HEPTACHLOR

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERIA DOCUMENT

HEPTACHLOR

CRITERIA

Aquatic Life

For heptachlor the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0015 µg/l as a 24-hour average and the concentration should not exceed 0.45 µg/l at any time.

For heptachlor the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.0036 µg/l as a 24-hour average and the concentration should not exceed 0.05 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to heptachlor through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of heptachlor estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100 thousand are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.23 ng/l, 0.023 ng/l, and 0.0023 ng/l, respectively.

HEPTACHLOR

Introduction

Heptachlor is a broad spectrum insecticide of the group of polycyclic chlorinated hydrocarbons called cyclodiene insecticides. It was introduced in 1948 as a contact insecticide under the trade names E 3314 and Velsicol 104. During the period 1971 to 1975 the most important use of heptachlor was to control soil insects for corn cultivation and other crop production. Since 1975 both the applications and production volume of heptachlor have undergone dramatic changes as a result of the sole producer's voluntary restriction of demestic use and the subsequent issuance by the Environmental Protection Agency of a registration suspension notice for all food crops and home use of heptachlor, effective August 2, 1976. However, significant commercial use of heptachlor for termite control or non-food plants continues and numerous formulation plants and packaging facilities have remained in operation.

Pure heptachlor is a white crystalline solid with a camphor-like odor having the molecular formula $C_{10}H_5Cl_7$, a molecular weight of 373.35, and a vapor pressure of 3×10^{-4} mm Hg at 25 degrees C (Metcalf, 1955; Windholz, 1976). It has a solubility in water of 0.056 mg/l at 25 to 29 degrees C and is readily soluble in relatively non-polar solvents (Metcalf, 1955). The chemical name for heptachlor is 1, 4, 5, 6, 7, 8, 8-heptachloro-3a, 4, 7, 7a-tetrahydro-4, 7-methanoindene. It is produced by means of a Diels-Alder addition reaction which joins cyclopentadiene to hexachlorocyclopentadiene (Windholz, 1976).

Technical grade heptachlor has the typical composition of approximately 73 percent heptachlor, 21 percent trans-(gamma) chlordane, 5 percent heptachlor, and 1 percent chlordene isomers (Anonymous, 1974). Technical heptachlor is a tan, soft, waxy solid with a melting point range of 46 to 74 degrees C. It has a vapor pressure of 4×10^{-4} mm Hg at 25 degrees C and a density of 1.65 to 1.67 g/ml at 25 degrees C.

In general, heptachlor is quite stable to chemical reactions such as dehydrochlorination, autooxidation, and thermal decomposition. However, in the environment, heptachlor undergoes numerous microbial, biochemical, and photochemical reactions.

Conversion of heptachlor to heptachlor epoxide has been reported in microorganisms (Miles, et al. 1969), in plants (Gannon and Decker, 1958), in soils (Lichtenstein, 1960; Lichtenstein, et al. 1970, 1971; Nash and Harris, 1972) and in mammals (Davidow and Radomski, 1953a; Radomski and Davidow, 1953) and represents the principal metabolite of heptachlor. Although it has been reported that heptachlor epoxide is less toxic in several invertebrate species than heptachlor (von Halacka and Polster, 1971), numerous other studies have demonstrated that the epoxide form is of equal toxicity (Schimmel, et al. 1976a) or greater toxicity (Georgacakis and Khan, 1971) than the parent compound in invertebrates, and two to ten times more toxic in mammals (Radomski and Davidow, 1953; Buck, et al. 1959).

The photodecomposition of heptachlor to photoheptachlor has been demonstrated in various solvent solutions using ultraviolet lamps, and as thin films using natural sunlight (Benson, et al. 1971). Although numerous photoisomers are produced, photoheptachlor (III) appears to predominate. Numerous investigations have demonstrated that photoheptachlor is two to five times more toxic than the parent compound to insects (Khan, et al. 1969) and aquatic vertebrates (Georgacakis and Khan, 1971; Khan, et al. 1973). Heptachlor epoxide has also been shown to undergo photodecomposition to photoheptachlor epoxide (IIIB) when exposed to UV light or sunlight (Graham, et al. 1973) and has been reported to exhibit greater toxicity than the epoxice (Ivie, et al. 1972).

Heptachlor can also be biologically converted to chlordene, 3-chlorochlordene, 1-hydroxychlordene, chlordene epoxide, 1-hydroxy-2, 3-epoxychlordene, and 2-chlorochlordene. However, these metabolites have been shown to be considerably less toxic to rats than heptachlor (Mastri, et al. 1969a,b).

Heptachlor was tentatively identified at levels greater than 0.002 µg/l in 15 of 96 river water samples tested by Weaver, et al. (1965). Heptachlor and/or heptachlor epoxide have been reported present in plankton-algae and aquatic insects (Hannon, et al. 1970), crayfish, crabs, shellfish and fish (Albright, et al. 1975; Casper, et al. 1969; Smith and Cole, 1970; Hannon, et al. 1970).

Heptachlor and heptachlor epoxide will bioconcentrate in numerous species and will accumulate in the food chain. Heptachlor/heptachlor epoxide bioconcentration factors as

high as 17,600 in the oyster, Crassostrea virginica (Stickel, 1968; Schimmel, et al. 1967a), have been reported.

Heptachlor epoxide is readily stored in the adipose tissue of rats and dogs but may also be found in liver, brain, and other tissues. It has been found in human milk samples and has also been detected in fetal blood and placenta.

The persistence of heptachlor and heptachlor epoxide in the environment is well known. Heptachlor also has been shown to be converted to the more toxic metabolite, heptachlor epoxide, in various soils (Gannon and Bigger, 1958; Lichtenstein, 1960; Lichtenstein, et al. 1971; Nash and Harris, 1972) and plants (Gannon and Decker, 1958).

Heptachlor has been demonstrated to be highly toxic to aquatic life, to persist for prolonged periods in the environment, to bioconcentrate in organisms at various trophic levels, and to exhibit carcinogenic activity in mice.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Heptachlor has been widely used for such purposes as fire ant and general insect control in much of the United States. Numerous studies on the acute toxicity of heptachlor to freshwater fish and invertebrate species have been conducted (Tables 1, 2, and 5). Most of these studies were carried out under static conditions with exposure levels based on unmeasured rather than measured concentrations. In most instances tests used technical-grade heptachlor as the toxicant. Technical-grade heptachlor usually consists of 72 percent heptachlor and 28 percent impurities. These impurities are primarily gamma chlordane and nonachlor. There are insufficient data to evaluate the relative toxicities of the various grades of heptachlor and the impact of the impurities on the toxicity determinations. Because of the unknown contribution of the impurities, all data included in this document are reported in concentrations of the actual material used for testing. Some authors used technical material in testing and then calculated

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

calculated concentrations as 100 percent heptachlor for data reporting. These data were converted back to concentrations of technical-grade heptachlor in this document.

Some studies have been reported on the impact of water hardness and temperature to acute toxicity (Henderson et al. 1959, 1960; Bridges, 1965; Macek, et al. 1969; Naqvi, 1973). In general, water hardness and temperature may have had some effect (see Acute Toxicity).

Heptachlor epoxide is the most commonly found degradation product of heptachlor. Both heptachlor and its epoxide have been reported in fish residues (Andrews, et al. 1966; Macek, et al. 1976). There are few data on the relative toxicity to freshwater organisms of these two materials. What is available suggests that the epoxide is not more toxic than heptachlor itself (Frear and Boyd, 1967). Because of the common occurrence of both materials and the inadequacy of the relative toxicity information, criteria should be based on the total concentration of heptachlor and its epoxide.

Acute Toxicity

In all but one case (Macek, et al. 1976) (Table 5), data on acute toxicity were obtained in static tests. In every case exposure concentrations were unmeasured. Values for standard tests with fish and invertebrate species are reported in Tables 1 and 2. Some additional acute mortality data are found in Table 5. Eight fish and ten invertebrate species have been tested.

In general, fish were less sensitive to heptachlor than were invertebrate species. Adjusted LC50 values for fish ranged from 3.8 µg/l for a 96-hour exposure with the rainbow trout to 175 µg/l for a 96-hour exposure with the goldfish (Table 1). Adjusted LC50 values for invertebrate species ranged from 0.8 µg/l for a 96-hour exposure with the stonefly, Pteronarcella badia, to 68 µg/l for a 48-hour exposure with the cladoceran, Simocephalus serrulatis (Table 2). Larvae of the Fowler's toad were tested by Sanders (1970) (Table 5); the 96-hour LC50 was 440 µg/l.

Many authors, cited in Tables 1 and 2, reported values for numerous other pesticides in addition to heptachlor. No clear relationship regarding the toxicity of heptaclor compared to other pesticides was found. For example, Sanders (1972) found that with the scud, Gammarus fasciatus, heptachlor was substantially less toxic than DDT and endrin. For the freshwater glass shrimp, however, there was little difference on toxicity of the three pesticides. For the stonefly, Pteronarcys californica, heptachlor was less toxic than endrin and more toxic than DDT (Sanders and Cope, 1968). Katz (1961) found with chinook salmon, Oncorhynchus tshawytscha, and coho salmon, Oncorhynchus kisutch, DDT and endrin were more toxic than heptachlor while with rainbow trout heptachlor was more toxic than DDT. It is difficult to determine how much of the variations in results are due to differences in species sensitivity and how much to test variability. However, it seems probable that species sensitivity varies considerably with different pesticides. It is also apparent from Tables 1 and 2 that heptachlor is generally highly toxic in an acute exposure.

Macek, et al. (1976) reported an incipient LC50 of 7.0 µg/l for the fathead minnow. This incipient LC50 was derived with flow-through testing procedures by determining when no additional significant mortality (less than 10 percent) was observed at any concentration during a 48-hour period. A linear regression equation was calculated by converting test concentrations and corresponding mortalities into logarithms and probits, respectively. This equation was then used to determine the incipient LC50. Due to analytical difficulties, however, actual concentration determinations were not made, but rather were based on nominal values.

Water hardness was found to have a possible slight effect on the toxicity of heptachlor (Henderson, et al. 1959). The adjusted 96-hour LC50 values for fathead minnows exposed to technical-grade heptachlor in soft and hard water were 71 µg/l and 43 µg/l, respectively.

Bridges (1965) found that toxicity to redear sunfish increased at higher temperatures (Table 1). Unadjusted 24-hour EC50 values decreased (toxicity increased) from 92 µg/l at 45° F to 22 µg/l at 85° F. Macek, et al. (1969) found an increase in toxicity to rainbow trout when tested at 7.2 and 12.7° C as compared to the toxicity at 1.6° C (Table 1). Naqvi (1973) found 100 percent mortality of tubificid worms, Branchiura sowerbyi, at 2,500 µg/l when tested at 4.4 and 32.2° C (Table 5). At 21.0° C no mortality occurred. Sanders and Cope (1966) found that with the cladoceran, Simocephalus serrulatus, the unadjusted 48-hour

EC50 values for heptachlor were 47 µg/l at 60° F and 80 µg/l at 70° F (Table 2).

Only one acceptable study was found that compared the relative toxicity of heptachlor to its common degradation product heptachlor epoxide. Frear and Boyd (1967), using an unspecified grade material, determined the 26-hour LC50 for Daphnia magna to be 50 µg/l for heptachlor and 120 µg/l for heptachlor epoxide (Table 5). There are insufficient data, therefore, to support the hypothesis that the epoxide degradation product is more toxic to aquatic life than the parent compound.

Many authors reported LC50 values for fish after 24, 48, and 96 hours of exposure to heptachlor. In general, toxicity increased slightly with time. However, considerable species variation existed. The ratios of 96-hour/24-hour and 96-hour/48-hour LC50 values ranged from 0.45 to 0.97 and 0.57 to 1.00, respectively. The geometric means of the ratios grouped by species were 0.62 for 96-hour/24-hour LC50 values and 0.78 for 96-hour/48-hour LC50 values. Considering the limited number of data points, these values are very close to the recommended Guideline values for adjustment of data to equivalent 96-hour values (0.66 and 0.81 for adjustment of 24- and 48-hour LC50 values, respectively). Guideline values were used where necessary.

The relationship of exposure time to LC50 values was more dramatic and variable for invertebrate species. The range of values for the ratio of 96-hour/24-hour LC50 values was 0.06 to 0.56. Exposure time, therefore, can significantly affect LC50

values for invertebrate species exposed to heptachlor. The geometric mean of the ratios was 0.20. Considering the wide variation in values, coupled with the limited data points, the Guideline value of 0.26 was used in the one instance where an adjustment factor for exposure period was necessary.

The absence of flow-through tests with measured exposure concentrations is primarily a function of the state-of-the-art of aquatic toxicology at the time when the majority of testing occurred. Improved test procedures would probably give a better picture of the acute toxicity of heptachlor.

The Final Fish and Invertebrate Acute Values were derived using values listed in Tables 1 and 2. Results from the literature were adjusted using Guideline procedures to be equivalent to 96-hour, flow-through toxicant-measured LC50 values. The final acute values were calculated according to Guideline procedures and were found to be 7.5 µg/l for fish and 0.45 µg/l for invertebrate species. Therefore, the Final Acute Value is 0.45 µg/l.

Chronic Toxicity

The only available chronic study was that of Macek, et al. (1976) with heptachlor and the fathead minnow (Table 3). This life-cycle test lasted 40 weeks during which growth, survival, and reproduction were monitored. Concentrations tested were 1.84, 0.86, 0.43, 0.20, 0.11, and 0.0 µg/l. All fish exposed to 1.84 µg/l were dead after 60 days. No adverse effects on parental fish or their offspring were noted at concentrations of 0.86 µg/l or lower. The maximum acceptable heptachlor concentration for

fathead minnows was estimated to be between 0.86 and 1.84 µg/l.

No valid chronic test data were available for any invertebrate species. However, in general, invertebrate acute values were considerably lower than fish acute values. In fact, some invertebrate LC50 values were lower than the fathead minnow chronic value. It is reasonable to expect, therefore, that some invertebrate chronic values would be lower than the available fish chronic value.

Data on the acute toxicity of heptachlor to fathead minnows indicate that this species is somewhat less sensitive than other fish species in general. Chronic tests with more sensitive species might have resulted in lower chronic effect levels. However, because there are no fathead minnow acute tests with measured exposure concentrations, no application factors can be calculated, and a quantitative relationship between acute and chronic values cannot be determined. It is difficult, therefore, to speculate on how the chronic value might be adjusted to take into account that more sensitive species other than by the recommended Guideline sensitivity factors. The Final Fish Chronic Value for heptachlor is 0.19 µg/l.

Plant Values

No studies using aquatic plants are available.

Residues

As part of the fathead minnow chronic study of Macek, et al. (1976), fish residue levels were determined. Residues in the

eviscerated carcasses of fish after 276 days of exposure were measured at each exposure concentration. Residues of heptachlor and heptachlor epoxide were combined. Heptachlor epoxide residues were reported as generally constituting 10 to 24 percent of the total residue. The amount of total residue accumulated was found to be approximately 20,000 times the concentration in the water. The residue was proportional to the level of exposure and reasonably linear over the range of concentrations tested.

It should be noted that no adverse effects were found with the fish which were used to determine accumulation in the above study. Fish at the high concentration (1.84 µg/l) were all dead after 60 days of exposure, and residue levels were not determined in these fish. Residues in fish at the next highest concentration (0.86 µg/l) were approximately 18 mg/kg with no measured detriment.

Current U.S. Food and Drug Administration guidelines limit the concentration of heptachlor in food for human consumption to 0.3 mg/kg and for domestic animals, 0.03 mg/kg. Only one measure of the equilibrium bioconcentration of heptachlor has been reported (Macek,et al. 1976). Based on the data from this one study, in order to prevent fish from exceeding FDA guidelines, a heptachlor concentration of 0.0015 µg/l should not be exceeded. The Residue Limited Toxicant Concentration (RLTC) is, therefore, 0.0015 µg/l (Table 4). The RLTC is the lowest value found for heptachlor exposures to aquatic life. The Final Chronic Value is, therefore, 0.0015 µg/l.

Miscellaneous

Andrews, et al. (1966) studied the impact of a single application of technical-grade heptachlor in several earthen ponds (Table 5). Initial concentrations as technical-grade heptachlor (rather than percent active ingredient as was done by the authors) in the test ponds ranged from 17.4 to 69.4 µg/l. Residue levels measured in stocked bluegills were not proportional to dosage. Time to peak residue levels depended on concentration with the lower concentrations peaking within 24 hours. Residue concentrations at all test levels decreased to below detectable limits by the end of 84 days. Although the data were not usable for calculating bioconcentration values in this document, maximum bioconcentration factors, based on peak residue levels for total heptachlor, heptachlor epoxide, and related compounds compared to initial dose concentrations in µg/l technical-grade heptachlor, ranged from 638 to 1,326. The highest level was at one of the intermediate level ponds.

In an additional study by Andrews, et al. (1966), bluegills in plastic pools were fed food containing heptachlor at either 25.0, 10.0, 5.0, or 0.0 mg/kg/day (Table 5). Tests were run in duplicate. Variable residue values were obtained that were not strictly dose-related. Although dosing through the diet was continuous, uptake rates peaked at the different exposure levels at various times, and in some cases secondary peak levels occurred. There was only one pool at 10 mg/kg/day in which residues were detected after 84 days. Apparently the fish reached a stage where removal rates exceeded uptake rates.

In vitro measurements of the effect of heptachlor on biochemical activity have also been reported by several authors (Table 5). The value of these data for criteria derivation is limited, however, since no environmental dose relationships were tested or derived.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 7.5 µg/l

Final Invertebrate Acute Value = 0.45 µg/l

Final Acute Value = 0.45 µg/l

Final Fish Chronic Value = 0.19 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = 0.0015 µg/l

Final Chronic Value = 0.0015 µg/l

0.44 x Final Acute Value = 0.20 µg/l

The maximum concentration of heptachlor is the Final Acute Value of 0.45 µg/l, which is based on the more acutely sensitive invertebrate organisms. Since 0.44 times the Final Acute Value (0.44 x 0.45 µg/l = 0.20 µg/l) is not lower than the Final Chronic Value (0.0015 µg/l), the latter is the recommended 24-hour average concentration.

CRITERION: For heptachlor the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0015 µg/l as a 24-hour average and the concentration should not exceed 0.45 µg/l at any time.

Table 1. Freshwater fish acute values for heptachlor

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs.)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Coho salmon, Oncorhynchus kisutch	S	U	Technical grade***	96	81.9	44.8	Katz, 1961
Chinook salmon, Oncorhynchus tshawytscha	S	U	Technical grade***	96	24.0	13.1	Katz, 1961
Rainbow trout, Salmo gairdneri	S	U	Technical grade***	96	26.9	14.7	Katz, 1961
Rainbow trout, Salmo gairdneri	S	U	Technical grade	96	7.7	4.2	Macek, et al. 1969
Rainbow trout, Salmo gairdneri	S	U	Technical grade	96	7.0	3.8	Macek, et al. 1969
Rainbow trout, Salmo gairdneri	S	U	Technical grade	96	7.3	4.0	Macek, et al. 1969
Goldfish, Carassius auratus	S	U	Technical grade	96	320	175	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	Technical grade	96	130	71	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	Technical grade	96	78	43	Henderson, et al. 1959
Guppy, Poecilia reticulata	S	U	Technical grade	96	148	81	Henderson, et al. 1959
Bluegill, Lepomis macrochirus	S	U	Technical grade	96	26	14	Henderson, et al. 1959
Redear, Lepomis microlophus	S	U	Technical grade	96	17	9	Bridges, 1965
Redear, Lepomis microlophus	S	U	Technical grade	24	92	33	Bridges, 1965
Redear, Lepomis microlophus	S	U	Technical grade	24	64	23	Bridges, 1965
Redear, Lepomis microlophus	S	U	Technical grade	24	47	17	Bridges, 1965

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs.)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Redear, Lepomis microlophus	S	U	Technical grade	24	22	8	Bridges, 1965

* S = static

** U = unmeasured

***Author converted from technical grade (72%) to 100% active ingredient. For the purpose of this criteria document, LC50 was converted back to technical grade.

Geometric mean of adjusted values = 29.4 µg/l $\frac{29.4}{3.9}$ = 7.5 µg/l

Table 2. Freshwater invertebrate acute values for heptachlor

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs.)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, Daphnia magna	S	U	99% heptachlor	48	78	66	Macek, et al. 1976
Cladoceran, Daphnia pulex	S	U	Unspecified grade	48	42	36	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S	U	Unspecified grade	48	47	40	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S	U	Unspecified grade	48	80	68	Sanders & Cope, 1966
Scud, Gammarus faciatus	S	U	Technical grade	96	56	47	Sanders, 1972
Scud, Gammarus faciatus	S	U	Technical grade	96	40	34	Sanders, 1972
Scud, Gammarus lacustris	S	U	Technical grade	96	29	25	Sanders, 1969
Crayfish, Orconectes nais	S	U	Technical grade	96	7.8	6.6	Sanders, 1972
Freshwater glass shrimp, Palaemonetes kadiakensis	S	U	Technical grade	96	1.80	1.52	Sanders, 1972
Freshwater glass shrimp, Palaemonetes kadiakensis	S	U	Technical grade	24	40.6	8.9	Naqvi & Ferguson, 1970
Stonefly, Claassenia sabulosa	S	U	Technical grade	96	2.8	2.4	Sanders & Cope, 1968
Stonefly, Pteronarcella badia	S	U	Technical grade	96	0.9	0.8	Sanders & Cope, 1968
Stonefly, Pteronarcys californica	S	U	Technical grade	96	1.1	0.9	Sanders & Cope, 1968

* S = static

** U = unmeasured

Geometric mean of adjusted values = 9.4 µg/l $\frac{9.4}{21}$ = 0.45 µg/l.

Table 3. Freshwater fish chronic values for heptachlor (Macek, et al. 1976)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Fathead minnow, *Pimephales promelas*	LC	0.86-1.84	1.26

* LC = life cycle or partial life cycle

Geometric mean of chronic values = 1.26 µg/l $\frac{1.26}{6.7}$ = 0.19 µg/l

Lowest chronic value = 1.26 µg/l

Table 4. Freshwater residues for heptachlor

Organism	Bioconcentration Factor	Time (days)	Reference
Fathead minnow, Pimephales promelas	20,000	276	Macek, et al. 1976

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Human	fish	0.3	U.S. FDA Admin. Guideline - 7420.08, 1973
Domestic animals	animal feed	0.03	U.S. FDA Admin. Guideline - 7426.04, 1977

Residue Limited Toxicant Concentration = $\frac{0.03}{20,000}$ = 0.0000015 mg/kg or 0.0015 µg/l

Table 5. Other freshwater data for heptachlor

Organism	Test Duration	Effect	Result ug/l	Reference
Rainbow trout, Salmo gairdneri	15 min	67% inhibition of NaK-ATPase	37,350	Davis, et al. 1972
Rainbow trout, Salmo gairdneri	15 min	31% inhibition of Mg-ATPase	3,735	Davis, et al. 1972
Atlantic salmon (juvenile), Salmo salar	24 hrs	Change in temperature selection	No effect up to 25	Peterson, 1976
Fathead minnow, Pimephales promelas	10 days	Incipient LC50	7.0	Macek, et al. 1976
Mosquitofish, Gambusia affinis	48 hrs	64% mortality in cages submerged in ponds dosed with emulsifiable concentrate	0.5 lbs/acre	Mulla, 1963
Mosquitofish, Gambusia affinis	36 hrs	LC50	70	Boyd & Ferguson, 1964
Bluegill, Lepomis macrochirus	171 days*	>90% mortality	69.4	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	171 days*	Growth and reproduction	No effect where fish survived	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	171 days*	Tissue accumulation	Maximum accumulation of 1326 x initial dose concentration; returned to normal after 84 days	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	171 days**	Increased mortality	10 mg/kg/day	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	171 days**	Dose-related growth decrease	5 to 25 mg/kg/day	Andrews, et al. 1966

Table 5. (Continued)

Organism	Test Duration	Effect	Result µg/l	Reference
Bluegill, Lepomis macrochirus	171 days**	Tissue accumulation	Accumulation peaked and subsequently declined to undetectable levels by day 112	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	25 min	65-69% inhibition of NaK- and Mg-ATPase	15,600	Cutkomp, et al. 1971
Bluegill, Lepomis macrochirus	25 min	45-47% inhibition of NaK- and Mg-ATPase	16,200	
Bluegill, Lepomis macrochirus	96 hrs	LC50 of heptachlor as emulsifiable concentrate in soft water	22	Henderson, et al. 1960
Bluegill, Lepomis macrochirus	96 hrs	LC50 of heptachlor as emulsifiable concentrate in hard water	18	Henderson, et al. 1960
Bluegill, Lepomis macrochirus	Unspecified	87% inhibition of O_2 utilization by mitochondria	370,000	Hiltibran, 1974
Bluegill, Lepomis macrochirus	Unspecified	29% inhibition of PO_4 utilization by mitochondria	370,000	Hiltibran, 1974
Bluegill, Lepomis macrochirus	Unspecified	50% inhibition of mitochondrial Mg-ATPase	6,790	Yap, et al. 1975
Bluegill, Lepomis macrochirus	Unspecified	50% inhibition of brain NaK-ATPase	16,434	Yap, et al. 1975

Table 5. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Bluegill, *Lepomis macrochirus*	Unspecified	50% inhibition of brain NaK-ATPase by heptachlor epoxide	8,179	Yap, et al. 1975
Fowler's toad (larva), *Bufo woodhousii fowleri*	96 hrs	LC50	440	Sanders, 1970
Bullfrog (larva), *Rana catesbeiana*	48 hrs	80% mortality in cages submerged in ponds dosed with emulsifiable concentrate	0.5 lbs/acre	Mulla, 1963
Tubificid worm, *Branchiura sowerbyi*	72 hrs	100% mortality at 4.4°C	2,500	Naqvi, 1973
Tubificid worm, *Branchiura sowerbyi*	72 hrs	0% mortality at 21.0°C	2,500	Naqvi, 1973
Tubificid worm, *Branchiura sowerbyi*	72 hrs	100% mortality at 32.2°C	2,500	Naqvi, 1973
Crayfish, *Procambarus clarkii*	Variable	Time to death after consuming contaminated tubificid worms; worms placed in clean water after exposure were not lethal	2 hr	Naqvi, 1973
Crayfish, *Procambarus clarkii*	Unspecified	10% inhibition of brain acetylcholinesterase	933	Guilbault, et al. 1972

Table 5. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Numerous miscellaneous invertebrates	171 days*	100% mortality in 24 hrs, returned to normal population levels by day 14	52.1	Andrews, et al. 1966
Cladoceran, Daphnia magna	26 hrs	LC50 (heptachlor)	52	Frear & Boyd, 1967
Cladoceran, Daphnia magna	26 hrs	LC50 (heptachlor epoxide)	120	Frear & Boyd, 1967

* Tested in ponds, dosed on day 1 only. Authors dosed with technical-grade heptachlor and reported as µg/l active ingredient. For the purposes of this document, values are reported as µg/l technical-grade heptachlor.

** Tested in small pools. Technical-grade heptachlor was incorporated into fish food only and fed for duration of test.

SALTWATER ORGANISMS

Introduction

Heptachlor is a chlorinated hydrocarbon pesticide that has had wide usage in the United States as a crop insecticide. It has been shown to be toxic to aquatic life, to accumulate in plant and animal tissues, and to persist in aquatic ecosystems.

Earlier studies reported toxicity of this material to freshwater organisms. More recently, pertinent studies have been completed that demonstrate acute and chronic toxicity and bioaccumulation potential to inhabitants of estuarine and marine waters.

Acute Toxicity

Heptachlor has been shown to be acutely toxic to a number of saltwater fish and invertebrate species. Many of the aquatic toxicity tests with heptachlor have used technical-grade material, containing approximately 72 percent heptachlor and a 22 to 28 percent mixture of trans-chlordane, cis-chlordane, nonachlor and related compounds. Heptachlor epoxide is a common metabolite of heptachlor. There are insufficient data to evaluate relative toxicity of these components. However, the data available suggest that toxicity of the technical material is attributable to the heptachlor and heptachlor epoxide components and that toxicities of heptachlor and heptachlor epoxide are similar (Schimmel, et al. 1976a).

The 96-hour LC50 values (Table 6) derived from flow-through tests with four fish species range from 0.85 to 10.5 µg/l (Hansen

and Parrish, 1977; Korn and Earnest, 1974; Schimmel, et al. 1976a). Results of static exposures of eight fish species are more variable and yield higher LC50 values than those from flow-through tests, i.e., 0.8 to 194 µg/l (Eisler, 1970a; Katz, 1961). LC50 values derived from tests utilizing aeration or static test procedures probably underestimate the toxicity of heptachlor, due to its probable high volatility during toxicity testing (Schimmel, et al. 1976a; Goodman, et al. 1978).

Saltwater invertebrate species seem to be more sensitive to heptachlor and its metabolite, heptachlor epoxide, than are fishes, and demonstrate a greater variability in sensitivity of species (Table 7). Of the seven species tested, the commercially valuable pink shrimp is especially sensitive with 96-hour LC50 values as low as 0.03 µg/l (Schimmel, et al. 1976a). Other species, such as the blue crab and American oyster are 2,100 to 950 times less sensitive, respectively, than the pink shrimp (Butler, 1963). As with fishes, 96-hour LC50 values derived from static exposures or exposures based on unmeasured concentrations probably underestimate toxicity of heptachlor and heptachlor epoxide to invertebrate species. For example, the 96-hour LC50 of heptachlor to the grass shrimp based on a static exposure using unmeasured concentrations is 440 µg/l (Eisler, 1969), whereas the results from a flow-through test with measured concentrations is 1.06 µg/l (Schimmel, et al. 1976a). The same relationship is true for the American oyster. Static test results (Butler, 1963) were 27 and 30 µg/l and, using flow-through procedures and measured concentrations, Schimmel, et al. (1976a) determined a 96-hour LC50

of 1.5 µg/l. These results demonstrate the need for adjustment factors for testing procedures. The range of unadjusted LC50 values for saltwater invertebrate species is from 0.03 to 440 µg/l and is similar to the comparable range of 0.9 to 80 µg/l for freshwater invertebrate species.

During toxicity testing with heptachlor, there is apparently an appreciable loss of heptachlor by volatilization due to aeration or mixing (Schimmel,et al. 1976a; Goodman,et al. 1978). This loss appears to be the principal cause of the variability in the data for the grass shrimp and American oyster due to different testing techniques as discussed above. It is felt that this loss is not adequately accounted for by the Guideline's adjustment factors for static vs. flow-through procedures and measured vs. unmeasured test concentrations. This may explain why the Final Fish Acute Value (0.85 µg/l) and Final Invertebrate Acute Value (0.05 µg/l) are based on the lowest test result with flow-through procedures and measured concentrations rather than the geometric mean LC50 values divided by the sensitivity factors. Unfortunately, there are too few data for heptachlor to derive adjustment factors specific to heptachlor.

Chronic Toxicity

The chronic toxicity of heptachlor to the sheepshead minnow (Tables 8 and 11) (Hansen and Parrish, 1977) was measured in an 18-week partial life-cycle exposure, begun with juveniles. Survival was affected at concentrations of 2.8 µg/l and greater. Egg production was significantly decreased at the lowest

concentration tested, 0.71 g/l, but not at the next highest concentration, 0.97 µg/l. However, significant impairment of egg production also occurred at test concentrations of 1.9 to 5.7 µg/l. Because of this anomaly in the data, test results were placed in Table 11 rather than Table 8. Significant effects on reproduction occurred at a concentration of 0.06 of the 96-hour LC50 obtained in this test (96-hour LC50 = 10.5 µg/l; Hansen and Parrish, 1977).

In a 28-day exposure starting with sheepshead minnow embryos, hatching was unaffected, but survival of fry was significantly reduced from that of controls at measured concentrations of 2.24 to 4.3 µg/l (Goodman, et al. 1978). Growth of fry was significantly reduced at concentrations of 2.04 µg/l and above. No detrimental effects were observed at 1.22 µg/l.

Comparison of data from the embryo-larval portion of the partial chronic exposure (Hansen and Parrish, 1977) with results of the 28-day embryo-larval test (Goodman, et al. 1978) shows survival of fry was reduced at a similar concentration in both exposures (2.8 µg/l and 2.24 µg/l, respectively). Therefore, for heptachlor, results from the embryo-fry exposure could be used to predict the results of a life-cycle toxicity test rather accurately.

The species sensitivity factor appears to be justified, since the sheepshead minnow has been shown to be generally less sensitive in acute studies with heptachlor than are other fishes (Table 6). No other fish can now be tested in life-cycle tests for comparison of chronic sensitivity. Therefore, 0.12 µg/l is the Final Fish Chronic Value.

No data are available on the chronic toxicity of saltwater crustaceans or other saltwater invertebrate species.

Plant Effects

Information on the sensitivity of aquatic plants, including algae and rooted vascular plants, is limited to one test using a 4-hour exposure of a natural phytoplankton community (Table 9). A concentration of 1,000 µg/l caused a 94.4 percent decrease in productivity (Butler, 1963) and is the Final Plant Value.

Residues

Heptachlor and heptachlor epoxide bioconcentrate from water into the tissues of marine organisms (Tables 10 and 11). The only bioconcentration factors (BCF) available at steady-state for heptachlor and heptachlor epoxide are those for fish (Table 10). Adult sheepshead minnows exposed to technical-grade material for 126 days accumulated heptachlor and heptachlor epoxide an average of 37,000 times that in the exposure water (Hansen and Parrish, 1977). Juvenile sheepshead minnows exposed in two separate experiments for 28 days to technical-grade material bioconcentrated 5,700 and 7,518 times the concentration in the water (Hansen and Parrish, 1977; Goodman, et al. 1976).

Spot exposed for 24 days to technical-grade material reached a maximum concentration of heptachlor in the tissues (whole body) after three days (BCF = 6,000; Schimmel, et al. 1976b). In the same exposure, maximum levels of heptachlor epoxide were reached in whole fish after 17 days. After a 28-day period of depuration,

less than 10 percent of the maximum amount of heptachlor remained in tissues; it was either lost or metabolized to the epoxide (Schimmel, et al. 1976b).

Data derived from Table 10 on saltwater residues for heptachlor and FDA maximum tissue concentrations of heptachlor allowable in animal feed (0.03 mg/kg), produce a Residue Limited Toxicant Concentration (RLTC) or 0.0036 µg/l. Of the four components used to establish the Final Chronic Value, as prescribed by the Guidelines, the RLTC is lowest and the Final Chronic Value is 0.0036 µg/l.

Miscellaneous

Other bioconcentration information (Table 11) available for heptachlor and heptachlor epoxide are based on short-term exposures and are probably not steady-state values (Schimmel, et al. 1976a). Two species of shrimp (Penaeus duorarum and Palaemonetes vulgaris) showed less bioconcentration in 96-hour exposures to technical heptachlor than did another invertebrate species, the American oyster, in a similar exposure (average BCF of 425 for shrimp and 6,200 for oysters). Three fish species exposed for 96-hours to technical heptachlor showed an average BCF of 9,333 (range 2,800 to 21,300) whereas three invertebrate species in a similar exposure had an average BCF of 2,350 (range 200 to 8,500). In contrast, the equilibrium fish bioconcentration factor averaged 12,000 (range 3,435 to 37,000; Table 10).

Schimmel, et al. (1976a) reported a 15 percent mortality of the pink shrimp at an unmeasured concentration of 0.0046 µg/l (Table 11), an amount of heptachlor that is not detectable in salt water using present technology. Therefore, it seems reasonable to be concerned about the adequacy of the RLTC to protect penaeid shrimp, or other very sensitive species, in a chronic or long-term exposure.

Table 11 contains no effect data at lower concentrations than those in previous tables, except the work of Hansen and Parrish (1977), which was discussed earlier.

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 0.85 µg/l

Final Invertebrate Value = 0.05 µg/l

Final Acute Value = 0.05 µg/l

Final Fish Chronic Value = 0.12 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 1,000 µg/l

Residue Limited Toxicant Concentration = 0.0036 µg/l

Final Chronic Value = 0.0036 µg/l

0.44 x Final Acute Value = 0.22 µg/l

Criterion Formulation

To derive the criterion, the maximum concentration is the Final Acute Value of 0.05 µg/l and the 24-hour average concentration is the Final Chronic Value of 0.0036 µg/l. No important adverse effects on marine aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration. But some data for the pink shrimp indicate concern for this and related species.

CRITERION: For heptachlor the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.0036 µg/l as a 24-hour average and the concentration should not exceed 0.05 µg/l at any time.

Table 6. Marine fish acute values for heptachlor

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American eel, Anguilla rostrata	S	U	***	96	10	5.47	Eisler, 1970a
Sheepshead minnow, Cyprinodon variegatus	FT	M	****	96	3.68	3.68	Schimmel, et al. 1976a
Sheepshead minnow, Cyprinodon variegatus	FT	M	****	96	10.5	10.5	Hansen & Parrish, 1977
Mummichog, Fundulus heteroclitus	S	U	***	96	50	27.3	Eisler, 1970a
Striped killifish, Fundulus majalis	S	U	***	96	32	17.5	Eisler, 1970a
Atlantic silverside, Menidia menidia	S	U	***	96	3	1.64	Eisler, 1970a
Threespine stickleback, Gasterosteus aculeatus	S	U	*****	96	111.9	61.2	Katz, 1961
Threespine stickleback, Gasterosteus aculeatus	S	U	*****	96	111.9	61.2	Katz, 1961
Striped bass, Morone saxatilis	FT	U	99+%	96	3	2.31	Korn & Earnest, 1974
Pinfish, Lagodon rhomboides	FT	M	****	96	3.77	3.77	Schimmel, et al. 1976a
Spot, Leiostomus xanthurus	FT	M	****	96	0.85	0.85	Schimmel, et al. 1976a
Spot, Leiostomus xanthurus	FT	M	99.8%	96	0.86	0.86	Schimmel, et al. 1976a
Bluehead, Thallassoma bifasciatum	S	U	***	96	0.8	0.44	Eisler, 1970a

Table 6. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
White mullet, Mugil curema	FT	U	--	48	3	1.67	Butler, 1963
Striped mullet, Mugil cephalus	S	U	**	96	194	106	Eisler, 1970a
Northern puffer, Sphaeroides maculatus	S	U	**	96	188	103	Eisler, 1970a

* S = static, FT = flow-through

** U = unmeasured, M = measured

*** Entomol. Soc. Am. reference standard

**** Technical material; also contains 22% trans-chlordane, 2% cis-chlordane, and 2% nonachlor

***** Technical material; 72% heptachlor and 28% related compounds

Geometric mean of adjusted values = 7.06 µg/l $\frac{7.06}{3.7}$ = 1.9 µg/l

Lowest value from a flow-through test with measured concentrations = 0.85 µg/l

Table 7. Marine invertebrate acute values for heptachlor

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American oyster, Crassostrea virginica	FT	U	--	96	27***	20.8	Butler, 1963
American oyster, Crassostrea virginica	FT	U	--	96	30***	23.1	Butler, 1963
American oyster, Crassostrea virginica	FT	M	****	96	1.5	1.5	Schimmel, et al. 1976a
Blue crab, Callinectes sapidus	FT	U	--	48	63***	20.8	Butler, 1963
Sand shrimp, Crangon septemspinosa	S	U	*****	96	8	6.8	Eisler, 1969
Hermit crab, Pagurus longicarpus	S	U	*****	96	55	46.6	Eisler, 1969
Korean shrimp, Palaemon macrodactylus	S	U	99%	96	14.5	12.3	Schoettger, 1970
Grass shrimp, Palaemonetes vulgaris	S	U	*****	96	440	373	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	FT	M	****	96	1.06	1.06	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	FT	M	****	96	0.11	0.11	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	FT	M	99.8%	96	0.03	0.03	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	FT	U	--	48	0.3***	0 10	Butler, 1963
Pink shrimp, Penaeus duorarum	FT	M	******	96	0.04	0.04	Schimmel, et al. 1976a

Table 7. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference

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* S = static, FT = flow-through

** U = unmeasured, M = measured

*** EC50: decreased growth of oyster or loss of equilibrium in pink shrimp or blue crabs

**** Technical material; also contains 22% trans-chlordane; 2% cis-chlordane, and 2% nonachlor

***** Entomol. Soc. Am. reference standard

****** Heptachlor epoxide, 99% pure

Geometric mean of adjusted values = 7.2 µg/l $\frac{7.2}{49}$ = 0.15 µg/l

Lowest species geometric mean from flow-through tests with measured concentrations = 0.05 µg/l

Table 8. Marine fish chronic values for heptachlor (Goodman, et al. 1978)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Sheepshead minnow, *Cyprinodon variegatus*	E-L	1.22-2.04**	0.79

* E-L = embryo-larval

** Technical material; also contains 27% trans-chlordane, 2% cis-chlordane, and 2% nonachlor

Geometric mean of chronic values = 0.79 µg/l $\quad \frac{0.79}{6.7} = 0.12$ µg/l

Lowest chronic value = 0.79 µg/l

Table 9. Marine plant effects for heptachlor (Butler, 1963)

Organism	Effect	Concentration (ug/l)
Natural phytoplankton communities	94.4% decrease in productivity.	1,000

Lowest plant value 1,000 µg/l

Table 10. Marine residues for heptachlor

Organism	Bioconcentration Factor	Time (days)	Reference
Sheepshead minnow (juvenile), Cyprinodon variegatus	5,700*	28	Hansen & Parrish, 1977
Sheepshead minnow (adult), Cyprinodon variegatus	37,000*	126	Hansen & Parrish, 1977
Sheepshead minnow (juvenile), Cyprinodon variegatus	7,518*	28	Goodman, et al. 1978
Spot, Leiostomus xanthurus	6,000**	24	Schimmel, et al. 1976b

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Domestic animals	animal feed	0.03	U.S. FDA Admin. Guideline - 7426.04, 1977

* Concentration of heptachlor, heptachlor epoxide, trans-chlordane, and cis-chlordane in whole fish divided by concentration of heptachlor and trans-chlordane measured in water.

** Concentration of heptachlor and heptachlor epoxide in whole fish divided by concentration of heptachlor in water.

Geometric mean bioconcentration factor for all species = 8,365

Lowest residue concentration = 0.03 mg/kg $\frac{0.03}{8,365}$ = 0.0000036 mg/kg or 0.0036 ug/l

Table 11. Other marine data for heptachlor

Organism	Test Duration	Effect	Result (ug/l)	Reference
American oyster, Crassostrea virginica	10 days	Bioconcentration factor = 17,600	-	Wilson, 1965
American oyster, Crassostrea virginica	96 hrs	Bioconcentration* factor = 3,900 to 8,500	-	Schimmel, et al. 1976a
Grass shrimp, Palaemonetes vulgaris	48 hrs	50-75% mortality 12 o/oo salinity	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	25-50% mortality 18 o/oo salinity	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	25-50% mortality 24 o/oo salinity	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	25-50% mortality 30 o/oo salinity	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	25-50% mortality 36 o/oo salinity	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	0-25% mortality 10°C	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	0% mortality 15°C	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	25-50% mortality 20°C	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	75-100% mortality 25°C	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	48 hrs	75-100% mortality 30°C	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	96 hrs	Bioconcentration* factor = 500 to 700	-	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	96 hrs	Bioconcentration* factor = 200 to 300	-	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	96 hrs	Bioconcentration** factor = 300 to 600	-	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	96 hrs	Bioconcentration*** factor = 200 to 1,700	-	Schimmel, et al. 1976a

Table 11. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Sheepshead minnow, Cyprinodon variegatus	96 hrs	Bioconcentration* factor = 7,400 to 21,300	-	Schimmel, et al. 1976a
Sheepshead minnow, Cyprinodon variegatus	126 days	decreased egg production	0.71	Hansen & Parrish, 1977
Mummichog, Fundulus heteroclitus	96 hrs	0-25% mortality 12 o/oo salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	0-25% mortality 18 o/oo salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	50-75% mortality 24 o/oo salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	25-50% mortality 30 o/oo salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	25-50% mortality 36 o/oo salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	0% mortality 10°C	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	0% mortality 15°C	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	0-25% mortality 20°C	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	50-75% mortality 25°C	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	96 hrs	0-25% mortality 30°C	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	240 hrs	LC50	11	Eisler, 1970b
Pinfish, Lagodon rhomboides	96 hrs	Bioconcentration* factor = 2,800 to 7,700	-	Schimmel, et al. 1976a
Spot, Leiostomus xanthurus	96 hrs	Bioconcentration* factor = 3,000 to 13,800	-	Schimmel, et al. 1976a

Table 11. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Spot, *Leiostomus xanthurus*	96 hrs	Bioconcentration** factor = 3,600 to 10,000	-	Schimmel, et al. 1976a

* Concentration of heptachlor in whole body divided by concentration of heptachlor in water. Organism exposed to technical heptachlor (65% heptachlor, 22% trans-chlordane, 2% cis-chlordane, and 2% nonachlor).

** Concentration of heptachlor in whole body divided by concentration of heptachlor in water. Organism exposed to analytical-grade heptachlor (99.8% heptachlor).

*** Concentration of heptachlor epoxide in whole body divided by concentration of heptachlor epoxide in water. Organism exposed to heptachlor epoxide (99%).

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Mammalian Toxicology and Human Health Effects

Exposure

Water. Heptachlor and/or heptachlor epoxide have been found in the major river basins within the United States. Weaver, et al. (1965) reported that from 96 river sampling points from around the U.S., 15 showed presumptive evidence of heptachlor residues. They also reported that heptachlor epoxide was not detectable in any of the samples taken. They explained the failure to find heptachlor epoxide in their samples by indicating that the analytical sensitivity for heptachlor was in the range of 0.002 to 0.010 µg/l, while only 0.075 µg/l for heptachlor epoxide. Breidenbach, et al. (1967) did an extensive survey of the water in the major river basins within the U.S. and in instances where they were detectable found levels of heptachlor ranging from 0.001 to 0.035 µg/l and heptachlor epoxide levels ranging from 0.001 to 0.020 µg/l, with a mean concentration for both of 0.0063 µg/l (U.S. EPA, 1976). They went on to add that 24 percent of the water grab samples taken in 1965 showed positive to presumptive evidence of heptachlor residues, and that heptachlor epoxide was present in 25 percent of their samples. Their level of analytical sensitivity was 0.001 µg/l for both heptachlor and heptachlor epoxide. Another survey conducted by the U.S. Geological Survey of 11 western U.S. streams showed heptachlor levels ranging from 0.005 µg/l to 0.015 µg/l when found and heptachlor epoxide levels ranging from 0.005 to 0.010 µg/l when found, with one sample showing 0.090 µg/l heptachlor epoxide (Brown and Nishioka, 1967).

Food. Food can add significantly to man's exposure to heptachlor and heptachlor epoxide. This occurs through biomagnification of heptachlor/heptachlor epoxide through the food chain. For example, U.S. EPA, (1976) reported data from Hannon, et al. (1970), which reported the average heptachlor/heptachlor epoxide residues in the Lake Poinsett, S. Dak. ecosystem as: 0.006 µg/l for water; 0.8 µg/kg for bottom sediment; 1.0 µg/kg for crayfish; 1.1 µg/kg for plankton-algae; 8.0 µg/kg for fish; and 312.0 µg/kg for aquatic insects. Additionally, there is an approximate ten to fifteenfold increase in heptachlor residues found in body fat, milk butterfat, and in the fat of eggs of poultry and livestock as compared to residue levels found in their normal food rations (U.S. EPA, 1976).

Since 1964 the Food and Drug Administration has reported pesticide residues in their Total Diet Study, sometimes called the "Market Basket Study" (Johnson and Manske, 1977). Their "market basket" of food represents the basic 2-week diet of 16 to 19-year-old males, statistically the Nation's highest percapita consumers, which is collected in each of several geographic areas. The foods analyzed in these studies are prepared in the manner in which they would be normally served and eaten. The latest published study covers food collected from August 1974 to July 1975 in 20 different cities (Johnson and Manshe, 1977). Their results showed that only three of the 12 food classes in this study contained detectable residues of heptachlor epoxide (Table 1). In these three instances, the heptachlor epoxide levels were found to range from 0.0006 to 0.003 ppm.

Nisbet (1977) calculated the average daily intake of heptachlor epoxide from the FDA's Market Basket Studies' standardized diet and estimated that the daily intake of heptachlor epoxide ranged from 1 to 3 µg/day between 1965 and 1970, and from 0.29 to 0.64 µg/day between 1971 and 1974. Nisbet questioned the calculated decrease in residue levels observed between the two time periods since the decrease coincided with FDA's change in analytical methodology. Nisbet (1977) stated that there was apparently a dilution effect taking place when FDA switched methodologies and he regards the total Diet Survey for heptachlor epoxide as only semi-quantitative. He states that the results suggest an overall mean daily intake, in the standardized diet, of the order of 1 ug/day of heptachlor epoxide.

The U.S. Department of Agriculture's Food Surveillance Program found heptachlor epoxide residues greater than 0.03 mg/kg in 19 percent of red meat, 17 percent of poultry, and 14 percent of dairy products in the years 1964 to 1974 (Nisbet, 1977).

The FDA and USDA studies address only food sold in interstate commerce. There is evidence that game fish may contribute to the daily dietary exposure of heptachlor and heptachlor epoxide in addition to that estimated for commercially bought fish. A national study by the U.S. Department of the Interior during the spring and fall of 1967 and the spring of 1968 reported that heptachlor and/or heptachlor epoxide was found in 32 percent of the 590 fish samples examined (Henderson, 1969). Results were reported as mg/kg wet weight whole fish, and ranged from 0.01 to 8.33 mg/kg when found. It must be noted that these results represent the whole fish, not just the portions man eats, so it is possible that much of the residues are accumulated in the uneaten portion (Henderson, 1969).

Table1 Heptachlor epoxide residues in food
(Johnson and Manske, 1977)

Food	class	Average Concentration ppm	Positive Composites		
			Total number	Number reported as trace	Range ppm
I	Dairy Products	0.0004	11	5	0.0006-0.003
II	Meat, Fish and Poultry	0.001	13	4	0.001-0.003
VIII	Garden Fruits	Trace	1	1	Trace

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

Measured steady-state bioconcentration factors were obtained for heptachlor using three species of fish:

Organism	BCF	Percent Lipids	Adjusted BCF	Reference
Sheepshead minnow (juvenile), *Cyprinodon variegatus*	5,700	5	2,662	Hansen & Parrish, 1977
Sheepshead minnow (adult), *Cyprinodon variegatus*	37,000	5	17,020	Hansen & Parrish, 1977
Sheepshead minnow (juvenile), *Cyprinodon variegatus*	7,518	5	3,458	Goodman, et al. 1978
Spot, *Leiostomus xanthuru*	6,000	3	4,600	Schimmel, et al. 1976b
Fathead minnow, *Pimephales promelas*	20,000	8	5,750	Macek, et al. 1976

Each of these measured BCF's was adjusted from the percent lipids of the test species to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. The geometric mean was obtained for each species and then for all species. Thus the weighted average bioconcentration factor for heptachlor and the edible portion of all aquatic organisms consumed by Americans is calculated to be 5,200.

Infants are exposed to heptachlor and heptachlor epoxide through mother's milk (Savage, 1976), cow's milk (Ritcey, et al. 1972; Johnson and Manske, 1977) and commercially prepared baby foods (Lipscomb, 1968). A recent nationwide study, done during 1975-76, indicates that 63.1 percent of the 1936 mothers' milk samples possessed heptachlor epoxide residues (Savage, 1976). The fat adjusted mean concentration for heptachlor epoxide in the mothers' milk with levels above the 1 µg/l sensitivity level, was 91.36 µg/l with a range of 15.24 to 2050 µg/l. It therefore appears that many nursing infants have been exposed to heptachlor epoxide and it is probable that a certain percentage have been exposed to levels that exceeded the levels in dairy products (Savage, 1976). Whole cow's milk and evaporated milk did not show a trace of heptachlor epoxide in the U.S. FDA's 1974-75 Market Basket Survey (Johnson and Manske, 1977), but a Canadian study which expressed the residues on a fat basis, reported heptachlor epoxide residue levels of 5.00 µg/l in evaporated milk (Ritcey, et al. 1972). Commercially prepared baby food was tested by the FDA during a period of July 1963 to June 1967 and heptachlor epoxide residues were found in 0.9 percent of 684 samples with most of the positive samples showing residues in the range of trace to 0.03 mg/kg (Lipscomb, 1968). Therefore it appears that infants raised on mothers' milk run a greater risk of ingesting heptachlor epoxide than if they were fed cow's milk and/or commercially prepared baby food.

Ritcey, et al. (1972) investigated the effects of cooking and heating poultry containing 28.1 mg of heptachlor epoxide per kg of tissue on a dry weight basis (U.S. EPA, 1976). They found baking reduced the residue level to 22.5 mg/kg; steaming to 22.1 mg/kg; and frying resulted in no change. They also found that heating in a closed container at 350°F for 60 to 90 minutes reduced the residue to 16.0 to 19.5 mg/kg.

Inhalation. Volatilization is a major route of loss of heptachlor from treated surfaces, plants and soils (Nisbet, 1977). It has been concluded, from various surveys, that heptachlor and to a lesser extent, heptachlor epoxide are widespread in our ambient air with typical mean concentrations of approximately 0.5 ng/m^3 (Nisbet, 1977). Levels of heptachlor and heptachlor epoxide in the air vary both geographically and seasonally (Stanley, et al. 1971). Higher levels have been found generally in rural agricultural areas where crop spraying was practiced (Stanley, et al. 1971; Nisbet, 1977). However, certain suburban areas have exhibited a substantial concentration of heptachlor in their ambient air (Nisbet, 1977).

Nisbet (1977) has reported air surveys where agricultural fields have been treated with technical heptachlor (2 lb/acre) and the air above and downwind from the fields showed heptachlor concentrations as high as 244 ng/m^3 immediately after application. After 3 weeks the concentrations remained as high as 15.4 ng/m^3. One survey reported heptachlor concentrations as high as 600 ng/m^3 in air over a treated field and this field showed high concentrations in the air throughout the growing season, at least from May to October (Nisbet, 1977).

Nisbet (1977) states that these "high concentrations found above and downwind from treated fields are obviously significant sources of exposure for persons living and working in or near the treated areas."

Arthur, et al. (1976) conducted a 3 year study in 1972-74 of Stoneville, Miss. which is reported as one of the highest pesticide usage areas of the U.S. due to intensive cotton production. They found heptachlor in 62 percent of their monthly samples with an average level of 0.25 ng/m^3 and a maximum concentration of 0.8 ng/m^3. Heptachlor epoxide was found in 36 percent of the monthly samples at an average level of 0.21 ng/m^3 and a maximum concentration of 9.3 ng/m^3 (Arthur, et al. 1976; Nisbet, 1977).

Stanley, et al. (1971) found heptachlor in only two out of nine U.S. localities studied and did not detect heptachlor epoxide in any of the localities. The localities showing residues were Iowa City, Iowa, and Orlando, Fla., with maximum heptachlor levels of 19.2 ng/m^3 and 2.3 ng/m^3, respectively.

Nisbet (1977) calculated the typical human exposure to heptachlor to be 0.01 µg/individual/day based on an ambient air mean concentration of 0.5 ng/m^3 and breathing 20 m^3 of air per day. He states further that even in Jackson, Miss., which has a mean air level as high as 6.3 ng/m^3, the average individual would inhale only 0.13 µg/day of heptachlor. The significance of these figures is dependent upon the efficiency of lung absorption of heptachlor and heptachlor epoxide which does not appear to be reported for humans (Nisbet, 1977). Based on the information presented here, it appears that inhalation is not a major route for human exposure

to heptachlor and its metabolites. However, an experiment by Arthur, et al. (1975) using rabbits, although controversial (Nisbet, 1977), suggests that inhalation may be a significant route of exposure even at ambient levels as low as 1.86 ng/m^3.

Dermal. Limited information is available regarding the dermal route of exposure to heptachlor and/or heptachlor epoxide. However, it may be assumed that persons handling this compound would be dermally exposed. Kazen, et al. (1974) found that chlordane, a compound structurally similar to heptachlor, could be found on a man's skin 2 years after occupational exposure. Gaines (1960) found that rats dermally exposed to technical grade heptachlor had LD_{50} values of 195 mg/kg for males and 250 mg/kg for females, while the LD_{50} values for orally exposed rats were 10.0 mg/kg for males and 162 mg/kg for females. Xylene was used as the vehicle to dissolve and apply the heptachlor and the solution was applied at a rate of 0.0016 ml/kg body weight.

It is significant to note that the U.S. EPA suspended most uses of heptachlor effective August 1, 1976 including most agricultural, home, and garden uses of technical grade heptachlor.

Pharmacokinetics

Absorption and distribution. Heptachlor and/or heptachlor epoxide are both readily absorbed from the gastrointestinal tract (Radomski and Davidow, 1953; Mizyukova and Kurchatov, 1970; Matsumura and Nelson, 1971). Mizyukova and Kurchatov (1970) showed that pure heptachlor reaches all organs and tissues of female rats within one-half to 1 hour after a single dose (120 mg/kg) of heptachlor was delivered directly into the stomach. After 4 hours the metabolite of heptachlor (heptachlor

epoxide) was found in the blood, liver, and fatty tissue. After a few days the concentration of heptachlor in all organs and tissues fell, while at the same time there was a rapid increase in heptachlor epoxide levels. By the end of 1 month only traces of heptachlor could be found in the fatty tissue, chiefly in the form of its metabolic products and no heptachlor or its metabolites could be found in the blood or kidneys. However, a small amount of heptachlor epoxide was found in the liver. After 3 to 6 months the level of heptachlor epoxide in fatty tissues became stabilized.

Radomski and Davidow (1953) used both dogs and rats and found, for rats, that after 2 months on a diet of 30-35 mg/kg of heptachlor, the highest concentration of heptachlor's metabolite (heptachlor epoxide) was found in the fat, with markedly lower amounts in the liver, kidney and muscle, and none was detected in the brain. Female dogs dosed at 1 mg/kg daily for a period of 12 to 18 months showed the same heptachlor epoxide distribution as did the rats except the dog livers appeared to contain more heptachlor epoxide than the kidneys and muscles. The lowest detectable concentration of heptachlor epoxide in this study was 0.6 mg/kg.

The degree to which heptachlor or heptachlor epoxide is absorbed by inhalation has not generally been reported (Nisbet, 1977). Arthur, et al. (1975) conducted a controversial study (Nisbet, 1977) where they exposed white rabbits to the ambient air of Stoneville, Miss., an area of high pesticide use. Their controls were housed indoors at Mississippi State University, an area of low pesticide usage. They found that between July 1972 and October 1972 the heptachlor epoxide level in the

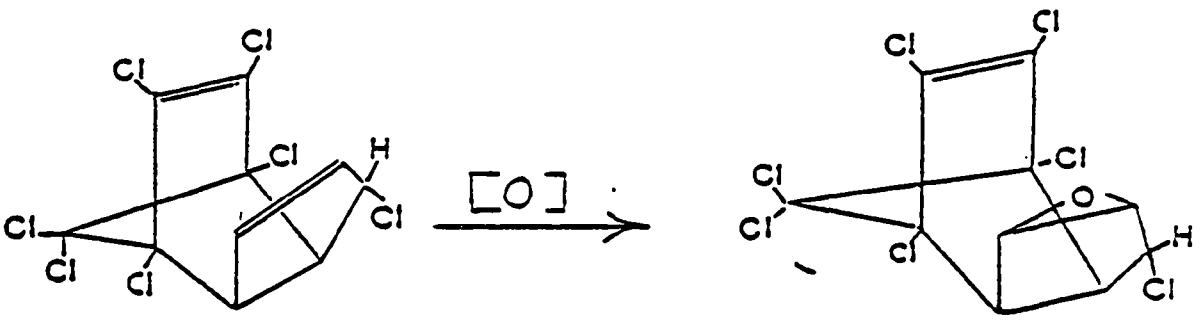
adipose tissue from Stoneville was 0.039 mg/kg while only 0.016 mg/kg was found in the same tissue in rabbits from Mississippi State. The air heptachlor epoxide level at Stoneville was reported to be 1.86 ng/m^3, while the Mississippi State University air heptachlor epoxide level was so low that they did not take air samples. The level of heptachlor in the air at both geographic locations was not given. They also stated that no heptachlor epoxide residues were detected in the feed of either group. They calculated the average daily respiratory intake for rabbits in Stoneville, Miss. as 0.002 µg/day. These data, even though controversial, indicate that heptachlor epoxide can be absorbed to a significant degree after inhalation as determined by rabbit adipose tissue residues.

Several studies released in the late 1960's indicate that the human placenta. that separates a growing fetus from the mother, does not provide adequate protection against chlorinated hydrocarbon pesticides such as heptachlor epoxide (Selby, et al. 1969; Zavon, et al. 1969; Curley, et al. 1969). Selby, et al. (1969) found that women who had high levels of heptachlor or heptachlor epoxide in their blood also had high levels of heptachlor and heptachlor epoxide in their placenta. They also reported a heptachlor epoxide distribution between the placenta and maternal blood in a ratio of 5.8:1 (placenta ppb:maternal blood ppb) based on the geometric means of 54 placental and 53 maternal blood samples. Polishuk, et al. (1977 b) has shown that heptachlor epoxide was higher in the extracted lipids of fetal blood and placenta than in the maternal blood and uterine muscle lipids. Zavon, et al. (1969) reported that fetal or neonatal tissue taken from stillborn or soon dead

children showed that heptachlor epoxide levels paralleled the concentrations found in adults. Curley, et al. (1969) conducted an extensive study using stillborn and soon dead infants, along with the cord blood of live neonates and found that the heptachlor epoxide levels in the various tissues and cord blood sampled varied greatly, but were within the range observed in adults. Therefore, any exposure of heptachlor or heptachlor epoxide to the mother will also expose the fetus to heptachlor epoxide.

Metabolism and excretion. Early studies carried out by Radomski and Davidow (Radomski and Davidow, 1953; Davidow and Radomski, 1953) show that both the rat and the dog rapidly metabolize ingested heptachlor to heptachlor epoxide by epoxidation (figure 1) and that heptachlor epoxide accumulates primarily in fat tissue. They also reported a positive relationship between the amount of heptachlor in the diet and the amount of heptachlor epoxide stored in the fat tissue. The female rats in this study accumulated approximately six times as much heptachlor epoxide in their fat tissue than did the males.

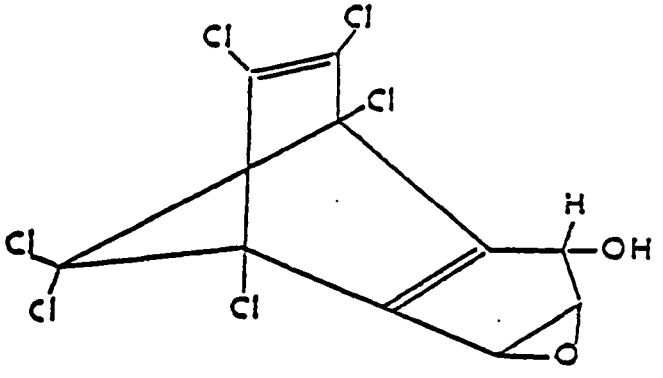
Matsumura and Nelson (1971) fed four male albino rats 10 mg/kg of heptachlor epoxide (99 percent pure) for 30 days (approximately 5 mg heptachlor epoxide/rat/30 days) and found that they excreted 950 ug of a fecal metabolite (figure 2) and 66 ug of heptachlor epoxide in the feces in the 30 day period. Mizyukova and Kurchatov (1971) found that the excretion of the non-stored heptachlor and its metabolites occurs within the first 5 days, chiefly through the gastrointestinal tract and to a smaller extent in the urine.



HEPTACHLOR

Heptachlor epoxide

Figure - 1



FAECAL METABOLITE

Figure - 2

Int. Agency Res. Cancer, 1974

One very important route of excretion of heptachlor and heptachlor epoxide for females is through lactation (Jonsson, et al. 1977). This study indicates that milk is a primary excretory route for heptachlor and its metabolites. It is also generally thought that the heptachlor epoxide concentration in mothers' milk is a good indicator of the body burden of heptachlor epoxide which is stored in the lactating mother's body (Jonsson, et al. 1977; Strassman and Kutz, 1977). Polishuk, et al. (1977 a) found that overweight women excreted lower quantities of pesticides such as heptachlor epoxide in their milk than did women of normal weight. They also found that women of the ages 20 to 29 excreted higher pesticides levels in their milk than did women of the ages 30 to 39, even though the younger women had lower pesticides levels in their plasma.

Kroger (1972) carried out a human milk study based on 53 samples collected from two Pennsylvania regions during 1970 and found that all of the samples contained heptachlor epoxide with an average concentration of 0.16 mg/l. Savage, et al. (1973) carried out a similar survey in Colorado in 1970-1971 with 40 human milk samples and found 25 percent of the samples contained heptachlor epoxide at levels ranging from trace amounts to 5 μg/l. Strassman and Kutz (1977) conducted a study in Arkansas and Mississippi in 1973-1974 containing 57 milk samples and found heptachlor epoxide residues in 35.1 percent of the samples and at least a trace amount of heptachlor epoxide in 64.9 percent of the samples. The levels in this study ranged from trace to 0.03 mg/l and the mean concentration was 0.004 mg/l. They also found trace to quantifiable amounts of trans-nonachlor, which indicates exposure to heptachlor or chlordane.

Savage (1976) reported the results of an extensive study involving 1436 human milk samples from selected sites within the continental U.S. conducted during 1975. He found that only 2 percent showed heptachlor residues, but 63.1 percent of the mothers' milk samples showed heptachlor epoxide residues that ranged from 15.24 to 2,050 µg/l on a fat adjusted basis, with a mean concentration of 91.36 µg/l. Savage also found that 11 percent of the high residue group of women were either occupationally exposed or lived in households where a household member was occupationally exposed. Jonsson, et al. (1977) reported that 24 percent of 51 human milk samples collected from St. Louis in 1977 contained an average heptachlor epoxide level of 0.0027 mg/l. Other studies concerning heptachlor epoxide in human milk in other countries include: Ritcey, et al. (1972); Polishuk, et al. (1977 a); and Bakkan and Seip (1976).

One major problem with the excretion of heptachlor epoxide in mothers' milk is that it becomes a major vehicle for exposing the neonate (Strassman and Kutz, 1977). This exposure to the neonate is an addition to the body burden which already exists due to exposure in-utero (Polishuk, et al. 1977 b; Zavon, et al. 1969; Selby, et al. 1969; Curley, et al. 1969).

Residues of heptachlor epoxide in adipose tissue and other tissues and fluids are indicative of the body burden and the exposure to heptachlor and heptachlor epoxide (Kutz, et al. 1977). Biopsied human adipose tissue was used by Burns (1974) to study the heptachlor epoxide levels in 302 hospital patients from 1969 to 1972 in the lower Rio Grande Valley in Texas. He found that over the study period 98 percent of the adipose samples possessed heptachlor epoxide residues with a mean value of 0.11 mg/kg. An extensive survey of human adipose tissue levels for

heptachlor epoxide has been published by Kutz, et al. (1977).. Tissues were collected during postmortem examinations and from surgical excisions and rejected samples collected from patients known or suspected of pesticide poisoning, cachectic patients, and patients institutionalized for extended periods. The samples were obtained within the conterminous 48 states and the sampling sites were picked to be representative of the U.S. populations. The five-year study showed that heptachlor epoxide can be found in over 90 percent of the U.S. population at approximate mean levels of 0.08 to 0.09 mg/kg (see Table 2).

In addition to the storage of heptachlor epoxide in human adipose tissue, a minor component (trans-nonachlor) of both technical heptachlor and technical chlordane has also been found (Sovocool and Lewis, 1975). They sampled nine composite human fat samples from nine census divisions of the U.S. and found eight of the nine samples possessed trans-nonachlor. Also found in lesser amounts were cis-nonachlor and "early-eluting" nonachlor. Five of the nine composite samples were also positive for heptachlor epoxide and oxychlordane. These data suggest that nonachlors may be more resistant to metabolism than heptachlor, and occurrence of the nonachlors in human tissues appears to be strong evidence of exposure to heptachlor or chlordane pesticides (Sovocool and Lewis, 1975).

Several other researchers have reported heptachlor epoxide residues in human adipose tissue in other countries including: Curley, et al. (1973); Wassermann, et al. (1974]; Abbott, et al. (1972]; and Wassermann, et al. (1972).

Table 2. Heptachlor epoxide residues in human adipose tissue

(Kutz, et al. 1977)

Survey year (fiscal)	Sample size	Percent positive	Geometric mean (mg/kg)	Maximum value mg/kg
1970	1412	94.76	0.09	10.62
1971	1615	96.22	0.09	1.53
1972	1913	90.28	0.08	1.21
1973	1095	97.72	0.09	0.84
1974	898	96.21	0.08	0.77

Health Effects

Acute, subacute and chronic toxicity. The acute toxicities of heptachlor and its metabolites have LD_{50} values ranging from 6 mg/kg to 531 mg/kg (Table 3) depending upon the animal species, toxicant used, and the mode of administration. Radomski and Davidow (1953) were the first to report that heptachlor epoxide is two to four times more toxic than heptachlor itself in mice when given intravenously. Buck, et al. (1959) later observed heptachlor epoxide to be approximately 10 times more toxic than heptachlor in dairy calves when given orally. The most toxic metabolite is photo-heptachlor epoxide [III B] (Ivie, et al. 1972) which is formed by exposure of heptachlor epoxide to ultraviolet light or sunlight with the presence of a photosensitizer on plants. Ivie, et al. (1972) reported the LD_{50} values for male Swiss-Webster mice to be 18 mg/kg for heptachlor epoxide; 36 mg/kg for the intermediate photo metabolite photo-heptachlor epoxide [II]; and 6 mg/kg for photo-heptachlor epoxide [III B]. Gaines (1960) conducted acute LD_{50} studies using oral doses of heptachlor in the Sherman Strain of rat and found LD_{50} values of 100 mg/kg in males and 162 mg/kg in females respectively, while the acute dermal LD_{50} toxicity of heptachlor in males was 195 mg/kg and 250 mg/kg for females. Harbison (1975) used neonatal and adult Sprague-Dawley rats (120 to 150 gm) to show that the newborn rat is more resistant to heptachlor than the adult. The intraperitoneal LD_{50} for the adult male rats was 71 mg/kg* while 531 mg/kg* was found for newborn rats. (*Assumed to be mg/kg body weight). Gak (1976) reported heptachlor LD_{50} values for the mouse, rat, and hamster to be 70 mg/kg, 105 mg/kg, and 100 mg/kg of body weight respectively.

Table 3 Heptachlor and heptachlor metabolites LD_{50}

Organism Sex & Strain	Compound	Route of Administration	LD_{50} (mg/kg)	Reference
Mouse (Swiss-Webster)	Heptachlor epoxide	i.p.	18	Ivie, et al, 1972
Mouse (Swiss-Webster)	Photo-heptachlor epoxide II	i.p.	36	Ivie, et al, 1972
Mouse (Swiss-Webster)	Photo-heptachlor epoxide (III B)	i.p.	6	Ivie, et al, 1972
Rat (M-Sherman)	Heptachlor	oral	100	Gaines, 1960
Rat (F-Sherman)	Heptachlor	oral	162	Gaines, 1960
Rat (M-Sherman)	Heptachlor	dermal	195	Gaines, 1960
Rat (F-Sherman)	Heptachlor	dermal	250	Gaines, 1960
Rat (M-Sprague-Dawley)	Heptachlor	i.p.	71*	Harbison, 1975
Rat (N-Sprague-Dawley)	Heptachlor	i.p.	531*	Harbison, 1975
Mouse	Heptachlor	oral	70	Gak, et al, 1976
Rat	Heptachlor	oral	105	Gak, et al, 1976
Hamster	Heptachlor	oral	100	Gak, et al. 1976

* = assumed to be mg/kg body weight
i.p. = intraperitoneally
M = male
F = female
N = neonate

Heptachlor is generally classified as a neurotoxin because it produces abnormal stimulation of the central nervous system when animals are exposed to high doses. In an attempt to elucidate the toxic action of heptachlor, numerous studies have taken place to demonstrate the biochemical changes induced by heptachlor toxicity. St. Omer (1971) studied the convulsions produced by heptachlor in rats and found that the intensity of the convulsions was directly correlated with the rise in brain ammonia and the periods between seizures were associated with decreased levels of brain ammonia. St. Omer and Ecobichon (1971) reported that acute administration of heptachlor in rats significantly elevated their brain acetylcholine content with some decrease in acetylcholine concentration during the period of severest seizure activity. They suggest that these changes seen in the brain level of ammonia and acetylcholine during heptachlor exposure may be part of the mechanism of convulsion induction. Hrdina, et al. (1974) administered heptachlor chronically for 45 days to rats and found the acetylcholine level in the cerebro-cortex to be decreased and the serotonin (5-HT) level significantly increased in the brain-stem. They also found that an acute dose of heptachlor (200 mg/kg) produced body hypothermia.

Changes in the energy-linked functions of the mitochondria have been studied by Pardini, et al. (1971) and Settlemire, et al (1974). Pardini, et al. (1971) reported that heptachlor (1μ mole/flask) depressed the mitochondrial succinoxidase system to 5.8 percent of the level of uninhibited controls and that heptachlor epoxide did not depress the system at all. Heptachlor also depressed the mitochondrial activity of NADH-oxidase to 8.6 percent of uninhibited controls, while heptachlor

epoxide again had no effect. They speculated that since heptachlor did not interact at any step in the electron transport chain after cytochrome C that the site of heptachlor interaction may be either at complex III or at complex I and II of the mitochondrial electron transport chain. Settlemire, et al. (1974) found that heptachlor caused dramatic changes in the membrane of mouse mitochondria at concentrations as low as 54 n moles. They stated that the increase in respiration (oxidation of succinate) observed when ADP and heptachlor were added was probably caused by increasing permeability of membranes to succinate or by producing conformational changes of such a nature that the intrinsic activity of the respiratory chain is increased.

Heptachlor and heptachlor epoxide induction of liver microsomal enzymes has been reported by Kinoshita and Kempf (1970) and Den Tonkelaar and Van Esch (1974). Kinoshita and Kempf (1970) found heptachlor and heptachlor epoxide to be very persistent inducers in rats of phosphorothioate detoxification, O-demethylase, and N-demethylase in a dose related manner. They also found that male rats were more sensitive to heptachlor while female rats were more sensitive to heptachlor epoxide. Den Toukelaar and Van Esch (1974) found that dietary heptachlor significantly induced aniline hydroxylase, aminopyrine demethylase, and hexobarbital oxidase in rats at levels of 2 to 50 mg/kg, 2 to 50 mg/kg, and 5 to 50 mg/kg, respectively. Both groups reported that approximately 1 mg/kg of heptachlor showed no effect on the induction of microsomal enzymes.

Krampl (1971) reported that heptachlor caused an increase in the enzymes glutamic-pyruvic transaminase (GPT) and aldolase (ALD) in the

serum of rats. Histologic examinations of the livers revealed that maximum alteration in hepatic morphology coincided with the days on which hepatic and serum GPT and ALD activities were different from normal. They stated that the increased enzyme activity was probably related to altered membrane permeability, which allowed intracellular enzymes to pass out of cells that were damaged but not necrotic. Welch, et al. (1971) found that heptachlor stimulated the metabolism of estrone by liver microsomal enzymes and inhibited the increase in uterine wet weight in treated female rats.

Several studies have been conducted concerning the effects of heptachlor on glucose homeostasis in the rat (Kacew and Singhal, 1973; Kacew and Singhal, 1974; Singhal and Kacew, 1976). It was reported that heptachlor administered either in small daily amounts over a prolonged period of time or in a single oral dose, caused significant increases in the activities of renal and hepatic pyruvate carboxylase, phosphoenol-pyruvate carboxykinase, fructose 1,6-diphosphatase, and glucose 6-phosphatase, as well as an elevation of blood and urinary glucose and serum urea levels, and a depression of liver glycogen. They also found that heptachlor caused a rise in the level of endogenous cyclic AMP and augmented the activity of hepatic and renal adenylate cyclase. They stated that their data support the hypothesis that the heptachlor-induced alterations in glucose homeostasis are related to an initial stimulation of cyclic AMP-adenylate cyclase system in liver and kidney cortex.

Dvorak and Halacka (1975) studied the ultrastructure of the liver cells of pigs after the administration of small doses (2 to 5 mg/kg of

body weight) of heptachlor and found a marked depletion of glycogen, morphological changes in the granular endoplasmic reticulum, and increases in the amount of agranular endoplasmic reticulum. With higher doses and a longer duration of administration of heptachlor a greater occurrence of liver lysosomes was also observed.

Reuber (1977 a) found that C3H male and female mice fed 10 mg/kg of heptachlor or heptachlor epoxide developed hepatic vein thrombosis. Heptachlor caused 15 percent of the females and 10 percent of the males to develop thrombi, while heptachlor epoxide caused 11 percent of the females and 7 percent of the males to develop thrombi. He also stated that seven mice of the 39 that exhibited hepatic vein thrombosis also possessed recent thrombi in the atria of the heart, while no thrombi were found in any organs of the control mice. Liver cirrhosis was also occasionally present in addition to liver carcinomas.

Mutagenicity. Marshall, et al. (1976) reported that both heptachlor and heptachlor epoxide were not mutagenic when tested with Salmonella typhimurium in the Ames assay. Cerey, et al. (1973) found that heptachlor in oral doses of 1 to 5 mg/kg caused dominant lethal changes in male rats, demonstrated by a statistically significant increase in the number of resorbed fetuses in intact pregnant rats. They confirmed this by finding a significant increase in the incidence of abnormal mitoses, abnormalities of chromatids, pulverization, and translocation in the bone marrow cells of their experimental animals. They concluded from the data that rat fetuses in early and late stages of embryonic development could be adversely affected by the use of heptachlor. Ahmed, et al. (1977) used SV-40 transformed human cells (VA-4) in culture to show that

both heptachlor and heptachlor epoxide induced unscheduled DNA synthesis in this system when metabolically activated with homogenized rat liver supernatant. Therefore heptachlor has been reported to be a mutagenic compound in mammalian studies but not in bacterial cell systems.

Teratogenicity. Mestitzova (1967) found that heptachlor administered to rats in food at 6 mg/kg body weight caused a marked decrease in litter size, both in several litters of one generation as well as in successive generations. The author also stated that the lifespan of suckling rats is significantly shortened with the death rate being highest during the first 24 to 48 hours. In long-term feeding studies with heptachlor the same author observed the development of cataracts of the lens, both in the offspring and the parent rats. Prolonged feeding of heptachlor increased the chances of cataracts occurring in the parents, while the cataracts in the offspring were observed shortly after their eyes opened. They stated that the sequence of occurrence of the cataracts excludes the possibility of recessive genetic traits or a vitamin B deficiency as the causative factor.

Synergism or Antagonism. It has been reported that the protein content in the diet can affect the acute toxicity of heptachlor in male weanling rats (Webb and Miranda, 1973; Miranda, et al. 1973; Miranda and Webb, 1974). These workers found that with a 10 percent dietary level of protein, heptachlor was less acutely toxic in rats fed an unsupplemented gluten diet than in animals pair-fed diets containing gluten plus supplemental amino acids or casein plus 0.2 percent DL-methionine. When the dietary protein level was raised to 18 percent, heptachlor was twice as toxic to rats pair-fed casein diets, as compared

to rats fed unsupplemented gluten. They also found that weight gain, microsomal proteins, and heptachlor metabolism were significantly reduced in the animals fed unsupplemented gluten and that animals pair-fed the casein diet had higher heptachlor epoxidase activities than those fed the gluten diet. Therefore, they suggest that low protein diets impair or slow heptachlor from being metabolized to the more toxic heptachlor epoxide. Weatherholtz, et al. (1969) reported that rats fed protein deficient diets are less susceptable to heptachlor toxicity and also suggested that this observation may be due to reduced in vivo conversion of the pesticide to the epoxide form.

Miranda and Webb also studied the effects of phenobarbital and SKF525-A on these protein diet regimens (Miranda, et al. 1973; Miranda and Webb, 1974). Their studies suggested an interaction of protein inadequacy with drug metabolism and its reduction or inhibition of heptachlor metabolism, but they believed further studies should be carried out to clarify their findings.

Harbison (1975) studied the effects of phenobarbital (PB) on neonatal rats. He found that PB potentiates the toxicity of heptachlor in newborn rats. The heptachlor LD_{50} for a newborn is 531 mg/kg, but the heptachlor LD_{50} for a newborn rat pretreated with PB was 133 mg/kg with the LD_{50} for an adult male un-pretreated rat being 71 mg/kg.

Carcinogenicity. Various studies regarding the carcinogenicity of heptachlor and heptachlor epoxide when administered to rats and mice have been conducted by the Kettering Laboratory, the Food and Drug Administration, Cabral, et al., International Research and Development Corporation sponsored by Velsicol, and the National Cancer Institute.

Two extensive reviews of these studies have been conducted by Epstein, (1976) and by the U.S. EPA (1977) and should be referred to for more specific information on each study. Tables 4 and 5 present summary data reported by Epstein (1976), and include the original authors' conclusions, any independent histological re-evaluation of the studies which have been conducted, and Dr. Epstein's comments on each study.

The 1955 Kettering study on heptachlor in rats was an unpublished study by the Kettering Laboratory under contract to the Velsicol Corporation. The U.S. EPA (1977) review of this study stated that the oral dosages were 0, 1.5, 3.0, 5.0, 7.0, and 10.0 mg/kg of heptachlor administered to a total of 120 male and 120 female Carworth Farm strain rats. The length of dietary administration was 110 weeks with a 57 percent mortality rate in the male groups and a 43 percent mortality rate in the female groups. The reviews of the report state that the majority of the deaths were due to incidental diseases, particularly respiratory (U.S. EPA, 1977; Epstein, 1976). Tumors were found both in controls and in exposed animals and the original authors interpreted their data as indicating no significant difference between the incidence of tumors in test and control groups (Epstein, 1976). Based on an independent statistical analysis of the data from this study, Epstein (1976) concluded that "the data in fact demonstrated a statistically significant incidence of multiple site and other tumors in the higher level female test groups."

Another Kettering study was carried out for the Velsicol Corp. in 1959 by Witherup, et al. (1959). This investigation evaluated heptachlor epoxide at dietary levels of 0, 0.5, 2.5, 5.0, 7.5, and 10 mg/kg administered to CFN (Carworth Farms, Nelson) rats for 108 weeks. Each dosage

Table 4 Summary of carcinogenicity data in rats

(taken from Table II of Epstein, 1976, with permission)

Authors	Strain	Formulation	Concentrations (ppm)			Carcinogenicity		Comments
		Heptachlor (H); epoxide (HE); chlordane (C)	H	HE	C	Authors conclusions	Independent histological re-evaluation	
Kettering, 1955	CF	H of unspecified purity	1.5; 3.0; 5.0; 7.0; 10.0	-		Tumor incidence "proportionately" distributed in all test and control groups	Not undertaken	1. Test diets prepared crudely and study poorly documented. 2. Author's data demonstrate statistically significant increase in malignant and any tumors in multiple sites in some female test groups.
Kettering, 1959	CFN	HE of unspecified purity	-	0.5; 2.5; 5.0; 7.5; 10.0	-	Tumor incidence "unrelated" to HE content in diets. Excess hepatomas in test animals is acknowledged, but discounted. Also unusual malignant tumors in males and females	Hepatocarcinogenic and multiple site malignant tumors	1. Test diets prepared crudely and study poorly documented. 2. Kettering data statistically significant, for incidence of total tumor-bearing animals and for liver and pituitary tumors. 3. Histological re-evaluation showed hepatocarcinomas. 4. Hepatocarcinogenicity statistically significant.
Kettering, 1966	CD	Mixture of 25% HE (99.9% pure), and 75% H (96.0 % pure)	5.0; 7.5; 10; 12.5		-	Incidence of tumors "qualitatively and quantitatively similar" in test and controls.	Not undertaken	1. Study poorly documented and methodologically unsound; female rats only tested. 2. Unacceptable as carcinogenicity test.

Table 4 (continued)

(taken from Table II of Epstein, 1976, with permission)

Authors	Strain	Formulation	Concentrations (ppm)			Carcinogenicity		Comments
		Heptachlor (H); epoxide (HE); chlordane (C)	H	HE	C	Authors conclusions	Independent histological re-evaluation	
Cabral, et al., 1972	Wistar	H Analytic Grade 96.8% pure	Total dosage 50 mg/kg	-	-	Not carcinogenic	Not undertaken	1. Perinatal dosage only. 2. Author's data demonstrate statistically significant increase in endocrine tumors in males and rare "lipomatous" renal tumors in 2 test females.
NCI, 1975	Osborne-Mendel	Technical H; consisting of 74% H and ca 26% alpha C	Males 38.9; 77.9 Females 18.9; 37.8	-	-	Final Report pending	Not undertaken	1. Relatively small number negative controls; uncertainties in dosage; high mortality in high dosage test groups. 2. NCI data shows excess hepatic nodules in males and females.

Table 5 Summary of carcinogenicity data in mice

(taken from Table I of Epstein, 1976, with permission)

Authors	Strain	Formulation	Concentrations (ppm)			Carcinogenicity		Comments
		Heptachlor (H); epoxide (HE); chlordane (C)	H	HE	C	Authors conclusions	Independent histological re-evaluation	
Davis, (FDA), 1965	C3H	H and HE of unspecified purity	10	10	-	"Benign hepatomas" induced by H and by HE	H and HE both hepatocarcinogenic	1. FDA data poorly documented. 2. FDA data statistically signficant for tumor incidences. 3. Histological re-evaluation demonstrated hepatocarcinogenicity. 4. Hepatocarcinogenic effects statistically significant.
IRDC, 1973	CD-1	Mixture of 25% H and 75% HE	1.0; 5.0; 10.0		-	Dose related nodular hyperplasia at 5.0 and 10.0 ppm	Hepatocarcinogenic	1. IRDC data statistically significant excess of nodular hyperplasias. 2. Histological re-evaluation found hepatocarcinomas. 3. Hepatocarcinogenicity statistically significant.
NCI, 1975	B6C3F1	Technical H; consisting of 74% H, and ca. 26% C	Males: 6.1; 13.8 Females 9.0; 18	-	-	Final report pending	Not undertaken	1. Relatively small number negative controls; non-concurrent experiments; uncertainties in dosage. 2. Revised data statistically significant for hepatocarcinogenicity.

group consisted of 25 males and 25 females. Mortality in males ranged from 32 percent for the controls to 52 percent at the dosage level of 2.5 mg/kg of diet and in the females ranged from 24 percent in controls to 52 percent at a dose level of 7.5 mg/kg of diet. They stated, however, that the increased mortality in the groups fed heptachlor epoxide was not significant. They also stated that the earliest tumor was discovered during the 13th month and that animals dying before that were examined, but were not included among the numbers capable of bearing tumors. The authors concluded that the tumor incidence was unrelated to the heptachlor epoxide content in the diet, although they acknowledge an excess of hepatomas in the test animals (Epstein, 1976). An independent statistical analysis of this data indicated that all the heptachlor epoxide dose levels except the 0.5 mg/kg level in the males, were significant at the $P = 0.05$ probability level.

Re-evaluation of tissue slides of the 1959 Kettering study by Dr. Melvin D. Reuber indicated that there was an increase in hyperplastic nodules and carcinomas of the liver in the treated animals when compared to control animals (U.S. EPA, 1977). He also found a greater incidence of carcinomas in females than in males, as the Kettering data had also indicated. In addition, he found highly malignant tumors in brain, thyroid, adrenal, kidney, lung, bone, and genital organs. Reuber concluded that because carcinomas of the liver in the untreated rats were infrequent, the presence of 28 liver carcinomas among 213 treated rats indicates that heptachlor epoxide is carcinogenic in rats at $P<10^{-8}$ (U.S. EPA, 1977).

Dr. Williams (U.S. EPA, 1977) also re-evaluated the Kettering tissue slides and he concluded that the study demonstrated an increased incidence of cancer in the livers of treated rats and an increase in hyperplastic nodules in the males only at the 10 mg/kg level. He considered the seven liver malignancies in the treated animals versus no malignancies in controls, to be strongly suggestive of a carcinogenic effect (U.S. EPA, 1977). Williams like Kettering and Reuber, also diagnosed a range of unusual malignant tumors in treated animals (Epstein, 1976).

The slides were re-evaluated by three other independent pathologists (Drs. Stewart, Squire and Popper) and all three diagnosed a higher incidence of carcinomas than that reported by the Kettering workers who found only two (U.S. EPA, 1977; Epstein, 1976).

In 1966 the Kettering Laboratory produced another unpublished report dealing with the administration of a mixture of 75 percent heptachlor and 25 percent heptachlor epoxide to female CD rats at doses of 0, 5.0, 7.5, 10.0, and 12.5 mg/kg in the diet (Jolley, et al. 1966). After 104 weeks of exposure various lesions in the pituitary gland, adrenal gland, mammary gland, and the liver were found but considered by the original investigators to be "spontaneous" because these lesions were found both in control and treated groups. The lesions of the pituitary glands and adrenal glands were considered hypertrophies rather than neoplasms. The lesions of the mammary gland were diagnosed as adenomas or fibroadenomas of mammary glands. The liver lesions were referred to as "clusters of enlarged hepatic cells" (Epstein, 1976, calls it centrilobular hepatocytomegaly), with cytoplasmic degranulation and

clusters of enlarged irregular vacuolated cells filled with lipid and distributed randomly in the lobules. They concluded that the experimental diet caused the changes in the liver which were qualitatively similar to but quantitatively different from lesions in control rats. Epstein, (1976) suggested that a re-evaluation of the liver histology in all test and control groups is necessary before the significance of these and other possible lesions can be assessed.

In 1965 FDA completed a 2 year study of heptachlor and heptachlor epoxide fed to C_3Heb/Fe/J mice (Davis, 1965). Three groups of 100 males and 100 females per group were fed 10 mg of heptachlor per kg of diet, 10 mg heptachlor epoxide per kg of diet, or a control diet. During the 2 year period survival rates of 34 percent, 30 percent, and 9.5 percent were reported for the control group and the heptachlor and heptachlor epoxide fed animals, respectively. Over the test period 30 control mice had benign tumors only and 21 controls had malignant tumors; heptachlor-treated mice had 51 benign tumors only and 10 malignant tumors; heptachlor epoxide-treated mice had 85 benign tumors only and 13 malignant tumors. Statistics were not run on this data by FDA because of incompleteness in the number of samples and the "arbitrariness of microscopic diagnoses" (Davis, 1965). Davis stated that the incidence of hepatic hyperplasia and benign hepatomas was approximately doubled in the test groups, but concluded that heptachlor and heptachlor epoxide do not have a significant effect on the incidence of malignant tumors.

The tissue slides from the 1965 FDA study were re-evaluated by Dr. Reuber. He found liver carcinomas in 64 out of 87 male mice (73 percent) and 57 out of 78 female mice (74 percent) ingesting heptachlor; in 73 out

of 79 male mice (92 percent) and 77 out of 81 female mice (95 percent) ingesting heptachlor epoxide; and in 22 out of 73 control male mice (30 percent) and in 2 out of 53 control female mice (4 percent) (Reuber, 1977 b). He also stated that the affected treated animals often had three to four carcinomas per liver with a size of 3 to 5 cm, while affected control animals had only solitary carcinomas of a size 5 mm or less. Reuber concluded that heptachlor and heptachlor epoxide diets caused the development of a highly significant incidence of carcinomas of the liver which were capable of invasion and metastasis.

Four other independent pathologists (Drs. Stewart, Squire, Williams, and Sternberg) were asked to review slides from 19 animals that Reuber had diagnosed as having hepatic carcinomas. Drs. Stewart, Squire and Sternberg agreed with Dr. Reuber that the 19 animals had heptatic carcinomas (U.S. EPA, 1977). Dr. Williams diagnosed eight carcinomas, 10 nodules or hyperplastic nodules, and one dysplastic area. However, Dr. Williams considers that hyperplastic nodules are induced only by carcinogens, therefore he considers them evidence of a carcinogenic effect on the liver (Epstein, 1976).

Cabral, et al. (1972) conducted a study using 95 Wistar rats force fed heptachlor in corn oil by gastric intubation. Heptachlor was administered at a level of 10 mg/kg of body weight five times on alternating days beginning at 10 days of age. It was observed that the incidence of tumors in males occurred at different sites and was not reproducible, while the tumors in females were in the adrenal, thyroid, and pituitary glands and were comparable in both control and treated groups. In the treated females, 9 of 28 rats developed 12 tumors in various organs,

including five mammary tumors and two renal lipomatous tumors. In the control group, 4 of 27 females developed four tumors, two of which were located in the breast. They concluded, that "in view of the different locations of the tumors and the lack of reproducibility of the findings among males, the results are not considered as evidence of carcinogenicity of heptachlor under the present experimental conditions." Epstein (1976) on the other hand, concluded that the study does show a statistically significant incidence of endocrine tumors in males.

In 1973 the International Research Development Corp. (IRDC) completed an unpublished 18 month study using CD-1 mice on a treatment diet mixture of 75 percent heptachlor epoxide and 25 percent heptachlor. The study was designed using one negative control, one positive dietary control of 2-Acetamidofluorene at 250 mg/kg, and three dietary treatment groups of 1.0, 5.0, and 10.0 mg/kg, respectively. Each group contained 100 males and 100 females. After 6 months on these treatments 10 males and 10 females were sacrificed from each group. It was found that the liver weights were significantly increased in the 5.0 and 10.0 mg/kg treatment groups in males and in the 10.0 mg/kg treatment group in females (IRDC, 1973). Also, the livers from males fed the 1.0, 5.0, and 10.0 mg/kg diets and from females fed the 5.0 and 10.0 mg/kg diets showed a dose related incidence and severity of hepatocytomegaly. A large number of compound related liver masses (nodular hyperplasias) were seen in mice that died during the study period or that were sacrificed at the end of the test period. These masses were thought to be extensions of the hepatocytomegaly lesions (IRDC, 1973). The mice fed the 1.0 mg/kg diet were considered to be free of compound-related nodular

hyperplasia, since the incidence of the lesion was similar to the untreated controls. No lesions were found suggestive of a compound effect in any tissue other than the liver and no mention was made of any carcinomas in any heptachlor epoxide/heptachlor test group.

Reuber also re-evaluated the histological material from the IRDC study (U.S. EPA, 1977; Epstein, 1976). His findings indicated a significant increase in the incidence of liver cancers induced by the heptachlor epoxide/heptachlor mixture in males in the 5.0 mg/kg group and in both males and females in the 10.0 mg/kg group. The incidence in these groups was comparable to or higher than the incidence in the positive (2-acetamedofluorene, 250 mg/kg) controls. It has been indicated that the majority of lesions diagnosed as nodular hyperplasias by IRDC, were diagnosed by Reuber as carcinomas (Epstein, 1976). It is interesting to note though that both IRDC and Reuber diagnosed a similar number of carcinomas in the positive controls, the discrepancies in diagnoses seem largely restricted to the test groups at the 5.0 and 10.0 mg/kg levels (Epstein, 1976).

Five additional pathologists reviewed slides from the IRDC study (two of the pathologists were consultants to the Velsicol Corporation) and found that the IRDC study had substantially underdiagnosed the number of carcinomas present (Epstein, 1976). Epstein (1976) concluded that the IRDC study demonstrated that the heptachlor epoxide/heptachlor mixture induced a dose-related incidence of nodular hepatic hyperplasias, and also demonstrated the hepatocarcinogenicity of heptachlor epoxide/heptachlor as evidenced by the histological re-evaluations.

The National Cancer Institute (NCI) released a preliminary report on the Gulf South Research Institute study on heptachlor in 1975. These preliminary findings have been reviewed by both Epstein (1976) and the U.S. EPA (1977). In 1977 the NCI released a final report which reported on contract work conducted first by the Gulf South Research Institute and more currently by Tracor Jitco Inc. (NCI, 1977). Both Osborne-Mendel rats and B6C3F1 mice were used to test the possible carcinogenicity of technical-grade heptachlor.

Groups of 50 rats of each sex were administered low and high doses of heptachlor for 80 weeks and then observed for 30 weeks. The doses of heptachlor to both males and females were lowered several times during the study due to toxic effects, and the time-weighted average doses used were 38.9 and 77.9 mg/kg of heptachlor in the diet for male rats and 25.7 and 51.3 mg/kg for female rats. Matched controls consisted of 10 untreated rats of each sex and pooled controls consisting of 50 untreated male and 50 untreated female rats from similar bioassays of five other compounds. All surviving rats were killed at 110 to 111 weeks and no hepatic tumors were observed. Neoplasms were found in test animals or with increased frequency when compared to control groups, but the nature, incidence, and severity of the lesions observed provide no clear evidence of a carcinogenic effect of heptachlor in Osborne-Mendel rats as reported by the pathologists.

In the second part of the NCI study, groups of 50 mice of each sex were administered heptachlor at low and high doses for 80 weeks and then observed for 10 weeks. The dose for males was reduced once while the dose for females was reduced twice due to toxic effects. The time-weighted

average dosages in the diet were 6.1 and 13.8 mg/kg of heptachlor for male mice, and 9 and 18 mg/kg of heptachlor for female mice. Matched controls consisted of 10 of each sex of untreated mice and pooled controls consisted of 90 untreated male and 70 untreated female mice from similar bioassays of five other compounds. Results of hepatocellular carcinomas in both male and female mice were found to show a highly significant dose-related trend. Twenty-six percent of matched male controls and 20 percent of matched female controls developed hepatic carcinomas; 18 percent of the pooled male controls and 4 percent of pooled female controls developed hepatic carcinomas; 24 percent of the low dose males and 6 percent of the low dose females developed hepatic carcinomas; and 72 percent of the high dose males and 71 percent of the high dose females developed hepatic carcinomas. It was concluded that heptachlor is carcinogenic in mice livers under the conditions of this assay at the high dosages given.

CRITERION FORMULATION

Existing Guidelines and Standards

Agency	Published Standard	Reference
Occup. Safety Health Admin.	500 $\mu g/m^3$* on skin from air	Natl. Inst. Occup. Safety Health, 1977
Am. Conf. Gov. Ind. Hyg. (TLV)	500 $\mu g/m^3$ inhaled	Am. Conf. Gov. Ind. Hyg., 1971
Fed. Republic Germany	500 $\mu g/m^3$ inhaled	Winell, 1975
Soviet Union	10 $\mu g/m^3$ ceiling value inhaled	Winell, 1975
World Health Organ.**	0.5 µg/kg/day acceptable daily intake in diet	Natl. Acad. Sci., 1977
U.S. Pub. Health Serv. Adv. Comm.	Recommended drinking water standard (1968) 18 µg/l of heptachlor and 18 µg/l heptachlor epoxide	Natl. Acad. Sci., 1977

* Time weighted average

** Maximum residue limits in certain foods can be found in Food Agric. Organ./World Health Organ. 1977, 1978

Current Levels of Exposure

Various investigators have detected heptachlor and/or heptachlor epoxide in the major river basins of the United States with a mean concentration of 0.0063 μg/l (U.S. EPA, 1976) for those instances of detection. Food can add to man's exposure to heptachlor and metabolites through biomagnification in the food chain. The FDA showed that in their market basket study covering August 1974-July 1975 for 20 different cities (Johnson and Manshe, 1977) three of 12 food classes contained residues of heptachlor epoxide ranging from 0.0006 to 0.003 ppm. A national study by the U.S. Department of Interior in 1967-1968 reported that heptachlor and/or heptachlor epoxide were found in 32 percent of the 590 fish samples examined (Henderson, 1969) with whole fish residues of from 0.01 to 8.33 mg/kg. Schimmel, et al. (1976) reported an average bioconcentration factor of 12,000 for the sheepshead minnow which will subsequently be used in risk calculations as being representative of fish bioconcentration potential.

Nisbet (1977) calculated the typical human exposure to heptachlor to be 0.01 μg/individual/day based on an ambient air mean concentration of 0.5 ng/m^3 and breathing 20 m^3 of air per day. He states further that even in Jackson, Miss., which has a mean air level as high as 6.3 ng/m^3, the average individual would inhale only 0.13 μg/day of heptachlor. The significance of these figures is dependent upon the efficiency of lung absorption which does not appear to be reported for humans (Nisbet, 1977). Based on this, it appears that inhalation is not a major route for human exposure to heptachlor.

Special Groups at Risk

Infants have been exposed to heptachlor and heptachlor epoxide through mothers' milk (Savage, 1976) cows' milk (Ritcey, et al. 1972), and commercially prepared baby foods (Lipscomb, 1968). It appears that infants raised on mothers' milk run a greater risk of ingesting haptachlor epoxide than if they were fed cows' milk and/or commercially prepared baby food. Nisbet (1977) found that persons living and working in or near heptachlor treated areas had a particularly high inhalation exposure potential.

Basis and Derivation for the Criterion

Heptachlor has been shown to exhibit numerous toxicological effects in animal systems. Acute toxicity of heptachlor and its metabolites has LD_{50} values ranging from 6 to 531 mg/kg depending upon the animal test system. Heptachlor is generally classified as a neurotoxin because it produces abnormal stimulation of the central nervous system when animals are exposed to high doses. Other effects on animal enzyme systems are referenced throughout the literature. Mutagenicity was not demonstrated with Salmonella typhimurium in the Ames assay; however, oral doses of heptachlor caused dominant lethal changes in male rats as demonstrated by an increase in the number of resorbed fetuses in intact pregnant rats. Heptachlor administered to rats caused a marked decrease in litter size, both in several litters of one generation as well as in successive generations.

Studies concerning the carcinogenicity of heptachlor and heptachlor epoxide when administered to rats and mice have been conducted by the Kettering Laboratory, the Food and Drug Administration, Cabral, et al., International Research and Development Corporation, and the National Cancer Institute. Heptachlor or its metabolites have induced hepatocellular carcinomas in three chronic mouse feeding studies and heptachlor epoxide has produced the same response in one rat study although no response was observed in four additional rat studies.

The weight of evidence for carcinogenicity is sufficient to conclude that heptachlor is likely to be a human carcinogen. As carcinogens are generally assumed to have a non-threshold dose/response characteristic, the carcinogenic effect is the most significant exposure effect from which to estimate an ambient water quality criterion value. A linear, non-threshold mathematic model is used in estimating human health risks associated with the ingestion of heptachlor (see appendix for model). Using the described model, the concentration of heptachlor in water may be calculated assuming an additional individual lifetime risk of 1/100,000, the ingestion of 2 l/day of water and 18.7 grams/day of contaminated fish products, a representative fish bioaccumulation factor of 12,000, and data for hepatocellular carcinoma incidence in the FDA female mouse. The calculation yields a concentration of 0.23 nanograms per liter as the desired ambient criterion level to maintain an additional risk of one cancer per 100,000 exposed individuals.

Basis for the Criterion

The proposed criterion for heptachlor/heptachlor epoxide in drinking water was derived from the extrapolation of the data presented in the carcinogenicity section of this document using a linear, non-threshold model. The extrapolation methodology can be found in the Methodology Document.

From this extrapolation the calculated dose of heptachlor/heptachlor epoxide in drinking water was found to be 0.23 nanogram per liter.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Heptachlor is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of heptachlor in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of heptachlor corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.0023 ng/l	0.023 ng/l	0.23 ng/l
Consumption of fish and shellfish only.	0	0.0023 ng/l	0.023 ng/l	0.23 ng/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document to the animal bioassay data presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) 98 percent of the heptachlor exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 5,200-fold. The remaining 2 percent of heptachlor exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to varius amounts of heptachlor, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding heptachlor concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding heptachlor concentrations.

Although total exposure information for heptachlor is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into amibient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

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APPENDIX I

Derivation of Criterion for Heptachlor

The lifetime carcinogenicity study of heptachlor epoxide at 10 ppm in the diet of C3Heb/Fe/J strain mice resulted in liver carcinomas in females in 77 of 81 treated animals and 2 of 54 controls (Davis, 1965). Using a fish bioaccumulation factor of 5,200, the water concentration estimated to result in a lifetime risk of 10^{-5} is calculated from the extrapolation model using the following parameters:

nt = 77	le = 104 weeks
NT = 81	d = $10 \times 10^{-6} \times 0.13 \times 10^{=6}$ mg food per day/kg body weight
nc = 2	= 1.3 mg/kg/day
NC = 54	w = 0.030 kg
Le = 104 weeks	L = 104 weeks
	R = 5,200

The result is that the water concentration corresponding to a lifetime risk of 10^{-5} is 0.23 (0.233) nanograms/liter.