United States
Environmental Protection
Agency

Office of Water
Regulations and Standards
Criteria and Standards Division
Washington DC 20460

EPA 440/5-80-052
October 1980

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EPA

Ambient Water Quality Criteria for Heptachlor

AMBIENT WATER QUALITY CRITERIA FOR

HEPTACHLOR

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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ACKNOWLEDGEMENTS

Aquatic Life Toxicology

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TABLE OF CONTENTS

CRITERIA SUMMARY

HEPTACHLOR

CRITERIA

Aquatic Life

For heptachlor the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0038 µg/l as a 24-hour average, and the concentration should not exceed 0.52 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 0.053 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of heptachlor through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criterion are 2.78 ng/l, 0.28 ng/l, and 0.028 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 2.85 ng/l, 0.29 ng/l, and 0.029 ng/l, respectively.

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 from 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 resulting from the sole producer's voluntary restriction of domestic use, and the subsequent issuance by the U.S. Environmental Protection Agency of a registration suspension notice for all food crops and home use of heptachlor, effective August 1, 1976. However, significant commercial use of heptachlor for termite control or in nonfood 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, a melting point of 95°C and a vapor pressure of 3×10^{-4} mm Hg at 25°C (Metcalf, 1955; Martin, 1972; Windholz, 1976). It has a solubility in water of 0.056 mg/l at 25 to 29°C and is readily soluble in relatively nonpolar 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 nonachlor, and 1 percent chlordene isomers (Martin, 1972). Technical heptachlor is a tan, soft, waxy solid with a melting point range from 46 to 74°C. It

has a vapor pressure of 4×10^{-4} mm Hg at 25°C and a density of 1.65 to 1.67 g/ml at 25°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,b). It represents the principal metabolite of heptachlor.

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. Heptachlor epoxide has also been shown to undergo photodecomposition to photoheptachlor epoxide (IIIB) when exposed to UV light or sunlight (Graham, et al. 1973).

Heptachlor can also be biologically converted to chlordene, 3-chlorochlordene, 1-hydroxychlordene, chlordene epoxide, 1-hydroxy-2, 3-epoxychlordene, and 2-chlorochlordene.

The persistence of heptachlor and heptachlor epoxide in the environment is well-known. Heptachlor also has been shown to be converted to the 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).

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Aquatic life Toxicology*

INTRODUCTION

Heptachlor is a chlorinated hydrocarbon pesticide that has had wide usage in the United States as a crop insecticide. It has been widely used for such purposes as fire ant and general insect control in much of the United States. 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 saltwater organisms. Most of these studies, however, were carried out under static conditions with results 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 trans-chlordane, cis-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 concentrations as 100 percent heptachlor for data reporting. These data were converted back to con-

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses 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 calculations for deriving various measures of toxicity as described in the Guidelines.

centrations of technical grade heptachlor in this document.

Some reported studies have examined the impact of water hardness and temperature on acute toxicity of heptachlor. Variable results were found regarding the effect of temperature on heptachlor toxicity, whereas water hardness had little effect on toxicity to fathead minnows in a single comparison.

Heptachlor epoxide is the most commonly found degradation product of heptachlor. Both heptachlor and heptachlor epoxide have been reported in fish residues. There are few data on the relative toxicity to aquatic organisms of these two materials. What data are available suggest that the epoxide is not more toxic than heptachlor itself.

EFFECTS

Acute Toxicity

In all but one case (Macek, et al. 1976)(Table 6), freshwater data on acute toxicity were obtained in static tests, and in every case exposure concentrations were unmeasured. Values for standard tests with fish and invertebrate species are reported in Table 1, and some additional acute toxicity data are given in Table 6. Ten freshwater invertebrate and eight fish species have been tested.

Many of the authors cited in Table 1 reported values for numerous other pesticides in addition to heptachlor. No clear relationship regarding the toxicity of heptachlor compared to other pesticides was found. For example, heptachlor is substantially less toxic to the scud, Gammarus fasciatus, than DDT and endrin; for the freshwater glass shrimp, however, there is little difference in toxicity among the three pesticides (Sanders, 1972). For the stonefly, Pteronarcys californica, heptachlor is less toxic than endrin and more toxic than DDT (Sanders and Cope, 1968). Katz (1961) found with chinook salmon and coho salmon that DDT and endrin are more toxic than

heptachlor, whereas with rainbow trout, heptachlor is more toxic than DDT. It is difficult to determine how many 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 the data in Table 1 that heptachlor is generally highly toxic in an acute exposure.

LC_{50} values for invertebrate species range from 0.9 µg/l for a 96-hour exposure with the stonefly, Pteronarcella badia, to 80 µg/l for a 48-hour exposure with the cladoceran, Simocephalus serrulatus (Table 1). Larvae of the Fowler's toad were tested by Sanders (1970)(Table 6); the 96-hour LC_{50} is 440 µg/l.

Freshwater fish species are generally less sensitive to heptachlor than are invertebrate species (Table 1). Ninety-six-hour LC_{50} values for fish species range from 10.0 µg/l for rainbow trout to 320 µg/l for goldfish (Table 1).

The Freshwater Final Acute Value for heptachlor, derived from the species mean acute values listed in Table 3 using the procedure described in the Guidelines, is 0.52 µg/l.

There is little information regarding the possible effect of water hardness on the toxicity of heptachlor. The 96-hour LC_{50} values for fathead minnows exposed to technical grade heptachlor in soft and hard water are 130 and 78 µg/l, respectively (Henderson, et al. 1959). It is difficult to formulate any conclusions regarding hardness-related effects on the basis of these tests.

Bridges (1965) found that toxicity to redear sunfish increased at higher temperatures (Table 6). Twenty-four-hour EC_{50} values decreased (toxicity increased) from 92 µg/l at 45°F to 22 µg/l at 85°F. Macek, et al. (1969) found essentially no difference in toxicity to rainbow trout when tested at

1.6, 7.2, and 12.7°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 6); at 21.0°C no mortality occurred. Sanders and Cope (1966) found that with the cladoceran, Simocephalus serrulatus, the 48-hour EC_{50} values for heptachlor were 47 µg/l at 60°F and 80 µg/l at 70°F (Table 1).

Only one acceptable freshwater 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 of material, determined the 26-hour LC_{50} for Daphnia magna to be 52 µg/l for heptachlor and 120 µg/l for heptachlor epoxide (Table 6).

Many authors reported LC_{50} values for freshwater fish species after 24, 48, and 96 hours of exposure to heptachlor. In general, toxicity increased slightly with time, although considerable variation existed among species. The ratios of 96-hour/24-hour and 96-hour/48-hour LC_{50} values ranged from 0.45 to 0.97 and 0.57 to 1.00, respectively. The relationship of LC_{50} values to exposure time was more dramatic and variable for invertebrate species. The range of values for the ratio of 96-hour/24-hour LC_{50} values was 0.06 to 0.56. Exposure time, therefore, can significantly affect LC_{50} values for invertebrate species exposed to heptachlor.

Heptachlor has been shown to be acutely toxic to saltwater fish and invertebrate species. Many of the saltwater toxicity tests with heptachlor have used technical grade material containing approximately 65 percent heptachlor, with the remaining 35 percent being a mixture of trans-chlordane, cis-chlordane, nonachlor, and related compounds. There are insufficient saltwater data to evaluate relative toxicity of heptachlor and heptachlor epoxide. However, the data available suggest that toxicity of the technical material is mostly attributable to heptachlor and that toxicities of heptachlor and heptachlor epoxide are similar (Schimmel, et al. 1976a). The tox-

icity of the several chlordane isomers is discussed in the criteria document for that compound and is, in general, 2 to 7 times less than that of heptachlor.

Saltwater invertebrate species seem to be more sensitive than fish species to heptachlor and heptachlor epoxide and demonstrate a greater variability in sensitivity between species (Table 1). Of the seven species tested, the commercially valuable pink shrimp is especially sensitive with 96-hour LC_{50} 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)(Tables 1 and 6). Ninety-six-hour LC_{50} 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 LC_{50} of heptachlor for the grass shrimp based on a static exposure using unmeasured concentrations is 440 µg/l (Eisler, 1969), whereas the result from a flow-through test with measured concentrations is 1.06 µg/l (Schimmel, et al. 1976a). A similar relationship is true for the American oyster. Test results from a flow-through exposure with unmeasured concentrations (Butler, 1963) were 27 and 30 µg/l and, using flow-through procedures and measured concentrations, Schimmel, et al. (1976a) determined a 96-hour EC_{50} of 1.5 µg/l. Generally toxicity data obtained from static tests or those in which concentrations were not measured yielded higher acute values for heptachlor than other tests. The range of LC_{50} values for saltwater invertebrate species is from 0.03 to 440 µg/l.

The 96-hour LC_{50} values (Table 1) derived from flow-through tests with four saltwater fish species range from 0.85 to 10.5 µg/l (Korn and Earnest, 1974; Schimmel, et al. 1976a; Hansen and Parrish, 1977). Results of static exposures of eight fish species are more variable and yield higher LC_{50}

values than those from flow-through tests; i.e., 0.8 to 194 µg/l (Katz, 1961; Eisler, 1970a). LC_{50} values derived from tests using aeration, static test procedures, or unmeasured concentrations probably underestimate the toxicity of heptachlor (Schimmel, et al. 1976a; Goodman, et al. 1978).

The Saltwater Final Acute Value for heptachlor, derived from the species mean acute values listed in Table 3 using the procedure described in the Guidelines, is 0.053 µg/l.

Chronic Toxicity

The only available freshwater chronic study on heptachlor was that of Macek, et al. (1976) using the fathead minnow (Table 2). 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, and 0.11 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. Analytical difficulties were encountered during the last 10 weeks of the 40-week exposure period. However, all effects found in the study occurred during the first 60 days, and so the analytical difficulties did not affect the reported chronic endpoint values. The chronic limits of heptachlor for fathead minnows are 0.86 and 1.84 µg/l. Data on the acute toxicity of heptachlor to fathead minnows indicate that this species is generally somewhat less sensitive than other fish species. There are no direct comparisons between the chronic results for fathead minnows and 96-hour LC_{50} values from tests conducted by the same author. However, by using the species mean acute value for fathead minnows, an acute-chronic ratio of 80 can be calculated for fathead minnows (Table 2).

No valid chronic test data were available for any freshwater invertebrate species. However, in general, invertebrate acute values are considerably lower than fish acute values (Table 1); indeed, some LC_{50} values for

invertebrate species were lower than the chronic value for fathead minnows. It is reasonable to expect, therefore, that some freshwater invertebrate chronic values would be lower than the available freshwater fish chronic value.

Insufficient data are available to calculate a Freshwater Final Chronic Value for heptachlor.

A 28-day life-cycle toxicity test (Table 6) was completed with a saltwater mysid shrimp, Mysidopsis bahia (U.S. EPA, 1980). Mortality of mysid shrimp exposed to measured concentrations of 0.17, 0.64, 1.3, and 3.1 µg/l was significantly greater than that in the control. Mortality of animals at an intermediate low concentration of 0.33 µg/l was not significantly different from controls. Because of this anomaly in the data, the more conservative estimate of effect on mortality is used (0.64 µg/l). Statistical analysis of data on cumulative number of offspring per female per day did not reveal significant differences between the control and any test concentration. Therefore, cumulative mortality of test animals exposed to 0.64 µg/l heptachlor was the most sensitive effect. Because this effect is based on anomalous data, test results are included in Table 6 rather than Table 2.

The chronic toxicity of technical heptachlor to the sheepshead minnow was measured in an 18-week partial life-cycle exposure begun with juveniles (Hansen and Parrish, 1977). Survival was affected at concentrations of 2.8 µg/l and greater (Table 6). Embryo production was significantly decreased at the lowest concentration tested, 0.71, and at test concentrations of 1.9 to 5.7 µg/l. An intermediate test concentration, 0.97 µg/l, did not cause reduced embryo production significantly different from controls. Because of this anomaly in the data, test results were included in Table 6 rather than Table 2.

The chronic toxicity of technical heptachlor to sheepshead minnows was also measured in a separate 28-day early life-stage test. 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). Comparison of these data with that from the early life-stage portion of the partial life-cycle exposure (Hansen and Parrish, 1977) shows survival of fry was reduced at a similar concentration in both exposures (2.24 and 2.8 µg/l, respectively). Growth of fry in the early life-stage test (Goodman, et al. 1978) was significantly reduced at concentrations of 2.04 µg/l and above. No detrimental effects were observed at 1.22 µg/l. If observed decreases in embryo production in the partial life-cycle test at 0.71 µg/l are an anomaly, then the results from the embryo-fry exposure predict the results of a life-cycle toxicity test rather accurately.

Chronic values for saltwater species can be obtained from only the sheepshead minnow early life-stage test (Table 2) and not the life-cycle tests on this fish species and mysid shrimp (Table 6). The chronic value from the early life-stage test is 1.58 µg/l, and the acute-chronic ratio is 3.9. If effects observed in the sheepshead minnow partial life-cycle test at 0.71 µg/l and in the mysid shrimp life-cycle test at 0.17 µg/l are considered anomalies, the acute-chronic ratios calculated using these two tests are 4.6 and 7.6, respectively. The range in acute-chronic ratios for the three tests is remarkably narrow, less than a factor of two.

Plant Effects

Two 96-hour tests with a freshwater algal species, Selenastrum capricornutum, have been conducted (Table 4). The EC_{50} values obtained are 39.4 and 26.7 µg/l. It should be noted that the exposure concentrations of heptachlor rapidly diminished during the course of the tests, and substantial

amounts of hydroxychlordene were present and may have contributed significantly to the toxic effect (Call and Brooke, 1980).

Information on the sensitivity of saltwater aquatic plants is limited to effects on five species of unicellular algae, or dinoflagellates and one study on a natural phytoplankton community (Tables 4 and 6).

Effects of heptachlor on three species of marine unicellular algae, Isochrysis galbana, Porphyridium cruentum, and Skeletonema costatum, are fairly similar. The 96-hour EC_{50} values range from 93 to 273 µg/l. The EC_{50} for a fourth species, Dunaliella tertiolecta, is 8 to 24 times higher (Table 4).

Toxicity tests with the marine dinoflagellate, Exuviella baltica, show effects of heptachlor at a concentration of 50 µg/l (Table 6). Cell density, chlorophyll a per unit volume of culture, ^{14}C uptake per cell, and carbon fixation per unit of chlorophyll a were reduced at this concentration after seven days. The natural phytoplankton community study was a 4-hour exposure at a single exposure concentration of 1,000 µg/l. This concentration of heptachlor caused a 94.4 percent decrease in productivity (Butler, 1963)(Table 6).

Residues

The only appropriate residue studies on freshwater species are those reported by Veith, et al. (1979). These studies used 32-day exposures of fathead minnows to heptachlor and heptachlor epoxide (Table 5). Bioconcentration factors (BCF) are 9,500 for heptachlor and 14,400 for heptachlor epoxide.

Andrews, et al. (1966) reported the results of tests in which bluegills held in plastic pools were fed food containing heptachlor at either 25.0, 10.0, 5.0, or 0.0 mg/kg/day (Table 6); tests were run in duplicate. Effects on survival, histopathology, and growth were monitored. In general, adverse

effects were found at a feeding rate of 10 mg/kg/day. In order to determine a maximum daily dietary intake level for wildlife, a value of 7.1 mg/kg/day (the geometric mean of 5 and 10 mg/kg/day) was calculated.

Data on the bioconcentration of heptachlor and heptachlor epoxide from water into the tissues of saltwater organisms are given in Tables 5 and 6. The only BCF values available at steady-state for heptachlor and heptachlor epoxide are those for fish species (Table 5).

The three studies (Schimmel, et al. 1976b; Hansen and Parrish, 1977; Goodman, et al. 1978) listed in Table 5 used technical heptachlor containing 65 percent heptachlor, 22 percent trans-chlordane, 2 percent cis-chlordane, 2 percent nonachlor, and 9 percent other unidentified compounds. Goodman, et al. (1978) and Hansen and Parrish (1977) measured both heptachlor and trans-chlordane in the exposure water. Schimmel, et al. (1976b) measured only heptachlor in the exposure water. Each study measured concentrations of heptachlor, heptachlor epoxide, trans-chlordane, and cis-chlordane in edible tissues or whole fish. Therefore, several calculations of BCF values are possible, and these are given in Table 5.

Spot exposed for 24 days to technical grade material reached a maximum concentration of heptachlor in whole body after three days (Schimmel, et al. 1976b). In the same exposure, maximum levels of heptachlor epoxide were reached in whole fish after 17 days. Whole body residues were generally 1.6 times higher than residues in edible portions of fish. 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).

Juvenile sheepshead minnows exposed in two separate experiments for 28 days to technical grade material had similar BCF values, i.e., 4,667 and 5,700 (Hansen and Parrish, 1977; Goodman, et al. 1978). Adult sheepshead

minnows exposed to technical grade material for 126 days accumulated heptachlor and heptachlor epoxide to a much greater extent, an average 37,000 times that in the exposure water (Hansen and Parrish, 1977). The BCF values derived in the above studies are from effect, as well as safe concentrations, and they appear similar.

The only BCF values considered appropriate for heptachlor for the derivation of a Final Residue Value were those based on the concentration of heptachlor in water and the total concentration of heptachlor and heptachlor epoxide in tissue. Dividing a BCF value by the percent lipid value for the same species provides a BCF value adjusted to 1 percent lipid content; this resultant BCF value is referred to as the normalized bioconcentration factor. The geometric mean of the appropriate normalized BCF values for heptachlor for freshwater and saltwater aquatic life is 5,222 (Table 5).

Dividing the U.S. Food and Drug Administration (FDA) action level of 0.3 mg/kg for edible fish and shellfish by the geometric mean of normalized BCF values (5,222) and by a percent lipid value of 15 for freshwater species (see Guidelines) gives a freshwater residue value of 0.0038 µg/l based on marketability for human consumption (Table 5). Dividing the FDA action level (0.3 mg/kg) by the geometric mean of normalized BCF values (5,222) and by a percent lipid value of 16 for saltwater species (see Guidelines) gives a saltwater residue value of 0.0036 µg/l. Also based on marketability for human consumption, using the FDA action level and the highest appropriate BCF for edible portion of a consumed species (3,435 for spot for saltwater), a saltwater residue value of 0.087 µg/l is obtained (Table 5). No appropriate BCF value for edible portion of a consumed species is available for freshwater. The Freshwater Final Residue Value is 0.0038 µg/l. The Saltwater Final Residue Value is the lower of the two calculated residue

values and is 0.0036 µg/l. It should be pointed out that the Final Residue Values may be too high because the average concentration in a high lipid species will be at the FDA action level.

Miscellaneous

Macek, et al. (1976) reported an incipent LC_{50} of 7.0 µg/l for a 10-day exposure of the fathead minnow (Table 6). This incipient LC_{50} was derived using 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 LC_{50}. Due to analytical difficulties, however, actual concentration measurements were not made; rather, concentration values were based on nominal values.

Andrews, et al. (1966) studied the impact of a single application of technical grade heptachlor in several earthen ponds (Table 6). Initial concentrations as technical grade heptachlor 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 BCF values in this document, maximum BCF values, based on peak residue levels for total heptachlor, heptachlor epoxide, and related compounds, compared to initial dose concentrations of technical grade heptachlor, ranged from 638 to 1,326 µg/l. The highest BCF value was for fish in one of the intermediate level ponds.

In vitro measurements of the effect of heptachlor on biochemical activity have also been reported by several authors (Table 6). The value of these data for criteria derivation is limited, however, since no environmental dose relationships were tested or derived.

A study by O'Kelley and Deason (1976) investigated the effect of heptachlor on the growth of 20 algal species isolates from Black Warrior River, Alabama (Table 6). Exposures were conducted in FW-1 algal media spiked with 10, 100 and 10,000 µg/l heptachlor. Effects on growth were determined by comparison with control values after two weeks of exposure. Variable species responses were found. At all three concentrations the majority of the species exhibited 51 to 110 percent growth compared to controls. At 10 and 100 µg/l there were no species that grew at less than 50 percent of controls. At 1,000 µg/l two species grew at less than 50 percent of controls, but there was also one species that grew at 151 to 190 percent of controls. The values for particular species were not specified.

Other saltwater BCF data (Table 6) available for heptachlor and heptachlor epoxide are based on short-term exposures and are probably not steady-state values (Wilson, 1965; Schimmel, et al. 1976a). These values are also measured at effect exposure concentrations. Two shrimp species, pink shrimp and grass shrimp, showed less bioconcentration in 96-hour exposures to technical heptachlor than did another invertebrate species, the American oyster (BCF values ranged from 200 to 700 for the shrimp and from 3,900 to 8,500 for oysters). A BCF of 17,600 was obtained in a separate 10-day exposure of oysters to technical heptachlor (Wilson, 1965). The BCF values for three fish species exposed for 96 hours to technical heptachlor ranged from 2,800 to 21,300.

Exposure to heptachlor as the technical material and to analytical grade heptachlor (99 percent pure heptachlor) gave comparable BCF values for two

species tested. The pink shrimp had BCF values of 200 to 300 when exposed to technical material and from 300 to 600 when exposed to analytical grade heptachlor. The spot had BCF values from 3,000 to 13,800 when exposed to technical material, as compared to 3,600 to 10,000 in an exposure to analytical material.

Table 6 contains no saltwater effect data at lower concentrations than those summarized in previous tables, except for the work of Hansen and Parrish (1977) and U.S. EPA (1980), which were discussed earlier.

Summary

Acute toxicity data are available for 18 freshwater invertebrate and fish species. Species mean acute values range from 0.9 to 78 µg/l for invertebrate species and from 13.1 to 320 µg/l for fish species. A single life-cycle test has been conducted with the fathead minnow, providing a chronic value of 1.26 µg/l and an acute-chronic ratio of 80 for this species. No chronic data are available for any freshwater invertebrate species.

Steady-state bioconcentration factors for fathead minnows are 9,500 for heptachlor and 14,400 for heptachlor epoxide. Adverse effects on bluegills were observed at a feeding rate of 10 mg/kg/day. EC_{50} values of 39.4 and 26.7 µg/l are available for a freshwater algal species, although hydroxychlordene was present in the test solutions and may have contributed significantly to the observed toxicity.

Acute toxicity data are available for 19 species of saltwater organisms. The range of species mean acute values is from 0.04 to 194 µg/l. The 96-hour LC_{50} values for pink shrimp from flow-through tests with measured concentrations are 0.11 µg/l using technical heptachlor and 0.03 µg/l using 99 percent pure heptachlor. Three saltwater chronic toxicity tests have been conducted, but the only acceptable one was an early life-stage test with the sheepshead minnow which resulted in a chronic value of 1.58 µg/l

and an acute-chronic ratio of 3.9. If the acute-chronic ratio for penaeid shrimp is similar to that of the tested species, then chronic effects might be expected to occur at concentrations less than 0.008 µg/l. EC_{50} values for four saltwater algal species range from 93 to 2,260 µg/l.

The saltwater bioconcentration data show that uptake of heptachlor is fairly rapid, reaching a maximum in one study in three days. However, heptachlor is readily metabolized in fish to heptachlor epoxide. The relative amount of heptachlor epoxide in tissues increased with length of exposure, with the maximum amount occurring by day 17. After a 28-day depuration, approximately 90 percent of the heptachlor was either eliminated or degraded to heptachlor epoxide.

Freshwater and Saltwater Final Residue Values of 0.0038 and 0.0036 µg/l, respectively, were derived. However, these Final Residue Values may be too high because the average concentration in a high lipid species will be at FDA action levels.

CRITERIA

For heptachlor the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0038 µg/l as a 24-hour average, and the concentration should not exceed 0.52 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 0.053 µg/l at any time.

Table 1. Acute values for heptachlor

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, Daphnia magna	S, U	Heptachlor (99%)	78	78	Macek, et al. 1976
Cladoceran, Daphnia pulex	S, U	Unspecified grade	42	42	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S, U	Unspecified grade	47	-	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S, U	Unspecified grade	80	61.3	Sanders & Cope, 1966
Scud, Gammarus fasciatus	S, U	Technical heptachlor (72%)	56	-	Sanders, 1972
Scud, Gammarus fasciatus	S, U	Technical heptachlor (72%)	40	47.3	Sanders, 1972
Scud, Gammarus lacustris	S, U	Technical heptachlor (72%)	29	29	Sanders, 1969
Crayfish, Orconectes nais	S, U	Technical heptachlor (72%)	7.8	7.8	Sanders, 1972
Glass shrimp, Palaemonetes kadiakensis	S, U	Technical heptachlor (72%)	1.8	1.8	Sanders, 1972
Stonefly, Claassenia sabulosa	S, U	Technical heptachlor (72%)	2.8	2.8	Sanders & Cope, 1968
Stonefly, Pteronarcella badia	S, U	Technical heptachlor (72%)	0.9	0.9	Sanders & Cope, 1968
Stonefly, Pteronarcys californica	S, U	Technical heptachlor (72%)	1.1	1.1	Sanders & Cope, 1968
Coho salmon, Oncorhynchus kisutch	S, U	Technical** heptachlor (72%)	81.9	81.9	Katz, 1961
Chinook salmon, Oncorhynchus tshawytscha	S, U	Technical** heptachlor (72%)	24.0	24.0	Katz, 1961

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Rainbow trout, Salmo gairdneri	S, U	Technical** heptachlor (72%)	26.9	-	Katz, 1961
Rainbow trout, Salmo gairdneri	S, U	Technical*** heptachlor (72%)	10.7	-	Macek, et al. 1969
Rainbow trout, Salmo gairdneri	S, U	Technical*** heptachlor (72%)	10.0	-	Macek, et al. 1969
Rainbow trout, Salmo gairdneri	S, U	Technical*** heptachlor (72%)	10.1	13.1	Macek, et al. 1969
Goldfish, Carassius auratus	S, U	Technical heptachlor (72%)	320	320	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S, U	Technical heptachlor (72%)	130	-	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S, U	Technical heptachlor (72%)	78	101	Henderson, et al. 1959
Guppy, Poecilia reticulata	S, U	Technical heptachlor (72%)	148	148	Henderson, et al. 1959
Bluegill, Lepomis macrochirus	S, U	Technical heptachlor (72%)	26	26	Henderson, et al. 1959
Redear sunfish, Lepomis microlophus	S, U	Technical** heptachlor (72%)	23.6	23.6	Bridges, 1965
		SALTWATER SPECIES			
American oyster, Crassostrea virginica	FT, U	Technical heptachlor (72%)	27[a]	-	Butler, 1963
American oyster, Crassostrea virginica	FT, U	Technical heptachlor (72%)	30[a]	-	Butler, 1963
American oyster, Crassostrea virginica	FT, M	Technical heptachlor (72%)	1.5[a]	1.5	Schimmel, et al. 1976a

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Mysid shrimp, Mysidopsis bahia	FT, M	Heptachlor (>99%)	3.4	3.4	U.S. EPA, 1980
Sand shrimp, Crangon septemspinosa	S, U	Heptachlor[b]	8	8	Eisler, 1969
Hermit crab, Pagurus longicarpus	S, U	Heptachlor[b]	55	55	Eisler, 1969
Korean shrimp, Palaemon macrodactylus	S, U	Heptachlor (>99%)	14.5	14.5	Schoettger, 1970
Grass shrimp, Palaemonetes vulgaris	S, U	Heptachlor[b]	440	-	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	FT, M	Technical[c] heptachlor	1.06	1.06	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	FT, M	Technical[c] heptachlor	0.11	-	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	FT, M	Heptachlor (>99%)	0.03	0.057	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	FT, M	Heptachlor epoxide (99%)	0.04	0.04	Schimmel, et al. 1976a
American eel, Anguilla rostrata	S, U	Heptachlor[b]	10	10	Eisler, 1970a
Sheepshead minnow, Cyprinodon variegatus	FT, M	Technical[c] heptachlor	3.68	-	Schimmel, et al. 1976a
Sheepshead minnow, Cyprinodon variegatus	FT, M	Technical[c] heptachlor	10.5	6.22	Hansen & Parrish, 1977
Mummichog, Fundulus heteroclitus	S, U	Heptachlor[b]	50	50	Eisler, 1970a
Striped killifish, Fundulus majalis	S, U	Heptachlor[b]	32	32	Eisler, 1970a

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Atlantic silverside, Menidia menidia	S, U	Heptachlor[b]	3	3	Eisler, 1970a
Threespine stickleback, Gasterosteus aculeatus	S, U	Technical heptachlor (72%)	111.9	-	Katz, 1961
Threespine stickleback, Gasterosteus aculeatus	S, U	Technical heptachlor (72%)	111.9	112	Katz, 1961
Striped bass, Morone saxatilis	FT, U	Heptachlor (>99%)	3	3	Korn & Earnest, 1974
Pinfish, Lagodon rhomboides	FT, M	Technical[c] heptachlor	3.77	3.77	Schimmel, et al. 1976a
Spot, Leiostomus xanthurus	FT, M	Technical[c] heptachlor	0.85	-	Schimmel, et al. 1976a
Spot, Leiostomus xanthurus	FT, M	Heptachlor (>99%)	0.86	0.86	Schimmel, et al. 1976a
Bluehead, Thallassoma bifasciatum	S, U	Heptachlor[b]	0.8	0.8	Eisler, 1970a
Striped mullet, Mugil cephalus	S, U	Heptachlor[b]	194	194	Eisler, 1970a
Northern puffer, Sphaeroides maculatus	S, U	Heptachlor[b]	188	188	Eisler, 1970a

* S = static, FT = flow-through, U = unmeasured, M = measured

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

***Authors converted from technical grade of unspecified percent heptachlor to 100% active ingredient. For this criterion document it was assumed that the technical grade was 72% and LC50 values were converted back to technical grade.

[a] EC50: amount of chemcal estimated to reduce shell growth by 50%.

[b] Entomol. Soc. Am. reference standard.

[c] Technical material: 65% heptachlor, 22% trans-chlordane, 2% cis-chlordane, 2% nonachlor, and 9% unidentified compounds.

Table 2. Chronic values for heptachlor

Species	Test*	Chemical	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES			
Fathead minnow, *Pimephales promelas*	LC	Heptachlor	0.86-1.84	1.26	Macek, et al. 1976
		SALTWATER SPECIES			
Sheepshead minnow, *Cyprinodon variegatus*	ELS	Technical** heptachlor	1.22-2.04	1.58	Goodman, et al. 1978

* LC = life cycle or partial life cycle, ELS = early life stage

**Technical material: 65% heptachlor, 22% trans-chlordane, 2% cis-chlordane, and <2% nonachlor

Acute-Chronic Ratios

Species	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Fathead minnow, *Pimephales promelas*	101	1.26	80
Sheepshead minnow, *Cyprinodon variegatus*	6.22	1.58	3.9

Table 3. Species mean acute values and acute-chronic ratios for heptachlor

Rank*	Species	Chemical**	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
		FRESHWATER SPECIES		
18	Goldfish, *Carassius auratus*	Technical heptachlor	320	-
17	Guppy, *Poecilia reticulata*	Technical heptachlor	148	-
16	Fathead minnow, *Pimephales promelas*	Technical heptachlor	101	80
15	Coho salmon, *Oncorhynchus kisutch*	Technical heptachlor	81.9	-
14	Cladoceran, *Daphnia magna*	Technical heptachlor	78	-
13	Cladoceran, *Simocephalus serrulatus*	Technical heptachlor	61.3	-
12	Scud, *Gammarus fasciatus*	Technical heptachlor	47.3	-
11	Cladoceran, *Daphnia pulex*	Technical heptachlor	42	-
10	Scud, *Gammarus lacustris*	Technical heptachlor	29	-
9	Bluegill, *Lepomis macrochirus*	Technical heptachlor	26	-
8	Chinook salmon, *Oncorhynchus tshawytscha*	Technical heptachlor	24	-
7	Redear sunfish, *Lepomis microlophus*	Technical heptachlor	23.6	-
6	Rainbow trout, *Salmo gairdneri*	Technical heptachlor	13.1	-

Table 3. (Continued)

Rank*	Species	Chemical**	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
5	Crayfish, *Orconectes nais*	Technical heptachlor	7.8	-
4	Stonefly, *Claassenia sabulosa*	Technical heptachlor	2.8	-
3	Glass shrimp, *Palaemonetes kadiakensis*	Technical heptachlor	1.8	-
2	Stonefly, *Pteronarcys californica*	Technical heptachlor	1.1	-
1	Stonefly, *Pteronarcella badia*	Technical heptachlor	0.9	-
		SALTWATER SPECIES		
19	Striped mullet, *Mugil cephalus*	Heptachlor***	194	-
18	Northern puffer, *Sphaeroides maculatus*	Heptachlor***	188	-
17	Threespine stickleback, *Gasterosteus aculeatus*	Technical heptachlor	112	-
16	Hermit crab, *Pagurus longicarpus*	Heptachlor***	55	-
15	Mummichog, *Fundulus heteroclitus*	Heptachlor***	50	-
14	Striped killifish, *Fundulus majalis*	Heptachlor***	32	-
13	Korean shrimp, *Palaemon macrodactylus*	Heptachlor (>99%)	14.5	-
12	American eel, *Anguilla rostrata*	Heptachlor***	10	-

Table 3. (Continued)

Rank*	Species	Chemical**	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
11	Sand shrimp, *Crangon septemspinosa*	Heptachlor***	8.	-
10	Sheepshead minnow, *Cyprinodon variegatus*	Technical**** heptachlor	6.22	3.9
9	Pinfish, *Lagodon rhomboides*	Technical**** heptachlor	3.77	-
8	Mysid shrimp, *Mysidopsis bahia*	Heptachlor (>99%)	3.4	-
7	Atlantic silverside, *Menidia menidia*	Heptachlor***	3	-
6	Striped bass, *Morone saxatilis*	Heptachlor (>99%)	3	-
5	American oyster, *Crassostrea virginica*	Technical heptachlor	1.5	-
4	Grass shrimp, *Palaemonetes vulgaris*	Heptachlor****	1.06	-
3	Spot, *Leiostomus xanthurus*	Heptachlor**** (Both technical and >99%)	0.86	-
2	Bluehead, *Thalassoma bifasciatum*	Heptachlor***	0.8	-
1	Pink shrimp, *Penaeus duorarum*	Heptachlor**** (Both technical and >99%)	0.057	-

* Ranked from least sensitive to most sensitive based on species mean acute value.

** Technical material: 72% heptachlor and 28% related compounds unless noted otherwise.

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

Table 3. (Continued)

****Technical material: 65% heptachlor, 22% trans-chlordane, 2% cis-chlordane, 2% nonachlor, and 9% unidentified compounds.

Freshwater Final Acute Value for heptachlor = 0.52 µg/l

Saltwater Final Acute Value for heptachlor = 0.053 µg/l

Table 4. Plant values for heptachlor

Species	Chemical	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	Heptachlor	96-hr EC50, growth inhibition	39.4*	Call & Brooke, 1980
Alga, *Selenastrum capricornutum*	Heptachlor	96-hr EC50, growth inhibition	26.7*	Call & Brooke, 1980
		SALTWATER SPECIES		
Alga, *Dunaliella tertiolecta*	Heptachlor (99%)	EC50, reduction in growth as measured by absorbance	2,260	U.S. EPA, 1980
Alga, *Isochrysis galbana*	Heptachlor (99%)	EC50, reduction in growth as measured by absorbance	157	U.S. EPA, 1980
Alga, *Porphyridium cruentum*	Heptachlor (99%)	EC50, reduction in growth as measured by aborbance	273	U.S. EPA, 1980
Alga, *Skeletonema costatum*	Heptachlor (99%)	EC50, reduction in growth as measured by absorbance	93	U.S. EPA, 1980

* Test solutions of heptachlor contained from 6 µg/l hydroxychlordene in the lowest test concentration of 8.6 µg/l to 25 µg/l hydroxychlordene in the highest tested concentration of 57 µg/l.

Table 5. Residues for heptachlor

Species	Tissue	Lipid (%)	Chemical	Bioconcentration Factor	Duration (days)	Reference
			FRESHWATER SPECIES			
Fathead minnow, Pimephales promelas	Whole body	7.6	Heptachlor	9,500	32	Veith, et al. 1979
Fathead minnow, Pimephales promelas	Whole body	7.6	Heptachlor epoxide	14,400	32	Veith, et al. 1979
			SALTWATER SPECIES			
Sheepshead minnow (juvenile), Cyprinodon variegatus	Whole body	-	Technical heptachlor*	3,582	28	Goodman, et al. 1978
Sheepshead minnow (juvenile), Cyprinodon variegatus	Whole body	-	Technical heptachlor**	6,456	28	Goodman, et al. 1978
Sheepshead minnow (juvenile), Cyprinodon variegatus	Whole body	-	Technical heptachlor***	4,953	28	Goodman, et al. 1978
Sheepshead minnow, (juvenile), Cyprinodon variegatus	Whole body	-	Technical heptachlor[a]	4,667	28	Goodman, et al. 1978
Sheepshead minnow (adult), Cyprinodon variegatus	Whole body	3.6[b]	Technical heptachlor[a]	37,000	126	Hansen & Parrish, 1977
Sheepshead minnow (juvenile), Cyprinodon variegatus	Whole body	-	Technical heptachlor[a]	5,700	28	Hansen & Parrish, 1977
Spot, Leiostomus xanthurus	Edible tissue	-	Technical heptachlor*	1,848	24	Schimmel, et al. 1976b
Spot, Leiostomus xanthurus	Whole body	1.1[b]	Technical heptachlor*	3,181	24	Schimmel, et al. 1976b
Spot, Leiostomus xanthurus	Edible tissue	-	Technical heptachlor**	3,435	24	Schimmel, et al. 1976b

Table 5. (Continued)

Species	Tissue	Lipid (%)	Chemical	Bioconcentration Factor	Duration (days)	Reference
Spot, *Leiostomus xanthurus*	Whole body	1.1[b]	Technical heptachlor**	5,744	24	Schimmel, et al. 1976b
Spot, *Leiostomus xanthurus*	Edible tissue	-	Technical heptachlor[c]	4,686	24	Schimmel, et al. 1976b
Spot, *Leiostomus xanthurus*	Whole body	1.1[b]	Technical heptachlor[c]	8,282	24	Schimmel, et al. 1976b

* Concentration of heptachlor in tissue divided by concentration of heptachlor in water.

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

***Concentration of heptachlor and trans-chlordane in tissue divided by concentration of heptachlor and trans-chlordane in water.

[a] Concentration of heptachlor, heptachlor epoxide, trans-chlordane and cis-chlordane in tissue divided by concentration of heptachlor and trans-chlordane in water.

[b] Percent lipid data from Hansen, 1980.

[c] Concentration of heptachlor, heptachlor epoxide, trans-chlordane and cis-chlordane in tissue divided by concentration of heptachlor in water.

Maximum Permissible Tissue Concentration

Action Level or Effect	Concentration (mg/kg)	Reference
Fish and shellfish	0.3	U.S. FDA Guideline 7420.08, 1979
Reduced survival, Bluegill, *Lepomis macrochirus*	7.1	Andrews, et al. 1966

Table 5. (Continued)

Geometric mean of appropriate normalized BCF values (see text) = 5,744/1.1 = 5,222

Marketability for human consumption: FDA action level for fish and shellfish = 0.3 mg/kg

Percent lipid value for freshwater species (see Guidelines) = 15

Percent lipid value for saltwater species (see Guidelines) = 16

Freshwater: $\frac{0.3}{5,222 \times 15}$ = 0.0000038 mg/kg = 0.0038 µg/l

Saltwater: $\frac{0.3}{5,222 \times 16}$ = 0.0000036 mg/kg = 0.0036 µg/l

Using highest appropriate BCF for edible portion of a consumed species

Saltwater: Spot = 4,686 (Schimmel, et al. 1976b)

$\frac{0.3}{3,435}$ = 0.000087 mg/kg = 0.087 µg/l

Freshwater Final Residue Value = 0.0038 µg/l

Saltwater Final Residue Value = 0.0036 µg/l

Table 6. Other data for heptachlor

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Twenty river algal species isolates	Heptachlor	2 wks	Reduction in growth in heptachlor-spiked FW-1 algal media	70% of species grew to 51-90% of controls 10 µg/l	O'Kelley and Deason, 1976
Numerous miscellaneous invertebrates	Heptachlor	171 days	100% mortality in 24 hrs; returned to normal population levels by day 14	52.1	Andrews, et al. 1966
Cladoceran, Daphnia magna	Heptachlor	26 hrs	LC50	52	Frear & Boyd, 1967
Cladoceran, Daphnia magna	Heptachlor epoxide	26 hrs	LC50	120	Frear & Boyd, 1967
Tubificid worm, Branchiura sowerbyi	Heptachlor	72 hrs	100% mortality at 4.4 C	2,500	Naqvi, 1973
Tubificid worm, Branchiura sowerbyi	Heptachlor	72 hrs	0% mortality at 21.0 C	2,500	Naqvi, 1973
Tubificid worm, Branchiura sowerbyi	Heptachlor	72 hrs	100% mortality at 32.2 C	2,500	Naqvi, 1973
Crayfish, Procambarus clarkii	Heptachlor	Variable	Time to death after consuming contaminated tubificid worms; worms placed in clean water after exposure were not lethal to crayfish	2	Naqvi, 1973
Crayfish, Procambarus clarkii	Heptachlor	Unspecified	10% inhibition of brain acetylcholinesterase	933	Guilbault, et al. 1972

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Glass shrimp, *Palaemonetes kadiakensis*	Heptachlor	24 hrs	LC50	40.6	Naqvi & Ferguson, 1970
Fowler's toad (larva), *Bufo woodhousii fowleri*	Heptachlor	96 hrs	LC50	440	Sanders, 1970
Bullfrog (larva), *Rana catesbeiana*	Heptachlor	48 hrs	80% mortality in cages submerged ponds dosed with emulsifiable concentrate	0.5 lbs/acre	Mulla, 1963
Rainbow trout, *Salmo gairdneri*	Heptachlor	15 min	67% inhibition of NaK-ATPase	37,350	Davis, et al. 1972
Rainbow trout, *Salmo gairdneri*	Heptachlor	15 min	31% inhibition of Mg-ATPase	3,735	Davis, et al. 1972
Atlantic salmon (juvenile), *Salmo salar*	Heptachlor	24 hrs	Change in temperature selection	No effect up to 25	Peterson, 1976
Fathead minnow, *Pimephales promelas*	Heptachlor	10 days	Incipient LC50	7.0	Macek, et al. 1976
Mosquitofish, *Gambusia affinis*	Heptachlor	48 hrs	64% mortality in cages submerged in ponds dosed with emulsifiable concentrate	0.5 lbs/acre	Mulla, 1963
Mosquitofish, *Gambusia affinis*	Heptachlor	36 hrs	LC50	70	Boyd & Ferguson, 1964
Bluegill, *Lepomis macrochirus*	Heptachlor	171 days*	>90% mortality	69.4	Andrews, et al. 1966
Bluegill, *Lepomis macrochirus*	Heptachlor	171 days*	Growth and reproduction	No effect where fish survived	Andrews, et al. 1966

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Bluegill, Lepomis macrochirus	Heptachlor	171 days*	Tissue accumulation	Maximum accumulation of 1,326x initial dose concentration; return to normal after 84 days	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	Heptachlor	171 days**	Increased mortality	10 mg/kg/day	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	Heptachlor	171 days**	Dose-related growth decrease	5 to 25 mg/kg/day	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	Heptachlor	171 days**	Tissue accumulation	Accumulation peaked and subsequently declined to undetectable levels by day 112	Andrews, et al. 1966
Bluegill, Lepomis macrochirus	Heptachlor	25 min	65-69% inhibition of NaK- and Mg-ATPase	15,600	Cutkomp, et al. 1971
Bluegill, Lepomis macrochirus	Heptachlor	25 min	45-47% inhibition of NaK- and Mg-ATPase	16,200	Cutkomp, et al. 1971
Bluegill, Lepomis macrochirus	Heptachlor	96 hrs	LC50 of heptachlor as emulsifiable concentrate in soft water	22	Henderson, et al. 1960
Bluegill, Lepomis macrochirus	Heptachlor	96 hrs	LC50 of heptachlor as emulsifiable concentrate in hard water	18	Henderson, et al. 1960

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Bluegill, Lepomis macrochirus	Heptachlor	Unspecified	87% inhibition of O_2 utilization by mitochondria	370,000	Hiltibran, 1974
Bluegill, Lepomis macrochirus	Heptachlor	Unspecified	29% inhibition of PO_4 utilization by mitochondria	370,000	Hiltibran, 1974
Bluegill, Lepomis macrochirus	Heptachlor	Unspecified	50% inhibition of mitochondrial Mg-ATPase	6,790	Yap, et al. 1975
Bluegill, Lepomis macrochirus	Heptachlor	Unspecified	50% inhibition of brain NaK-ATPase	16,434	Yap, et al. 1975
Bluegill, Lepomis macrochirus	Heptachlor	Unspecified	50% inhibition of brain NaK-ATPase	8,179	Yap, et al. 1975
Redear sunfish, Lepomis microlophus	Heptachlor	24 hrs	EC50 at 45 F	92	Bridges, 1965
Redear sunfish, Lepomis microlophus	Heptachlor	24 hrs	EC50 at 55 F	64	Bridges, 1965
Redear sunfish, Lepomis microlophus	Heptachlor	24 hrs	EC50 at 65 F	47	Bridges, 1965
Redear sunfish, Lepomis microlophus	Heptachlor	24 hrs	EC50 at 75 F	34	Bridges, 1965
Redear sunfish, Lepomis microlophus	Heptachlor	24 hrs	EC50 at 85 F	22	Bridges, 1965
		SALTWATER SPECIES			
Natural phytoplankton communities	Technical heptachlor***	4 hrs	94.4% decrease in productivity	1,000	Butler, 1963

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Dinoflagellate, *Exuviella baltica*	Technical heptachlor***	7 days	Reduced cell density, chlorophyll *a* per unit volume of culture, ^{14}C uptake per cell and carbon fixation per unit of chlorophyll *a*	50	Magnani, et al. 1978
American oyster, *Crassostrea virginica*	Technical heptachlor***	10 days	Bioconcentration factor = 17,600[b]	-	Wilson, 1965
American oyster, *Crassostrea virginica*	Technical heptachlor****	96 hrs	Bioconcentration factor = 3,900 to 8,500[b]	-	Schimmel, et al. 1976a
Mysid shrimp, *Mysidopsis bahia*	Heptachlor (99%)	28 days	Reduced survival	0.64	U.S. EPA, 1980
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	50-75% mortality 12 g/kg salinity	400	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	25-50% mortality 18 g/kg salinity	400	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	25-50% mortality 24 g/kg salinity	400	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	25-50% mortality 30 g/kg salinity	400	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	25-50% mortality 36 g/kg salinity	400	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	0-25% mortality 10 C	400	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	0% mortality 15 C	400	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	Heptachlor[a]	48 hrs	25-50% mortality 20 C	400	Eisler, 1969

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Grass shrimp, Palaemonetes vulgaris	Heptachlor[a]	48 hrs	75-100% mortality 25 C	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	Heptachlor[a]	48 hrs	75-100% mortality 30 C	400	Eisler, 1969
Grass shrimp, Palaemonetes vulgaris	Technical heptachlor****	96 hrs	Bioconcentration factor = 500 to 700[b]	-	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	Technical heptachlor***	48 hrs	EC50: loss of equilibrium	0.3	Butler, 1963
Pink shrimp, Penaeus duorarum	Technical heptachlor****	96 hrs	Bioconcentration factor = 200 to 300[b]	-	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	Heptachlor (99%)	96 hrs	Bioconcentration factor = 300 to 600[c]	-	Schimmel, et al. 1976a
Pink shrimp, Penaeus duorarum	Heptachlor epoxide (99%)	96 hrs	Bioconcentration factor = 200 to 1,700[d]	-	Schimmel, et al. 1976a
Blue crab (juvenile), Callinectes sapidus	Technical heptachlor***	48 hrs	EC50: loss of equilibrium	63	Butler, 1963
Sheepshead minnow, Cyprinodon variegatus	Technical heptachlor****	96 hrs	Bioconcentration factor = 7,400 to 21,300[b]	-	Schimmel, et al. 1976a
Sheepshead minnow, Cyprinodon variegatus	Technical heptachlor****	126 days	Decreased embryo production	0.71	Hansen & Parrish, 1977
Mummichog, Fundulus heteroclitus	Heptachlor[a]	96 hrs	0-25% mortality 12 g/kg salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	Heptachlor[a]	96 hrs	0-25% mortality 18 g/kg salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	Heptachlor[a]	96 hrs	50-75% mortality 24 g/kg salinity	50	Eisler, 1970b
Mummichog, Fundulus heteroclitus	Heptachlor[a]	96 hrs	25-50% mortality 30 g/kg salinity	50	Eisler, 1970b

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Mummichog, *Fundulus heteroclitus*	Heptachlor[a]	96 hrs	25-50% mortality 36 g/kg salinity	50	Eisler, 1970b
Mummichog, *Fundulus heteroclitus*	Heptachlor[a]	96 hrs	0% mortality 10 C	50	Eisler, 1970b
Mummichog, *Fundulus heteroclitus*	Heptachlor[a]	96 hrs	0% mortality 15 C	50	Eisler, 1970b
Mummichog, *Fundulus heteroclitus*	Heptachlor[a]	96 hrs	0-25% mortality 20 C	50	Eisler, 1970b
Mummichog, *Fundulus heteroclitus*	Heptachlor[a]	96 hrs	50-75% mortality 25 C	50	Eisler, 1970b
Mummichog, *Fundulus heteroclitus*	Heptachlor[a]	96 hrs	0-25% mortality 30 C	50	Eisler, 1970b
Mummichog, *Fundulus heteroclitus*	Heptachlor[a]	240 hrs	LC50	11	Eisler, 1970b
Pinfish, *Lagodon rhomboides*	Technical heptachlor****	96 hrs	Bioconcentration factor = 2,800 to 7,700[b]	-	Schimmel, et al. 1976a
Spot, *Leiostomus xanthurus*	Technical heptachlor****	96 hrs	Bioconcentration factor = 3,000 to 13,800[b]	-	Schimmel, et al. 1976a
Spot, *Leiostomus xanthurus*	Heptachlor (99%)	96 hrs	Bioconcentration factor = 3,600 to 10,000[c]	-	Schimmel, et al. 1976a
White mullet (juvenile), *Mugil curema*	Technical heptachlor***	48 hrs	LC50	3	Butler, 1963

* Tested in ponds, dosed on day 1 only. Authors dosed with technical grade heptachlor and reported as µg/l active ingredient. For the purpose 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.

Table 6. (Continued)

*** Technical material: contains 74% heptachlor and 26% other chemicals, including trans-chlordane, cis-chlordane, nonachlor, and others.

****Technical material: contains 65% heptachlor, 22% trans-chlordane, 2% cis-chlordane, 2% nonachlor, and 9% others.

a Heptachlor; Entomol. Soc. Am. reference standard.

b 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).

c Concentration of heptachlor in whole body divided by concentration of heptachlor in water. Organism exposed to analytical-grade heptachlor (99% heptachlor).

d 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

Ingestion from 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 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 detection limit for heptachlor was in the range of 0.002 to 0.010 µg/l, but was 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 added 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).

Ingestion from 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, the U.S. EPA (1976) cited data from Hannon, et al. (1970), who reported that average heptachlor/heptachlor epoxide residues in the Lake Poinsett, S. Dakota ecosystem were: 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 10-fold to 15-fold increase in heptachlor residues found in body fat, milk butterfat, and the fat of eggs and livestock as compared to residue levels found in normal food rations (U.S. EPA, 1976).

Since 1964, the Food and Drug Administration (FDA) has reported pesticide residues in their Total Diet Study, sometimes called the "Market Basket Study" (Johnson and Manske, 1977). Their "market basket" of food, which is collected in each of several geographic areas, represents the basic 2-week diet of 16- to 19-year-old males, statistically the nation's highest per capita consumers. The foods analyzed in these studies were 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 Manske, 1977). Their results showed that only 3 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.

TABLE 1

Heptachlor Epoxide Residues in Food*

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	0.001-0.0003
VIII	Garden Fruits	Trace	1	1	Trace

*Source: Johnson and Manske, 1977

Nisbet (1977) calculated the average daily intake of heptachlor epoxide from the FDA's Market Basket Study 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, because 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 regarded the total Diet Survey for heptachlor epoxide as only semi-quantitative. He stated that the results suggest an overall mean daily intake, in the standardized diet, of the order of 1 µg/day of heptachlor epoxide.

The U.S. Department of Agriculture's (USDA) 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, et al. 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 that man eats, so it is possible that much of the residues are accumulated in the uneaten portion (Henderson, et al. 1969).

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

Several laboratory studies, in which percent lipids and a steady-state BCF were measured, have been conducted on heptachlor. The mean of the BCF values, after normalization to 1 percent lipids, is 3,747 (see Table in Aquatic Life Toxicology, Section B). An adjustment factor of 3 can be used to adjust the mean normalized BCF to the 3.0 percent lipids that is the weighted average

for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for heptachlor and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 11,200.

Infants are exposed to heptachlor and heptachlor epoxide through mothers' milk (Savage, 1976), cows' milk (Ritcey, et al. 1972; Johnson and Manske, 1977), and commercially prepared baby foods (Lipscomb, 1968). A recent nationwide study, conducted during 1975-1976, indicates that 63.1 percent of the 1,936 mothers' milk samples possessed heptachlor epoxide residues (Savage, 1976). The adjusted mean fat 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 2,050 µg/l. Therefore, it 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 cows' milk and evaporated milk did not show a trace of heptachlor epoxide in the U.S. FDA's 1974-1975 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 cows' 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 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). The air above and downwind from the fields showed heptachlor concentrations as high as 244 ng/m^3 immediately after application.

After three 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, with the field showing 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 from 1972 to 1974 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, Florida 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 stated 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 has not been 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 two 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 100 mg/kg for males and 162 mg/kg for females. Xylene was used as the vehicle to dissolve and apply the heptachlor, with the solution 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 pure heptachlor reaches all organs and tissues of female rats within one-half to one hour after a single dose (120 mg/kg) of heptachlor was delivered directly into the stomach. After four 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 decreased, while at the same time there was a rapid increase in heptachlor epoxide levels. By the end of one month, only traces of heptachlor could be found in the fatty tissue, chiefly in the form of its metabolic products. Heptachlor or its metabolites could not be found in the blood or kidneys. However, a small amount of heptachlor epoxide was found in the liver. After three to six months the level of heptachlor epoxide in fatty tissues became stabilized.

Radomski and Davidow (1953) used both dogs and rats. In rats, after two months on a diet of 30 to 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, with none being detected in the brain. Female dogs, dosed at 1 mg/kg daily for a period from 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.

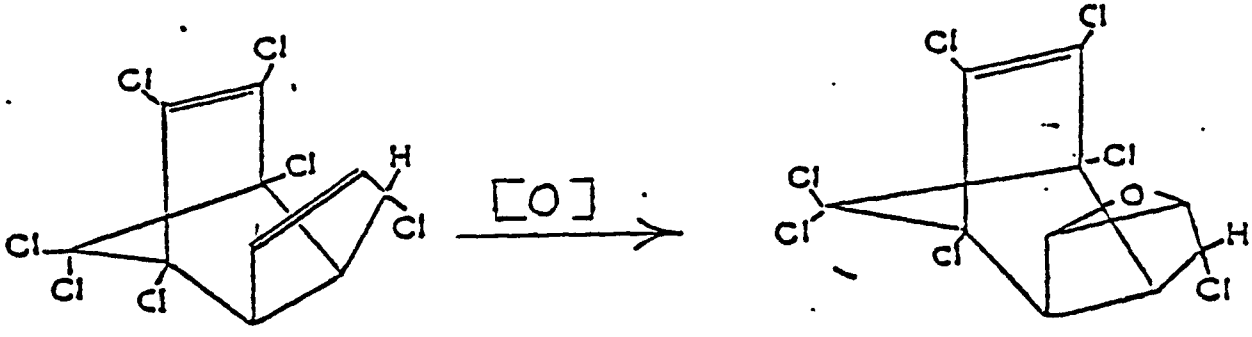
The degree to which heptachlor or heptachlor epoxide is absorbed by inhalation has not generally been reported (Nisbet, 1977). Arthur, et al. (1975) conducted a now controversial study where they exposed white rabbits to the ambient air of Stoneville, Miss., an area of high pesticide use. Their controls were housed indoors at Mississippi State University, an area of low pesticide use. They found that between July 1972 and October 1972 the heptachlor epoxide level in the rabbits' 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 heptachlor epoxide level in air at Stoneville was reported to be 1.86 ng/m^3, while the Mississippi State University 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 of heptachlor 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 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 both in their placenta. They also reported 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. (1977b) 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 (Radomski and Davidow, 1953; Davidow and Radomski, 1953) show that both the rat and the dog metabolize ingested heptachlor rapidly 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 in the fat tissue. In this study, the female rats accumulated approximately six times as much heptachlor epoxide in their fat tissue as did the males.



HEPTACHLOR

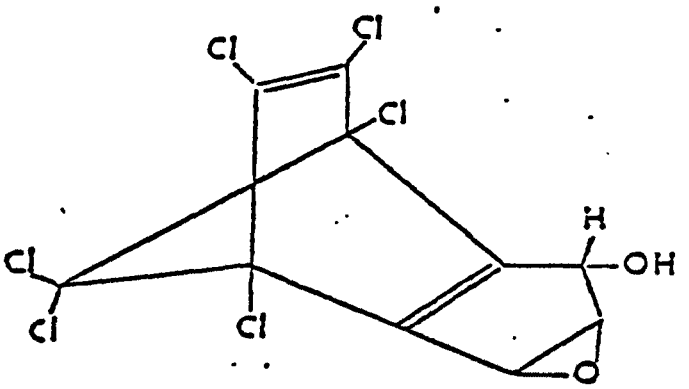
HEPTACHLOR EPOXIDE

FIGURE 1

Matsumura and Nelson (1971) fed four male albino rats 10 mg/kg of 99 percent pure heptachlor epoxide for 30 days (approximately 5 mg heptachlor epoxide/rat/30 days) and found that they excreted 950 µg of a fecal metabolite (Figure 2), and 66 µg of heptachlor epoxide in the feces in the 30-day period. Mizyukova and Kurchatov (1970) found that the excretion of the nonstored heptachlor and its metabolites occurs within the first five days, chiefly through the gastrointestinal tract and to a smaller extent in the urine.

One very important route of excretion of heptachlor and heptachlor epoxide in females is through lactation (Jonsson, et al. 1977). This study indicates that milk is a primary excretory route for heptachlor and its metabolites. Generally, heptachlor epoxide concentration in mothers' milk is a good indicator of the body burden of heptachlor epoxide stored in the lactating mothers' body (Jonsson, et al. 1977; Strassman and Kutz, 1977). Polishuk, et al. (1977a) 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 from ages 20 to 29 years old excreted higher pesticides levels in their milk than did women from the ages 30 to 39, even though the younger women had lower pesticides levels in their plasma.

In a human milk study of 53 samples collected from two Pennsylvania regions during 1970, Kroger (1972) found all of the samples contained heptachlor epoxide at an average concentration of 0.16 mg/l. Savage, et al. (1973) performed a similar survey in Colorado in 1970-1971 with 40 human milk samples, and found 25



HEPTACHLOR
FECAL METABOLITE

FIGURE 2

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 of 57 milk samples and found heptachlor epoxide residues in 35.1 percent of the samples with 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 conducted during 1975 involving 1,436 human milk samples from selected sites within the continental U.S. He found that only 2 percent showed heptachlor residues, but 63.1 percent of the mothers' milk samples showed heptachlor epoxide residues ranging 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 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 from other countries include: Ritcey, et al. (1972); Polishuk, et al. (1977a); 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 is an addition

to the body burden which already exists due to exposure *in utero* (Polishuk, et al. 1977b; 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 of 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. During the study period, he found 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 coterminous 48 states, and the sampling sites were randomly selected to be representative of the U.S. populations. The 5-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 (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 studied nine composite human fat samples from nine census divisions of the U.S. and found eight of

TABLE 2

Heptachlor Epoxide Residues in Human Adipose Tissue*

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

*Source: Kutz, et al. 1977

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 indicate 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 (Curley, et al. 1973; Wasserman, et al. 1974; Abbott, et al. 1972; Wasserman, et al. 1972) have reported heptachlor epoxide residues in human adipose tissue in other countries.

EFFECTS

Acute, Subacute, and Chronic Toxicity

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 when given intravenously in mice. 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 photoheptachlor epoxide [III B] (Ivie, et al. 1972), which is formed by exposure of heptachlor epoxide to ultraviolet light or sunlight in 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

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
M = male
F = female
N = neonate
i.p. = intraperitoneally

for the intermediate photo metabolite photoheptachlor epoxide [II]; and 6 mg/kg for photoheptachlor 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, while the acute dermal LD_{50} of heptachlor in males was 195 mg/kg and 250 mg/kg for females. Harbison (1975) used neonatal and adult (120 to 150 g) Sprague-Dawley rats 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*, but was 531 mg/kg* for newborn rats. Gak, et al. (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.

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. 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 to rats significantly elevated their brain acetylcholine content, with some decrease in acetylcholine concentration

*Assumed to be mg/kg body weight.

during the period of severest seizure activity. They suggested that these changes 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 cerebral 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 (1 μmole/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 again heptachlor epoxide had no effect. They speculated that since heptachlor did not interact at any step in the electron transport chain after cytochrome C, 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 lower concentrations of heptachlor caused dramatic changes in the membrane of mouse mitochondria. They stated that the increase in respiration (oxidation of succinate), observed when ADP and heptachlor were added, was probably caused by increased permeability of membranes to succinate,

or by conformational changes of such a nature that the intrinsic activity of the respiratory chain was increased.

Induction of liver microsomal enzymes by heptachlor and heptachlor epoxide 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 Tonkelaar 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, phosphoenolpyruvate carboxykinase, fructose 1,6-diphosphatase, and glucose 6-phosphatase, 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 the 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 (1977a) 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 7 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 given to male rats caused dominant lethal changes as 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 mitosis, abnormalities of chromatids, pulverization, and translocation of chromosomes in the bone marrow cells of their experimental animals. They concluded from the results mentioned above that rat fetuses in early and late stages of embryonic development could be adversely affected by heptachlor. Ahmed, et al. (1977) used SV-40 transformed human cells (VA4) 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.

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 life span of suckling rats was 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. Mestitzova stated that the sequence of occurrence of the cataracts excluded the possibility of recessive genetic traits or a vitamin B deficiency as the causative factor.

Synergism and/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. There-

fore, they suggested that low protein diets impaired or slowed metabolism of heptachlor to the more toxic heptachlor epoxide. Weatherholtz, et al. (1969) reported that rats fed protein deficient diets were less susceptable to heptachlor toxicity and also suggested that this observation may have been 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 deficient diets (Miranda, et al. 1973; Miranda and Webb, 1974). Their studies suggested an interaction of protein inadequacy with drug metabolism and with 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. For heptachlor, LD_{50} values for a newborn rat, for a newborn pretreated with PB, and for an adult male untreated rat, were 531 mg/kg, 133 mg/kg, and 7 mg/kg, respectively.

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 FDA, Cabral, et al. 1972, International Research and Development Corporation (IRDC) sponsored by Velsicol, and the National Cancer Institute (NCI). Two extensive reviews of these studies have been conducted

by Epstein (1976) and by the U.S. EPA (1977) and should be consulted for more specific information on each study. Tables 4 and 5 present summary data reported by Epstein (1976), and include the original authors's 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 of heptachlor administered in the diet were 0, 1.5, 3.0, 5.0, 7.0, and 10.0 mg/kg. These dosages were 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 diseases (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 conducted for the Velsicol Corp. in 1959 by Witherup, et al. (1959). This investigation evaluated

TABLE 4

Summary of Carcinogenicity Data in Rats*

Authors	Strain	Formulation Heptachlor (H); Epoxide (HE); Chlordane (C)	Concentrations (ppm) H	HE	C	Carcinogenicity Authors Conclusions	Carcinogenicity Independent Histological Re-evaluation	Comments
Kettering, 1955	CF	H of unspecified purity	1.5; 3.0; 5.0; 7.0; 10.0	-	-	Tumor incidence "proportionately" distributed in all tests 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; 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 tota tumor-bearing animalsl 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 methodolog cally unsound; femaleirats only tested. 2. Unacceptable as carcinogenicity test.

TABLE 4 (Continued)

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, 1977	Osborne-Mendel	Technical H; consisting of 74% H and ca 26% alpha C	Males 38.9; 77.9. Females 25.7; 51.3	-	-	Carcinogenic under conditions of assay**	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.

* Source: Epstein, 1976

**The conclusions of NCI state that there is no clear evidence of carcinogenic effect of heptachlor.

TABLE 5

Summary of Carcinogenicity Data in Mice*

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 HE	H and HE both hepatocarcinogenic	1. FDA data poorly documented. 2. FDA data statistically significant for tumor incidences. 3. Histological re-evaluation demonstrated hepatocarcinogenicity. 4. Hepatocarcinogenic effects statistically significant.
IRDC, 1973	CD-1	Mixture of 25% H and 75%	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, 1977	B6C3F1	Technical H; consisting of 74% H, and ca, 26%C	Males 6.1; - 13.8 Females 9.0; 18		-	Carcinogenic under conditions of assay	Not undertaken	1. Relatively small number negative controls non-concurrent experiments; uncertainties in dosage. 2. Revised data statistically significant for hepatocarcinogenicity.

*Source: Epstein, 1976

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 group consisted of 25 males and 25 females. Mortality in males ranged from 32 percent for the controls to 52 percent at 2.5 mg/kg of diet, and in the females ranged from 24 percent in controls to 52 percent at 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 the earliest tumor was discovered during the 13th month and 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 acknowledged 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 $p = 0.55$ probability level.

Re-evaluation of tissue slides by Dr. Melvin D. Reuber of a 1959 unpublished Kettering study 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 indicated

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 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 the lesions were found in both control and treated groups. The lesions of the pituitary and adrenal glands were considered hypertrophies rather than neoplasms. The lesions of the mammary gland were diagnosed as adenomas or fibro-

adenomas 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 which were 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 and 21 controls had malignant tumors; heptachlor-treated mice had 51 benign tumors and 10 malignant tumors; heptachlor epoxide treated mice had 85 benign tumors and 13 malignant tumors. Statistics were not performed 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 of 87 male mice (74 percent) and 57 of 78 female mice (73 percent) ingesting heptachlor; in 73 of 79 male mice (92 percent) and 77 of 81 female mice (95 percent) ingesting heptachlor epoxide; and in 22 of 73 control male mice (30 percent) and in 2 of 53 control female mice (4 percent) (Reuber, 1977b). 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 hepatic 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. Hepta-

chlor 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 Cabral, et al. (1972) study does show a statistically significant incidence of endocrine tumors in males.

In 1973, the IRDC completed an unpublished 18-month study using CD-1 mice on a treatment diet containing a 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 six 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-acetamidifluorene, 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 that though both IRDC and Reuber diagnosed a similar number of carcinomas in the positive controls, the discrepancies in the 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 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 NCI released a preliminary report on the Gulf South Research Institute study on heptachlor in 1975. These preliminary findings were 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 $B6C3F_1$ 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 consisted 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 at 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.

Epidemiological studies conducted to date have uncovered no evidence of increased cancer mortality among workers occupation-

ally exposed in the manufacture of chlordane and heptachlor (Shindell, 1977; Wang and MacMahon, 1979a,b). Wang and MacMahon (1979a) investigated mortalities in a cohort of professional pesticide applicators. There were 311 deaths between 1967 and 1976 in the population of 16,126 males, giving a standard mortality rate (SMR) of 84. SMRs for cancers of the lung, liver and bladder did not differ significantly from 100 at the 95 percent confidence level. In fact, SMRs for termite control operators, exposed routinely to heptachlor and chlordane, were somehwat lower than SMRs for general pesticide operators, who received much less exposure to heptachlor and chlordane.

Wang and MacMahon (1979b) reported on 1,403 white male workers who were employed for at least three months in the manufacture of chlordane and heptachlor in two U.S. plants between 1946 and 1976. Their study observed 113 deaths from the study group, compared to 157 expected, giving a standardized mortality ratio of 72. They also observed no overall excess of deaths from cancer, even in workers followed for 20 or more years from entry into the occupation. A small nonsignificant increase in lung cancer deaths was seen (12 observed, 9.0 expected), which was not distributed by duration of exposure or latency in any pattern suggesting an etiologic role. Unfortunately, cigarette smoking data were not available for this exposed population. The Wang and MacMahon (1979b) data would indicate that chlordane and heptachlor do not increase the cancer mortality among these workers, but the

authors express that "the study population is too small and the period of followup too short to translate this into a statement that there is no excess risk of cancer associated with exposure in man."

CRITERION FORMULATION

Existing Guidelines and Standards

Source	Published Standard	Reference
Occup. Safety Health Admin.	500 µg/m^3*	Natl. Inst. Occup. Safety Health, 1977
Am. Conf. Gov. Ind. Hyg.	500 µg/m^3 inhaled (TLV)	Am. Conf. Gov. Ind. Hyg., 1971
Fed. Republic Germany	500 µg/m^3 inhaled	Winell, 1975
USSR	10 µg/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 at a mean concentration of 0.0063 µg/l (U.S. EPA, 1976) for those instances of detection. Food can be a significant factor in 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 to July 1975 for 20 different cities (Johnson and Manshe, 1977), 3 of 12 food classes contained residues of heptachlor epoxide ranging from trace amounts in the garden fruits class to 0.0006 to 0.003 ppm in the dairy products and the meats, fish, and poultry classes, respectively. A national study by the U.S. Department of Interior in 1967 to 1968 reported that heptachlor and/or heptachlor epoxide were found in 32 percent of the 590 fish samples examined (Henderson, et al. 1969), with whole fish residues from 0.01 to 8.33 mg/kg.

Nisbet (1977) calculated the typical human exposure to heptachlor to be 0.01 µg/individual/day, based on a mean ambient air concentration of 0.5 ng/m^3 and a respiratory volume of 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 have been reported for humans (Nisbet, 1977). Based on this research, 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 of Criteria

Heptachlor has been shown to exhibit numerous toxicological effects in animal systems. Heptachlor and its metabolites have 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 FDA, Cabral, et al. 1972, the IRDC, and the NCI. Heptachlor or its metabolites have induced hepatocellular carcinomas in three chronic feeding studies in mice 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 carcinogencity is sufficient to conclude that heptachlor is likely to be a human carcinogen. As

carcinogens are generally assumed to have a nonthreshold dose/response characteristic, the carcinogenic effect is the most significant exposure effect from which to estimate an ambient water quality criterion value. A linearized multistage model, as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document, is used in estimating human health risks associated with the ingestion of heptachlor. Using the described model, the concentration of heptachlor in water may be calculated from the incidence data for hepatocellular carcinomas in the NCI $B6C3F_1$ mouse study, by assuming an additional individual lifetime risk of 1/100,000, the daily ingestion of 2 liters of water and 6.5 grams of contaminated fish products, and a weighted average bioconcentration factor of 11,200.

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 6.5 grams fish and shellfish. (2)	0	0.028 ng/l	0.28 ng/l	2.78 ng/l
Consumption of fish and shellfish only	0	0.029 ng/l	0.29 ng/l	2.85 ng/l

(1) Calculated by applying a linearized multistage model as described above to the animal bioassay data presented in the Appendix. 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

(2) Ninety-seven percent of the heptachlor exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 11,200-fold. The remaining 3 percent of heptachlor exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various 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, these data will not be factored into ambient water quality criteria formulations until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

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APPENDIX

Derivation of Criterion for Heptachlor

Heptachlor fed to $B6C3F_1$ mice for nearly a lifetime induced hepatocellular carcinomas wtih high frequency in both sexes at two doses (NCI, 1977). The data for males and additional parameters, as shown below, were used to calculate the criterion:

Dose (mg/kg/day)	Incidence (# responding/# tested)
0.0	5/19
0.79	11/46
1.79	34/47

le = 546 days w = 0.036

Le = 630 days R = 11,200

L = 630 days

With these parameters the carcinogenic potency for humans, q_1^*, is 3.37 $(mg/kg/day)^{-1}$. The result is that the water concentration corresponding to a lifetime risk of 10^{-5} is 2.8 ng/l.

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