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Criteria and Standards Division
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Ambient Water Quality Criteria for Toxaphene

AMBIENT WATER QUALITY CRITERIA FOR

TOXAPHENE

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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TOXAPHENE

CRITERIA

Aquatic Life

For toxaphene the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.013 µg/l as a 24-hour average, and the concentration should not exceed 1.6 µg/l at any time.

For saltwater aquatic life the concentration of toxaphene should not exceed 0.070 µg/l at any time. No data are available concerning the chronic toxicity of toxaphene to sensitive saltwater aquatic life.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of toxaphene 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 criteria are 7.1 ng/l, 0.71 ng/l, and 0.07 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, including consumption of water, the levels are 7.3 ng/l, 0.73 ng/l, and 0.07 ng/l, respectively.

INTRODUCTION

Toxaphene is a commercially produced, broad spectrum, chlorinated hydrocarbon pesticide consisting primarily of chlorinated camphene and a mixture of related compounds and isomers. It was introduced in the United States in 1948 as a contact insecticide under various trade names and is currently the most heavily used insecticide in the United States, having replaced many of the agricultural applications of DDT, for which registration has been cancelled. Annual production of toxaphene exceeds 100 million pounds, with primary usage in agricultural crop application, mainly cotton.

On May 25, 1977, the U.S. EPA issued a notice of rebuttable presumption against registration and continued registration of pesticide products containing toxaphene (42 FR 26860).

Toxaphene is a complex mixture of polychlorinated camphenes and bornanes with the typical empirical formula $C_{10}H_{10}C_{18}$ and an average molecular weight of 414. It is an amber, waxy solid with a mild terpene odor, a melting point range of 65 to 90°C, a vapor pressure 0.17 to 0.40 mm Hg at 25°C, and a density of 1.64 at 25°C (Brooks, 1974; Metcalf, 1966). Toxaphene has a solubility in water of approximately 0.4 to 3.0 mg/l and is readily soluble in relatively nonpolar solvents, with an octanol/water partition coefficient of 825 (Brooks, 1974; Edwards, 1973; Metcalf, 1966; Sanborn, et al. 1976). Paris, et al. (1977) reported a toxaphene partition coefficient value of 3,300. Gas chromatographic analysis suggests the presence of approximately 177 components in technical toxaphene (Holmstead, et al. 1974). Infrared absorptivity at 7.2 microns

aids in distinguishing toxaphene from other chlorinated terpene products such as strobane. Although tricyclene may accompany the camphene, the commercial mixture contains less than 5 percent of other terpenes.

Toxaphene is commercially produced by reacting camphene with chlorine in the presence of ultraviolet radiation and certain catalysts to yield chlorinated camphene with a chlorine content of 67 to 69 percent (Metcalf, 1966). The chlorine content of the commercial product is limited to this narrow range since the insecticidal activity peaks sharply at those percentage levels. Toxaphene is available in various formulations as an emulsifiable concentrate, wettable powder, or dust.

The commercial product is relatively stable but may dehydrochlorinate upon prolonged exposure to sunlight, alkali, or temperatures above 120^{o}C (Metcalf, 1966; Brooks, 1974).

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Aquatic Life Toxicology*

INTRODUCTION

Toxaphene has been used as an insecticide for many years. Its acute toxicity, particularly to fishes, prompted its use to control populations of undesirable fishes. Toxaphene is a mixture of numerous chlorinated terpenes, but which terpenes are most toxic to aquatic biota is unknown because they have not been tested individually.

The acute toxicity, persistence, and bioconcentration potential of toxaphene have been well documented. Chronic toxicity of toxaphene to freshwater and saltwater fish and invertebrate species has been documented only recently.

EFFECTS

Acute Toxicity

Available data for freshwater invertebrate species (Table 1) include 13 acute values for 11 species; six species represent rather different decapods and insects. There are toxicity data from only three tests using flow-through procedures. LC_{50} values range from 1.3 to 180 µg/l. The stonefly, Claassenia sabulosa, is the most sensitive species among those tested; the midge, Chironomous plumosus, is least sensitive.

As shown in Table 1, 57 acute toxicity values are available for 18 species of freshwater fishes. Nine of the 57 LC_{50} values are from flow-through tests, and the remainder are from static tests. Johnson and Julin (1980) showed that exposures of bluegill and channel catfish to toxaphene in

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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.

flow-through test systems did not produce an appreciable increase in toxicity values over static test systems; however, fathead minnows were three times more susceptible to toxaphene poisoning in the flow-through system. Channel catfish was the most sensitive species, with a 96-hour LC_{50} value of 0.8 µg/l, and goldfish was least sensitive, with a 96-hour LC_{50} value of 28 µg/l.

The Freshwater Final Acute Value for toxaphene, derived from the species mean acute values listed in Table 3 using the procedure described in the Guidelines, is 1.6 µg/l.

The 10 saltwater invertebrate species tested were highly disparate in species sensitivity to toxaphene (Table 1). Crustaceans varied greatly in species sensitivity. The blue crab was relatively insensitive; the 96-hour LC_{50} values range from 370 to 2,700 µg/l (McKenzie, 1970). Several life stages of the pink shrimp were nearly identical in sensitivity to toxaphene, with the 96-hour LC_{50} values in the range from 1.4 to 2.2 µg/l (Courtenay and Roberts, 1973; Schimmel, et al. 1977). However, sensitivity of individuals of five early life stages of the drift-line crab exposed to toxaphene in 96-hour toxicity tests was inversely related to the age of the crabs tested. For example, the 96-hour LC_{50} of stage I larvae was 0.054 µg/l; that for megalopa (the oldest stage tested) was 8.4 µg/l (Table 1). Other than stage I drift-line crab larvae, the most sensitive crustacean tested was the copepod, Acartia tonsa, with a 96-hour LC_{50} value of 0.11 µg/l (Khattat and Farley, 1976). The hard clam, Mercenaria mercenaria, was the least sensitive species (Table 1) with a species mean acute value of 1,120 µg/l (Davis and Hidu, 1969).

In flow-through toxicity tests with five saltwater fish species (Tables 1 and 6), 96-hour LC_{50} values were in the range from 0.5 to 8.6 µg/l

(Katz, 1961; Korn and Earnest, 1974; Schimmel, et al. 1977). Katz (1961) exposed the threespine stickleback to toxaphene in static tests at 5 and 25 g/kg salinity and reported 96-hour LC_{50} values of 8.6 and 7.8 µg/l, respectively.

The Saltwater Final Acute Value for toxaphene, derived from the species mean acute values listed in Table 3 using the procedure described in the Guidelines, is 0.07 µg/l.

Chronic Toxicity

Chronic data are available for three freshwater invertebrate species (Table 2). The chronic values for Daphnia magna, scud (Gammarus pseudolimnaeus), and midge (Chironomus plumosus) are 0.09, 0.18, and 1.8 µg/l, respectively. These differ by a factor of 20, indicating a sensitivity difference among the tested species. Acute-chronic ratios for the three invertebrate species tested were in the range from 100 to 133 (Table 2).

Two chronic tests have been conducted with freshwater fish species, providing chronic values of 0.037 and 0.059 µg/l for fathead minnow and channel catfish, respectively (Table 2). Acute-chronic ratios are 265 for fathead minnow and 71 for channel catfish. A third chronic test result with brook trout is included in Table 6 because even at the lowest concentration tested there was an effect on growth.

The geometric mean of acute-chronic ratios for freshwater species is 123. Dividing the value of 123 into the Freshwater Final Acute Value of 1.6 µg/l provides the Freshwater Final Chronic Value of 0.013 µg/l (Table 3).

Chronic studies on toxaphene with saltwater fish species indicate that concentrations that do not affect individuals in their early stages differ little from 96-hour LC_{50} values. Goodman, et al. (1978) conducted an early-life-stage study with the sheepshead minnow in which toxaphene was not

lethal to embryos at concentrations as high as 2.5 µg/l. Combined embryo and larval mortality during a 28-day exposure to 2.5 µg/l was significantly greater than control mortality, but at 1.1 µg/l mortality was not greater. Therefore, concentrations not affecting survival or growth of sheepshead minnows in an early-life-stage test (Table 2) (Goodman, et al. 1978) were similar to the 96-hour LC_{50} (1.1 µg/l) of toxaphene to juvenile sheepshead minnows (Table 1) (Schimmel, et al. 1977). The acute-chronic ratio for sheepshead minnow is 0.66, two orders of magnitude lower than the freshwater ratios.

The chronic data for the saltwater sheepshead minnow contrast sharply with chronic test data for freshwater fish species (Table 2). The acute value of toxaphene for the channel catfish (4.2 µg/l) was 85 times the highest concentration that produced no observable deleterious effects in a chronic study; that for the fathead minnow (9.8 µg/l) was nearly 400 times. Data for four other pesticides support the hypothesis that differences between acute and chronic effect concentrations in freshwater and saltwater fish species are similar (Parrish, et al. 1978). Possibly the early-life-stage test was not a sensitive measure of chronic effects, or it may be that saltwater fish species differ from freshwater fish species in chronic sensitivity to toxaphene due to innate differences between saltwater and freshwater fishes or to phylogenetic factors such as those reported by Macek and McAllister (1970).

In another early-life-stage study with a saltwater fish species, Schimmel, et al. (1977) exposed the embryos and larvae of the longnose killifish, Fundulus similis, to toxaphene for 28 days (Table 6). The results of the test could not be used to establish a chronic value because the lowest concentration tested caused substantial mortality.

The acute-chronic ratio for sheepshead minnow was not used because it was two orders of magnitude lower than the other five values, and therefore a Saltwater Final Chronic Value was not calculated.

Plant Effects

A single test on a freshwater algal species, Selenastrum capricornutum (Table 4) provided an EC_{50} of 0.38 µg/l (U.S. EPA, 1980). Ukeles (1962) found that five species of saltwater algae varied greatly in sensitivity to toxaphene (Table 4). The most sensitive organism was the dinoflagellate, Monochrysis lutheri, its growth being inhibited at a concentration of 0.15 µg/l. Data from Butler (1963) indicated that 1,000 µg/l caused a 90.8 percent decrease in productivity of natural phytoplankton communities.

Residues

Table 5 contains steady-state bioconcentration data for three freshwater fish species. Bioconcentration factors (BCF) ranged from 3,400 for brook trout (Mayer, et al. 1975) to 52,000 for fathead minnow (Mayer, et al. 1977).

The bioconcentration of toxaphene in tissues of saltwater animals has been well studied (Table 5). Lowe, et al. (1970) exposed eastern oysters, Crassostrea virginica, to a concentration of 0.7 µg/l for 36 weeks, followed by a 12-week depuration period. The maximum BCF, 32,800, was attained after 24 weeks. No toxaphene was found in oyster tissues after the 12-week depuration period. Goodman, et al. (1978) exposed sheepshead minnow embryos and fry to toxaphene for 28 days and reported an average BCF of 9,800. Schimmel, et al. (1977) exposed newly-hatched and juvenile longnose killifish for 28 days and reported average BCF values of 27,900 and 29,400, respectively.

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 normalized BCF values for toxaphene for freshwater and saltwater aquatic life is 4,372 (Table 5).

Dividing the U.S. Food and Drug Administration (FDA) action level of 5.0 mg/kg for edible fish by the geometric mean of normalized BCF values (4,372) and by a percent lipid value of 15 for freshwater species (see Guidelines) gives a freshwater residue value based on marketability for human consumption of 0.076 µg/l. Dividing the FDA action level (5.0 mg/kg) by the geometric mean of normalized BCF values (4,372) and by a percent lipid value of 16 for saltwater species (see Guidelines) gives a saltwater residue value of 0.071 µg/l. Also based on marketability for human consumption using the FDA action level and the highest BCF for edible portion of a consumed fish species (7,800 for channel catfish for freshwater), a freshwater residue value of 0.64 µg/l is obtained (Table 5). No appropriate BCF value for edible portion of a consumed fish species is available for saltwater.

The lowest freshwater residue value of those calculated becomes the Freshwater Final Residue Value of 0.076 µg/l. The Saltwater Final Residue Value is 0.071 µg/l. The Final Residue Values may be too high because, on the average, the concenration in 50 percent of species similar to those used to derive the values will exceed the FDA action level.

Miscellaneous

Table 6, containing data for other effects not listed in the first five tables, does not indicate any significant effect levels that would alter the conclusions discussed previously.

Summary

The freshwater acute data base for toxaphene contains data for 11 invertebrate and 18 fish species. Acute values for invertebrate species range from 1.3 µg/l for the stonefly, Claassenia sabulosa, to 180 µg/l for the

midge, Chironomus plumosus. Species mean acute values for fish species range from 2 µg/l for largemouth bass to 20 µg/l for guppy. Chronic values are available for three freshwater invertebrate and two fish species, and range from 0.037 µg/l for the fathead minnow to 1.8 µg/l for midge, Chironomus plumosus. Acute-chronic ratios for freshwater species were in the range from 71 to 265.

The saltwater acute data base for toxaphene contains data for 10 invertebrate and four fish species. Species mean acute values for invertebrate species range from 0.11 µg/l for a copepod, Acartia tonsa, to 1,120 µg/l for the hard clam, Mercenaria mercenaria. Acute values for fish species range from 0.5 µg/l for pinfish to 8.2 µg/l for the threespine stickleback. A chronic value of 1.66 µg/l is available for the sheepshead minnow.

A single EC_{50} value of 0.38 µg/l is available for a freshwater algal species, and a wide range of toxaphene concentrations (0.15 to 1,000 µg/l) has been reported to cause deleterious effects to saltwater plant species.

Bioconcentration factors for toxaphene and freshwater fish species range from 3,400 for brook trout fillets to 52,000 for whole body fathead minnow. The bioconcentration factor for a single saltwater invertebrate species, Eastern oyster, is 32,800 in edible tissue; bioconcentration factors in saltwater fish species range from 1,270 in ova of exposed adult longnose killifish to 29,400 in juvenile longnose killifish. Freshwater and Saltwater Final Residue Values of 0.076 and 0.071 µg/l were calculated. It should be pointed out that these 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 value will exceed the FDA action level.

CRITERIA

For toxaphene the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.013 µg/l as a 24-hour average, and the concentration should not exceed 1.6 µg/l at any time.

For saltwater aquatic life the concentration of toxaphene should not exceed 0.070 µg/l at any time. No data are available concerning the chronic toxicity of toxaphene to sensitive saltwater aquatic life.

Table 1. Acute values for toxaphene

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Simocephalus serrulatus*	S, U	19	-	Sanders & Cope, 1966
Cladoceran, *Simocephalus serrulatus*	S, U	10	14	Sanders & Cope, 1966
Cladoceran, *Daphnia pulex*	S, U	15	15	Sanders & Cope, 1966
Cladoceran, *Daphnia magna*	FT, M	10	10	Sanders, 1980
Scud, *Gammarus fasciatus*	S, U	35	-	Sanders, 1972
Scud, *Gammarus fasciatus*	S, U	.6	14	Sanders, 1972
Scud, *Gammarus lacustris*	S, U	26	26	Sanders, 1969
Scud, *Gammarus pseudolimnaeus*	FT, M	24	24	Sanders, 1980
Glass shrimp, *Palaemonetes kadiakensis*	S, U	28	28	Sanders, 1972
Midge (larvae), *Chironomus plumosus*	FT, M	180	180	Sanders, 1980
Stonefly, *Pteronarcys californica*	S, U	2.3	2.3	Sanders & Cope, 1968
Stonefly, *Pteronarcella badia*	S, U	3.0	3.0	Sanders & Cope, 1968
Stonefly, *Claassenia sabulosa*	S, U	1.3	1.3	Sanders & Cope, 1968
Coho salmon, *Oncorhynchus kisutch*	S, U	9.4	-	Katz, 1961

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Coho salmon, Oncorhynchus kisutch	S, U	8	8.7	Macek & McAllister, 1970
Chinook salmon, Oncorhynchus tshawytscha	S, U	2.5	2.5	Katz, 1961
Rainbow trout, Salmo gairdneri	S, U	8.4	-	Katz, 1961
Rainbow trout, Salmo gairdneri	S, U	8.4	-	Mahdi, 1966
Rainbow trout, Salmo gairdneri	S, U	11	9.2	Macek & McAllister, 1970
Brown trout, Salmo trutta	S, U	3	3	Macek & McAllister, 1970
Brook trout, Salvelinus fontinalis	FT, M	10.8	11	Mayer, et al. 1975
Stoneroller, Campostoma anomalum	S, U	14	14	Mahdi, 1966
Goldfish, Carassius auratus	S, U	5.6	-	Henderson, et al. 1959
Goldfish, Carassius auratus	S, U	28	-	Mahdi, 1966
Goldfish, Carassius auratus	S, U	14	13	Macek & McAllister, 1970
Carp, Cyprinus carpio	S, U	4	4	Macek & McAllister, 1970
Golden shiner, Notemigonus crysoleucas	S, U	6	6	Mahdi, 1966
Bluntnose minnow, Pimephales notatus	S, U	6.3	6.3	Mahdi, 1966

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Fathead minnow, Pimephales promelas	S, U	7.5	-	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	FT, U	7.2	-	Mayer, et al, 1977
Fathead minnow, Pimephales promelas	S, U	5.1	-	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S, U	14	-	Macek & McAllister, 1970
Fathead minnow, Pimephales promelas	S, U	13	-	Cohen, et al. 1960
Fathead minnow, Pimephales promelas	S, U	20	-	Johnson & Julin, 1980
Fathead minnow, Pimephales promelas	S, U	23	-	Johnson & Julin, 1980
Fathead minnow, Pimephales promelas	FT, U	7.0	-	Johnson & Julin, 1980
Fathead minnow, Pimephales promelas	FT, U	5.0	9.8	Johnson & Julin, 1980
Black bullhead, Ictalurus melas	S, U	1.8	-	Mahdi, 1966
Black bullhead, Ictalurus melas	S, U	5	3.0	Macek & McAllister, 1970
Channel catfish, Ictalurus punctatus	S, U	13	-	Macek & McAllister, 1970
Channel catfish, Ictalurus punctatus	FT, U	16.5	-	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	FT, U	5.5	-	Johnson & Julin, 1980

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Channel catfish, *Ictalurus punctatus*	FT, U	7.5	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	2.8	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	0.8	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	4.7	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	4.2	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	3.7	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	2.7	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	3.4	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	3.0	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	3.9	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	3.2	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	3.9	-	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	S, U	4.7	4.2	Johnson & Julin, 1980
Guppy, *Poecilia reticulata*	S, U	20	20	Henderson, et al. 1959

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Bluegill, *Lepomis macrochirus*	S, U	3.2	-	Macek, et al. 1969
Bluegill, *Lepomis macrochirus*	S, U	2.6	-	Macek, et al. 1969
Bluegill, *Lepomis macrochirus*	S, U	2.4	-	Macek, et al. 1969
Bluegill, *Lepomis macrochirus*	S, U	5.0	-	Isensee, et al. 1979
Bluegill, *Lepomis macrochirus*	S, U	7.8	-	Isensee, et al. 1979
Bluegill, *Lepomis macrochirus*	S, U	3.5	-	Henderson, et al. 1959
Bluegill, *Lepomis macrochirus*	S, U	18	-	Macek & McAllister, 1970
Bluegill, *Lepomis macrochirus*	S, U	2.4	-	Johnson & Julin, 1980
Bluegill, *Lepomis macrochirus*	S, U	2.6	-	Johnson & Julin, 1980
Bluegill, *Lepomis macrochirus*	FT, U	3.4	-	Johnson & Julin, 1980
Bluegill, *Lepomis macrochirus*	FT, U	4.7	4.1	Johnson & Julin, 1980
Redear sunfish, *Lepomis microlophus*	S, U	13	13	Macek & McAllister, 1970
Largemouth bass, *Micropterus salmoides*	S, U	2	2	Macek & McAllister, 1970
Yellow perch, *Perca flavescens*	S, U	12	12	Macek & McAllister, 1970

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		SALTWATER SPECIES		
Eastern oyster, Crassostrea virginica	FT, M	16	-	Schimmel, et al. 1977
Eastern oyster, Crassostrea virginica	FT, U	63	-	Butler, 1963
Eastern oyster, Crassostrea virginica	FT, U	57	16	Butler, 1963
Hard clam (embryo), Mercenaria mercenaria	S, U	1,120	1,120	Davis & Hidu, 1969
Copepod, Acartia tonsa	S, U	0.11**	0.11	Khattat & Farley, 1976
Mysid shrimp (juvenile), Mysidopsis bahia	FT, M	6.32	-	Nimmo, 1977
Mysid shrimp (adult), Mysidopsis bahia	FT, M	3.19	4.5	Nimmo, 1977
Blue crab, Callinectes sapidus	S, U	580	-	McKenzie, 1970
Blue crab, Callinectes sapidus	S, U	900	-	McKenzie, 1970
Blue crab, Callinectes sapidus	S, U	370	-	McKenzie, 1970
Blue crab, Callinectes sapidus	S, U	960	-	McKenzie, 1970
Blue crab, Callinectes sapidus	S, U	380	-	McKenzie, 1970
Blue crab, Callinectes sapidus	S, U	770	-	McKenzie, 1970

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Blue crab, *Callinectes sapidus*	S, U	1,200	-	McKenzie, 1970
Blue crab, *Callinectes sapidus*	S, U	2,700	-	McKenzie, 1970
Blue crab, *Callinectes sapidus*	S, U	1,000	824	McKenzie, 1970
Korean shrimp, *Palaemon macrodactylus*	S, U	20.3	-	Schoettger, 1970
Korean shrimp, *Palaemon macrodactylus*	FT, U	20.8	21	Schoettger, 1970
Grass shrimp, *Palaemonetes pugio*	FT, M	4.4	4.4	Schimmel, et al. 1977
Pink shrimp, *Penaeus duorarum*	FT, M	1.4	-	Schimmel, et al. 1977
Pink shrimp (nauplius), *Penaeus dourarum*	S, U	2.2	-	Courtenay & Roberts, 1973
Pink shrimp (protozoea), *Penaeus duorarum*	S, U	1.8	-	Courtenay & Roberts, 1973
Pink shrimp (mysis), *Penaeus duorarum*	S, U	1.4	1.4	Courtenay & Roberts, 1973
Mud crab (stage I larva), *Rhithropanopeus harrisii*	S, U	43.75	43.8	Courtenay & Roberts, 1973
Drift-line crab (stage I larva), *Sesarma cinereum*	S, U	0.054	-	Courtenay & Roberts, 1973
Drift-line crab (stage II larva), *Sesarma cinereum*	S, U	0.76	-	Courtenay & Roberts, 1973

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Drift-line crab (stage III larva), *Sesarma cinereum*	S, U	0.74	-	Courtenay & Roberts, 1973
Drift-line crab (stage IV larva), *Sesarma cinereum*	S, U	6.8	-	Courtenay & Roberts, 1973
Drift-line crab (megalopa), *Sesarma cinereum*	S, U	8.4	1.1	Courtenay & Roberts, 1973
Sheepshead minnow, *Cyprinodon variegatus*	FT, M	1.1	1.1	Schimmel, et al. 1977
Threespine stickleback, *Gasterosteus aculeatus*	S, U	8.6	-	Katz, 1961
Threespine stickleback, *Gasterosteus aculeatus*	S, U	7.8	8.2	Katz, 1961
Striped bass, *Morone saxatilis*	FT, U	4.4	4.4	Korn & Earnest, 1974
Pinfish, *Lagodon rhomboides*	FT, M	0.5	0.5	Schimmel, et al. 1977

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

**LC50 recalculated using probit analysis method of Finney (1971).

Table 2. Chronic values for toxaphene

Species	Test*	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	LC	0.07-0.12	0.09	Sanders, 1980
Scud, *Gammarus pseudolimnaeus*	LC	0.13-0.25	0.18	Sanders, 1980
Midge (larva), *Chironomus plumosus*	LC	1.0-3.2	1.8	Sanders, 1980
Fathead minnow, *Pimephales promelas*	LC	0.025-0.054	0.037	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	LC	0.049-0.072	0.059	Mayer, et al. 1977
		SALTWATER SPECIES		
Sheepshead minnow, *Cyprinodon variegatus*	ELS	1.1-2.5	1.66	Goodman, et al. 1978

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

Acute-Chronic Ratios

Species	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Cladoceran, *Daphnia magna*	10	0.09	111
Scud, *Gammarus pseudolimnaeus*	24	0.18	133

Table 2. (Continued)

Species	Acute-Chronic Ratios: Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Midge (larvae), Chironomus plumosus	180	1.8	100
Fathead minnow, Pimephales promelas	9.8	0.037	265
Channel catfish, Ictalurus punctatus	4.2	0.059	71
Sheepshead minnow, Cyprinodon variegatus	1.1	1.66	0.66

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

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
		FRESHWATER SPECIES	
29	Midge, *Chironomus plumosus*	180	100
28	Glass shrimp, *Palaemonetes kadiakensis*	28	-
27	Scud, *Gammarus lacustris*	26	-
26	Scud, *Gammarus pseudolimnaeus*	24	133
25	Guppy, *Poecilia reticulata*	20	-
24	Cladoceran, *Daphnia pulex*	15	-
23	Scud, *Gammarus fasciatus*	14	-
22	Stoneroller, *Campostoma anomalum*	14	-
21	Cladoceran, *Simocephalus serrulatus*	14	-
20	Goldfish, *Carassius auratus*	13	-
19	Redear sunfish, *Lepomis microlophus*	13	-
18	Yellow perch, *Perca flavescens*	12	-
17	Brook trout, *Salvelinus fontinalis*	11	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
16	Cladoceran, *Daphnia magna*	10	111
15	Fathead minnow, *Pimephales promelas*	9.8	265
14	Rainbow trout, *Salmo gairdneri*	9.2	-
13	Coho salmon, *Oncorhynchus kisutch*	8.7	-
12	Bluntnose minnow, *Pimephales notatus*	6.3	-
11	Golden shiner, *Notemigonus crysoleucas,*	6	-
10	Channel catfish, *Ictalurus punctatus*	4.2	71
9	Bluegill, *Lepomis macrochirus*	4.1	-
8	Carp, *Cyprinus carpio*	4	-
7	Black bullhead, *Ictalurus melas*	3.0	-
6	Stonefly, *Pteronarcella badia*	3.0	-
5	Brown trout, *Salmo trutta*	3	-
4	Chinook salmon, *Oncorhynchus tshawytscha*	2.5	-
3	Stonefly, *Pteronarcys californica*	2.3	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
2	Largemouth bass, Micropterus salmoides	2	-
1	Stonefly, Claassenia sabulosa	1.3	-
	SALTWATER SPECIES		
14	Hard clam, Mercenaria mercenaria	1,120	-
13	Blue crab, Callinectes sapidus	824	-
12	Mud crab, Rhithropanopeus harrisii	43.8	-
11	Korean shrimp, Palaemon macrodactylus	21	-
10	Eastern oyster, Crassostrea virginica	16	-
9	Threespine stickleback, Gasterosteus aculeatus	8.2	-
8	Mysid shrimp, Mysidopsis bahia	4.5	-
7	Grass shrimp, Palaemonetes pugio	4.4	-
6	Striped bass, Morone saxatilis	4.4	-
5	Pink shrimp, Penaeus duorarum	1.4	-
4	Drift-line crab, Sesarma cinereum	1.1	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
3	Sheepshead minnow, *Cyprinodon variegatus*	1.1	0.66
2	Pinfish, *Lagodon rhomboides*	0.5	-
1	Copepod, *Acartia tonsa*	0.11	-

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

Freshwater Acute-Chronic Ratio = 123

Freshwater Final Acute Value = 1.6 µg/l

Freshwater Final Chronic Value = 1.6 µg/l ÷ 123 = 0.013 µg/l

Saltwater Final Acute Value = 0.07 µg/l

Table 4. Plant values for toxaphene

Species	Effect	Result (µg/l)	Reference
	FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	EC50	0.38	U.S. EPA, 1980
	SALTWATER SPECIES		
Alga, *Chlorella* sp.	No growth	70	Ukeles, 1962
Dinoflagellate, *Dunaliella euchlora*	Lethal	150	Ukeles, 1962
Dinoflagellate, *Monochrysis lutheri*	No growth	0.15	Ukeles, 1962
Alga, *Phaecodactylum tricornutum*	Lethal	40	Ukeles, 1962
Alga, *Protococcus* sp.	No growth	150	Ukeles, 1962
Natural phytoplankton communities	90.8% decrease in productivity; ^{14}C	1,000	Butler, 1963

Table 5. Residues for toxaphene

Species	Tissue	Lipid (%)	Bioconcentration Factor	Duration (days)	Reference
		FRESHWATER SPECIES			
Brook trout, Salvelinus fontinalis	Whole body	-	10,000	140	Mayer, et al. 1975
Brook trout, Salvelinus fontinalis	Fillet	-	3,400	161	Mayer, et al. 1975
Fathead minnow, Pimephales promelas	Whole body	9.3	52,000	98	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	Whole body	7.8	22,000	100	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	Fillet	-	7,800	137	Mayer, et al. 1977
Channel catfish fry, Ictalurus punctatus	Whole body	4.7	40,000	90	Mayer, et al. 1977
		SALTWATER SPECIES			
Eastern oyster, Crassostrea virginica	Edible tissue	-	32,800	168	Lowe, et al. 1970
Sheepshead minnow, Cyprinodon variegatus	Whole body	3.6*	9,800	28	Goodman, et al. 1978
Longnose killifish (fry), Fundulus similis	Whole body	-	27,900	28	Schimmel, et al. 1977
Longnose killifish (juvenile), Fundulus similis	Whole body	-	29,400	28	Schimmel, et al. 1977
Longnose killifish (adult), Fundulus similis	Whole body	-	5,400	32	Schimmel, et al. 1977
Longnose killifish, Fundulus similis	Ova of exposed adults	-	1,270	14	Schimmel, et al. 1977

Table 5. (Continued)

Species	Tissue	Lipid (%)	Bioconcentration Factor	Duration (days)	Reference
Longnose killifish, Fundulus similis	Ova of exposed adults	-	3,700	32	Schimmel, et al. 1977

* Percent lipid data from Hansen, 1980

Maximum Permissible Tissue Concentration

Action Level	Concentration (mg/kg)	Reference
Fish	5.0	U.S. FDA Guideline 7420.08, 1979

Geometric mean of normalized BCF values (see text) = 4,372

Marketability for human consumption: FDA action level for fish = 5.0 mg/kg

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

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

Freshwater: $\frac{5.0}{4,372 \times 15}$ = 0.000076 mg/kg = 0.076 µg/l

Saltwater: $\frac{5.0}{4,372 \times 16}$ = 0.000071 mg/kg = 0.071 ug/l

Using highest BCF for edible portion of a consumed species

Freshwater: Channel catfish = 7,800 (Mayer, et al. 1977)

$\frac{5.0}{7,800}$ = 0.00064 mg/kg = 0.64 µg/l

Table 5. (Continued)

Freshwater Final Residue Value = 0.076 µg/l

Saltwater Final Residue Value = 0.071 µg/l

Table 6. Other data for toxaphene

Species	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	14 days	Reduced reproduction	0.12	Sanders, 1980
Midge, *Chironomus plumosus*	20 days	Delayed emergence	3.2	Sanders, 1980
Brook trout, *Salvelinus fontinalis*	161 days	Growth inhibition and mortality	0.288	Mayer, et al. 1975
Brook trout, *Salvelinus fontinalis*	11 days	LTC*	4.1	Mayer, et al, 1975
Brook trout, *Salvelinus fontinalis*	161 days	Decreased reproduction (embryo viability)	0.068	Mayer, et al. 1975
Fathead minnow, *Pimephales promelas*	30 days	Growth inhibition	0.097	Mayer, et al. 1977
Fathead minnow (fry), *Pimephales promelas*	30 days	Growth inhibition	0.054	Mayer, et al. 1977
Fathead minnow, *Pimephales promelas*	7 days	LTC	5.3	Mayer, et al. 1977
Fathead minnow, *Pimephales promelas*	24 days	LTC	2.6	Johnson & Julin, 1980
Fathead minnow, *Pimephales promelas*	16 days	LTC	1.5	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	5 days	LTC	15.2	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	12 days	LTC	3.7	Johnson & Julin, 1980
Channel catfish, *Ictalurus punctatus*	29 days	LTC	1.9	Johnson & Julin, 1980

Table 6. (Continued)

Species	Duration	Effect	Result (µg/l)	Reference
Channel catfish, *Ictalurus punctatus*	30 days	Growth inhibition	0.299	Mayer, et al. 1977
Channel catfish (fry), *Ictalurus punctatus*	15 days	Backbone quality	0.072	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	34 days	LTC	0.7	Johnson & Julin, 1980
Bluegill, *Lepomis macrochirus*	7 days	LTC	1.4	Johnson & Julin, 1980
		SALTWATER SPECIES		
Eastern oyster, *Crassostrea virginica*	24 hrs	Growth inhibition	100	Butler, 1960
Eastern oyster, *Crassostrea virginica*	4 days	Bioconcentration factor = 11,250	-	Schimmel, et al. 1977
Mactrid clam, *Rangia cuneata*	4 days	LC50	460,000	Chaiyarach, et al. 1975
Blue crab, *Callinectes sapidus*	2 days	EC50	330	Butler, 1963
Grass shrimp, *Palaemonetes pugio*	4 days	Bioconcentration factor = 960	-	Schimmel, et al. 1977
Pink shrimp, *Penaeus duorarum*	4 days	Bioconcentration factor = 550	-	Schimmel, et al. 1977
Brown shrimp, *Penaeus aztecus*	2 days	EC50	4.9	Butler, 1963
Mysid shrimp, *Mysidopsis bahia*	Life cycle	82% decrease in number of young produced	0.14	Nimmo, et al. 1977
Sheepshead minnow, *Cyprinodon variegatus*	4 days	Bioconcentration factor = 7,620	-	Schimmel, et al. 1977

Table 6. (Continued)

Species	Duration	Effect	Result (µg/l)	Reference
Longnose killifish (fry 48 hrs), *Fundulus similis*	28 days	LC50	1.3	Schimmel, et al. 1977
Longnose killifish (juvenile), *Fundulus similis*	28 days	LC50	0.9	Schimmel, et al. 1977
Longnose killifish (adult), *Fundulus similis*	14 days	95% mortality	1.7	Schimmel, et al. 1977
Spot, *Leiostomus xanthurus*	144 hrs	50% mortality	0.5	Lowe, 1964
Spot, *Leiostomus xanthurus*	2 days	LC50	1.0	Butler, 1964
White mullet, *Mugil curema*	2 days	LC50	5.5	Butler, 1963

* LTC = lethal threshold concentration

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

Several routine monitoring studies of United States surface waters conducted prior to 1975 did not detect toxaphene (Brown and Nishioka, 1967; Lichtenberg, et al. 1970; Manigold and Schulze, 1969; Mattraw, 1975; Schafer, et al. 1969; Schulze, et al. 1973; Weaver, et al. 1965). Lichtenberg (1971) and Schulze, et al. (1973) placed the toxaphene lower detection limit at 0.5 to 1.0 µg/l, whereas other organochlorides can be detected near concentrations two orders of magnitude lower.

Toxaphene, however, had been detected before 1975 in water around areas where it was applied to crops as an insecticide. In California, Johnston, et al. (1967) detected toxaphene residues in 60 of 61 analyses of surface effluents in Panoche Drain Water (average 2.009 µg/l and range of 0.100 to 7.900 µg/l) and in 13 of 66 analyses of San Joaquin Valley tile drainage effluents (average 0.528 µg/l and range of 0.130 to 0.950 µg/l). Also, in California, Bailey and Hannum (1967) found toxaphene in 17 of 26 surface water samples (average concentration 0.23 µg/l). The San Joaquin District, California Department of Water Resources (1963-1969) detected toxaphene in 51 of 422 (12 percent) tile drainage effluents (0.02 to 0.5 µg/l), in 216 of 447 (48 percent) surface drains in Central Valley (0.04 to 71.00 µg/l), in 88 of 712 (12 percent) of Central Valley surface waters (0.02 to 0.93 µg/l), and in 8 of 200 (4 percent) California bays and surface waters.

In Alabama, the Flint Creek watershed was monitored during the years 1959 to 1965 (Cohen, et al. 1961; Grzenda and Nicholson, 1965; Grzenda, et al. 1964; Nicholson, 1969; Nicholson, et al. 1964, 1966). This watershed drains an agricultural district where the major pesticide source is from small cotton farms which are major users of toxaphene (Nicholson, et al. 1964). During this study, toxaphene was detected (carbon absorption followed by chloroform extraction) in paired samples of raw Flint Creek water and treated drinking water obtained from Flint Creek. Toxaphene concentrations ranged from the limits of detection to 0.410 µg/l, with a mean of approximately 0.07 µg/l. However, since the recovery was approximately 50 percent (i.e., 48 percent for the 1 ng/l spiked samples and 42 percent for the 0.5 ng/l samples), actual residues may have averaged about 0.14 µg/l. The toxaphene concentrations in treated and untreated water samples were not significantly different, indicating that treatment of drinking water does not reduce toxaphene concentrations.

Although Mattraw (1975) did not detect toxaphene in surface water in an organochlorine residue survey in Florida, toxaphene was found in 3.2 percent of the sediment samples (claimed lower detection limit of 0.05 µg/l). Barthel, et al. (1969) also found detectable toxaphene residues in sediments at 11 sites on the lower Mississippi River. Herring and Cotton (1970) detected toxaphene in 11 of 20 Mississippi Delta Lakes at a maximum concentration of 1.92 µg/l. Sediments from 10 of these lakes had a maximum toxaphene concentration of 2.46 µg/l.

Toxaphene contamination also has been documented in an area surrounding a toxaphene manufacturing plant. The University of Georgia Marine Institute (Reimold, 1974; Reimold and Durant, 1972a,b, 1974; Durant and Reimold, 1972) has monitored toxaphene contamination in surface waters, sediment, and biota of waters receiving the effluent of the Hercules, Inc. plant which is located on Terry Creek, Brunswick, Georgia and is the largest producer of toxaphene in the United States. The average monthly toxaphene concentration in the plant's effluent has decreased from a high of 2,332 µg/l in August 1970 to a low of 6.4 µg/l in June 1974. Dye experiments have shown that the effluent is diluted by a factor of 10 after it reaches Terry Creek (Reimold, 1974). The Institute (Reimold and Durant, 1972a,b; Durant and Reimold, 1972) analyzed sediment at three locations downstream of the plant outfall. Samples were collected prior to a dredging operation in June 1971 at three sites downstream: 0.2 miles from the outfall at a location 50 yards from an intersection with another creek; 0.8 miles from the plant outfall; and 1.4 miles from the plant outfall and 50 yards from the end of Terry Creek (junction with Back River). Reimold and Durant (1972b) measured 32.56 µg/l as the average toxaphene concentration in sediment cores within Terry Creek Marsh. The highest residue concentration measured in the surrounding water was 15 µg/l before dredging.

Recently, a survey of commercial drinking water samples conducted by the U.S. EPA (1976a) during 1975 and 1976 found no detectable levels of toxaphene in 58 samples; the limit of detection was 0.05 µg/l.

Ingestion from Food

Estimates of toxaphene exposure from dietary intake can be made from the U.S. Food and Drug Administration (FDA) market basket survey, the FDA survey of unprocessed food and feed samples, and the U.S. Department of Agriculture (USDA) survey of meat and poultry. In the FDA market basket survey, food samples are prepared for consumption (i.e., cooked or otherwise processed) prior to monitoring for pesticide residues (Duggan and McFarland, 1967). The market basket items are grouped by commodity class (e.g., dairy products, leafy vegetables, legume vegetables) and are intended to represent a 2-week diet for a 16- to 19-year-old male (Duggan and Corneluissen, 1972). The results of these surveys, from their inception to the most recently published report, are summarized in Table 1. From 1964 to 1972, food samples were obtained from five cities: Boston, Mass., Baltimore, Md., Los Angeles, Calif., Kansas City, Mo., and Minneapolis, Minn. Of the 26 positive samples encountered during this period, there were 19 in Los Angeles, 4 in Baltimore, and 1 each in Boston, Minneapolis and Kansas City. Based on the estimates of daily intake made by Duggan and Corneluissen (1972) and assuming an average body weight of 70 kg, the estimated daily dose of dietary toxaphene over the period of June 1964 to April 1970 was 0.021 µg toxaphene/kg body weight/day. This estimate is based on food samples from a limited number of cities, most of which are not located in areas of high toxaphene usage. The more recent (1972 to 1975) results of the market basket survey suggest that the current daily dietary dose may be substantially lower; however, it is equally possible that the dietary doses for

TABLE 1

Toxaphene Residues Found in Food and Drug Administration Market Basket Survey, 1964 to 1975*

Monitoring Period	No. of Composits	No. of Composits Positive	% Occurrence	Commodities Contaminated (No. of composits of each commodity contaminated)	Range of Levels (mg/kg)	Daily Intake	Reference
June 1964-April 1965	216	0	0.0	--	--	0	Duggan, et al. 1966
June 1965-April 1966	312	3	1.0	Leafy vegetables(1) and garden fruits(2)	0.048-0.38	0.002	Duggan, et al. 1967
June 1966-April 1967	360	0	0.0	--	--	0	Martin and Duggan, 1968
June 1967-April 1968	360	4	1.1	Meat, fish, or poultry(1), leafy vegetables(1), and garden fruits(2)	0.064-0.375	0.002	Corneliussen, 1969
June 1968-April 1969	360	13	3.6	Garden fruits(6), meat, fish, or poultry(1), legume vegetables(2), root vegetables (1), and leafy vegetables(3)	0.022-0.33	0.004	Corneliussen, 1970
June 1969-April 1970	360	4	1.1	Leafy vegetables(2) and garden fruits(2)	0.080-0.132	0.001	Corneliussen, 1972
June 1970-April 1971	360	1	0.3	Root vegetables(1)	trace		Manske and Corneliussen, 1974
June 1971-July 1972	420	1	0.2	Leafy vegetables(1)	0.1		Manske and Johnson, 1975
Aug. 1972-July 1973	360	0(1)**	0.0	--	(0.005)**		Johnson and Manske, 1975
Aug. 1973-July 1974	360	3	0.8	Garden fruits(3)	trace-0.163		Manske and Johnson, 1976
Aug. 1974-July 1975	240	1	0.4	Leafy vegetables(1)	0.118		Johnson and Manske, 1977

*Source: Duggan and Corneliussen, 1972
**Strobane

individuals located in the Mississippi Delta (an area of high toxaphene usage) could be substantially higher.

The U.S. EPA (1977) recently compiled the results of the FDA survey on unprocessed food and feed samples. As indicated in Table 2, the percent of occurrence of toxaphene contamination suggests a low incidence of contamination.

The only published information encountered in the USDA survey of meat and poultry is contained in the World Health Organization (WHO, 1974a) monograph on toxaphene. This information is summarized in Table 3.

Similar but unpublished information covering the years 1973 to 1978 has been obtained from the USDA (1978) and is summarized in Table 4. These data indicate that toxaphene is found consistently from year to year in the fat of cattle, although the incidence of contamination is extremely low. During this survey period, only six samples were in excess of the tolerance limit (7.0 mg/kg; see Existing Guidelines and Standards section). Of these six violations, five were in fat samples from cattle, one of which occurred in the first quarter of 1978. The data summarized in Tables 3 and 4 indicate that toxaphene is not a widespread contaminant in meat and poultry products.

As detailed in the Aquatic Toxicology section of this criteria document, toxaphene in water can be bioconcentrated in fish by factors of 50,000 and more, based on laboratory studies and measurements of whole body residues. However, in assessing potential human dietary exposure, the primary concern is with residues bioconcentrated in the edible portion or fillet. Working with adult

TABLE 2

Toxaphene Residues Found in Food and Drug Administration Survey of Unprocessed Food and Feed Samples, 1972 to 1976*

Year	No. of Commodities Contaminated	No. of Samples Checked	No. of Positive Samples	No. of Occurrence	Commodity most Frequently Contaminated
1972	10	3516	118	3.3	Leaf & Stem Vegetables
1973	15	2906	150	4.8	Leaf & Stem Vegetables
1974	8	1919	109	4.6	Fish
1975	12	2317	118	5.0	Fish
1976	15	4228	257	6.0	Fish

*Source: U.S. EPA, 1977.

TABLE 3

Residues of Toxaphene in Meat and Poultry Products[a]

Species	No. of Tissues Analyzed		No. with a Residue		No. with Toxaphene	
	1969	1970(6 mos)	1969	1970 (6 mos)	1969	1970
Meat						
Cattle	739	583	712	NA*	2	0
Calves	142	67	141	NA	0	0
Swine	1964	1076	1741	NA	0	2
Sheep	312	137	303	NA	0	1
Goats	12	8	10	NA	0	0
TOTAL	3169	1871	2907	1721	2	3
Poultry						
Young chickens	1909	1405	1898	NA	2	0
Mature chickens	78	-	77	NA	0	0
Turkeys	169	67	164	NA	0	0
Ducks	42	8	41	NA	0	0
Geese	1	2	1	NA	0	0
Other	-	4	-	NA	0	0
TOTAL	2199	1486	2181	1472	2	0

[a]Source: World Health Organization, 1974a
*Breakdown by species not available from 1970 interim report

TABLE 4

Residues of Toxaphene in Fat Samples of Meat and Poultry Products at Slaughter in the United States[a]

Animal	Number of Positive Samples/Total Number of Samples (%)											
	1973		1974		1975		1976		1977		1978*	
Cattle	9/710	(1.27)	2/1117	(0.18)	3/1733	(0.17)	3/1785	(0.17)	4/880	(0.45)	1/432	(0.23)
Calves	1/84	(1.19)	0/284	(0.0)	0/269	(0.0)	0/327	(0.0)	0/124	(0.0)	0/62	(0.0)
Sheep & Goats	2/289	(0.69)**	1/371	(0.27)	0/356	(0.0)	0/250	(0.0)	0/100	(0.0)	0/36	(0.0)
Swine	4/232	(1.72)	2/329	(0.61)	0/324	(0.0)	1/442	(0.23)	0/215	(0.0)	0/179	(0.0)
Chicken	3/530	(0.57)	1/1138	(0.09)	0/777	(0.0)	0/927	(0.0)	1/375	(0.27)	0/191	(0.0)
Turkeys	3/517	(0.58)	0/735	(0.0)	0/554	(0.0)	0/456	(0.0)	0/303	(0.0)	0/64	(0.0)
Ducks & Geese	0/95	(0.0)	0/148	(0.0)	0/246	(0.0)	0/267	(0.0)	0/186	(0.0)	0/39	(0.0)
Rabbits	0/19	(0.0)			0/11	(0.0)	0/65	(0.0)	0/21	(0.0)	0/14	(0.0)
Horses	0/44	(0.0)	3/266	(1.13)	0/261	(0.0)	0/217	(0.0)	0/112	(0.0)	0/20	(0.0)
TOTAL	22/2520	(0.87)	9/4388	(0.21)	3/3971	(0.08)	4/4736	(0.08)	5/3216	(0.22)	1/1037	(0.10)

[a]Source: U.S. Department of Agriculture, 1978
*first two quarters only
**listed as lamb

brook trout, Mayer, et al. (1975) found that toxaphene was bioconcentrated in the fillet by a factor of 8,000 when fish were kept in water containing toxaphene at 0.5 µg/l for 161 days. The bioconcentration factor for the fillet was less than 2,400. Toxaphene residues found in fish from toxaphene-treated lakes are generally consistent with levels obtained during laboratory studies and indicate that fish bioconcentrate toxaphene by a factor of several thousand. For example, Terriere, et al. (1966) found that total mean body residues in rainbow trout in lakewater were several µg/g compared to approximatley 0.5 µg/l in water (bioconcentration factor of 9,000 to 19,000), which is comparable to the bioconcentration observed experimentally by Mayer, et al. (1975) with total body residues in brook trout.

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 percent lipids and a steady-state BCF were measured, have been conducted on toxaphene. The mean of the BCF values, after normalization to 1 percent lipids, is 4,372 (see Table 5 in Aquatic 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 toxaphene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 13,100.

Inhalation

The highest toxaphene residues in air have been found in areas where toxaphene is applied for agricultural purposes (especially cotton production) (Arthur, et al. 1976; Miss. Agric. Exp. Sta., 1976; Stanley, et al. 1971; Tabor, 1965 and 1966). Studies in cotton growing areas demonstrate that airborne residues are highest during the cotton growing season and decrease to lower levels after harvesting, but spring tilling releases soil residues to the air. The recent identification of toxaphene at ng/m^3 concentrations over the Atlantic Ocean, where it has not been applied, indicates that toxaphene residues move with air currents analagous to DDT (Bidleman, et al. 1976; Bidleman and Olney, 1975).

Arthur, et al. (1976) reported a 3-year (January 1972 to December 1974) study of toxaphene air residues at Stoneville, Miss., which is located in the southern cotton belt. Over this period, toxaphene concentrations were highest in August (1,540.0, 268.8, and 903.6 ng/m^3) and lowest in January (0.0, 0.0, 10.9 ng/m^3). The mean monthly concentration was 167 ng/m^3. In a more recent unpublished survey of the Mississippi area, conducted from January 1976 to July 1976, the mean measured toxaphene concentration in air was 18.7 ng/m^3, with the highest concentration found during June and July (42.09 ng/m^3) (Miss. Agric. Exp. Sta., 1976). Earlier studies (Tabor, 1965, 1966) conducted in seven southern agricultural communities detected toxaphene at only two sites: Leland, Miss., where toxaphene levels ranging from 1.2 to 7.5 ng/m^3 were found in 6 of 15 samples from July to September 1963; and Newellton, Tex., where toxaphene levels ranging from 3.1 to 15 ng/m^3 were found in 6 of 10 samples. Both of these communities were in cotton growing areas.

Comparative geographic studies of toxaphene air concentrations suggest that toxaphene contamination is most pervasive in southern states. From 1967 to 1968 Stanley, et al. (1971) attempted to monitor toxaphene at nine locations: Baltimore, Md.; Buffalo, N.Y.; Dothan, Ala.; Fresno, Calif.; Iowa City, Iowa; Orlando, Fla.; Riverside, Calif.; Salt Lake City, Utah; and Stoneville, Miss. Toxaphene was found in only three locations, all in the southern part of the country: Dothan (11 of 90 samples at 27.3 to 79.0 ng/m^3), Orlando (9 of 79 samples at 20.0 to 2,520 ng/m^3), and Stoneville (57 of 98 samples at 16.0 to 111.0 ng/m^3). Similarly,

Bidleman, et al. (1976) monitored toxaphene at five sites in North America. As indicated in Table 5, the more southern sites evidenced considerably higher concentrations of toxaphene.

Toxaphene has also been monitored in the atmosphere over the east coast of the U.S., near Bermuda, and over the open ocean (Bidleman and Olney, 1975). With respect to the above discussion of geographic distribution and since substantial amounts of toxaphene are used in the South on cotton, it is not too surprising that a sample taken at Sapelo Island, Ga. is substantially greater (mean of 2.8 ng/m^3) than the samples taken at Bermuda (mean of 0.79 ng/m^3) or over the open ocean (mean of 0.53 ng/m^3).

These monitoring studies clearly suggest that toxaphene is a prevalent atmospheric contaminant in areas where this pesticide is used, particularly in the southern United States. Taking the mean monthly toxaphene concentration of 167 ng/m^3 noted by Arthur, et al. (1976) over a 3-year period in Stoneville, Miss., and assuming (1) that the average human weighs 70 kg and breathes 24 m^3 of air per day and (2) that all of the toxaphene breathed into the lungs is absorbed,* the average daily dose of toxaphene from air is approximately 0.057 µg/kg.** This is approximately twice the estimated daily intake of toxaphene from the diet (see Ingestion from Food section) based on the FDA 1964 to 1970 market basket survey. An

*Assuming 100 percent absorption is common EPA policy, but in this case is very conservative since human studies of occupationally exposed individuals suggest no absorption (see Absorption section).

**It should be noted that 0.057 µg/kg is a maximum or worst case value due to (1) assumption of 100 percent absorption and (2) use of a mean monthly toxaphene concentration from a high toxaphene use area.

TABLE 5

Toxaphene Residues in Air Samples at Five North American Sites*

Location and Date	Number of Samples	Range (ng/m^3)
Kingston, Rhode Island, 1975	6	0.04 - 0.4
Sapelo Island, Georgia, 1975	6	1.7 - 5.2
Organ Pipe Cactus National Park, Arizona, 1974	6	2.7 - 7.0
Hays, Kansas, 1974	3	0.083 - 2.6
Northwest Territories, Canada, 1974	3	0.04 - 0.13

*Source: Bidleman, et al. 1976

average national level of toxaphene exposure from air cannot be estimated from the available data. However, taking the average concentration monitored by Bidleman and Olney (1975) over the open ocean (0.53 ng/m^3), the daily intake of toxaphene from air would be 0.18 ng/kg.

Dermal

No direct information is available on the importance of dermal absorption in total human exposure to toxaphene. Data from toxicity studies with laboratory mammals (see Acute, Subacute, and Chronic Toxicity section) indicate that toxaphene can be absorbed across the skin in toxic amounts by humans. However, incidences of dermal absorption of toxaphene by humans are restricted to occupational or accidental exposures to large amounts of toxaphene. For those exposed to only background levels of toxaphene, dermal absorption is not likely to be a significant route of entry.

PHARMACOKINETICS

Absorption

The recently completed U.S. EPA (1978) study suggests that inhalation exposures to toxaphene do not result in sufficient absorption by humans to cause quantifiable levels in the blood. The study found no detectable levels of toxaphene in the blood of 54 workers occupationally exposed to toxaphene. However, of 53 personal air samples analyzed, 30 had quantifiable levels of toxaphene and 19 had trace levels. In the same study, one individual not occupationally exposed to toxaphene was found to have elevated toxaphene blood levels associated with the consumption of toxaphene-contaminated fish (see Excretion section), indicating significant absorption after oral exposure.

Inferences on the absorption of toxaphene by laboratory mammals can be made from some of the available toxicity data. Absorption across the alimentary tract, skin, and respiratory tract is indicated by the adverse effects elicited by toxaphene after oral, dermal, and inhalation exposures. Based on toxicity studies detailed in the Acute, Subacute, and Chronic Toxicity section, the vehicle used in the administration of toxaphene has a marked influence on lethality. This effect is probably attributable to differences in the extent and/or rate of absorption. In oral exposures, toxaphene has a much lower LD_{50} when administered in a readily absorbed vehicle, e.g., corn oil or peanut oil, than when given in an indigestible vehicle such as kerosene. Similarly, dermal applications of toxaphene in solution with mineral oil, dimethyl phthalate, or water are much more toxic than similar applications of toxaphene in powder preparations (Lackey, 1949a,b; Conley, 1952). Documented cases of human poisoning by toxaphene indicate that man may absorb toxic levels following oral, dermal, or inhalation exposures (McGee, et al. 1952; Pollock, 1958; Warraki, 1963). When administered or applied in comparable lipophilic solvents, the ratio of oral LD_{50} to dermal LD_{50} is about 0.1 (Tables 6 and 7). This suggests that toxaphene is absorbed more completely and/or more rapidly from the alimentary tract than from the skin. The pronounced variability in time to death after toxaphene ingestion indicates marked individual differences in the rate of toxaphene absorption and/or differences in susceptibility to toxaphene intoxication.

TABLE 6

Acute Oral Toxicity of Technical Toxaphene to Laboratory Mammals

Organism	Vehicle	LD_{50} (mg/kg)	Reference
Rats:			
Unspecified strain	Unspecified	69	Lehman, 1951
Wistar, male, (3-4 weeks, 50-60 g) fasted	Cottonseed oil	220 ± 33*	Boyd and Taylor, 1971
Sherman, male, (>90 days, > 175 g) fasted	Peanut oil	90(67-122)**	Gaines, 1960
Sherman, female, (>90 days, > 175 g) fasted	Peanut oil	80(70-91)**	Gaines, 1960
	Peanut oil	40	Shelanski and Gellhorn, undated
	Peanut oil	90	Hercules Inc., undated
	Corn oil	120-125	Shelanski and Gellhorn, undated
	Corn oil	60	Hercules Inc., undated
Mice	Corn oil	112	Hercules Inc., undated
	Unspecified oil	80	Rico, 1961
Cats	Peanut oil	25-40	Hercules Inc., undated
	Unspecified oil	100	Rico, 1961
Dogs	Peanut oil	25	Lackey, 1949a
	Corn oil	49	Hercules Inc., undated
	Unspecified oil	100	Rico, 1961
Rabbits	Peanut oil	75-100	Hercules Inc., undated
Guinea Pigs	Corn oil	270	Hercules Inc., undated
	Unspecified oil	80	Rico, 1961

*+ standard error.
**95 percent confidence interval.

TABLE 7

Acute Dermal Toxicity of Toxaphene to Laboratory Mammals

Organism	Vehicle	Dose (mg/kg)	Response	Reference
Rats				
Sherman, male, (>90 days, >175 g) unfasted	Xylene	1075 (717-1613)	LD_{50} (95% Confidence Interval)	Gaines, 1960 and 1969
Rats				
Sherman, female, (>90 days, >175 g)	Xylene	780 (600-1014)	LD_{50} (95% Confidence Interval)	Gaines, 1960 and 1969
Rats	Xylene	930	LD_{50}	Hercules, Inc., undated
Rabbits	Dust	>4000	LD_{50}	Hercules, Inc., undated
Rabbits	Peanut oil	<250	LD_{50}	Hercules, Inc., undated

Distribution

Toxaphene is readily distributed throughout the body, with highest residues found in fat tissue. Three hours after single intubations of ^{36}Cl labeled toxaphene in a mixture of peanut oil and acacia, rats had detectable levels of ^{36}Cl activity in all tissues examined (kidney, muscle, fat, testes, brain, blood, liver, intestines, esophagus, spleen, and stomach). The highest levels were found in the stomach and blood. By nine days after dosing, 6.57 percent of the administered dose (measured as ^{36}Cl activity) remained in the organism, with most of the activity found in the fat, blood, liver, and intestines (Crowder and Dindal, 1974). In a similar single dose study using rats, with corn oil as the vehicle (Ohsawa, et al. 1975), both ^{14}C labeled toxaphene (8.5 mg/kg) and ^{14}C labeled 2,2,5-endo-, 6-exo-, 8,9,10-heptachloroborane (2.6 mg/kg) (a component of toxaphene) were found primarily in the fat, liver, kidneys, and blood after 14 and 9 days, respectively. These patterns are consistent with toxaphene redistribution from the fat via the circulatory system to kidneys and liver prior to urinary and fecal elimination (see Metabolism and Excretion sections).

The predominance of fat storage has also been demonstrated in 12-week feeding studies with rats (Clapp, et al. 1971) and 2-year feeding studies with rats and dogs (Lehman, 1952a; Hercules, Inc., undated). In all these studies, toxaphene residues were highest in fat tissue but remained below the levels administered in the diet. This is consistent with the relatively rapid elimination of toxaphene by mammals (see Excretion section).

Metabolism

Toxaphene undergoes reductive dechlorination, dehydrochlorination, and hydroxylation in mammalian systems.

In the study by Crowder and Dindal (1974) using ^{36}Cl labeled toxaphene, about 68 percent of the activity was recovered as ionic chloride. Similarly, Ohsawa, et al. (1975) found that of seven ^{36}Cl labeled toxaphene fractions administered by intubation to rats, all were dechlorinated by about 50 percent. Based on the recovery of both ^{14}C and ^{36}Cl labeled toxaphene, these investigators concluded that only 3 percent of the original dose is excreted unchanged and only 2 percent is eliminated as carbon dioxide.

For technical (i.e., commercial grade) toxaphene, both reductive dechlorination and dehydrochlorination occur in reduced bovine blood hematin solutions, and 50 percent dechlorination has been noted in toxaphene incubated with rat liver microsomes and reduced nicotinamide adenine dinucleotide phosphate (NADPH) under anaerobic conditions (Khalifa, et al. 1976). Reductive dechlorination has also been demonstrated for heptachloroborane, a component of toxaphene (Saleh, et al. 1977; Chandurkar, 1977; Pollock, 1978).

Toxaphene has been shown to yield a type I binding spectra with hepatic cytochrome P-450 of rats, mice, and rabbits, which suggests that toxaphene may serve as a substrate for the hepatic microsomal mixed-function oxidase system (Kulkarni, et al. 1975). Type II binding has not been observed. Metabolism by the hepatic microsomal mixed function oxidase system is further suggested by the potentiation of toxaphene by piperonyl butoxide (Saleh, et al.

1977) and the demonstrated NADPH dependence for the *in vitro* hydroxylation of nonachloroborane (a toxaphene component) by rat liver microsomes (Chandurkar, 1977).

In comparing the chromatographic patterns of toxaphene residues found in the liver, feces, and fats, both Pollock (1978) and Saleh, et al. (1977) have noted that only fat residues approximate those of whole toxaphene, while residues in both the liver and feces are consistently more polar.

Excretion

The half-life of ^{14}C or ^{36}Cl labeled toxaphene in rats after single oral doses appears to be from 1 to 3 days, with most of the elimination occurring via the urine and feces (Crowder and Dindal, 1974; Ohsawa, et al. 1975). Only a small portion of the urine and fecal metabolites are eliminated as glucuronide or sulfate conjugates (Chandurkar, 1977).

As mentioned in the Absorption section, elevated toxaphene blood levels in one individual in the U.S. EPA (1978) study were associated with the consumption of toxaphene-contaminated fish (catfish fillet with a toxaphene residue of 52 µg/g wet weight). On the first day that blood samples were taken, toxaphene was found in the blood of this individual at a concentration of 142 µg/l. Eleven days after this measurement, the concentration of toxaphene in the blood had fallen to 47 µg/l. By 14 days after the initial measurement, toxaphene blood levels were below the limit of detection (30 µg/l).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Information on the acute oral toxicity of toxaphene to laboratory animals is summarized in Table 6. In cases of acute intoxication, toxaphene, like most chlorinated hydrocarbon insecticides, appears to act as a central nervous system stimulant. However, unlike DDT, toxaphene does not significantly affect conduction in the rat superior cervical ganglion (Whitcomb and Santolucito, 1976). Published reports of cases of acute poisoning of humans by ingestion of toxaphene are summarized in Table 8. In these cases, convulsions are the most consistent clinical signs of intoxication. Similar effects have been observed in both rats and dogs (Lehman, 1951). Along with convulsions, hyperreflexia has been noted in dogs (Lackey, 1949a,b), rats (Boyd and Taylor, 1971), and humans (Haun and Cueto, 1967). Additional unpublished reports (U.S. EPA, 1976d) of poisoning in humans describe the major symptoms of oral intoxication as vomiting, convulsions, cyanosis, and coma. Based on a review of the acute toxicity of toxaphene to experimental mammals and cases of human poisoning, Conley (1952) has estimated the minimum lethal oral dose of toxaphene for man to be between 30 and 103 mg/kg body weight. In rats, pathological effects of toxaphene include cloudy swelling and congestion of the kidneys, fatty degeneration and necrosis of the liver, and decreased spermatogenesis (Boyd and Taylor, 1971). Mehendale (1978) has reported that toxaphene (100 mg/kg in the diet for eight days) inhibits hepatobiliary function in rats.

TABLE 8

Case Studies of Toxaphene Poisoning in Humans in which Ingestion is the Primary Route of Entry

Case No.	1*	2*	3*	4*	5*	6*	7**
Subject(s)	Male, 2 yrs 8 mo	Male, 4 yrs	Male, 1 yr 5 mo	Male, 2 yrs	Female, 20 yrs Female, 16 yrs Female, 12 yrs	Male, adult Male, young Female, adult	Female, 9 mo.
Nature of toxaphene	Wax	Emulsion in water	60% in solvents	20% in solution	Residue of spray in food	Residue of spray in food	Powder, 13.8% toxaphene, 7.04% DDT
Dose	Unknown	Unknown	100 mg/kg	Unknown	9.5-47 mg/kg	Unknown	Unknown
Time to react to onset of symptoms	~7 hours	2 hours	N]S]	N]S]	1.5-4 hours	4 hours	A few hours
Symptoms	Convulsions	Convulsions 2-5 minute intervals	Convulsions intermittent	Convulsions, intermittent; mild cerebral excitement; aimless jerking motion and excessive muscular tensions of extremities, marked pharyngeal and laryngeal spasms; labored respiration; cyanosis	Nausea; vomiting convulsions	No nausea; spontaneous vomiting; convulsions jerking and transitory movements; muscular rigidity; periods of unconsciousness; amnesia(?)	Vomiting; diarrhea; convulsions; hyperreflexia; tachycardia; b.p. 140/100; labored respiration; respiratory failure
Outcome	Death	Death	Death	Recovery	Recovery	Recovery	Death
Time to death or recovery	9.5 hours	6 hours	11 hours	12 hours	~12 hours	<1 day(?)	~9 hours

*McGee, et al. 1952
**Haun and Cueto, 1967

The acute dermal toxicity of toxaphene is summarized in Table 7. Toxaphene appears to be somewhat less toxic when administered dermally. In rats the ratios of dermal to oral LD_{50}s range from 10 to 12 (Gaines, 1960, 1969; Hercules, Inc., undated). Without providing documentation, Hayes (1963) estimates the hazardous dermal dose for humans at 46 g. For a 70 kg man, this is approximately 660 mg/kg. Dermal LD_{50}s for rats range from 780 to 1075 mg/kg (Gaines, 1960, 1969; Hercules Inc., undated).

Table 9 summarizes the effects of subacute oral administration of toxaphene to laboratory mammals. Except for convulsions observed in dogs given 5 mg/kg/day, none of the exposures detailed in Table 9 resulted in clinical signs of toxaphene poisoning. The ability of dogs to tolerate large cumulative doses (176 to 424 mg/kg) when given at 4 mg/kg/day suggests a rather sharp threshold level for central nervous system stimulation. This is consistent with information discussed in the Excretion section, showing that toxaphene is eliminated relatively rapidly. A similar pattern is seen in rats on intraperitoneal injection. Ohsawa and coworkers (1975) have found that male rats injected with 50 mg toxaphene (approximately 300 mg/kg) every 48 hours tolerated cumulative doses of 700 to 2,000 mg/kg (over 10 times the single oral LD_{50} dose) before marked lethality occurred.

In subacute exposures that do not cause apparent central nervous system stimulation, no increases in mortality are noted. However, pathological changes of the kidneys and liver, as well as changes in blood chemistry, seem to be common features of subclinical toxaphene intoxication.

TABLE 9

Subacute Oral Toxicity of Toxaphene

Organism	Vehicle	Duration	Dose mg/kg/day or ppm in diet)	Estimated cumulative dose (mg/kg)	Response*	Reference
Mice, both albino and wild strains	Diet	Several weeks or months	50 mg/kg/day (250-480 ppm)	300	Changes in blood chemistry and urine protein	Baeumler, 1975
Rats	Diet	12 weeks	189 ppm		No apparent adverse effects	Clapp, et al. 1971
Rats	N.S.**	7 months	1.2-4.8 mg/kg/day	250-1000	Temporary change in blood chemistry	Grebenyuk, 1970
Rats, Sherman, male and female, ~100 g	Diet	2-9 months	50 and 200 ppm		Questionable liver pathology	Ortega, et al. 1957
Rats and guinea pigs	Diet	6 months	100-800 ppm		No significant effect	Shelanski and Gellhorn, undated
Dogs	Corn oil	"A few days"	5 mg/kg/day	~15-35	Convulsion	Lackey, 1949a
	Corn oil	44 days	4 mg/kg/day	176	Questionable liver pathology: renal tubular degeneration	Lackey, 1949a
	Corn oil	106 days	4 mg/kg/day	424	Questionable liver pathology: renal tubular degeneration	Lackey, 1949a

*See text for details.
**N.S. - not specified.

Ortega, et al. (1957) (using rats) and Lackey (1949a) (using dogs) have noted similar changes in liver histology after toxaphene administration. Morphologically, these changes appear as vacuoles of plasma with occasional red blood cells found within hepatic cells. This condition, referred to as hydropic accumulation, is distinct from fatty degeneration. In neither rats nor dogs was hydropic accumulation associated with the destruction of hepatic cells. However, Ortega, et al. (1957) also noted occasional masses of red blood cells invading the cytoplasm of liver cells in areas of hypertrophy and margination. In addition to liver damage, Lackey (1949a) also noted widespread degeneration of the tubular epithelium, occasionally accompanied by inflammation of the pelvis of the kidney. Identical pathological changes were seen in dogs surviving prolonged dermal exposures to toxaphene (Lackey, 1949b). Ortega, et al. (1957), however, did not note any pathological changes attributable to toxaphene in the kidneys of rats.

As noted in Table 9, alterations in clinical chemistry have also been seen in subacute oral toxaphene exposures. Mice with no clinical signs of intoxication evidenced consistent increases in serum acid phosphatase, glutamicpyruvic transaminase, and gamma-glutyamyl transpeptidase activities, along with increased neutrophil counts and changes in urine protein (Baeumler, 1975). At a much lower daily dose, rats had only a transient increase in serum alkaline phosphatase during the fifth month of ingestion and showed no variation in urine hippuric acid (Grebenyuk, 1970). Increases in all of the above enzyme activities are consistent with the mild liver pathology associated with subacute toxaphene exposure.

Lehman (1952b) states that the 90-day dermal LD_{50} of toxaphene (as a dry wax) is 40 mg/kg in rabbits. No details of symptoms or pathology are provided.

Hercules Inc. (undated) has exposed human volunteers to toxaphene. Both dermal and inhalation routes of exposure were used. Toxaphene doses of 300 mg/day applied to the skin of 50 volunteers for 30 days produced no observable toxic effects. Similarily, cotton patches treated with toxaphene produced neither sensitization nor primary skin irritation when applied to the skin of 200 subjects. Shelanski (1974) indicates that humans exposed to toxaphene mists of 500 mg/m^3 of air for 30 minutes daily for 10 consecutive days followed by three daily exposures three weeks later showed no adverse effects, based on physical examinations as well as blood and urine tests.

However, Warraki (1963) has attributed two cases of acute bronchitis with miliary lung shadows to inhalation of toxaphene during applications of toxaphene formulation spray. Warraki does not specify the carriers used during the toxaphene spray applications of the cases that he summarized. However, he did indicate that toxaphene is usually applied as an emulsifiable concentrate containing 60 percent toxaphene, 35 percent kerosene, 3 percent xylol, and 2 percent emulsifier. Both individuals, male adults, had been exposed to toxaphene sprays from 1.5 to 2 months before the onset of pulmonary insufficiency. Maximum breathing capacity was between 19 and 22 percent of normal. Both adverse affects observed (pulmonary insufficiency and lung lesions) were reversible within three months after toxaphene exposure was discontinued. No

central nervous system effects were noted. One case of allergic rhinitis in a worker exposed to toxaphene by inhalation has been reported. However, details on the duration of his exposure were not given (U.S. EPA, 1976d). As with most reports of occupational poisoning, the possible role of exposure to other compounds complicates the interpretation of these case studies.

Long-term exposures to low dietary levels of toxaphene are summarized in Table 10. All studies note some form of liver pathology in rats at dietary levels of 100 mg/kg or above. At 100 mg/kg, cytoplasmic vacuolization similar to that seen on subacute oral exposure was noted by Kennedy, et al. (1973). Lehman (1952a) noted both cytoplasmic vacuolization and fatty degeneration of the liver in rats fed 100 mg/kg. With a 25 mg/kg diet, Fitzhugh and Nelson (1951) observed increased liver weight with minimal liver cell enlargement. Unpublished studies on rats, dogs, and monkeys by Hercules Inc. (undated) are in general agreement with the above published reports. The lowest dietary level of toxaphene producing unequivocal liver damage over a 2-year feeding period is 20 mg/kg diet. Only at relatively high concentrations, i.e., 1,000 mg/kg diet, does chronic toxaphene exposure elicit central nervous system effects characteristic of acute intoxication.

No cases of chronic human intoxication have been encountered in the literature.

Synergism and/or Antagonism

Induction of hepatic microsomal mixed-function oxidase appears to account for most of the interactions of toxaphene with other compounds. In rats pretreated with aldrin or dieldrin and

TABLE 10

Chronic Toxicity of Toxaphene at Low Dietary Levels to Laboratory Mammals

Organism	Duration of Feeding	Toxaphene Concentration in Diet	Response*	Reference
Rats, Sprague-Dawley	3 generations	25 mg/kg**	No effect	Kennedy, et al. 1973
		100 mg/kg	Liver pathology	
Rats	Lifetime	25 mg/kg	No effect	Lehman, 1952a
		100 mg/kg	Liver pathology	
Rats	Lifetime	25 mg/kg	Liver pathology	Fitzhugh and Nelson, 1951
Rats	2 years	25 mg/kg	No effect	Hercules, Inc., undated
	2 years	100 mg/kg	Slight liver damage	
		1000-1600 mg/kg	CNS stimulation	
Dogs	2 years	5-20 mg/kg	No effect	Hercules, Inc., undated
Dogs	2 years	40 mg/kg	Slight liver degeneration	Hercules, Inc., undated
		200 mg/kg	Moderate liver degeneration	Hercules, Inc., undated
Dogs	1360 days (3.7 years)	5 mg/kg/day*	Liver necrosis	Hercules, Inc., undated
Monkeys	2 years	10-15 mg/kg (0.64-0.78 mg/kg/day)	No clinical or histological effects	Hercules, Inc., undated

*Administered in capsules containing toxaphene dose in corn oil; 5 mg/kg/day equivalent to 200 mg/kg in diet.
**Diets prepared fresh weekly. (The other studies in this table did not specify frequency).

evidencing increased liver O-dealkylase and O-demethylase activities, toxaphene 96-hour LD_{50} values were approximately two times higher (indicating decreased toxicity) than those of rats given no pretreatment. Similarly, pretreatment with DDT, a known inducer of hepatic microsomal mixed-function oxidase, resulted in a 3-fold increase in the 96-hour LD_{50} of toxaphene in rats (Deichmann and Keplinger, 1970). Piperonyl butoxide, which inhibits the metabolism of many toxicants by mixed-function oxidase, has been shown to potentiate the toxicity of toxaphene in house flies (Saleh, et al. 1977).

When administered by intubation to rats, equitoxic combinations of toxaphene with parathion, diazinon, or trithion were less toxic than would be expected, based on the assumption of simple similar action (Keplinger and Deichmann, 1967).

Cases of acute human intoxication by toxaphene-lindane mixtures have been reported. In one instance, (Pollock, 1958) a 70-year-old male had his hands in contact with a toxaphene-lindane solution for two hours. After 10 hours, the following symptoms developed: headache, poor coordination, lassitude, severe nausea, and vomiting. Over the next week, this individual exhibited mild hyperthermia, flaccid musculature, and decreased response to stimuli. Only after nine days did the individual become semicomatose. At no time were convulsions or hyperreflexia noted. These signs and symptoms are not characteristic of toxaphene or lindane poisoning (Matsumura, 1975) and differ markedly from the previously described cases of acute oral toxaphene poisoning in humans. While clinical signs of intoxication may be expected to show some varia-

tion with different routes of entry, such profound variation is uncommon with the chlorinated insecticides. Gaines (1960, 1969) noted no difference between signs of intoxication in rats orally and dermally exposed to a variety of pesticides. Lackey (1949a,b) similarly noted no remarkable differences in the response of dogs to subacute oral and dermal doses of toxaphene.

Two cases of acute aplastic anemia associated with dermal exposure to toxaphene/lindane mixtures have been reported (U.S. EPA, 1976d). One of these cases resulted in death due to acute myelomonocytic leukemia which was presumed to be secondary to the development of aplastic anemia. Thus, while toxic anemia has not been reported in laboratory mammals experiencing acute toxaphene poisoning, such an effect may be hazardous in man in instances also involving lindane exposure.

Teratogenicity

In a study by Kennedy, et al. (1973), male and female rats were fed toxaphene at dietary levels of 25 and 100 mg/kg. Gross and microscopic pathology of F_3 weanlings revealed no indication of teratogenic effects. Further, no statistically signficiant variations from controls were noted in either dose group for any of the following parameters: mating index, fertility index, pregnancy index, parturition index, mean viable litter size, live birth index, 5-day survival index, lactation index, or weaning body weights of offspring. One of sixteen females from each dose group resorbed an entire litter. This was not seen in any of the 32 control females but did occur in tests with another pesticide, Delnav®.

In multigeneration studies of mice given toxaphene at 25 mg/kg diet, no effects on fertility, gestation, viability, lactation, or survival indices were observed (Keplinger, et al. 1970).

In addition to these long-term dietary studies, one study (Chernoff and Carver, 1976) has been conducted in which toxaphene in corn oil was administered to pregnant female rats and mice from days 7 to 16 of gestation at doses of 15, 25, and 35 mg/kg/day. All doses produced signs of maternal and fetal toxicity but did not produce teratogenic effects.

DiPasquale (1977) has examined the effects of toxaphene on fetal guinea pig development. In this study, toxaphene was administered to pregnant females at a dose of 15 mg/kg body weight orally from day 21 to day 35 of gestation. No effects were noted on anatomical development of the fetus. The only sign of fetotoxicity was a decrease in collagen-containing structures. This was attributed to a functional deficiency of vitamin C related to mixed-function oxidase induction. Maternal guinea pigs showed a slight loss of body weight, but no effects attributable to toxaphene exposure were seen on maternal liver weight or mortality.

Mutagenicity

Epstein, et al. (1972) have used a modified dominant lethal assay in mice to evaluate the mutagenic potential of a variety of chemical agents including toxaphene. In this study, four groups of male ICR/Ha Swiss mice were given toxaphene either intraperitoneally (single doses of 36 mg/kg or 180 mg/kg) or orally (five doses of 8 mg/kg/dose or 16 mg/kg/dose). After dosing, the treated males were mated to groups of untreated females over an 8-week period.

Based on measurements of early fetal deaths per pregnancy and the percent of females with early fetal deaths, the toxaphene-treated groups did not differ significantly from controls. Thus, in this strain of mice, toxaphene apparently does not produce chromosomal abnormalities that preclude zygote development.

Hill (1977) has summarized information on the mutagenicity testing of toxaphene in bacterial systems. Ames tests have been conducted on Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with and without metabolic activation by noninduced mammalian liver fractions. Positive results were obtained for strains TA 98 (frameshift mutation) and TA 100 (base pair substitution) only in tests without metabolic activation. All other tests were negative. A "high temperature" toxaphene has elicited positive dose response increases in strains TA 98 and TA 100 only with metabolic activation. All the above tests were conducted by Litton Bionetics Inc. for Hercules, Inc.

In addition to these studies, work has been conducted on the mutagenicity of toxaphene in the Salmonella system by Dr. Kim Hooper of Bruce Ames' group in Berkeley, Calif. (Hill, 1977). His results indicate that toxaphene and toxaphene subfractions are mutagenic to strain TA 100 with and without activation by Aroclor® induced rat microsomes. Mutagenic activity was decreased in those tests using microsomal activation.

A recently completed study by U.S. EPA (1978) found no significant differences in the rates of chromosomal aberrations in leukocytes between groups of individuals occupationally exposed to toxaphene and groups with no occupational exposures to toxaphene.

Carcinogenicity

Under contract to the National Cancer Institute (NCI), Gulf South Research Institute has recently completed a carcinogenicity bioassay of toxaphene (NCI, 1979). It should be noted that this study, which was conducted from 1971 to 1973, did not follow current NCI protocols (NCI, 1977). Specifically, only 10 animals were used in each matched control group, and were not pair-fed. In this study, groups of Osborne-Mendel rats and B6C3F_1 hybrid mice were exposed to technical-grade toxaphene in the diet for 80 weeks. Details of the dose schedule and number of animals used are provided in Tables 11 and 12.

Toxaphene was added to the feed in acetone. In addition, 2 percent corn oil was added to the diet as a dust suppressant. Actual dietary toxaphene concentrations, which were confirmed by gas-liquid chromotography, did not deviate from the nominal concentration by more than 6.9 percent. In addition to the matched control groups indicated in these tables, pooled control groups were used in the statistical analyses. For rats, pooled controls consisted of matched controls from similar bioassays on captan, chloraben, lindane, malathion, and picloram, as well as the matched controls from the toxaphene bioassay. For mice, pooled controls consisted of matched controls from similar bioassays on lindane, malathion, phosphamidon, and tetrachlorvinphos, as well as the matched controls from the toxaphene study. Organisms used in all pooled control groups were of the same strains, from the same suppliers, and examined by the same pathologists.

TABLE 11

Toxaphene Chronic Feeding Studies in Rats[a]

Sex and Test Group	Initial No. of Animals(b)	Toxaphene in Diet(c) (mg/kg)	Time on Study (weeks) Dosed(d)	Time on Study (weeks) Observed(e)	Time-Weighted Average Dose(f) ppm
Male					
Matched-Control	10	0		108-109	
Low-Dose	50	1,280	2		556
		640	53		
		320	25		
		0		28	
High-Dose	50	2,560	2		1,112
		1,280	53		
		640	25		
		0		28	
Female					
Matched-Control	10	0		108-109	
Low-Dose	50	640	55		540
		320	25		
		0		30	
High-Dose	50	1,280	55		1,080
		640	25		
		0		30	

[a]Source: National Cancer Institute, 1979.

[b]All animals were 5 weeks of age when placed on study.

[c]Initial doses shown were toxic; therefore, doses were lowered after 2 weeks and again at 53 or 55 weeks, as shown.

[d]All animals were started on study on the same day.

[e]When diets containing toxaphene were discontinued, dosed rats and their matched controls were fed control diets without corn oil for 20 weeks, then control diets (2 percent corn oil added) for an additional 8 weeks.

[f]Time-weighted average dose = $\frac{\sum(\text{dose in ppm x no. of weeks at that dose})}{\sum(\text{no. of weeks receiving each dose})}$

TABLE 12

Toxaphene Chronic Feeding Studies in Mice[a]

Sex and Test Group	Initial No. of Animals(b)	Toxaphene in Diet(c) (mg/kg)	Time on Study (weeks) Dosed(d)	Time on Study (weeks) Observed(e)	Time-Weighted Average Dose(f) ppm
Male					
Matched-Control	10	0		90-91	
Low-Dose	50	160	19		99
		80	61		
		0		11	
High-Dose	50	320	19		198
		160	61		
		0		10	
Female					
Matched-Control	10	0		90-91	
Low-Dose	50	160	19		99
		80	61		
		0		11	
High-Dose	50	320	19		198
		160	61		
		0		10	

[a]Source: National Cancer Institute, 1979.

[b]All animals were 5 weeks of age when placed on study.

[c]Initial doses shown were toxic; therefore, doses were lowered at 19 weeks, as shown.

[d]All animals were started on study on the same day.

[e]When diets containing toxaphene were discontinued, dosed mice and their matched controls were fed control diets without corn oil for 7 weeks, then control diets (2 percent corn oil added) for an additional 3 to 4 weeks.

[f]Time-weighted average dose = $\frac{\Sigma(\text{dose in ppm} \times \text{no. of weeks at that dose})}{\Sigma \text{ (no. of weeks receiving each dose)}}$

During the course of this study, both rats and mice evidenced signs of general toxic effects. Both male and female rats in the high-dose group developed body tremors at week 53. From week 52 to week 80, other clinical signs, which occurred primarily in toxaphene-dosed rats, included diarrhea, dyspnea, pale mucous membranes, alopecia, rough hair coats, dermatitis, ataxia, leg paralysis, epistasis, hematuria, abdominal distention, and vaginal bleeding. Female rats in both dose groups had lower mean body weights than the matched controls. No dose-related effect on mortality was noted in any of the rat test groups. In mice, males and females in each dose group displayed a significant increase in mortality when compared to the matched controls. In high-dose male mice, mean body weights were generally lower than those in the matched control group. Clinical signs of toxicity in mice included abdominal distention, diarrhea, alopecia, rough hair coats, and dyspnea.

The effects of dietary toxaphene on tumor incidence in male rats, female rats, male mice, and female mice are summarized in Tables 13, 14, 15, and 16, respectively.

In male rats in the high dose group, a significant increase was noted in the incidence of follicular-cell carcinomas or adenomas of the thyroid. Of the nine thyroid tumors that were found in this group, two were carcinomas. A significant increase of follicular-cell adenomas of the thyroid was also noted in the high-dose group of female rats; however, no carcinomas were found. In both of these groups, the development of thyroid tumors was dose-related. A significant increase was also noted in the incidence of chromophobe adenomas, chromophobe carcinomas, and adenomas of the

TABLE 13

Analyses of the Incidence of Primary Tumors in Male Rats Fed Toxaphene in the Diet[a,b]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Neoplastic Nodule(c)	1/9 (11)	1/52 (2)	6/44 (14)	4/45 (9)
p Values(d)	N.S.	N.S.	p = 0.034**	N.S.
Weeks to First Observed Tumor	109	--	p = 108	94
Pituitary: Chromophobe Adenoma, Carcinoma, NOS, or Adenoma, NOS(c)	3/7 (43)	8/46 (17)	13/42 (31)	5/31 (16)
p Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	102	--	85	95
Adrenal: Adenoma, NOS, Cortical Adenoma, or Carcinoma	4/9 (44)	5/52 (10)	5/41 (12)	3/37 (8)
p Values(d,e)	p = 0.019 (N)	N.S.	p = 0.043 (N)*	p = 0.020 (N)*
Weeks to First Observed Tumor	--	--	p = 85	p = 85
Spleen: Hemangioma(c)	0/9 (0)	0/49 (0)	3/45 (7)	3/42 (7)
p Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	83	85
Thyroid: Follicular-cell Carcinoma or Adenoma(c)	1/7 (14)	2/44 (5)	7/41 (17)	9/35 (26)
p Values(d)	N.S.	p = 0.007	N.S.	p = 0.008**
Weeks to First Observed Tumor	109	--	104	56

[a]Source: National Cancer Institute, 1979.
[b]Dosed groups received time-weighted average doses of 556 or 1,112 ppm.
[c]Number of tumor-bearing animals/number of animals examined at site (percent).
[d]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when p less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparisons of that dosed group with the matched-control group (*) or with the pooled-control group (**) when p less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.
[e]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

TABLE 14

Analyses of the Incidence of Primary Tumors in Female Rats Fed Toxaphene in the Diet[a,b]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Integumentary System: Malignant Fibrous Histiocytoma of the Subcutaneous Tissue(c)	0/10 (0)	0/55 (0)	1/50 (2)	3/49 (6)
p Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--		105	83
Mammary Gland: Fibroadenoma(c)	1/10 (10)	6/55 (11)	10/50 (20)	10/49 (20)
p Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	87	--	19	67
Liver: Hepatocellular Carcinoma or Neoplastic Nodule(c)	1/10 (10)	1/55 (2)	5/42 (12)	4/40 (10)
p Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	109	--	108	109
Pituitary: Chromophobe Adenoma, Carcinoma, or Adenoma, NOS(c)	3/8 (38)	17/51 (33)	15/41 (37)	23/39 (59)
p Values(d)	p = 0.046	p = 0.012	N.S.	p = 0.013**
Weeks to First Observed Tumor	85	--	75	79
Thyroid: Follicular-cell Adenoma(c)	0/6 (0)	1/46 (2)	1/43 (2)	7/42 (17)
p Values(d)	p = 0.022	p = 0.008	N.S.	p = 0.021**
Weeks to First Observed Tumor	--	--	102	105

TABLE 14 (continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Adrenal: Cortical Adenoma or Carcinoma(c)	0/8 (0)	3/50 (6)	3/44 (7)	6/43 (14)
p Values(d)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	104	87
Uterus: Endometrial Stromal Polyp(b)	0/9 (0)	5/53 (9)	9/41 (22)	5/45 (11)
p Values(c)	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	87	109

[a]Source: National Cancer Institute, 1979.

[b]Dosed groups received time-weighted average doses of 540 or 1,080 mg/kg.

[c]Number of tumor-bearing animals/number of animals examined at site (percent).

[d]Beaneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when p less than 0.05; otherwise not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when p less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

TABLE 15

Analyses of the Incidence of Primary Tumors in Male Mice Fed Toxaphene in the Diet[a,b]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma(c)	0/10 (0)	4/48 (8)	34/49 (69)	45/46 (98)
p Values(d)	$p < 0.001$	$p < 0.001$	$p < 0.001$*	$p < 0.001$*
			$p < 0.001$**	$p < 0.001$**
Weeks to First Observed Tumor	--	--	73	59
Liver: Hepatocellular Carcinoma or Neoplastic Nodule(c)	2/10 (20)	7/48 (15)	40/49 (82)	45/46 (98)
p Values(d)	$p < 0.001$	$p < 0.001$	$p < 0.001$*	$p < 0.001$*
			$p < 0.001$**	$p < 0.001$**
Weeks to First Observed Tumor	90	--	73	59

[a]Source: National Cancer Institute, 1979.

[b]Dosed groups received time-weighted average doses of 99 or 198 mg/kg.

[c]Number of tumor-bearing animals/number of animals examined at site (percent).

[d]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when p less than 0.05; otherwise not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when p less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

TABLE 16

Analyses of the Incidence of Primary Tumors in Female Mice Fed Toxaphene in the Diet[a,b]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma(c)	0/9 (0)	0/48 (0)	5/49 (10)	34/49 (69)
p Values(d)	$p < 0.001$	$p < 0.001$	$p = 0.030$**	$p < 0.001$* $p < 0.001$**
Weeks to First Observed Tumor	--	--	89	72
Liver: Hepatocellular Carcinoma or Neoplastic Nodule(c)	0/9 (0)	0/48 (0)	18/49 (37)	40/49 (82)
p Values (d)	$p < 0.001$	$p < 0.001$	$p = 0.026$* $p < 0.001$**	$p < 0.001$* $p < 0.001$**
Weeks to First Observed Tumor	--	--	89	72

[a]Source: National Cancer Institute, 1979.

[b]Dosed groups received time-weighted average doses of 99 or 198 mg/kg.

[c]Number of tumor-bearing animals/number of animals examined at site (percent).

[d]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when p less than 0.05; otherwise not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group (*) or with the pooled-control group (**) when p less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

pituitary in the high-dose group of female rats. However, an examination of historical control data on the incidence of pituitary tumors in female rats suggested that an association between the administration of toxaphene and the development of pituitary tumors could not be maintained.

In both male and female mice, significant increases were noted in the incidence of hepatocellular carcinomas and in the incidence of hepatocellular carcinomas combined with neoplastic nodules of the liver. Based on the results of this study, the NCI (1979) has concluded: "Toxaphene is carcinogenic in male and female $B6C3F_1$ mice, causing increased incidences of hepatocellular carcinomas. The test results also suggest carcinogenicity of toxaphene for the thyroid of male and female Osborne-Mendel rats."

Litton Bionetics, Inc. (1978) reported a study in the $B6C3F_1$ strain of male and female mice fed at doses of 7, 20, and 50 ppm toxaphene in the diet. This study showed a statistically significant excess of hepatocellular tumors (hepatocellular adenoma plus hepatocellular carcinoma) in male mice, but only at the 50 ppm dose. Toxaphene in a corn oil premix was added to the basal diet and blended; the control diets contained an equal amount of added corn oil. Animals were maintained on dietary toxaphene treatment for 18 months, followed by a 6-month period of observation (Table 17). At the end of this 2-year study, surviving animals were sacrificed and histopathologic examination of the major organs was initiated. Intercurrent deaths were evaluated by histopathology as they occurred.

TABLE 17

Toxaphene Chronic Feeding Studies in Mice*

Sex and Test Group		Initial No. of Animals**	Toxaphene in Diet (mg/kg)	Dosed (weeks)	Observed (weeks)
	Male				
Group 1	Matched-Control	54	0	78	105
Group 2	Low-Dose	54	7	78	105
Group 3	Med-Dose	54	20	78	105
Group 4	High-Dose	54	50	78	105
	Female				
Group 1	Matched-Control	54	0	78	105
Group 2	Low-Dose	54	7	78	105
Group 3	Med-Dose	54	20	78	105
Group 4	High-Dose	53	50	78	105

*Source: Litton Bionetics, Inc., 1978.

**Weanling $B6C3F_1$ mice were placed on study following seven days of acclimation.

Analysis of the combined hepatocellular tumor incidence indicated a statistically significant increase (Fisher Exact Test) in male mice treated with 50 ppm levels of toxaphene (Table 18). A dose-related increase in the incidence of this tumor type was determined using the Cochran Armitage Trend Test. Female mice did not show a significant increase in hepatocellular tumor incidence at any level of toxaphene treatment (Table 19).

The major increase in tumor incidence for male mice administered 50 ppm levels of toxaphene was in hepatocellular adenomas. This nonmalignant tumor type occurs with increasing age in controls of the $B6C3F_1$ strain of mice.

TABLE 18

Analysis of the Incidence of Hepatocellular Tumors in Male Mice Fed Toxaphene*

SEX	MALES			MALES		
GROUP NUMBER	GROUP 1			GROUP 2		
TYPE OF DEATH	T	I	T + I	T	I	T + I
NUMBER OF LIVERS EXAMINED	(44)	(9)	(53)	(47)	(7)	(54)
Hepatocellular adenomas	3	0	3	0	0	0
Hepatocellular carcinomas	5	2	7	9	2	11
Total hepatocellular tumors	8	2	10	9	2	11
Total number of livers bearing hepatocellular tumors		10/53 (19%)++			10/54 (19%)++	

SEX	MALES			MALES		
GROUP NUMBER	GROUP 3			GROUP 4		
TYPE OF DEATH	T	I	T + I	T	I	T + I
NUMBER OF LIVERS EXAMINED	(45)	(8)	(53)	(46)	(5)	(51)
Hepatocellular adenomas	2	0	2	11	0	11
Hepatocellular carcinomas	10	2	12	11	1	12
Total hepatocellular tumors	12	2	14	22	1	23
Total number of livers bearing hepatocellular tumors		12/53 (23%)++			18/51 (35%)+,++	

*Source: Litton Bionetics, Inc., 1978

T = Terminal kill

I = Intercurrent death

+ = Fisher's Exact Test (Group 4 compared to Group 1): P = 0.048 (1 tailed)

++ = Cochran Armitage Trend Test: P = 0.020

TABLE 19

Analysis of the Incidence of Hepatocellular Tumors in Female Mice Fed Toxaphene*

SEX	FEMALES			FEMALES		
GROUP NUMBER	GROUP 1			GROUP 2		
TYPE OF DEATH	T	I	T + I	T	I	T + I
NUMBER OF LIVERS EXAMINED	(46)	(7)	(53)	(46)	(7)	(53)
Hepatocellular adenomas	1	0	1	1	0	1
Hepatocellular carcinomas	1	0	1	1	0	1
Total hepatocellular tumors	2	0	2	2	0	2
Total number of livers bearing hepatocellular tumors		2/53 (4%)			2/53 (4%)	

SEX	FEMALES			FEMALES		
GROUP NUMBER	GROUP 3			GROUP 4		
TYPE OF DEATH	T	I	T + I	T	I	T + I
NUMBER OF LIVERS EXAMINED	(43)	(9)	(52)	(45)	(7)	(52)
Hepatocellular adenomas	1	0	1	3	0	3
hepatocellular carcinomas	3	0	3	2	1	3
Total hepatocellular tumors	4	0	4	5	1	6
Total number of livers bearing hepatocellular tumors		4/52 (8%)			6/52 (12%)	

*Source: Litton Bionetics, Inc., 1978

T = Terminal kill

I = Intercurrent death

CRITERION FORMULATION

Existing Guidelines and Standards

Standards for toxaphene in air, water, and food have been established or recommended by many groups. However, all these standards were set before the results of the NCI bioassay of toxaphene for carcinogenicity were available.

Both the Occupational Safety and Health Administration (39 FR 23540) and the American Conference of Governmental Industrial Hygienists (ACGIH, 1977a) established a time-weighted average value of 500 $\mu g/m^3$ for toxaphene in the air of the working environment. The ACGIH (1977b) based this standard on unpublished acute and chronic toxicity studies conducted in the 1950's and on comparisons of the toxicity of toxaphene with DDT and lindane. In addition, this group set a tentative short-term exposure limit for toxaphene of 1.0 mg/m^3 (ACGIH, 1977a).

The national interim primary drinking water standard for toxaphene is 5 µg/l (40 FR 11990; U.S. EPA 1976b,c). This standard is based on the reported organoleptic effects of toxaphene at concentrations above 5 µg/l (Cohen, et al. 1961; Sigworth, 1965). A standard of 25 µg/l was also calculated based on minimal or no effects in rats after they were fed toxaphene at a concentration of 10 mg/kg in the diet, which was estimated to give an average daily dose of 1 mg/kg body weight (Lehman, 1965). This latter calculation used the following assumptions:

weight of rat = 300 g
daily food consumption of rat = 50 g
weight of average human adult = 70 kg
average daily water intake for man = 2 liters
safety factor = 500
dietary intake = trace (assume zero)

From these assumptions, the maximum safe daily dose for human was estimated to be 3.4 µg/kg body weight (U.S. EPA, 1976b). It should be noted, however, that the assumption of 50 g daily food consumption for a 300 g rat is probably excessively high.

The National Academy of Sciences (NAS, 1977) estimated the acceptable daily intake of toxaphene for man at 1.25 µg/kg. This was based on a study by Fitzhugh and Nelson (1951), summarized in Table 10, in which rats evidenced increased liver weight and hepatic cell enlargement after exposure to toxaphene at 25 mg/kg diet for two years. In their estimation NAS assumed the daily dose in rats during the Fitzhugh and Nelson study was equivalent to 1.25 mg/kg body weight, and the application of a safety factor of 1,000 was appropriate. Then, assuming a human body weight of 70 kg and a daily water consumption of 2 liters, NAS set the suggested no-adverse-effect level from water at 8.75 µg/l (assigning 20 percent of the total ADI to water) or 0.44 µg/l (assigning 1 percent of the total ADI to water).

Tolerances established by the FDA for toxaphene residues in various agricultural products are given in Table 20.

In Canada, the tolerance for toxaphene in citrus fruits is 7.0 mg/kg. In both the Netherlands and West Germany, the corresponding standard is 0.4 mg/kg (Gunther, 1969).

WHO has not yet established an acceptable daily intake level for toxaphene (WHO, 1974a,b, 1976). The following information is considered necessary by WHO (1974b) before an acceptable daily intake can be established:

TABLE 20

Tolerances for Toxaphene Residues in Various Agricultural Products

Residue level (mg/kg)	Product	Reference
7	Fat of meat from cattle, goats, and sheep	22 FR 4615
	Fat of meat from hogs	24 FR 4727
	Fat of meat from horses	27 FR 7492
	Cranberries, hazelnuts, hickory nuts, horseradish, parsnips, pecans, peppers, pimentos, rutabagas, walnuts	22 FR 4615
	Collards, kale, spinach	27 FR 7492
6	Crude soybean oil	31 FR 12435
5	Barley, oats, rice, rye, and wheat	23 FR 477
	Sorghum grain	25 FR 5335
	Cottonseed	26 FR 11799
3	Pineapple and bananas*	27 FR 4913
2	Soybeans, dry form	31 FR 9453
0.1	Sunflower seeds	U.S. EPA, 1977

*Of which not more than 0.3 mg/kg shall be in pulp after the peel is removed and discarded.

1. Adequate toxicological information on camphechlor (toxaphene) as currently marketed, including a carcinogenicity study.

2. Comparative studies evaluating the toxicological hazard associated with polychlorinated camphene of different manufacture used in worldwide agriculture.

3. Before recommendations can be made concerning residues from the use of camphechlor, other than that conforming to FAO specifications, information is needed on the composition, uses, and residues arising from such products.

Nonetheless, the guideline levels for toxaphene in specified foods have been recommended by WHO (1974a) (Table 21). These recommendations are based on levels that might be expected if good application practices are followed and do not reflect a judgment concerning potential human hazard.

The International Joint Commission of the United States and Canada (1977) has recommended a water standard of 0.008 µg/l for the protection of aquatic life. This standard is based on the study by Mayer, et al. (1975) which found that toxaphene at 0.039 µg/l caused a significant increase in mortality and a significant decrease in growth in brook trout fry over a 90-day period. The standard of 0.008 µg/l is obtained by applying a safety factor of 5.

Finally, effluent standards for toxaphene manufacturers have been set at 1.5 µg/l for existing facilities and 0.1 µg/l for new facilities (41 FR 23576).

TABLE 21

Guideline Levels for Toxaphene in Specified Foods*

Food	Level	
Fat of meat of cattle, sheep, goats, and pigs	5	mg/kg
Broccoli, brussels sprouts, cabbage, celery, collards, eggplant, kale, kohlrabi, lettuce, okra, peppers, pimentos, spinach, tomatoes, barley, rice (rough), rye, sorghum, bananas (whole), pineapple, beans (snap, dry, lima), peas, cauliflower, oats, wheat, shelled nuts, carrots, onions, parsnips, radishes, rutabagas	2	mg/kg
Soybeans, peanuts (ground-nut), cotton-seed oil (refined), rape-seed oil (refined), soybean oil (refined), peanut oil (refined), maize, rice (finished)	0.5	mg/kg
Milk and milk products (fat basis)	0.5	mg/kg

*Source: World Health Organization, 1974a

Current Levels of Exposure

Quantitative estimates of human exposure to toxaphene are extremely difficult to make based on the data presented in the Exposure section. The three major obstacles are:

1. The wide variation in toxaphene concentrations noted in food, water, and air.
2. Conflicting information concerning the trend of toxaphene residues in food.
3. The marked seasonal and geographic difference in toxaphene concentrations found in air and food.

Given these problems, a conservative approach in estimating exposure to toxaphene is necessary.

An early estimate of dietary intake of toxaphene was 0.021 µg/kg/day, based on the FDA's market basket surveys between 1964 and 1970 (Duggan and Corneliussen, 1972). Although more recent market basket surveys indicate a decrease in the incidence of toxaphene contamination (see Table 1) and although the USDA survey suggests that the incidence of toxaphene contamination of raw meat has remained relatively stable since 1969 (see Tables 2 and 3), the FDA survey of unprocessed food samples shows an almost 2-fold increase in the incidence of toxaphene contamination between 1972 and 1976 (see Table 2). Given this conflicting information, the current dietary intake is estimated to be 0.042 µg/kg/day, twice that noted by Duggan and Corneliussen (1972).

No satisfactory estimate can be made of average national inhalation exposures. In areas where toxaphene is not used, inhalation

exposure may be negligible. Even in areas of high use, the apparent low absorption of toxaphene across the lungs suggests that inhalation may not be a significant source of exposure.

These admittedly tenuous exposure estimates are summarized as follows:

Source	Estimated Intake
Water	no estimate
Food	0.042 µg/kg/day
Air	0

Special Groups at Risk

Individuals working with toxaphene or living in areas where toxaphene is used or produced would seem to be at higher risk than the general population. However, as indicated previously (see Mutagenicity section), an increased incidence of chromosomal aberration has not been noted in groups with occupational exposure to toxaphene (U.S. EPA, 1978). Further, of 32 samples of human adipose tissue obtained in areas of high toxaphene usage from autopsy or surgery cases, only one sample contained detectable levels of toxaphene (0.13 ppm) (U.S. EPA, 1978). It appears, then, that individuals who live in areas of high toxaphene use or who have occupational exposure to toxaphene are not at greater risk than the general population.

Basis and Derivation of Criterion

Various water concentrations have already been recommended for toxaphene (see Existing Guidelines and Standards section). These concentrations, with the rationale, are summarized in Table 22.

TABLE 22

Water Concentrations for Toxaphene

Standard	Rationale	Source
5.0 µg/l	Organoleptic effects	U.S. EPA, 1976b
8.75 µg/l	Noncarcinogenic mammalian toxicity	NAS, 1977
0.44 µg/l	Noncarcinogenic mammalian toxicity	NAS, 1977
0.008 µg/l	Aquatic toxicity data	Int. Joint Comm., 1977

Since the results of the NCI bioassay of toxaphene for carcinogenicity were positive (see Appendix I), estimated risk levels for toxaphene in water can also be calculated using a linearized multistage model as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice that announced the availability of this document.

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." Toxaphene is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of toxaphene 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 toxaphene 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, U.S. EPA stated that it is con-

sidering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following table.

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	0.071 ng/l	0.71 ng/l	7.1 ng/l
Consumption of fish and shellfish only.	0	0.073 ng/l	0.73 ng/l	7.3 ng/l

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

(2) Approximately 98 percent of the toxaphene exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 13,100-fold. The remaining 2 percent of toxaphene exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of toxaphene (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing

the corresponding toxaphene concentrations and (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding toxaphene concentrations. Because data indicating other sources of toxaphene 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 I

Summary and Conclusions Regarding the Carcinogenicity of Toxaphene*

Toxaphene is a mixture of polychlorinated camphenes. It was found to be mutagenic for Salmonella typhimurium strains TA 98 and TA 100 without metabolic activation. Two studies, (1) the National Cancer Institute (NCI) bioassay (dietary study) on toxaphene in mice and rats, and (2) the Bionetics Research Laboratory dietary study (sponsored by Hercules, Inc.) in mice, have demonstrated that toxaphene is carcinogenic to both mice and rats.

The NCI dietary study using male and female $B6C3F_1$ mice at doses of 99 and 198 ppm revealed a statistically significant excess of hepatocellular carcinomas in male and female mice at both dose levels. The Bionetics Research Laboratory study in the same strain ($B6C3F_1$) of male and female mice fed at doses of 7, 20, and 50 ppm in the diet showed a statistically significant excess of hepatocellular tumors (hepatocellular adenoma plus hepatocellular carcinoma) in male mice, but only at the 50 ppm dose.

The NCI bioassay study also showed a carcinogenic response induced by toxaphene in both male and female Osborne-Mendel rats only at the high dose level (1,080 ppm), consisting of a statistically significant excess of follicular-cell carcinomas and adenomas of the thyroid.

In summary, carcinogenic responses have been induced in mice and rats by toxaphene. These results, together with the positive mutagenic response, constitute substantial evidence that toxaphene is likely to be a human carcinogen.

The water quality criterion for toxaphene is based on incidence of hepatocellular carcinomas and neoplastic nodules from the Litton Bionetics $B6C3F_1$ male mice bioassay. It is concluded that the water concentration of toxaphene should be less than 7.1 ng/l in order to keep the lifetime cancer risk below 10^{-5}.

*This summary has been prepared by the Carcinogens Assessment Group, EPA, on June 15, 1979.

Derivation of the Water Quality Criterion for Toxaphene

The water quality criterion for toxaphene is derived from the development of hepatocellular carcinomas and neoplastic nodules in the $B6C3F_1$ male mice given several doses of toxaphene in the Litton Bionetics bioassay (Litton Bionetics, 1978). The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0.0	10/53
0.91	11/54
2.6	12/53
6.5	18/51

le = 540 days
Le = 735 days
L = 735 days
w = 0.030 kg
R = 13,100 l/kg

With these parameters, the carcinogenic potency factor for humans, q_1^* is 1.131 $(mg/kg/day)^{-1}$. The resulting water concentration of toxaphene calculated to keep the individual risk below 10^{-5} is 7.1 ng/l.

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