United States
Environmental Protection
Agency

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

EPA 440/5-80-027
October 1980

C. 2

EPA

Ambient Water Quality Criteria for Chlordane

AMBIENT WATER QUALITY CRITERIA FOR

CHLORDANE

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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

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CRITERIA DOCUMENT

CHLORDANE

CRITERIA

Aquatic Life

For chlordane the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0043 μg/l as a 24-hour average, and the concentration should not exceed 2.4 μg/l at any time.

For chlordane the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.0040 μg/l as a 24-hour average, and the concentration should not exceed 0.09 μg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure to chlordane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the nonthreshold 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 criteria are 4.6 ng/l, 0.46 ng/l, and 0.046 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 4.8 ng/l, 0.48 ng/l, and 0.048 ng/l, respectively.

INTRODUCTION

Chlordane is a broad spectrum insecticide of the group of polycyclic chlorinated hydrocarbons called cyclodiene insecticides. Chlordane has been used extensively over the past 30 years for termite control, as an insecticide for homes and gardens, and as a control for soil insects during the production of crops such as corn. Production of chlordane in the United States approached 10,000 metric tons per year in 1974 (41 FR 7558). Both the uses and the production volume of chlordane have decreased extensively since the issuance of a registration suspension notice for all food crops and home and garden uses of chlordane by the U.S. EPA (40 FR 34456). However, significant commercial use of chlordane for termite control continues. In addition, under the terms of a recent settlement which terminated chlordane registration cancellation proceedings, chlordane will be permitted for limited usage through 1980 as an agricultural insecticide (43 FR 12372).

Pure chlordane is a pale yellow liquid having the molecular formula $C_{10}H_6Cl_8$ and a molecular weight of 409.8 (Windholz, 1976; Whetstone, 1972). The chemical name for chlordane is 1,2,4,5,6,7,8,8-octachloro-2,3,-3a,4,7,7a-hexahydro-4,7-methanoindene (Windholz, 1976). Pure chlordane is composed of a mixture of stereoisomers, with the cis and trans forms predominating and referred to as alpha and gamma isomers, respectively (Brooks, 1974). Brooks (1974) reported the solubility of chlordane in water to be approximately 9 μg/l at 25°C.

Chlordane is produced by the chlorination of chlordene which, in turn, is a product of hexachlorocyclopentadiene and cyclopentadiene (Whetstone, 1972).

Technical grade chlordane is a mixture of various chlorinated hydrocarbons with a typical composition of approximately 24 percent trans(gamma)-chlordane, 19 percent cis(alpha)chlordane, 10 percent heptachlor, 21.5 percent chlordene isomers, 7 percent nonachlor, and 18.5 percent closely related chlorinated hydrocarbon compounds (Velsicol Chemical Corp., 1971). Technical chlordane is a viscous, amber-colored liquid with a cedar-like odor and is relatively nonvolatile, having a vapor pressure of 1×10^{-5} mm Hg at 25°C; it is soluble in water (150 to 220 μg/l at 22°C) and has a density greater than that of water, approximately 1.65 g/ml at 16°C (Metcalf, 1955; Whetstone, 1972; Cardwell, et al. 1977).

Chlordane has been detected at various concentrations in ambient water, finished drinking water, rainwater, and soils. Chlordane is readily soluble in natural fats and fat soluble substances (Brooks, 1974). Chlorane has been found in plankton, earthworms, shellfish, fish, birds, bird eggs, man, and several other mammals.

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Aquatic Life Toxicology*

INTRODUCTION

Although chlordane has been used as an insecticide for many years, our knowledge of its toxicity to aquatic life is less complete than for other chlorinated hydrocarbon insecticides such as DDT and dieldrin. Early freshwater studies (Henderson, et al. 1959; Katz, 1961) using static test procedures showed it to be substantially less toxic than endrin, dieldrin, DDT, and toxaphene. Perhaps as a result, few additional data appeared in the literature until the 1970's. Chronic data were published recently, but dealt with only a few species. Data for bioconcentration likewise is mostly of recent origin. The effect on aquatic plants is not well documented.

The chlordane data base for saltwater organisms is less than for freshwater organisms. The data are insufficient to determine the importance of salinity, temperature, or other water quality factors to the toxicity of this insecticide.

The toxicities of major chemicals in technical chlordane have not been studied, and relative toxicity of each chemical responsible for the effects of chlordane has not been identified.

EFFECTS

Acute Toxicity

Data from 25 tests on five freshwater invertebrate and nine fish species met Guideline requirements for inclusion in Table 1; these data are inadequate to show a general difference in susceptibility between freshwater fish

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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 understand this section better. The attached tables contain pertinent available data, and at the bottoms of the appropriate tables are calculations deriving vari- ous measures of toxicity as described in the Guidelines.

and invertebrate species. The susceptibility ranking in Table 3 appears to show the invertebrate species to be more sensitive, but the ranked location of the carp and Daphnia magna and the variation among tests on the same species (Table 1) offset any attempt to rank susceptibility by large taxonomic groups. The LC_{50} values of the tested aquatic animals range from 3 µg/l for carp to 190 µg/l for guppy; however, most species mean acute values lie between 15 and 60 µg/l (Table 3). The Freshwater Final Acute Value for chlordane, derived from the species mean acute values listed in Table 3 using the calculation procedure described in the Guidelines, is 2.4 µg/l.

Acute values for saltwater invertebrate species range from 0.4 to 480 µg/l (Tables 1 and 5). Blue crab, in a 48-hour test (Table 5), were over 1,000 times more tolerant than pink shrimp in a 96-hour test (Table 1). Adult Dungeness crabs were also tolerant of acute chlordane exposure, with an LC_{50} value of 220 µg/l (Caldwell, 1977), but Dungeness crab zoeae had a much lower LC_{50} of 1.3 µg/l (Table 1).

Five species of saltwater fishes have been tested for the acute effects of chlordane (Tables 1 and 5). In flow-through exposures, the 96-hour LC_{50} values for three species range from 6.4 to 24.5 µg/l (Korn and Earnest, 1974; Parrish, et al. 1976, 1978). Two LC_{50} values for threespine stickleback from static tests with unmeasured concentrations were 90 and 160 µg/l. The LC_{50} values for fish species differed by a factor of more than 25.

The minimum data base requirements for deriving a Saltwater Final Acute Value have not been met (96-hour LC_{50} values are available for four instead of the required five invertebrate families); however, data are available for eight species (four invertebrate and four fish species). Moreover, it is unlikely that the Saltwater Final Chronic Value (see Chronic

Toxicity section) would be significantly influenced by one more acute value for an invertebrate species. Accordingly, a Saltwater Final Acute Value for chlordane of 0.09 µg/l was derived from the species mean acute values listed in Table 3 using the procedure described in the Guidelines.

Chronic Toxicity

Freshwater chronic tests have been conducted by Cardwell, et al. (1977) on *Daphnia magna* and bluegill, providing chronic values for these species of 16 and 1.6 µg/l, respectively; acute-chronic ratios for these two species are 3.6 and 37, respectively (Table 2). The only other freshwater chronic tests reported were also conducted by Cardwell, et al. (1977) on fathead minnow, brook trout, *Hyallela azteca*, and *Chironomus* No. 51 (Table 5). The fathead minnow test produced no statistically significant difference at the highest concentration tested (6.03 µg/l). Reduced embryo viability was observed in brook trout during a 13-month exposure to 0.32 µg/l. Effects on the invertebrate species occurred at concentrations as low as 1.7 µg/l; this concentration caused mortality of chironomid larvae in a 25-day exposure (Table 5).

No reports of life-cycle chronic tests with any saltwater invertebrate species were found. In extended exposures of Dungeness crab zoeae and adults to chlordane (Caldwell, 1977), 0.15 µg/l affected moulting and was lethal to 50 percent after 37 days of exposure. Survival and moulting were unaffected in chlordane concentrations of 0.015 µg/l. Most adult crabs died after a 90-day continuous exposure to 10 µg/l, but survival in 1 µg/l did not differ from controls (Table 5).

Chlordane was chronically toxic to the saltwater sheepshead minnow (Table 2) in a full life-cycle exposure at concentrations $\geq$0.8 µg/l (Parrish, et al. 1978). Survival of juveniles was reduced at 18 µg/l, and their

survival through adulthood was reduced at 2.8 µg/l (Parrish, et al. 1978). Reproduction of exposed adults was not impaired, but hatching of embryos was decreased at 0.8 µg/l, and juvenile survival decreased at 1.7 µg/l. No significant effects were observed on survival, growth, or reproduction at a chlordane concentration of 0.5 µg/l. The concentration not affecting sheepshead minnows in this chronic exposure was 0.04 of the 96-hour LC_{50}. In an early-life-stage test on the same species, 17 µg/l was lethal to fry, but 7.1 µg/l was not (Parrish, et al. 1976). Usually, results of early-life-stage toxicity tests can be used to predict results of life-cycle tests. Chlordane, because of its effects on adult fish and their progeny, is an exception to this general relationship. Therefore, the results of the life-cycle test, rather than those of the early-life-stage test, should be used as a measure of chlordane's chronic toxicity to this saltwater fish species.

The Final Acute-Chronic Ratio for chlordane of 14 is the geometric mean of the three acute-chronic ratios (Tables 2 and 3). The Freshwater Final Acute Value of 2.4 µg/l divided by the Final Acute-Chronic Ratio of 14 results in the Freshwater Final Chronic Value for chlordane of 0.17 µg/l. The Saltwater Final Acute Value of 0.09 µg/l divided by the Final Acute-Chronic Ratio of 14 results in the Saltwater Final Chronic Value for chlordane of 0.0064 µg/l.

Plant Effects

Glooschenko and Lott (1977) found that 0.1 µg/l stimulated growth of a freshwater algal species (Table 5). No data are available showing other effects on freshwater plant species. Information on the sensitivity of saltwater aquatic plants, including algae and rooted vascular plants, is limited to one test using a 4-hour exposure of a mixed phytoplankton community (Table 5).

Residues

Table 4 contains bioconcentration data for a freshwater fish and an invertebrate species. For Hyallela azteca, Cardwell, et al. (1977) reported factors for each of seven major constituents of technical chlordane; the bioconcentration factor (BCF) of 5,200 for technical chlordane shown in Table 4 was obtained by multiplying the arithmetic mean of each constituent's BCF value by its percentage composition in technical chlordane, then adding the products of each constituent. A BCF of 3,800 for Daphnia magna (Cardwell, et al. 1977), shown in Table 5, was calculated in the same manner as the Hyallela azteca factor, but the datum was not included in Table 4 because of the short duration (7 days) of the exposure.

Whole-body BCF values for the saltwater fish species, sheepshead minnow, ranged from 6,600 to 16,000 (Table 4). Bioconcentration factors in juvenile fish ranged from 8,500 to 12,300 after 28 days of exposure to technical chlordane (Parrish, et al. 1976). Adult fish exposed to technical chlordane for 189 days had BCF values ranging from 13,000 to 22,000, and a 28-day-old progeny from the same experiment contained 6,500 to 22,000 times as much chlordane as was measured in the test solution (Parrish, et al. 1978). Sheepshead minnows exposed to technical heptachlor, which contains trans-chlordane, accumulated the trans-chlordane 2,000 to 11,700 times the concentration in water (Goodman, et al. 1978).

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 BCF. Percent lipid values are available for fathead minnows (Veith, 1980) and adult sheepshead minnows (Hansen, 1980). Dividing the percent lipid value of 7.6 for fathead minnows into the BCF of 37,800 gives a normalized BCF of 4,974. Dividing the percent lipid

value at 3.6 for sheepshead minnows into the BCF of 16,000 gives a normalized BCF of 4,444. The geometric mean of these normalized BCF values is 4,702 (Table 4).

To protect the marketability of edible fish, the concentration of chlordane in edible tissue cannot exceed the action level of 0.3 mg/kg established by the U.S. Food and Drug Administration (FDA) for chlordane. The Freshwater Final Residue Value is derived by dividing the FDA action level of 0.3 mg/kg by the geometric mean of the normalized BCF values (4,702) and by a percent lipid value of 15 for freshwater species (see Guidelines). The Freshwater Final Residue Value thus obtained is 0.0043 µg/l (Table 4). The Saltwater Final Residue Value (Table 4) is 0.0040 µg/l, obtained by dividing the FDA action level (0.3 mg/kg) by the geometric mean of normalized BCF values (4,702) and by a percent lipid value of 16 for saltwater species (see Guidelines). The Final Residue Value may be too high because, on the average, the concentration in 50 percent of species similar to those need to derive the values will exceed the FDA action level.

Miscellaneous

No other data from Table 5 suggest any more sensitive effects or greater accumulation of chlordane than those already discussed.

Summary

Acute toxicity of chlordane to freshwater fish and invertebrate species occurs at concentrations ranging from 3 to 190 µg/l, with most values falling between 15 and 60 µg/l. Freshwater chronic values are available for one fish (1.6 µg/l) and one invertebrate (16 µg/l) species. Bioconcentration factors of 37,800 and 5,200 are available for one freshwater fish and one invertebrate species, respectively. No appropriate data are available for chlordane and any freshwater plant species. The Freshwater Final Acute Val-

ue is 2.4 μg/l, the Freshwater Final Chronic Value is 0.17 μg/l, and the Freshwater Final Residue Value is 0.0043 μg/l based on the FDA action level for edible fish.

Acute toxicity of chlordane to saltwater fish and invertebrate species occurs at concentrations ranging from 0.4 to 480 μg/l, with the pink shrimp being the most sensitive species. A life-cycle chronic test on the sheepshead minnow provided a chronic value for this species of 0.63 μg/l. No chronic data are available for chlordane and any saltwater invertebrate species, and no appropriate data are available for any saltwater plant species. Bioconcentration factors for chlordane in the sheepshead minnow ranged from 6,600 to 16,000. The data base for acute toxicity of chlordane to saltwater species lacks one invertebrate family to fulfill the minimum data base requirements according to the Guidelines. However, because acute data are available for eight species and because it is unlikely that the Saltwater Final Chronic Value would be significantly influenced by one more acute value for an invertebrae species, a Saltwater Final Acute Value was derived for chlordane and was calculated to be 0.09 μg/l. The Saltwater Final Chronic Value is 0.0064 μg/l, and the Saltwater Final Residue value is 0.0040 μg/l based on the FDA action level for edible fish.

It should be noted that the Final Residue Values may be too high because, on the average the concentration in 50 percent of species similar to those used to derive the values will exceed the FDA action level.

CRITERIA

For chlordane the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0043 μg/l as a 24-hour average, and the concentration should not exceed 2.4 μg/l at any time.

For chlordane the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.0040 µg/l as a 24-hour average, and the concentration should not exceed 0.09 µg/l at any time.

Table 1. Acute values for chlordane

Species	Method*	Chemical**	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, M	Technical chlordane	35	-	U.S. EPA, 1980
Cladoceran, *Daphnia magna*	S, U	Technical chlordane	97	58	Randall, et al. 1979
Scud, *Gammarus fasciatus*	S, U	Technical chlordane	40	40	Sanders, 1972
Scud, *Gammarus lacustris*	S, U	Technical chlordane	26	26	Sanders, 1969
Freshwater shrimp, *Palaemonetes kadiakensis*	S, U	Technical chlordane	10	-	Sanders, 1972
Freshwater shrimp, *Palaemonetes kadiakensis*	FT, U	Technical chlordane	4	6.3	Sanders, 1972
Stonefly, *Pteronarcys californica*	S, U	Technical chlordane	15	15	Sanders & Cope, 1968
Coho salmon (age 0), *Oncorhynchus kisutch*	S, U	Chlordane 100% A.I.	56	56	Katz, 1961
Chinook salmon (age 0), *Oncorhynchus tshawytscha*	S, U	Chlordane 100% A.I.	57	57	Katz, 1961
Rainbow trout (age 0), *Salmo gairdneri*	S, U	Chlordane 100% A.I.	44	-	Katz, 1961
Rainbow trout, *Salmo gairdneri*	S, U	Technical chlordane	47	-	Mehrle, et al. 1974
Rainbow trout, *Salmo gairdneri*	S, U	Technical chlordane	8	25	Mehrle, et al. 1974
Brook trout (adult), *Salvelinus fontinalis*	FT, M	Technical chlordane	45	45	Cardwell, et al. 1977
Goldfish, *Carassius auratus*	S, U	Chlordane 100% A.I.	82	82	Henderson, et al. 1959

Table 1. (Continued)

Species	Method*	Chemical**	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Carp, *Cyprinus carpio*	S, U	Chlordane 75% E.C.	3	3	Rao, et al. 1975
Fathead minnow, *Pimephales promelas*	S, U	Chlordane 100% A.I.	52	-	Henderson, et al. 1959
Fathead minnow, *Pimephales promelas*	S, U	Chlordane 100% A.I.	69	-	Henderson, et al. 1959
Fathead minnow (juvenile), *Pimephales promelas*	FT, M	Technical chlordane	37	37	Cardwell, et al. 1977
Guppy, *Poecilia reticulata*	S, U	Chlordane 100% A.I.	190	190	Henderson, et al. 1959
Bluegill, *Lepomis macrochirus*	S, U	Chlordane 100% A.I.	22	-	Henderson, et al. 1959
Bluegill, *Lepomis macrochirus*	S, U	Technical chlordane	77	-	Macek, et al. 1969
Bluegill, *Lepomis macrochirus*	S, U	Technical chlordane	77	-	Macek, et al. 1969
Bluegill, *Lepomis macrochirus*	S, U	Technical chlordane	85	-	Macek, et al. 1969
Bluegill, *Lepomis macrochirus*	FT, M	Technical chlordane	59	-	Cardwell, et al. 1977
Bluegill, *Lepomis macrochirus*	S, U	Technical chlordane	41	59	Randall, et al. 1979
		SALTWATER SPECIES			
Eastern oyster, *Crassostrea virginica*	FT, U	-	7	-	Butler, 1963
Eastern oyster, *Crassostrea virginica*	FT, U	-	10	-	Butler, 1963

Table 1. (Continued)

Species	Method*	Chemical**	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Eastern oyster, *Crassostrea virginica*	FT, M	-	6.2	6.2	Parrish, et al. 1976
Pink shrimp, *Penaeus duorarum*	FT, M	-	0.4	0.4	Parrish, et al. 1976
Grass shrimp, *Palaemonetes pugio*	FT, M	-	4.8	4.8	Parrish, et al. 1976
Dungeness crab (zoeae), *Cancer magister*	S, U	-	1.3	-	Caldwell, 1977
Dungeness crab (adult), *Cancer magister*	S, U	-	220	16.9	Caldwell, 1977
Sheepshead minnow, *Cyprinodon variegatus*	FT, M	-	24.5	-	Parrish, et al. 1976
Sheepshead minnow, *Cyprinodon variegatus*	FT, M	-	12.5	17.5	Parrish, et al. 1978
Threespine stickleback (adult), *Gasterosteus aculeatus*	S, U	-	90	-	Katz, 1961
Threespine stickleback (adult), *Gasterosteus aculeatus*	S, U	-	160	120	Katz, 1961
Striped bass, *Morone saxatilis*	FT, U	-	11.8	11.8	Korn & Earnest, 1974
Pinfish, *Lagodon rhomboides*	FT, M	-	6.4	6.4	Parrish, et al. 1976

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

**A.I. = active ingredient, E.C. = effective concentration

Table 2. Chronic values for chlordane

Species	Test*	Chemical	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	LC	Technical chlordane	12.1-21.6	16	Cardwell, et al. 1977
Bluegill, *Lepomis macrochirus*	LC	Technical chlordane	1.22-2.20	1.6	Cardwell, et al. 1977
		SALTWATER SPECIES			
Sheepshead minnow, *Cyprinodon variegatus*	ELS	Chlordane	7.1-17	11	Parrish, et al. 1976
Sheepshead minnow, *Cyprinodon variegatus*	LC	Chlordane	0.5-0.8	0.63	Parrish, et al. 1978

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

Acute-Chronic Ratios

Species	Chemical	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Cladoceran, *Daphnia magna*	Technical chlordane	58	16	3.6
Bluegill, *Lepomis macrochirus*	Technical chlordane	59	1.6	37
Sheepshead minnow, *Cyprinodon variegatus*	Chlordane	12.5	0.63	20

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

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	FRESHWATER SPECIES		
14	Guppy, *Poecilia reticulata*	190	-
13	Goldfish, *Carassius auratus*	82	-
12	Bluegill, *Lepomis macrochirus*	59	37
11	Cladoceran, *Daphnia magna*	58	3.6
10	Chinook salmon, *Oncorhynchus tshawytscha*	57	-
9	Coho salmon, *Oncorhynchus kisutch*	56	-
8	Brook trout, *Salvelinus fontinalis*	45	-
7	Scud, *Gammarus fasciatus*	40	-
6	Fathead minnow, *Pimephales promelas*	37	-
5	Scud, *Gammarus lacustris*	26	-
4	Rainbow trout, *Salmo gairdneri*	25	-
3	Stonefly, *Pteronarcys californica*	15	-
2	Freshwater shrimp, *Palaemontes kadiakensis*	6.3	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
1	Carp, *Cyprinus carpio*	3	-
	SALTWATER SPECIES		
8	Threespine stickleback, *Gasterosteus aculeatus*	120	-
7	Sheepshead minnow, *Cyprinodon variegatus*	17.5	20
6	Dungeness crab, *Cancer magister*	16.9	-
5	Striped bass, *Morone saxatilis*	11.8	-
4	Pinfish, *Lagodon rhomboides*	6.4	-
3	Eastern oyster, *Crassostrea virginica*	6.2	-
2	Grass shrimp, *Palaemonetes pugio*	4.8	-
1	Pink shrimp, *Penaeus duorarum*	0.4	-

Table 3. (Continued)

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

Final Acute-Chronic Ratio = 14

Freshwater Final Acute Value = 2.4 µg/l

Freshwater Final Chronic Value = 2.4 µg/l ÷ 14 = 0.17 µg/l

Saltwater Final Acute Value = 0.09 µg/l

Saltwater Final Chronic Value = 0.09 µg/l ÷ 14 = 0.0064 µg/l

Table 4. Residues for chlordane

Species	Tissue	Lipid (%)	Chemical	Bioconcentration Factor	Duration (days)	Reference
			FRESHWATER SPECIES			
Scud, *Hyallela azteca*	Whole body	-	Technical chlordane	5,200*	65	Cardwell, et al. 1977
Fathead minnow, *Pimephales promelas*	Whole body	7.6**	Technical chlordane	37,800	32	Veith, et al. 1979
			SALTWATER SPECIES			
Sheepshead minnow (juvenile), *Cyprinodon variegatus*	Whole body	-	Technical chlordane	10,300	28	Parrish, et al. 1976
Sheepshead minnow (adult), *Cyprinodon variegatus*	Whole body	3.6***	Technical chlordane	16,000	189	Parrish, et al. 1978
Sheepshead minnow (juvenile), *Cyprinodon variegatus*	Whole body	-	Technical chlordane	15,300	28	Parrish, et al. 1978
Sheepshead minnow (juvenile), *Cyprinodon variegatus*	Whole body	-	trans-Chlordane	6,600	28	Goodman, et al. 1978

* Adjusted for wet weight. Total of the seven predominant constituents. Each constituent's bioconcentration adjusted for its percent composition in technical chlordane.

** Percent lipid data from Veith, 1980.

***Percent lipid data from Hansen, 1980.

Maximum Permissible Tissue Concentration

Action Level	Concentration (mg/kg)	Reference
Fish	0.3	U.S. FDA Guideline 7420.08, 1979

Table 4. (Continued)

Geometric mean of normalized bioconcentration factors = 4,702

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

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

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

Freshwater: $\frac{0.3}{4{,}702 \times 15}$ = 0.0000043 mg/kg = 0.0043 µg/l

Saltwater: $\frac{0.3}{4{,}702 \times 16}$ = 0.0000040 mg/kg = 0.0040 µg/l

Freshwater Final Residue Value = 0.0043 µg/l

Saltwater Final Residue Value = 0.0040 µg/l

Table 5. Other data for chlordane

Species	Chemical*	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Alga, *Scenedesmus quadricauda*	Technical chlordane	7 days	Stimulated cell division	0.1	Glooschenko & Lott, 1977
Cladoceran, *Daphnia magna*	Technical chlordane	96 hrs	LC50	28.4	Cardwell, et al. 1977
Cladoceran, *Daphnia magna*	Technical chlordane	7 days	Bioconcentration of chlordane = 3,800**	-	Cardwell, et al. 1977
Tubificid worm, *Tubifex tubifex*	Chlordane	24 hrs	LC50	10,000	Ludemann & Neumann, 1962
Tubificid worm, *Branchiura sowerbyi*	Technical chlordane	72 hrs	100% mortality	500	Naqvi, 1973
Scud, *Hyallela azteca*	Technical chlordane	168 hrs	LC50	97.1	Cardwell, et al. 1977
Scud, *Hyallela azteca*	Technical chlordane	65 days	Reduced growth and survival	11.5	Cardwell, et al. 1977
Freshwater shrimp, *Palaemonetes kadiakensis*	Technical chlordane	24 hrs	LC50	13.6	Naqvi & Ferguson, 1970
Freshwater shrimp, *Palaemonetes kadiakensis*	Technical chlordane	120 hrs	LC50	2.5	Sanders, 1972
Midge (larva), *Chironomus plumosus*	Chlordane	24 hrs	LC50	10	Ludemann & Neumann, 1962
Midge, *Chironomus* No. 51	Technical chlordane	25 days	Larval mortality	1.7	Cardwell, et al. 1977
Rainbow trout, *Salmo gairdneri*	Technical chlordane	5 hrs	Death or distress	100	Applegate, et al. 1957
Rainbow trout, *Salmo gairdneri*	Chlordane	24 hrs	LC100	1,000	Ludemann & Neumann, 1961

Table 5. (Continued)

Species	Chemical*	Duration	Effect	Result (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	Chlordane (emulsifiable concentrate, 75% A.I.)	24 hrs	60% mortality	250	Mayhew, 1955
Brook trout, *Salvelinus fontinalis*	Technical chlordane	13 mos	Reduced embryo viability	0.32	Cardwell, et al. 1977
Northern pike, *Esox lucius*	Chlordane	24 hrs	LC100	50	Ludemann & Neumann, 1961
Fathead minnow, *Pimephales promelas*	Technical chlordane	11 mos	Survival, growth, reproduction	>6.03	Cardwell, et al. 1977
Green sunfish, *Lepomis cyanellus*	Chlordane (emulsifiable concentrate, 75% A.I.)	<35 min	Avoidance	5,000	Summerfelt & Lewis, 1967
Channel catfish, *Ictalurus punctatus*	Chlordane	96 hrs	LD50	500	Clemens & Sneed, 1959
Carp (fry), *Cyprinus carpio*	Chlordane (emulsifiable concentrate, 72% A.I.)	91 hrs	Accelerated development	1.0	Malone & Blaylock, 1970
Carp, *Cyprinus carpio*	Chlordane	48 hrs	LC50	1,160	Ludemann & Neumann, 1960
Carp (fry), *Cyprinus carpio*	Chlordane (emulsifiable concentrate, 72% A.I.)	96 hrs	93.7% mortality	5,000	Malone & Blaylock, 1970
Largemouth bass, *Micropterus salmoides*	Chlordane 47.2% A.I.	33 hrs	Increased opercular rate	30	Morgan, 1975
Frog, *Bufo bufo*	Chlordane	24 hrs	LC50	2,000	Ludemann & Neumann, 1962

Table 5. (Continued)

Species	Chemical*	Duration	Effect	Result (µg/l)	Reference
		SALTWATER SPECIES			
Natural phytoplankton community	Chlordane	4 hrs	94% decrease in productivity	1,000	Butler, 1963
Eastern oyster, *Crassostrea virginica*	Chlordane	24 hrs	Growth affected	10	Butler, et al. 1960
Eastern oyster, *Crassostrea virginica*	Chlordane	96 hrs	Bioconcentration factor = 5,522	-	Parrish, et al. 1976
Brown shrimp, *Penaeus aztecus*	Chlordane	48 hrs	EC50	4.4	Butler, 1963
Pink shrimp, *Penaeus duorarum*	Chlordane	96 hrs	Bioconcentration factor = 4,564	-	Parrish, et al. 1976
Grass shrimp, *Palaemonetes pugio*	Chlordane	96 hrs	Bioconcentration factor = 2,117	-	Parrish, et al. 1976
Blue crab, *Callinectes sapidus*	Chlordane	48 hrs	EC50	480	Butler, 1963
Dungeness crab (zoeae), *Cancer magister*	Chlordane	96 hrs	LC50	>10	Caldwell, 1977
Dungeness crab, *Cancer magister*	Chlordane	>70 days	50% larval mortality in 37 days, retardation of molting	0.15	Caldwell, 1977
Dungeness crab, *Cancer magister*	Chlordane	>70 days	No effect	0.015	Caldwell, 1977
Dungeness crab, *Cancer magister*	Chlordane	90 days	Survival not affected	1	Caldwell, 1977
Sheepshead minnow, *Cyprinodon variegatus*	Chlordane	96 hrs	Bioconcentration factor = 15,250	-	Parrish, et al. 1976
Sheepshead minnow, *Cyprinodon variegatus*	Chlordane	96 hrs	Bioconcentration factor = 12,900	-	Schimmel, et al. 1976a

Table 5. (Continued)

Species	Chemical*	Duration	Effect	Result (µg/l)	Reference
Pinfish, *Lagodon rhomboides*	Chlordane	96 hrs	Bioconcentration factor = 6,227	-	Parrish, et al. 1976
Spot, *Leiostomus xanthurus*	Chlordane	96 hrs	Bioconcentration factor = 9,250	-	Schimmel, et al. 1976a
Spot, *Leiostomus xanthurus*	Chlordane	72 hrs	Bioconcentration factor = 4,600	-	Schimmel, et al. 1976b
White mullet, *Mugil curema*	Chlordane	48 hrs	LC50	5.5	Butler, 1963

* A.I. = active ingredient

**Adjusted for wet weight. Total of the seven predominant constituents. Each constituent's bioconcentration adjusted for its percent composition in technical chlordane.

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

The lowest detectable concentrations for a number of chemicals were reviewed, and it was concluded that the limit for chlordane is 1 µg/l for an analyst using standardized procedures, with 0.3 µg/l being the most sensitive detection level using more sophisticated techniques (Ballinger, personal communication). By using unusually large quantities of sample and concentration measures, the sensitivity may be increased.

A study of the persistence of technical chlordane in river water showed 85 percent remaining after eight weeks (Eichelberger and Lichtenberg, 1971). Of the major components of technical chlordane, cis- and trans-chlordane were completely stable over the 8-week period. All but two of the remaining components were at least partially changed.

Schafer, et al. (1969) examined over 500 grab samples from water supplies of the Mississippi and Missouri Rivers. Chlordane was detected in over 20 percent of the finished waters, with the maximum concentration being 8 µg/l. An extensive search of the literature and U.S. EPA reports generated from the Agency's analytical activities resulted in a list of organic compounds in drinking water of the United States (U.S. EPA, 1975). The highest concentration reported for chlordane did not exceed that reported by Schafer, et al. (1969). Chlordane has also been detected in rainwater (Bevenue, et al. 1972; 41 FR 7552).

Although reports occasionally are received of individual household wells becoming contaminated after a house is treated with chlordane for termite control, only one report has been published of the contamination of a municipal water system (Harrington, et al. 1978). On March 24, 1976 a section of the public water system supplying 105 persons in Chattanooga, Tenn. became contaminated. Back siphonage apparently occurred while diluting a chlordane concentrate with a hose during a period of negative pressure. Of the 71 residents affected, 13 had symptoms of mild acute chlordane toxicity. None of the residents has had prolonged sequelae from the exposure.

Ingestion from Food

The Food and Drug Administration (FDA) has been systematically monitoring chlordane in the food supply of the United States since 1965. Chlordane has been found infrequently during the 11 years of survey (Nisbet, 1976). The only quantifiable sample collected was 0.059 mg/kg measured in a sample of grain in 1972 (Manske and Johnson, 1975). In the most recent published results chlordane was not detected, even in trace amounts (Johnson and Manske, 1977). Nisbet (1976) discussed the problems of compositing and analytical methods. Residues of technical chlordane are multi-component, so that the practical detection limit is several times higher than the 0.003 mg/kg stated for single components. Using data from FDA and others, Nisbet calculated an average chlordane intake from fish of 1 μg/day and concluded that fish represent the most significant dietary exposure to chlordane.

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 seems 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 was 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.

Two laboratory studies, in which percentage of lipids and a steady-state BCF were measured, have been conducted on chlordane. The mean of the BCF values, after normalization to 1 percent lipids, is 4,707 (see Table 5 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 chlordane and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 14,100.

The National Academy of Sciences (NAS, 1977) in reviewing the results of Moore (1975) reported that of 200 samples of milk collected in Illinois during the period 1971-1973, 87 percent were positive for chlordane. The average concentration was 50 µg/l. Cyclodienes, such as chlordane, apparently are ingested with forage and tend to concentrate in lipids. Oxychlordane, a major mammalian metabolite of chlordane and heptachlor, was found in 46 percent of 57 human milk samples collected during 1973-1974 in Arkansas and Mississippi. The mean value was 5 µg/l and the maximum was 20 µg/l (Strassman and Kutz, 1977).

Inhalation

In a survey of the extent of atmospheric contamination by pesticides, air was sampled at nine localities representative of both urban and agricultural areas. At least one chlorinated pesticide was found at all locations, but chlordane was not found in any samples (Stanley, et al. 1971). In a larger survey summarized by Nisbet (1976), 2,479 samples were collected at 45 sites in 16 states. Chlordane was detected in only two samples, with concentrations of 84 and 204 ng/m^3.

Dermal

Chlordane can be absorbed through the skin and produce toxic effects (Gosselin, et al. 1976). Dermal exposure would be expected to occur only with occupational manufacture or use of the pesticide. Absorption can range from negligible to that producing acute effects, depending on the degree of exposure. For the general population, dermal exposure would be negligible. Persons using chlordane could have the pesticide persist on their skin for

long periods. In one study, hexane rinsings of the hands of a former pest control operator contained chlordane two years after his last known exposure (Kazen, et al. 1974).

PHARMACOKINETICS

Absorption

Cis- and trans-chlordane are the primary components of the insecticide. Both are stable when held under ambient conditions or mixed with the feed of experimental animals. A single oral dose of chlordane administered to rats resulted in approximately 6 percent absorption (Barnett and Dorough, 1974). Small daily doses result in greater absorption values approximating 10 to 15 percent. Feeding the pure cis- and trans-isomers separately indicates that the cis- isomer is more effectively eliminated from the rats than the trans-isomer. Although the difference is not extensive, the data indicate that in long-term exposure situations, trans-chlordane would contribute a relatively greater amount to the body burden of the exposed animal than would the cis-isomer.

Distribution

Barnett and Dorough (1974) also studied the distribution of chlordane and metabolites in rats using radioactive carbon. The levels of residues in the tissues were generally low, except in the fat. Levels of chlordane residues in the fat of the rats, after being fed 1, 5, and 25 mg/kg in their diet for 56 days, were approximately three times the concentration in the diet. Concentrations in the liver, kidney, brain, and muscle were 12, 10, 4, and 2 percent, respectively, of the concentration in the feed.

Once the chlordane was removed from the diet, all residues declined steadily for four weeks, at which time the concentrations were reduced approximately 60 percent. During the following four weeks, the residues declined only slightly. Treatment with trans-chlordane resulted in higher concentrations of residues in the tissues than did treatment with the cis-isomer.

Dorough and Hemken (1973) fed three levels of chlordane to cows for 60 days and tested the milk periodically. Milk levels of chlordane and the metabolite oxychlordane increased sharply the first week and more slowly thereafter. When chlordane was removed from the diet, the milk residues dropped rapidly during the week following termination of treatment and stabilized after two weeks.

Metabolism

Polen, et al. (1971) and Street and Blau (1972) found oxychlordane to be a mammalian metabolite of chlordane, and to persist in adipose tissue. Street and Blau (1972) observed that the toxicity of oxychlordane was greater than the parent compound. Barnett and Dorough (1974) tentatively identified several hydroxylated metabolites of chlordane in rat excreta in addition to oxychlordane and concluded that the metabolism of chlordane takes place via a series of oxidative enzyme reactions.

Tashiro and Matsumura (1977) attempted to isolate and positively identify the metabolic by-products of chlordane to establish the route of its metabolism. The major route of metabolism for both cis- and trans-chlordane is via dichlorochlordene and oxychlordane. These metabolic intermediates are further converted

to two key metabolites, 1-exo-hydroxy-2-chlorochlordene and 1-exo-hydroxy-2-endo-chloro-2,3-exo-epoxychlordene, which are readily degraded further. Trans-chlordane is more readily metabolized through this route.

There is yet another major metabolic route for cis-chlordane which involves more direct hydroxylation reactions to form 1-exo-hydroxydihydrochlordenes and 1,2-trans-dihydroxydihydrochlordene. Cis-chlordane is more readily degraded through this latter route. As judged by a toxicity test on mosquito larvae, none of the metabolic end products appear to be more toxic than the original chlordanes or the intermediates.

Excretion

Most chlordane is excreted in the feces of rats. Only about 6 percent of the total intake is voided in the urine. Rabbits, however, provide a different pattern. Urinary elimination of chlordane in rabbits is greater than excretion in the feces. Nye and Dorough (1976) suggest that the conjugative metabolism system is more efficient in rabbits than in rats. The patterns of excretion following inhalation of chlordane by rats follow the patterns reported for oral administration (Nye and Dorough, 1976).

Human half-life data were obtained when chlordane was accidently ingested by a young boy (Curley and Garrettson, 1969). A whole body value of 21 days was calculated, which is long compared to drugs used in therapy, but quite short when compared to other chlorinated insecticides. This compares to a half-life of about 23 days obtained by Barnett and Dorough (1974) in studies with rats fed chlordane for 56 days. After the levels reached 60 per-

cent, further reduction was slight. Serum half-life of chlordane in a young girl was found to be 88 days by Aldrich and Holmes (1969).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Human toxicity data for chlordane usually is obtained after accidental exposure to the compound. Curley and Garrettson (1969) reported that shortly after a 20-month-old boy accidently drank an unknown amount of chlordane, he vomited and began a series of convulsions lasting 3 to 5 minutes each. After being given 14 mg/kg body weight phenobarbital, the seizures stopped. Body temperature rose to 102°F and then gradually decreased to normal. At no time was there evidence of pulmonary disease. Neurological examination at the time seizures were occurring revealed brisk deep tendon reflexes in all extremities. Cranial nerve function was intact and nystagmus was absent. An EEG taken 48 hours after exposure was normal. Three months after exposure, all tests appeared normal. Similar cases were reported by Dadey and Krammer (1953) and Aldrich and Holmes (1969). Barnes (1967) reported that intermittent dermal exposure of a nursery worker to chlordane as a soil insecticide produced symptoms including repeated seizures, electroencephalographic dysrhythmia, convulsions, and twitching. After cessation of contact with chlordane, all symptoms disappeared.

Purified chlordane at a concentration of 100 μg/l was reported to induce cytotoxic effects in human HeLa cell cultures by inhibiting growth and altering cell morphology (Gabliks, 1965).

A number of studies have been conducted to determine chlordane LD_{50} values for laboratory animals. Claude, et al. (1976) reported the oral LD_{50} of chlordane to be 350 mg/kg in rats, 390 mg/kg in mice, and 1,720 mg/kg in hamsters. Studies by Harbison (1975) showed the intraperitoneal LD_{50} of analytical chlordane to be 343 mg/kg for the adult rat, 1,121 mg/kg for newborn rats, and 539 mg/kg for newborn rats pretreated with 40 mg/kg sodium phenobarbital. Ben-Dyke, et al. (1970) reported an oral LD_{50} value of 283 mg technical grade chlordane/kg body weight for the rat. Ambrose, et al. (1953) reported a chlordane oral LD_{50} value of 590 mg/kg for the rat. Daily oral doses of 25 mg/kg or less for 15 days produced no toxic symptoms.

A review of the literature by the National Institute for Occupational Safety and Health (NIOSH, 1976) indicated a range of chlordane LD_{50} values from 100 mg/kg for rabbits with oral administration to 700 mg/kg for rats with dermal administration. Gaines (1960) reported technical grade chlordane oral LD_{50} values of 335 mg/kg for male rats and 430 mg/kg for females and a dermal LD_{50} of 530 mg/kg for the female rat. The National Academy of Sciences (1977) reported dermal LD_{50} values of 840 and 690 mg/kg for male and female rats, respectively. Chlordane fed to rats at 2.5 mg/kg in the diet caused slight liver damage.

Wazeter, et al. (1968) reported acute oral LD_{50} values of 392 mg/kg, 327 mg/kg, and 371 mg/kg for cis(alpha)chlordane, trans(gamma)chlordane, and an equal mixture of the two isomers, respectively, in the male rat. Thus, the data indicate that technical grade chlordane and the individual purified chlordane iso-

mers exhibit approximately equal toxicity. Boyd and Taylor (1969) observed that chlordane toxicity is increased in rats fed low protein diets. Oral LD_{50} values for reference grade technical chlordane ranged from 137 mg/kg for rats fed a low protein diet, to 311 mg/kg for rats fed a normal protein diet.

Mice receiving 0.075 and 0.15 mg of cis- or trans-chlordane on days 2, 3, and 4 of life exhibited a delay in general maturation (Talamantes and Jang, 1977). Chlordane administered at 25 to 75 mg/kg in the Indian desert gerbil produced hyperglycemia and lowered the glucose tolerance, indicating an impairment in the uptake and utilization of glucose (Saxena and Karel, 1976). Repeated doses of 2.5 mg/kg chlordane to these animals produced changes in serum proteins, blood glucose, and alkaline and acid phosphatase activity (Karel and Saxena, 1976). The no-effect level, as indicated by induction of microsomal liver enzymes in male rats receiving chlordane in their diets over two weeks, was 5 mg/kg (Den Tonkelaar and Van Esch, 1974).

Hyde and Falkenberg (1976) studied neuroelectrical disturbances in rats as a result of injections of chlordane. Intraperitoneal injection of 350 mg/kg resulted in mild tremors and disorientation within a few minutes and death in one hour. Daily injection of 0.15, 1.75, and 25 mg/kg in adult rats resulted in dose-dependent alterations of brain potentials without behavioral signs of chronic toxicity. Changes were directly related to length of exposure, indicating that chlordane may be a cumulative neurotoxin.

Mammalian metabolism of the chlordane isomers results in the formation of the toxic metabolite oxychlordane (Street and Blau, 1972; Barnett and Dorough, 1974). Oxychlordane has been demonstrated to be approximately 20 times more toxic than the parent compound, with an acute oral LD_{50} value of approximately 19 mg/kg in male and female rats (Mastri, et al. 1969). Furthermore, oxychlordane has been demonstrated to be the most persistent metabolite stored in rat adipose tissue (Street and Blau, 1972). The other products of chlordane isomer metabolism in rats are much less toxic (Mastri, et al. 1969).

Synergism and/or Antagonism

Histologic slides prepared from rats pretreated with 25 mg/kg chlordane and then injected with 0.5 ml of a 25 percent solution of carbon tetrachloride in olive oil, revealed more extensive hepatocellular necrosis in the chlordane-pretreated rats than was found in the carbon tetrachloride treatment alone (Stenger, et al. 1975).

Ludke (1976) found that quail, treated with chlordane followed by endrin, had considerably more chlordane residues in their brains than did birds treated with chlordane alone, suggesting an increased uptake of chlordane in brains of birds post-treated with endrin. Quail pretreated with 10 mg/kg chlordane exhibited decreased susceptibility (antagonism) to parathion but not to paraoxon dosage, as measured by cholinesterase activity (Ludke, 1977).

Teratogenicity

Chlordane was found not to be teratogenic in rats when fed at concentrations of 150 to 300 mg/kg in the diet during pregnancy (Ingle, 1952).

Mutagenicity

Arnold, et al. (1977) administered chlordane to Charles River CD-1 male mice in a single dose of 50 or 100 mg/kg. The males were subsequently mated with untreated female mice. No dominant lethal changes were produced. Studies by Ahmed, et al. (1977) with the SV-40 transformed human fibroblast cell line VA-4 showed that chlordane induced unscheduled DNA synthesis, indicating that chlordane is a potential genotoxic agent. Metabolic activation eliminated the induction of unscheduled DNA synthesis. Simmon, et al. (1977) found that neither pure cis-chlordane nor trans-chlordane were mutagenic in the Ames *Salmonella* microsome assay. Technical grade chlordane, however, was found to be mutagenic in *Salmonella typhimurium* strains TA 1535, TA 98 and TA 100. An S-9 liver activation mix did not enhance the mutagenic activity.

Carcinogenicity

A retrospective epidemiological study of 1,403 workers employed in the manufacture of chlordane and heptachlor showed no statistically significant excess cancer mortality (Wang and MacMahon, 1979a). Cancer of the lung was the only tumor type found in excess of expected values, and the excess was not associated with duration of exposure or latency in such a way as to suggest an etiologic relationship between the lung cancer and occupational exposure to heptachlor and chlordane. It should be noted that

the authors considered the study population size too small and the period of follow-up too short to translate these negative findings into a statement that there is not excess risk of cancer associated with heptachlor and chlordane exposure in man (Wang and MacMahon, 1979a).

In their study of manufacturing workers, Wang and MacMahon (1979a) did note a substantial and statistically significant excess of deaths due to cerebrovascular disease. This excess was not seen, however, in their prospective epidemiological study of 16,126 pesticide applicators Wang and MacMahon (1979b). This cohort included "termite control operators" (TCOs) who would be expected to have had exposures to chlordane and heptachlor in excess of the general population. Although TCOs showed no statistically significant excess of cancer relative to expected values, Wang and MacMahon (1979b) noted that their study was limited as it related to cancer experience, since relatively few workers had substantial work experience and could be followed for long periods after first employment.

A dose-dependent incidence of hepatocellular carcinoma in male and female strain B6C3F1 mice fed diets containing analytical grade chlordane was reported by the National Cancer Institute (NCI, 1977), and the results of their investigation are summarized in Table 1. This bioassay of chlordane for possible carcinogenicity was conducted by Gulf South Research Institute under contract to the National Cancer Institute. The batch tested contained 71.7 percent cis-chlordane, 23.1 percent trans-chlordane, 0.3 percent

TABLE 1

Liver Carcinomas in Mice Associated With the Oral Feeding of Chlordane

	% Positive (No. Tested)[1]		% Positive (No. Tested)[2]	
Dose (ppm)	Male	Female	Male	Female
63.8		69(49)		
56.2	88(49)			
50			82(39)	70(37)
30.1		6(47)		
29.9	33(48)			
25			79(52)	64(50)
5			9(55)	0(61)
0(controls)	11(18)	0(19)	9(33)	0(45)
0(controls)[3]	18(92)	4(78)		

(1) National Cancer Institute, 1977
(2) Epstein, 1976
(3) Pooled controls consisted of matched controls combined with other untreated mice.

heptachlor, 0.6 percent nonachlor, 1.1 percent hexachlorocyclopentadiene, 0.25 percent chlordene isomers, and 2.95 percent unspecified chlorinated compounds. The material was incorporated into the feed of B6C3F1 hybrid mice.

Groups of 50 mice of each sex at 35 days of age were administered the test material at two concentrations for 80 weeks and then observed for 10 weeks. Matched controls were used during the tests. Since similar bioassays were conducted on five other compounds, the results were also given for the pooled controls. Hepatocellular carcinoma showed a highly significant dose-related trend for the mice. Male mice fed a time-weighted average concentration of 56.2 mg/kg chlordane in the diet for 80 weeks exhibited an 87.8 percent (43/49) incidence of liver tumors, compared with an 11.1 percent (2/18) incidence in matched male controls and an 18.5 percent (17/92) incidence in pooled male controls from other experiments. In the same investigation, males fed a time-weighted average concentration of 29.9 mg/kg chlordane in the diet for 80 weeks exhibited a 33.3 percent (16/48) incidence of liver tumors. Female mice fed a time-weighted average concentration of 63.8 mg/kg chlordane in the diet for 80 weeks exhibited a 69.4 percent (34/49) incidence of liver tumors, as compared with a 0 percent (0/19) incidence in matched female controls and a 3.8 percent (3/78) incidence in pooled female controls from other experiments. Female mice fed a time-weighted average concentration of 30.1 mg/kg chlordane in the diet for 80 weeks exhibited a 6.4 percent (3/47) incidence of liver tumors.

Similar studies were conducted by Gulf South with analytical grade chlordane, using Osborne-Mendel strain rats. Groups of 50 rats of each sex were administered low or high concentrations for 80 weeks and then observed for 29 weeks. Time-weighted average doses used for the male rats were 203.5 and 407.0 mg/kg, while the female rats received 120.8 and 241.5 mg/kg. The effects of chlordane on body weights and other clinical signs indicated that the dosages used were near the maximum permissible. In contrast to findings with mice, hepatocellular carcinomas failed to appear at a significant rate of incidence in rats administered chlordane. Further, the number of lesions of the liver in rats did not become significant with the inclusion of nodular neoplasia or with the application of life-table adjustment to the data.

In another bioassay, the International Research and Development Corp. (IRDC), using Analytical Reference Standard Chlordane (Technical), fed groups of 100 male and 100 female Charles River CD-1 mice dietary levels of 5, 25, and 50 mg/kg food. Feeding commenced at six weeks of age and continued for 18 months (Epstein, 1976). The IRDC report, reviewed by Epstein, made no inference and drew no conclusion regarding carcinogenicity, in spite of its conclusion that chlordane induced a statistically significant increase of nodular hyperplasias in the 25 and 50 mg/kg groups. The report also noted an increased incidence of hepatomas in the male 5 and 25 mg/kg groups. Epstein also reviewed the data of Reuber, who conducted a histological re-evaluation of the IRDC slides and found that most of the histological material designated by IRDC as nodules were in fact carcinomas of

the liver. Reuber's diagnoses were corroborated by three other independent pathologists and are summarized in the previous Table 1. Thus, chlordane was found to produce liver cancer in both sexes of two different strains of mice.

Becker and Sell (1979) recently reported an elevated incidence of hepatic alterations in C57BL/6N male mice that were given 25 and 50 ppm chlordane in their diet. (The chlordane used was greater than 90 percent heptachlor.) Both primary hepatocellular carcinomas and "benign proliferative lesions" were seen in the treated animals; animals receiving the control diet developed neither histological alterations of the liver nor gross tumors. The total absence of tumors in the controls was not surprising in view of the fact that the C57BL/6N mouse has been reported to demonstrate virtually no spontaneous tumors of the liver and to require substantial exposure to known carcinogens for the production of tumors (Becker and Sell, 1979). This observation was borne out by the findings of Becker and Sell upon dietary administration of 0.045 or 0.03 percent acetylaminofluorene (AAF) to the C57BL/6N mouse. While both primary hepatocellular carcinomas and benign proliferative lesions were seen with AAF, the incidence associated with this demonstrated animal carcinogen was relatively low; in fact, it was lower than the incidence associated with chlordane treatment.

CRITERION FORMULATION

Existing Guidelines and Standards

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) adopted a time-weighted average value of 0.5 mg/m^3 for chlordane based on inhalation exposure. The short-term exposure limit (15 minutes) was set at 2 mg/m^3.

An acceptable daily dose for man has been estimated to be 0.001 mg/kg body weight (Food Agric. Organ., 1968). Although a limit of 3 µg/l was originally suggested for chlordane under the proposed Interim Primary Drinking Water Standards (40 FR 11990), the final U.S. EPA regulations (40 FR 59566) did not include a limit in view of the cancellation proceedings under the Federal Insecticide, Fungicide, and Rodenticide Act (40 FR 59566). Canadian Drinking Water Standards (Dept. Natl. Health Welfare, 1968) list a tentative maximum permissible limit for chlordane of 3 µg/l, which is applicable to raw water supplies in Canada.

Current Levels of Exposure and Special Groups at Risk

Nisbet (1976) estimated total daily intake of chlordane from all possible sources by back-calculating from the level of oxychlordane stored in tissue. A value of 9 µg/day chlordane intake was obtained. Nisbet also identified highly exposed segments of the general population: children as a result of milk consumed; fishermen and their families because of the high consumption of fish and shellfish, especially freshwater fish; persons living downwind from treated fields; and persons living in houses treated with chlordane pesticide control agents.

Basis and Derivation of Criterion

Several approaches are available to estimate a criterion level for chlordane in ambient water. Using the Food and Agricultural Organization/World Health Organization (FAO/WHO) value of 0.001 mg/kg of body weight as the maximum daily human intake, and assuming an average body weight of 70 kg, the allowable intake would be 70 µg/day. Further, subtracting Nisbet's (1976) value of 9 µg as the daily intake from fish, shellfish, milk, inhalation, etc., and assuming that the contribution from drinking water is a negligible part of this value, the ambient water criterion becomes 61 µg/day. At 2 l/day consumption, the maximum allowable concentration would be 30 µg/l.

The proposed U.S. EPA drinking water regulations (40 FR 11990), the Canadian standards, and the National Technical Advisory Committee (Fed. Water Pollut. Control Admin., 1968) all suggest a chlordane limit of 3 µg/l for drinking water. The latter report specifically indicates that the water treatment process has little effect on chlordane.

Although there are limitations to the procedure, the industrial inhalation exposure limit of the American Conference of Governmental Industrial Hygienists (1977) may be converted to a limit for ingestion (Stokinger and Woodward, 1958). Assuming absorption via the GI tract for chlordane is one-fifth the absorption by inhalation:

$$\frac{0.5\ \text{mg}}{\text{m}^3} \times \frac{10\text{m}^3}{\text{workday}} \times \frac{5\ \text{day work week}}{7\ \text{day/wk}} \times \frac{1}{5} = 0.7\ \text{mg/day}.$$

Consumption of 2 liters of water daily and the consumption of 6.5 g of contaminated fish which have a bioconcentration factor of 14,100 result in a maximum permissible concentration of 7.5 µg/l for the ingested water.

The use of inhalation data assumes an 8-hour day, time-weighted average occupational exposure in the working place with workers inhaling the toxic substance throughout such a period. Exposures for the general population should be considerably less. Such worker-exposure inhalation standards are inappropriate for the general population, since they presume an exposure limited to an 8-hour day, an age bracket of the population that excludes the very young and the very old, and a healthy worker prior to exposure. Ingestion data is superior to inhalation data when the risks associated with the food and water of the water environment are being considered.

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." Chlordane is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of chlordane 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 chlordane corresponding to several incre-

mental 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 g fish and shellfish. (2)	0	0.046 ng/l	0.46 ng/l	4.6 ng/l
Consumption of fish and shellfish only.	0	0.048 ng/l	0.48 ng/l	4.8 ng/l

(1) Calculated by applying 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, to the animal bioassay data presented in Appendix and in Table 1. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to

the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Ninety-eight percent of the chlordane exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 14,100-fold. The remaining 2 percent of chlordane exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of chlordane (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding chlordane concentrations and (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding chlordane concentrations. Because data indicating other sources of chlordane exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

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APPENDIX

Derivation of Criterion for Chlordane

The IRDC lifetime study of chlordane in the diet of CD-1 mice resulted in liver carcinomas in males as shown below, according to Dr. Reuber's re-analysis of slides from the IRDC bioassay (Epstein, 1976). Using a fish bioconcentration factor of 14,100 the water concentration estimated to result in a lifetime risk of 10^{-5} is calculated from the linearized multistage model using the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0.0	3/33
0.65	5/55
3.25	41/52
6.5	32/39

le = 546 days w = 0.041 kg

Le = 546 days R = 14,100 l/kg

L = 546 days

With these parameters the carcinogenic potency factor for humans, q_1^*, is 1.6075 $(mg/kg/day)^{-1}$. The result is that the water concentration corresponding to a lifetime risk of 10^{-5} is 4.6 ng/l.

U S GOVERNMENT PRINTING OFFICE 1980 720-016/4374