estimates, $Q_1^* = 16 \; (mg/kg/day)^{-1}$, was estimated as the potency for the general population (U.S. EPA, 1987).
- 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 that concentrations of 0.219, 0.0219 and 0.00219 ug dieldrin per liter may result in excess cancer risk of 10^{-4} , 10^{-5} and 10^{-6} , respectively.
- * The linearized multistage model is only one method of estimating carcinogenic risk. From the data contained in U.S. EPA (1987), it was determined that five of the thirteen data sets were suitable for determining slope estimates for the probit, logit, Weibull and gammamultihit models. Using the geometric mean of these slope estimates (13 for multistage, 5 for other models) at their upper 95% confidence limits, the following comparisons of unit risk (i.e., a 70-kg man consuming 2 liters of water per day containing 1 ug/L of dieldrin over a lifetime) can be made: multistage, 4.78 x 10-4; probit, 7.7 x 10-12; logit, 5.09 x 10-6; Weibull, 1.13 x 10-4; multihit, 5.68 x 10-4. Each model is based on different assumptions. No current understanding of the biological mechanisms of carcinogenesis is able to predict which of these models is more accurate than another.
- While recognized as statistically alternative approaches, the range of risks described by using any of these modelling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach.
- IARC (1982) concluded that there is limited evidence that dieldrin is carcinogenic in laboratory animals.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- ACGIH (1984) has established a short-term exposure limit (STEL) of 0.75 mg/m³ and an 8-hour Threshold Limit Value (TLV)-TWA exposure 0.25 mg/m³ for dieldrin.
- U.S. EPA (1980) has recommended ambient water quality criteria of
 0.71 ng/L for dieldrin. It is based on a carcinogenic potency factor

- (q_1^*) of 30.37 $(mg/kg/day)^{-1}$ derived from the incidence of hepatocellular carcinoma in a mouse feeding study conducted by Walker et al. (1972).
- Residue tolerances ranging from 0.02 to 0.1 ppm have been established for dieldrin in or on agricultural commodities (U.S. EPA, 1985).
- WHO (1982) established guidance of 0.03 ug dieldrin/L in drinking water.

VII. ANALYTICAL METHODS

Determination of dieldrin is by a liquid-liquid extraction gas chromatographic (GC) procedure (U.S. EPA, 1984a). In this procedure, a 1-liter sample is extracted with methylene chloride using a separatory funnel. The methylene chloride extract is dried and exchanged to hexane during concentration to a volume of 10 mL or less. The extract is separated by GC, and the components are then measured with an electron-capture detector. Identification may be corroborated through the use of two unlike columns or by gas chromatography-mass spectroscopy (GC-MS). A GC-MS procedure is available (U.S. EPA, 1984b) that allows for the qualitative and quantitative confirmation of results obtained by the GC procedure.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that reverse osmosis (RO), granular-activated carbon (GAC) adsorption, ozonation and conventional treatment will remove dieldrin from water. The percent removal efficiency ranges from 50 to 99+%.
- Laboratory studies indicate that RO is a promising treatment method for dieldrin-contaminated waters. Chian et al. (1975) reported 99+% removal efficiency for two types of membranes operating at 600 psig and a flux rate of 8 to 12 gal/ft²/day. Membrane adsorption, however, is a major concern and must be considered, since breakthrough of dieldrin would probably occur once the adsorption potential of the membrane was exhausted.
- GAC is effective for dieldrin removal. Pirbazari and Weber (1983) reported 99+% dieldrin removal efficiency of a GAC column operating at an empty bed contact time (EBCT) of 15 minutes and a hydraulic loading of 1.4 gal/ft²/min, for the entire test period (approximately 7.5 months).
- Pirbazari and Weber (1983) determined adsorption isotherms using GAC on dieldrin in water solutions. Resin adsorption was also found to remove dieldrin from water. The Freundlich values determined by The authors indicate that the tested resins are not quite as effective as GAC in the removal of dieldrin from water.

- Ozonation treatment appears to be an effective dieldrin removal method. Treatment with 36 mg/L ozone (03) removed 50% of dieldrin while 11 mg/L 03 removed only 15% of dieldrin (Robeck et al., 1965).
- Conventional water-treatment techniques using alum coagulation, sedimentation and filtration proved to be 55% effective in removing dieldrin from contaminated potable water supplies (Robeck et al., 1965). Lime- and soda-ash softening with ferric chloride as a coagulant did not improve upon the removal efficiency achieved with alum alone.
- Oxidation with chlorine and potassium permanganate is ineffective in degrading dieldrin (Robeck et al., 1965).
- Treatment technologies for the removal of dieldrin from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt dieldrin removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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