March 31, 1987

HEPTACHLOR AND HEPTACHLOR EPOXIDE

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.

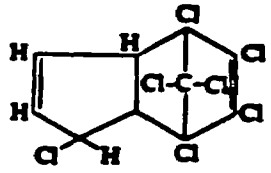
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from 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 can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Heptachlor, Heptachlor Epoxide and Chlordane (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117991/AS. The toll free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 76-44-8

Structural Formula



A. Heptachlor

Synonyms

3-Chlorochlordene; 3,4,5,6,7,8,8a-heptachlorodicyclopentadiene; 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-endomethanoindene.

Use

Insecticide

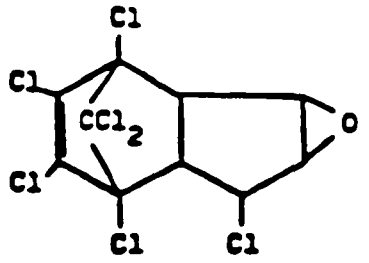
Properties

Chemical Formula	$C_{10}H_5Cl_7$
Molecular Weight	373.32
Physical State (room temp.)	white, crystalline solid
Boiling Point	135-145°C (at 1-1.5 mm Hg)
Melting Point	93°C
Density	--
Vapor Pressure	3×10^{-4} mm Hg (at 25°C)
Water Solubility	0.056 mg/L (at 25°C)
Log Octanol/Water Partition Coefficient	3.87
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

B. Heptachlor Epoxide

CAS No. 1024-57-3

Structural Formula



Synonyms

- 1,4,5,6,7,8,8,-Heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-4,7-methanoindan

Use

- Insecticide

Properties

Chemical Formula	$C_{10}H_5Cl_7O$
Molecular Weight	389.32
Physical State (room temp.)	solid
Boiling Point	--
Melting Point	160-161.5°C (99.5% pure)
Density	--
Vapor Pressure	3×10^{-4} mm Hg (at 25°C)
Water Solubility	0.35 mg/L (at 25°C)
Log Octanol/Water Partition Coefficient	2.65, 4.43, 5.40 (by 3 methods)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Heptachlor is an insecticide which in the past has been used on corn, alfalfa, hay and vegetables, and as a termiticide. During the mid-70s, use of heptachlor on food crops was phased out due to the persistence of the chemical and its epoxide. Currently, heptachlor is used only as a termiticide and on a very limited number of crops.

- Heptachlor is considered to be a moderately persistent compound, with a half life in soil of 6 months. However, heptachlor is biotransformed to an epoxide which is very resistant to further biological or chemical change. The half lives of heptachlor epoxide in various soils have been reported to be as long as several years. Heptachlor and its epoxide bind to soil and migrate slowly.

- Heptachlor has been analyzed for in a number of national and regional surveys of drinking water supplies. However, heptachlor has not been detected in any of the surveys. Heptachlor and its epoxide have been detected in private drinking water wells at levels of less than 0.02 ug/L. Heptachlor has been found at similar levels in a few surface water samples (not drinking water).

- Heptachlor epoxide, but not heptachlor itself, is a common low level contaminant in food. Heptachlor has been detected in air at very low levels, approximately 1 ppt. However, the available data are insufficient to evaluate exposures from these areas or to determine if drinking water is a significant route of exposure.

III. PHARMACOKINETICS

Absorption

- Heptachlor was absorbed rapidly from the gastrointestinal tract of rats following intragastric administration as evidenced by its detection in blood within one hour after dosing (Mizyukova and Kurchatov, 1970).

Distribution

- In female rats, intragastrically administered heptachlor was detected in blood, liver, kidney and adipose tissue within one hour. After four hours, heptachlor epoxide was detected in blood, liver and fat, persisting in adipose tissue for 3 to 6 months (Mizyukova and Kurchatov, 1970). With dietary administration of heptachlor to rats for two months or to dogs by capsule for 12 to 18 months, Radomski and Davidow (1953) reported similar tissue distribution. Heptachlor epoxide levels in the fat of female rats, however, were about 5 to 10 times higher than those in male rats. Retention in adipose tissue was 6 and 8 weeks for male and female rats respectively.

- Heptachlor epoxide has been detected in tissue samples from 77 autopsies performed from 1966 to 1968 at 1 to 32 ppb per whole tissue, with highest concentrations in bone marrow and liver (Klemmer et al., 1977).

- Heptachlor epoxide has been detected in human adipose tissue in surveys conducted in Great Britain (Abbott et al., 1972; 1981), Brazil (Wassermann et al., 1972), Japan (Curley et al., 1973), Israel (Wassermann et al., 1974), Texas (Burns, 1974), Louisiana (Greer et al., 1980) and the United States (Kutz et al., 1979; Sovocool and Lewis, 1975).

- Evidence of transplacental transfer of heptachlor or heptachlor epoxide in humans (levels of 0.01-0.3 mg/kg in fat; 0.001 mg/L in blood) comes from a study by Curley et al. (1969), who detected heptachlor epoxide in adipose tissue, brain, adrenals, lungs, heart, liver, kidney and spleen of ten stillborn babies and two babies who died soon after birth and in 27 of 30 samples of cord blood from healthy neonates.

Metabolism

- Metabolism of heptachlor to heptachlor epoxide *in vitro* was similar using rat and human liver microsomal preparations. A major species difference was that four times more heptachlor epoxide was formed in the rat system than in the human system (Tashiro and Matsumura, 1978).

- The major fecal metabolites of orally administered heptachlor in rats include heptachlor epoxide, 1-hydroxychlordene, and 1-hydroxy-2,3-epoxychlordene (Tashiro and Matsumura, 1978).

Excretion

- The major route of heptachlor elimination by rats is via the feces, amounting up to 50% of the administered oral dose over 10 days (Tashiro and Matsumura, 1978). Urinary excretion of metabolites amounted to <5% of the dose.

- The only information available on human excretion of heptachlor are reports of heptachlor epoxide detected in milk of lactating women (Kroger, 1972; Ritcey et al., 1972; Savage et al., 1973; Bakken and Seip, 1976; Polishuk et al., 1977; Strassman and Kutz, 1977; Takahashi et al., 1981).

IV. HEALTH EFFECTS

Humans

- Clinical case studies of acute exposure (via ingestion, dermal or inhalation routes) to chlordane containing heptachlor document a pattern of CNS effects similar to that found in animals (e.g., irritability, salivation, labored respiration, muscle tremors, convulsions, etc.)(Dadey and Kammer, 1953; Derbes et al., 1955).

- Several blood dyscrasias (e.g., anemias and leukemias) are associated with inhalation and dermal exposure of humans to heptachlor (Furie and Trubowitz, 1976; Klemmer et al., 1977; Infante et al., 1978).

- Wang and McMahon (1979) reported a non-significant increased incidence of lung cancer and a statistically significant increased incidence of cerebrovascular disease in a cohort of 1403 white male workers employed for 73 months in the production of chlordane and heptachlor.

Animals

Short-term Exposure

- Symptoms of acute intoxication from heptachlor or heptachlor epoxide include tremors, convulsions, paralysis and hypothermia (Hrdina et al., 1974; Yamaguchi et al., 1980).

- Acute oral LD_{50} values in rats for heptachlor range from 40 mg/kg for a commercial formulation (Ben-Dyke et al., 1970) to 162 mg/kg for technical grade heptachlor (Gaines et al., 1960).

- The acute oral LD_{50} value for heptachlor epoxide in rats ranged from 46.5 to 60 mg/kg (NAS, 1977; Sperling and Ewinike, 1969; Podowski et al., 1979).

- A single, acute oral dose of 60 mg/kg heptachlor in rats was associated with increased levels of serum GPT and serum aldolase, and moderate to severe histological liver damage (Krampl, 1971).

- Evidence of significant liver damage and altered liver function was reported in rats maintained on diets containing heptachlor at 7 to 12 mg/kg bw/day for up to 14 days (Krampl, 1971) and 10 mg/kg diet for 5 to 7 days (Enan et al., 1982).

- A dose-related significant induction of liver microsomal enzymes, at dietary levels of heptachlor of 2 to 50 mg/kg diet for 14 days, was observed in rats (Den Tonkelaar and Van Esch, 1974).

Long-term Exposure

- At dietary levels of 10 mg/kg of heptachlor or heptachlor epoxide in mice for 2 years, Reuber (1977a) diagnosed hepatic vein thrombosis and cirrhosis of the liver from slides of the Davis (1965) study.

- In the IRDC (1973) study, reviewed by Epstein (1976), a 75% heptachlor epoxide and 25% heptachlor mixture was fed to mice for 18 months; females and males had dose-related significantly increased mean liver weights and hepatocytomegaly at 1, 5 and 10 mg/kg diet.

- Jolley et al. (1966) found dose-related increased mortality in rats fed 5 to 12.5 mg/kg diet levels of a 75% heptachlor and 25% heptachlor epoxide mixture for 2 years.

- Witherup et al. (1955) found non-neoplastic lesions in rats at dietary levels $\geq$7.0 mg/kg diet of heptachlor for 110 weeks. Treated males had dose-related increased liver weights at levels of 3 to 10 mg/kg diet.

- Dose-related liver weight increases, hepatocytomegaly and hepatic cell vacuolization were observed in rats maintained for 108 weeks on diets containing heptachlor epoxide at 0.5-10 mg/kg diet (Witherup et al., 1959).

- Dose-related changes in clinical measurements related to liver function and microscopic changes in liver were noted in dogs administered heptachlor epoxide in the diet at dose levels of 3, 5, 7 and 10 mg/kg/day for 2 years (U.S. EPA, 1971; IRDC, 1973).

- Beagle dogs from 23 to 27 weeks of age were given diets containing 0, 0.5, 2.5, 5 or 7.5 mg/kg/day of heptachlor epoxide for 60 weeks. Results included liver weight to body weight ratios which were significantly increased in a treatment-related fashion. Effects were noted for both males and females at the dose of 0.5 ppm. No NOEL was determined from this study (U.S. EPA, 1958, Kettering Laboratory).

Reproductive Effects

- No information was found in the available literature on the reproductive effects of heptachlor or heptachlor epoxide.

Developmental Effects

- No information was found in the available literature on the developmental effects of heptachlor or heptachlor epoxide.

Mutagenicity

- Heptachlor has been tested for mutagenicity in a number of systems. Negative results have been obtained in bacterial systems (Moriya et al., 1983; Probst et al., 1981; Gentile et al., 1982; Shirasu et al., 1976), in mitotic gene conversion (Gentile et al., 1982), in the recessive lethal assay in fruit flies (Benes and Sram, 1969), in assays for unscheduled DNA synthesis in rat, mouse and hamster primary hepatocyte cultures (Probst et al., 1981; Maslansky and Williams, 1981), and for the dominant lethal assay in mice (Arnold et al., 1977).

- Positive results were reported for unscheduled DNA synthesis in transformed human fibroblasts with S-9 activation (Ahmed et al., 1977) and in the dominant lethal assay in rats (Cerey et al., 1973).
- Heptachlor epoxide was negative in bacterial systems (Moriya et al., 1983; Marshall et al., 1976), in the recessive lethal assay in fruit flies (Benes and Sram, 1969) and in the dominant lethal assay in mice (Arnold et al., 1977).

- Heptachlor epoxide was positive for unscheduled DNA synthesis in human fibroblasts in the presence of S-9 (Ahmed et al., 1977).

Carcinogenicity

- In a National Cancer Institute bioassay (NCI, 1977), heptachlor was tested for possible carcinogenicity in male and female mice and rats. Male $B6C3F_1$ mice received heptachlor at dietary concentrations of 0, 6.1 and 13.8 mg/kg diet and female $B6C3F_1$ mice received diets containing 0, 9.0 and 18.0 mg/kg diet, both for 80 weeks. The incidence of hepatocellular carcinomas was statistically significant in the high-dose males, while a highly significant dose-related trend also was observed between high- and low-dose females. Heptachlor was not carcinogenic in male and female Osborne-Mendel rats similarly treated with concentrations of 25.7 to 77.9 mg/kg diet.

- Re-analysis of the study results reported by Witherup et al. (1955), indicate that administration of heptachlor to male and female CF rats at dietary levels of 1.5 to 10.0 ppm (mg/kg diet) for 110 weeks resulted in a statistically significant increase in malignant and any tumors in multiple sites in some female test groups (Epstein, 1976).

- Significantly increased incidences of hepatic carcinoma were determined by Reuber and Williams (Epstein, 1976) upon re-analysis of histologic slides from the Witherup et al. (1959) study. Witherup administered heptachlor epoxide to male and female CFN rats at doses of 0, 0.5, 2.5, 5.0, 7.5 and 10.0 mg/kg diet for 108 weeks. The incidences were significantly different from controls for female rats at the 5 and 10 mg/kg dietary concentrations (Epstein, 1976).

- Histological re-examination of the slides from the Davis (1965) study resulted in a conclusion of significantly increased incidence of hepatocellular carcinoma in C3H mice receiving 10 mg/kg diet of heptachlor epoxide for 728 days (Reuber, 1977b).

- Histological re-examination of the slides of the IRDC (1973) study resulted in a conclusion of significantly increased incidence of hepatocellular carcinoma in CD-1 mice administered a 75:25 mixture of heptachlor epoxide:heptachlor in the diet at concentrations of 1.0, 5.0 or 10.0 ppm (mg/kg diet) for 18 months (Reuber, 1977b).

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:

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

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

There are insufficient toxicological data available to derive a One-day HA for heptachlor or heptachlor epoxide. The Ten-day HA, however, would be protective for a One-day exposure period for heptachlor of 0.01 mg/L.

Ten-day Health Advisory

A Ten-day HA for heptachlor can be derived from a study conducted by Enan et al. (1982) in which rats were administered heptachlor at 1.0 mg/kg/day (10 ppm) in the feed for 14 days. Exposure resulted in evidence of liver damage and altered liver function: increased blood urea, increased blood glucose, decreased liver glycogen content, and increased acid and alkaline phosphatase levels when compared with controls. Using 1.0 mg/kg/day as the LOAEL, the Ten-day HA for the 10 kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(1.0 \text{ mg/kg/day})(10 \text{ kg})}{(1{,}000)\ (1 \text{ L/day})} = 0.010 \text{ mg/L } (10 \text{ ug/L})$$

where:

1.0 mg/kg/day = LOAEL based on liver effects in rats.

10 kg = Assumed body weight of a child.

100 = Uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = Assumed daily water consumption of a child.

No data are available from which to derive a Ten-day HA for heptachlor epoxide.

Longer-term Health Advisory

There are insufficient toxicological data available to derive a Longer-term HA for heptachlor or heptachlor epoxide. The DWEL of 0.0015 mg/L adjusted for a 10-kg child is recommended as a conservative estimate for a longer-term exposure.

Lifetime Health Advisory for Heptachlor

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 classifed 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 by Witherup et al. (1955) is the most appropriate from which to derive the DWEL. Investigators studied the effects of heptachlor on

groups of 20 male and 20 female CF rats. The compound was administered at dietary concentrations of 0, 1.5, 3, 5, 7 or 10 ppm (10 mg/kg/dose) of heptachlor. Mortality among test groups was not dose-related. Loss of body weight, decreased food consumption and increased liver weights were seen among treated males. Lesions in the liver were limited to 7 ppm and above and were characteristic of chlorinated hydrocarbons, i.e., hepatocellular swelling, homogeneity of the cytoplasm and peripheral arrangements of the cytoplasmic granuled of cells of the central zone of the liver lobules. The NOEL for increased liver to body weight for males only was 3 ppm and LEL was 5 ppm. [Note: A re-analysis of the Witherup et al. (1955) dietary study on the toxicity of heptachlor to rats (by the OPP, RfD Work Group, 1987) indicated that the NOEL of 3 ppm (0.15 mg/kg/day) for increased liver to body weight for male rats was the most appropriate for a Lifetime Health Advisory for heptachlor.] Using this NOEL, the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.15 \text{ mg/kg/day})}{(300)} = 0.0005 \text{ mg/kg/day}$$

where:

0.15 mg/kg/day (3 ppm) = NOEL based on absence of increased liver to body weight for male rats.

300 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study (also RfD meeting, April 16, 1987).

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

$$DWEL = \frac{(0.0005 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.0175 \text{ mg/L } (17.5 \text{ ug/L})$$

where:

0.0005 mg/kg/day = RfD.

70 kg = assumed weight of an adult.

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

Heptachlor is classified as Group B: Probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing heptachlor at 17.5 ug/L is approximately 3×10^{-4}. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group 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.

Lifetime Health Advisory for Heptachlor Epoxide

Two studies in dogs are the most appropriate from which to derive the DWEL. In the 60-week dog feeding study (U.S. EPA, 1958) beagle dogs from 23 to 27 weeks of age were divided into five groups (three females and two males) and were given diets containing 0, 0.5, 2.5, 5 or 7.5 ppm of heptachlor epoxide. Results included liver weight to body weight ratios which were significantly increased in a treatment-related fashion. Effects were noted for both males and females at the 0.5 ppm (0.0125 mg/kg/day) dose level of heptachlor epoxide. No NOEL was determined for the study. In another two-generation reproduction study in dogs (U.S. EPA, 1971) animals were administered diets containing various dose levels of heptachlor epoxide. The dose levels were 0, 1, 3, 5, 7 or 10 ppm of heptachlor epoxide in the diet. This study was designed to investigate reproduction parameters associated with heptacnlor epoxide administration. The OPP and the RfD Work Group considered that the former study in dogs, 60-week dog feeding study providing the LEL of 0.5 ppm (0.0125 mg/kg/day) is the most appropriate for the derivation of the DWEL. Using this LEL, the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.0125\ mg/kg/day)}{(1,000)} = 0.000013\ mg/kg/day$$

Where:

0.0125 mg/kg/day = Low Effect Level (LEL).

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

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

$$DWEL = \frac{(0.000013\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.00044\ mg/L\ (0.4\ ug/L)$$

Where:

0.000013 mg/kg/day = RfD.

70 kg = assumed weight of an adult.

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

Heptachlor epoxide is classified in Group B: Probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing heptachlor epoxide at 0.4 ug/L is approximately 2×10^{-3}. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group 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

- The U.S. EPA (1987) derived a human carcinogenic potency factor, q_1^*, of 4.5 $(mg/kg/day)^{-1}$ for heptachlor. This derivation was based on the geometric mean of four potency estimates which were based on the incidence of hepatocellular carcinoma in male and female CH3 mice (Davis, 1965, as diagnosed by Reuber, 1977b) and male and female $B6C3F_1$ mice (NCI, 1977). this estimate supersedes the potency of 3.37 $(mg/kg/day)^{-1}$ previously calculated by the U.S. EPA (1980). The concentrations in drinking water corresponding to increased lifetime risk levels of 10^{-4}, 10^{-5} and 10^{-6} for a 70 kg human consuming 2 L/day are 7.6, 0.76 and 0.076 ug/L, respectively (U.S. EPA, 1987).

- Cancer risk estimates (95% upper limit) with other models are presented for comparison with that derived with the multistage. For example, one excess cancer per 1,000,000 (10^{-6}) is associated with exposure to heptachlor epoxide at levels pf <0.0001 ug/L (probit), <0.00001 ug/L (logit) and <0.0001 ug/L (Weibull).

- The U.S. EPA (1987) derived a human carcinogenic potency factor, q_1^*, of 9.1 $(mg/kg/day)^{-1}$ for heptachlor epoxide. This derivation was based on the geometric mean of four potency estimates which were based on the incidence of hepatocellular carcinoma in male and female CH3 mice (Davis, 1965, as diagnosed by Reuber, 1977b) and male and female CD-1 mice (IRDC, 1973). this estimate supersedes the potency of 5.786 $(mg/kg/day)^{-1}$ previously calculated by the U.S. EPA. The concentrations in water corresponding to increased lifetime risk levels of 10^{-4}, 10^{-5} and 10^{-6} for a 70 kg human consuming 2 L/day are 3.8, 0.38 and 0.038 ug/L, respectively (U.S. EPA, 1987).

- The NAS (1977) determined 0.119 ug/L for heptachlor as the water concentration corresponding to an increased lifetime risk of cancer of 10^{-5}. NAS (1977) categorizes heptachlor epoxide as a suspect animal carcinogen, but noted that there are insufficient data to permit a statistical extrapolation of risk.

- IARC (1979) classified heptachlor as Group 3: inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals. The IARC (1979) position on heptachlor epoxide is that there is limited evidence that heptachlor epoxide is carcinogenic in experimental animals.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), heptachlor and heptachlor epoxide is classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- In 1980, EPA estimated a range of excess cancer risks for lifetime exposure to heptachlor when developing ambient water quality criteria

(U.S. EPA, 1980). This range was 2.78 ng/L, 0.28 ng/L and 0.028 ng/L, respectively, for risks of 10^{-5}, 10^{-6} and 10^{-7}, assuming consumption of 2 liters of water and 6.5 grams of contaminated fish per day by a 70 kg adult.

- FAO/WHO recommended an ADI value of 0.5 ug/kg bw for heptachlor or heptachlor epoxide. This recommendation was established by the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO, 1978).

- A guideline value of 0.1 ug/L in drinking water also was recommended by the WHO (1984), based upon this level as one percent of the ADI.

- The American Conference of Governmental Industrial Hygienists (ACGIH, 1983) has adopted TWA-TLVs of 0.5 mg/m^3 for heptachlor in workroom air.

- It should be noted that an estimated concentration for detection by taste and odor in water for heptachlor was 0.02 mg/L (Sigworth, 1965).

VII. ANALYTICAL METHODS

- Determination of heptachlor is by a liquid-liquid extraction gas chromatographic procedure (U.S. EPA, 1978; Standard Methods, 1985). Specifically, the procedure involves the use of 15% methylene chloride in hexane for sample extraction, followed by drying with anhydrous sodium sulfate, concentration of the extract and identification by gas chromatography. Detection and measurement is accomplished by electron capture, microcoulometric or electrolytic conductivity gas chromatography. Identification may be corroborated through the use of two unlike columns or by gas chromatography-mass spectroscopy (GC-MS). The method sensitivity is 0.001 to 0.010 ug/L for single component pesticides and 0.050 to 1.0 ug/L for multiple component pesticides when analyzing a 1-liter sample with the electron capture detector.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which are capable of removing heptachlor from drinking water include adsorption by granular activated carbon (GAC) and ozone (O_3) or ozone/ultraviolet oxidation (O_3/UV).

- Dobbs and Cohen (1980) developed adsorption isotherms for a number of organic chemicals in drinking water, including heptachlor. Based on the isotherm data, they reported that the activated carbon Filtrasorb® 300 exhibited adsorptive capacities of 45 mg, 18 mg and 8 mg of heptachlor per gm of carbon at equilibrium concentrations of 100 ug/L, 10 ug/L, and 1 ug/L, respectively.

- The GAC system in U.S. EPA's Hazardous Materials Spills Treatment Trailer was used to treat 104,000 gal of pesticide-contaminated water containing heptachlor. Water analysis showed 6.1 ug/L of heptachlor

in the contaminated water. Ninety-nine percent heptachlor removal was achieved at a contact time of 17 minutes (U.S. EPA, 1985b).

- Hansen (1977) reported on the efficiency of GAC used in Mount Clements water treatment plant to remove synthetic organic chemicals from the raw water source. Heptachlor epoxide was detected in the raw water at concentrations of 220 ng/L. The GAC column reportedly was capable of removing 99.9+ percent (below its detectable limit) of the heptachlor epoxide.

- Gilbert (as referenced in U.S. EPA, 1985b) summarized the results presented by a number of different researchers on the ability of ozone to remove several SOCs from drinking water, including heptachlor. The results indicate that greater than 99% of the heptachlor was removed by ozone oxidation, while heptachlor epoxide was only partially removed (i.e., 26%) at an applied ozone dose of 17 mg/L.

- Treatment technologies for the removal of heptachlor from drinking water have not been extensively evaluated (except on an experimental level). An evaluation of some of the physical and/or chemical properties of heptachlor indicates that the following techniques would be candidates for further investigation: adsorption by granular activated carbon and ozone oxidation. Whichever individual or combinations of technologies for heptachlor reduction are used, it must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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