

**TOXICOLOGICAL PROFILE FOR  
TOXAPHENE**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**Public Health Service**  
Agency for Toxic Substances and Disease Registry

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## UPDATE STATEMENT

A Toxicological Profile for toxaphene was released in August 1994. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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Division of Toxicology/Toxicology Information Branch  
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## FOREWORD

This toxicological profile is prepared in accordance with guidelines\* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audience for the toxicological profiles is health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

[Redacted]

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## \*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Super-fund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on April 29, 1996 (61 FR 18744). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(l)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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### THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.
2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.
3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRL.





## PEER REVIEW

A peer review panel was assembled for toxaphene. The panel consisted of the following members:

1. Dr. William Buck, Private Consultant, Consul-Tox, Inc., 1206B County Road, 800N., Tolono, Illinois;
2. Mr. Anthony Donigian Jr., Private Consultant, AQUATERRA Consultants, 2672 Bayshore Parkway, Suite 1001, Mountain View, California; and
3. Dr. Donald Morgan, Private Consultant, 326 Highland Drive, Iowa City, Iowa.

These experts collectively have knowledge of toxaphene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.



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## 1. PUBLIC HEALTH STATEMENT

This public health statement tells you about toxaphene and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Toxaphene has been found in at least 58 of the 1,430 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with toxaphene may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to toxaphene, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

### 1.1 WHAT IS TOXAPHENE?

Toxaphene, also known as camphechlor, chlorocamphene, polychlorocamphene, and chlorinated camphene, is a manufactured insecticide containing over 670 chemicals. Toxaphene is usually found as a solid or gas. In its original form, toxaphene is a yellow to amber waxy solid that smells like turpentine. It does not burn and evaporates when in solid form or when mixed with liquids.

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Toxaphene was one of the most heavily used insecticides in the United States until 1982. It was used primarily in the southern United States to control insect pests on cotton and other crops.

Toxaphene was also used to control insect pests on livestock and to kill unwanted fish in lakes.

### 1.2 WHAT HAPPENS TO TOXAPHENE WHEN IT ENTERS THE ENVIRONMENT?

Toxaphene enters the environment after it is applied to a crop or poured into a lake. Toxaphene can enter the air (by evaporation), the soil (by sticking to soil particles), and the water (from runoff after rains). Toxaphene may also enter the environment from hazardous waste sites or when it accidentally spills or leaks during storage or transport. It does not dissolve well in water, so it is more likely to be found in air, soil, or the sediment at the bottom of lakes and streams. If toxaphene is found in surface water or groundwater, it is usually at very low levels. Once toxaphene is in the environment, it can last for years because it breaks down very slowly. This means there is still the chance of being exposed to toxaphene in the United States even though it has not been widely used for over 10 years. Because toxaphene breaks down slowly, exposure will probably be to the original material. For more information on the chemical and physical properties of toxaphene, refer to Chapter 3.

Levels may be high in some predatory fish and mammals because toxaphene accumulates in fatty tissues. For example, when a raccoon eats a contaminated fish, some of the toxaphene in the fish is transferred to the raccoon. The more contaminated fish the raccoon eats, the more toxaphene it acquires. This means that even when toxaphene levels are low or confined to a certain area, they could be high in individual animals. For more information on toxaphene in the environment, see Chapter 5.

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### 1.3 HOW MIGHT I BE EXPOSED TO TOXAPHENE?

Since the use of toxaphene is banned in the United States, you can probably only be exposed to it in areas where it is concentrated (such as a waste site). In those areas, there is a greater chance of breathing or directly contacting the chemical. People may also be exposed to toxaphene by eating contaminated soil. Infants and toddlers have the greatest risk because they are likely to put things in their mouths. People who eat large quantities of fish and shellfish, or game animals such as raccoons taken in areas contaminated by toxaphene may experience somewhat higher intakes of toxaphene because those animals tend to concentrate toxaphene in their fatty tissues. You can also be exposed to toxaphene by breathing contaminated air, but concentrations in outdoor air are very low so you are not likely to be exposed to unhealthy levels in air. For more information on human exposure to toxaphene, see Chapter 5.

### 1.4 HOW CAN TOXAPHENE ENTER AND LEAVE MY BODY?

Toxaphene can enter the body through eating contaminated food or soil, through the skin after direct contact with contaminated substances, and through the lungs after breathing its vapors. Once toxaphene enters the body, it rapidly spreads to all organs. Toxaphene is quickly broken down in the body and excreted in urine and feces. Nearly all (approximately 90%) of the toxaphene is eliminated from the body within 24 to 36 hours after entering the body. However, studies in animals show that low levels of toxaphene may remain in fat for months. Chapter 2 contains more detailed information on how toxaphene enters and leaves the body.

### 1.5 HOW CAN TOXAPHENE AFFECT MY HEALTH?

Breathing, eating, or drinking high levels of toxaphene has been reported to damage the lungs, nervous system, liver, and kidneys, and can cause death. Of course, how severe the effects are depends on how much toxaphene is absorbed. Because toxaphene is no longer used, the chances of high-level exposure are small. However, exposure to low levels can occur in some places because it may last a long time in the environment. For this reason, if exposure occurs, it is likely to be to environmental or low levels and probably over a long time (that is, more than

## 1. PUBLIC HEALTH STATEMENT

1 year). Scientists have no information about how low-level exposure for a long time affects humans; however, animal studies have been conducted to try to answer that question.

Studies in animals show that long-term exposure (1-2 years) to toxaphene can damage the liver, kidneys, adrenal glands, and immune system, and may cause minor changes in fetal development. Toxaphene may also cause cancer in laboratory animals. The results of studies where animals were exposed to relatively high levels of toxaphene for most of their lives show that the thyroid gland in some of the animals developed cancerous cell types. The EPA has determined that toxaphene is a probable human carcinogen. The National Toxicology Program also concludes that there is a reasonable chance that toxaphene is a human carcinogen. However, most people will never be exposed to toxaphene for a long time (more than 1 year), and not everyone exposed to it will develop cancer. In fact, there is no evidence that toxaphene has caused cancer in people, but animal evidence suggests that it may cause cancer in humans. See Chapter 2 for more information on toxaphene and cancer.

### **1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TOXAPHENE?**

Toxaphene and its breakdown products can be detected in blood, urine, breast milk, and body tissues. Because samples are easy to take, urine and blood tests are the most common way to tell if a person has been exposed to toxaphene. Neither of these tests is routinely available at a doctor's office because special equipment is needed to detect toxaphene, but your doctor can send samples to a special laboratory that performs those tests. The tests cannot determine how much toxaphene you have been exposed to. Toxaphene leaves the body quickly, so the tests can only detect it within several days after exposure. Also, if you are exposed to other chemicals at the same time, the test results could be misinterpreted.

Blood and urine tests can confirm that a person has been exposed to toxaphene, but these tests cannot yet predict the kind or severity of any health effects that might occur. See Chapters 2 and 6 for specific information about the tests used to detect toxaphene in the body.

## 1. PUBLIC HEALTH STATEMENT

**1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?**

In 1990, the EPA banned all uses of toxaphene in the United States or any of its territories because of scientific evidence that it harms humans and animals. In 1993, the EPA banned the importation of food containing toxaphene residues into the United States or any of its territories. The federal government has developed regulatory standards and guidelines to protect individuals from the potential harmful health effects of toxaphene in drinking water and food. The EPA concludes that the amount of toxaphene in drinking water should not exceed 0.005 parts of toxaphene per million parts (ppm) of water and that any release to the environment greater than one pound should be reported. The EPA has also established limits on how much toxaphene can be released from a factory into waste water. The limit is set at 0-1 .5 milligrams (mg) of toxaphene per liter (approximately a quart) of water. The EPA has determined that toxaphene is a “hazardous air pollutant” under the Clean Air Act, but the agency has not yet established standards for it. For short-term exposures, EPA concludes that drinking water levels should not exceed 0.5 ppm for 1 day or 0.04 ppm for 10 days. The Food and Drug Administration has set a limit of 6 ppm of toxaphene in crude soybean oil, and EPA has set limits that range from 0.1 to 7 ppm for other raw agricultural products such as sunflower seeds, soybeans, grains, cottonseed, vegetables, and fruits (including bananas and pineapples). Since the EPA has banned the importation of all food containing toxaphene residues, and toxaphene can no longer be used in the United States or its territories, the likelihood of eating contaminated food is small.

The Occupational Safety and Health Administration (OSHA) has set a legally enforceable limit (permissible exposure limit or PEL) of 0.5 milligrams of toxaphene per cubic meter of air in workroom air to protect workers during an 8-hour shift over a 40-hour workweek. For more information on criteria and standards for toxaphene exposure, see Chapter 7.

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**1.8 WHERE CAN I GET MORE INFORMATION?**

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road NE, E-29  
Atlanta, Georgia 30333  
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.



## 2. HEALTH EFFECTS

### 2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of toxaphene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Toxaphene is a manufactured pesticide that is composed of over 670 different constituents; the relative proportions of the major components of the pesticide are essentially the same in different formulations. The use of toxaphene has been banned in the United States and all of its territories since 1990 (EPA 1990b). Moreover, toxaphene residues are not allowed on any food imported to the United States (EPA 1993b). Nevertheless, because of its earlier widespread use, persistence in the environment, and storage in waste sites, exposure to toxaphene is still possible. U.S. manufacturers can legally produce pesticides for export that are currently banned or not registered for domestic use (FASE 1996). It is not known whether toxaphene is still being produced in the United States for export purposes or whether occupational exposures are likely during production.

Two major metabolites of toxaphene, toxicants A and B, have been isolated and found to possess toxicity that is 6 and 14 times greater, respectively, than the technical toxaphene mixture as measured by comparing intraperitoneal LD<sub>50</sub> values in mice (Casida et al. 1974).

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

### 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure -inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

## 2. HEALTH EFFECTS

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the LSE tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of toxaphene are indicated in Table 2-2 and Figure 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 ( $10^{-4}$  to  $10^{-7}$ ), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for toxaphene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect

## 2. HEALTH EFFECTS

or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

### 2.2.1 Inhalation Exposure

Very little information is available regarding the health effects of toxaphene following inhalation exposure in humans. Most of the existing data come from case reports and long-term studies of pesticide workers and are of limited value. In such studies, precise levels of exposure are usually not provided, and concurrent exposure to several pesticides confounds the interpretation of the results.

#### 2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to toxaphene.

The concentration of 40% toxaphene dust that caused death in about one-half of an exposed group of rats in 1 hour was 3,400 mg/m<sup>3</sup> (Boots Hercules Agrochemicals n.d.).

## 2. HEALTH EFFECTS

**2.2.1.2 Systemic Effects**

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, endocrine, or ocular effects in humans or animals following inhalation exposure to toxaphene.

One controlled human study was found that investigated the general effects of inhaled toxaphene. Keplinger (1963) reported that no toxic effects were seen in 25 humans exposed to an aerosol containing a maximum of 500 mg/m<sup>3</sup> for 30 minutes per day for 10 days. The author calculated the exposure dose to be as much as 60 mg per person per day. After a 3-week period, these same subjects were exposed for three more 30-minute periods. Examination of these subjects before and after exposures by a dermatologist and an internist (some of them using blood tests and urinalysis) indicated no effects. Due to the limited information reported in this study and the unusual exposure conditions, it is difficult to assess the adequacy of these data. Nevertheless, the study is referenced below for the appropriate systemic end points.

The highest NOAEL values for humans for each effect are recorded in Table 2-1 and plotted in Figure 2-1.

**Respiratory Effects.** Pulmonary hypersensitivity reactions to toxaphene were suspected in two Egyptian agricultural pesticide workers in 1958. In these cases, men involved in the spraying of toxaphene (formulated as 60% toxaphene, 35% kerosene, 3% xylol, and 2% emulsifier) for approximately 2 months suffered from acute pulmonary insufficiency (Warraki 1963). Chest X-rays revealed extensive miliary shadows, and one man exhibited marked bilateral hilar lymphadenopathy. The diagnosis in both cases was extensive bilateral allergic bronchopneumonia as a result of insecticide exposure. Both patients recovered quickly and completely with cortisone, streptomycin, and isoniazid treatment. Although the clinical sequelae observed in these two patients could be associated with toxaphene exposure, the effects could have been caused by other components of the spray. No similar cases have been reported since 1958.

No studies were located regarding respiratory effects in animals following inhalation exposure to toxaphene

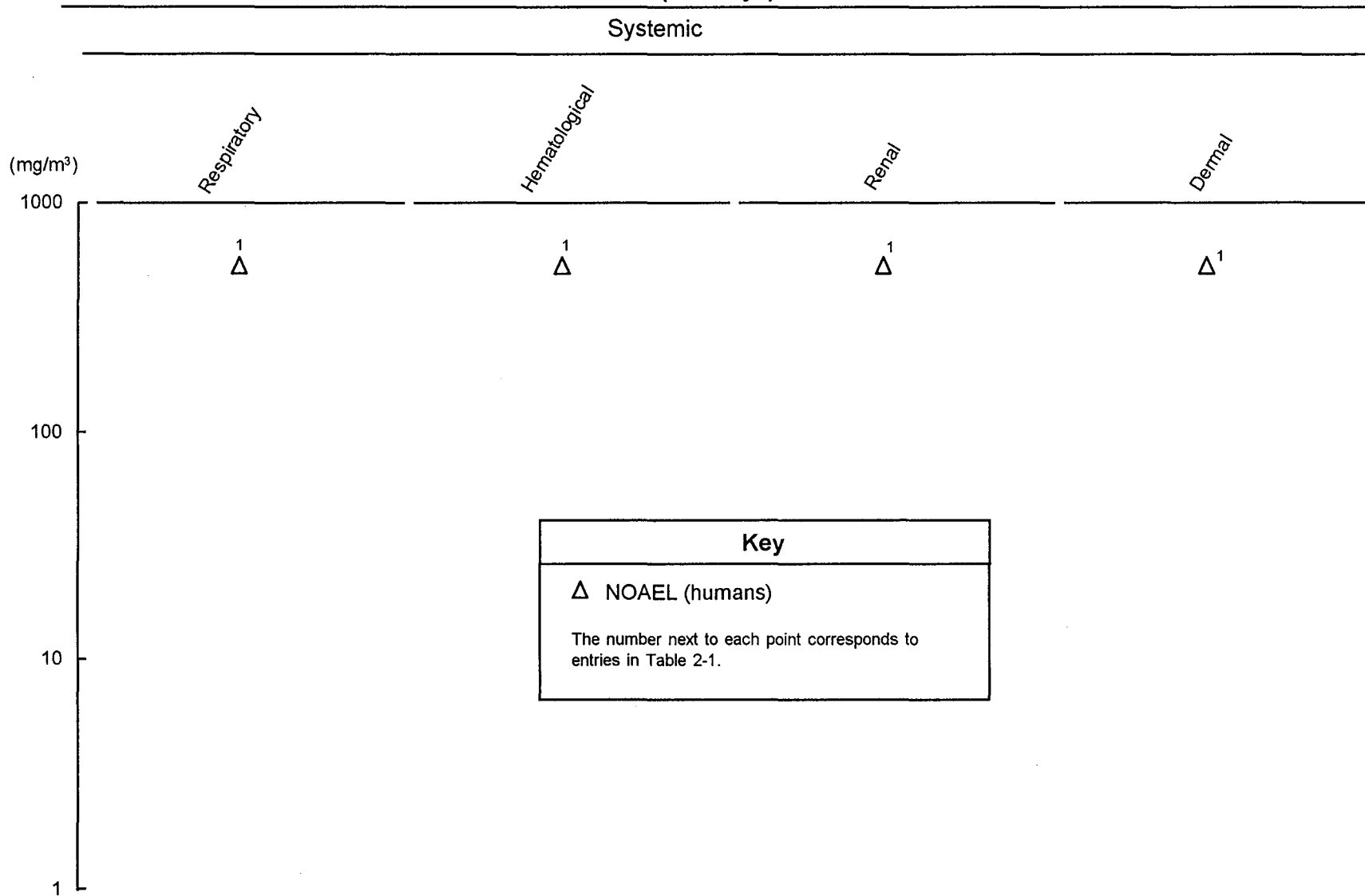
Table 2-1. Levels of Significant Exposure to Toxaphene - Inhalation

Key to figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL mg/m3	LOAEL		Reference
					Less serious mg/m3	Serious mg/m3	
<b>ACUTE EXPOSURE</b>							
<b>Systemic</b>							
1	Human	10 d 30 min/d	Resp	500			Keplinger 1963
			Hemato	500			
			Renal	500			
			Dermal	500			

d = day(s); Hemato = hematological; LOAEL = lowest-observable-adverse-effect level; min = minute(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory

**Figure 2-1. Levels of Significant Exposure to Toxaphene - Inhalation**

**Acute ( $\leq 14$  days)**



## 2. HEALTH EFFECTS

**Hematological Effects.** Blood tests conducted on humans exposed to a toxaphene spray indicated that the pesticide did not cause blood abnormalities (Keplinger 1963). However, the exact dose to which the subjects were exposed could not be determined. Other clinical findings included elevated sedimentation rates, the presence of blood eosinophilia, and high serum globulin (Warraki 1963).

No primary source studies were located that described adverse hematological effects in animals following inhalation exposure to toxaphene. However, no toxaphene-related hematological effects were noted in rats, rabbits, dogs and guinea pigs exposed to toxaphene dust or mist (unpublished observations 195.5, 1964, 1965, as cited in Boots Hercules Agrochemicals n.d.). These data are limited because only summaries of unpublished data cited in a secondary unpublished bulletin were available for review, thus precluding an assessment of their adequacy.

**Hepatic Effects.** No studies were located regarding hepatic effects in humans following inhalation exposure to toxaphene.

Slight hepatocellular necrosis was observed in some female rats that survived inhalation exposure to 0.004, 0.012, or 0.04 mg/L (4, 12, or 40 mg/m<sup>3</sup>) toxaphene dust for 3 months (unpublished observations as cited in Boots Hercules Agrochemicals n.d.). These data are limited because only summaries of unpublished data cited in a secondary unpublished bulletin were available for review, thus precluding an assessment of their adequacy.

**Renal Effects.** Urinalysis results from humans exposed to a toxaphene spray (approximately 500 mg/m<sup>3</sup>) indicated that the pesticide did not affect kidney function (Keplinger 1963). However, the actual dose to which the subjects were exposed could not be determined.

No animal studies describing toxaphene-related renal toxicity following inhalation exposure were found.

**Dermal Effects.** No toxic effects were seen in humans exposed to an aerosol containing a maximum of 500 mg/m<sup>3</sup> toxaphene for 30 minutes/day for 10 days (Keplinger 1963).

No animal studies describing toxaphene-related dermal toxicity following inhalation exposure were found.

## 2. HEALTH EFFECTS

**Body Weight Effects.** No studies were located regarding body weight effects in humans following inhalation exposure to toxaphene.

In rats, acute exposure to toxaphene at 15 ppm resulted in decreased body weight; intermediate exposure to toxaphene in rats, guinea pigs, and dogs has also been shown to decrease body weight (unpublished observations, as cited in Boots Hercules Agrochemicals n.d.). These data are limited because only summaries of unpublished data cited in a secondary unpublished bulletin were available for review, thus precluding an assessment of their adequacy.

### 2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to toxaphene.

### 2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to toxaphene.

Dogs, rats, guinea pigs, and rabbits exposed to an aerosol of toxaphene dust (5 mg/L, 15% respirable or 750 mg/m<sup>3</sup>) for 6 hours per day, 5 days per week for 1 week exhibited hyperactivity, tremors, salivation, lacrimation, and tonic-clonic convulsions (Industrial Biotest 1965). It should be noted that some studies conducted by Industrial Biotest have been shown to be less than reliable.

### 2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following inhalation exposure to toxaphene.



## 2. HEALTH EFFECTS

### 2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to toxaphene.

### 2.2.1.7 Genotoxic Effects

A higher incidence of chromosomal aberrations was observed in cultured lymphocytes taken from the blood of eight women exposed to toxaphene than in lymphocytes taken from unexposed women (Samosh 1974). The exposed women had entered a field that had recently been sprayed with an analog of toxaphene and were described as presenting “mild to moderate” clinical symptoms. The nature of the symptoms was not reported by Samosh. The women were likely to have been exposed by both the inhalation and dermal routes. The degree of exposure was not known. It is unclear whether the chromosomal aberrations observed in the lymphocytes of these women were directly attributable to the toxaphene exposure.

No studies were located regarding the genotoxic effects in animals following inhalation exposure to toxaphene. Other genotoxicity studies are discussed in Section 2.5.

### 2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals following inhalation exposure to toxaphene.

## 2.2.2 Oral Exposure

Toxaphene is toxic following short-term, high-dose oral exposure. Several cases of fatal and nonfatal poisoning have been reported in humans following the accidental or intentional ingestion of toxaphene or food contaminated with large amounts (gram quantities) of toxaphene. In such instances of acute poisoning, toxaphene stimulates the central nervous system like other chlorinated hydrocarbon pesticides. Long-term studies using high doses indicate that toxaphene causes central nervous system toxicosis and hepatic hypertrophy accompanied by increased microsomal enzyme activity and histological changes in liver cells. The kidneys, spleen, and adrenal gland have also been identified as target organs of toxaphene-induced toxicity.

## 2. HEALTH EFFECTS

**2.2.2.1 Death**

Ingestion of large doses of toxaphene by humans can be fatal. Six case studies of acute poisoning were reported, three of which (all children) were fatal (McGee et al. 1952). In all cases, an unknown quantity of toxaphene was ingested, either alone or as a residue of spray on food. Symptoms were usually abruptly manifested by 7 hours post-ingestion and consisted of intermittent convulsions, generally without abdominal pain, vomiting, or diarrhea. Death was attributed to respiratory failure resulting from the seizures. It is estimated that the approximate minimum lethal dose in humans is 2-7 g (Hayes 1963); however, the data used to calculate that dose range was not presented.

The oral LD<sub>50</sub> values obtained in laboratory animals can vary according to species, solvent used, nutritional status, and, perhaps, the manufacturing source of toxaphene. LD<sub>50</sub> values in rats range from approximately 80 to 293 mg/kg when administered by gavage (Boyd and Taylor 1971; Gaines 1969; Jones et al. 1968). The administration of 80 mg/kg/day toxaphene for 5 days to male mice by gavage resulted in 75% mortality (Epstein et al. 1972). Pregnant rats (Chernoff et al. 1990; Chemoff and Carver 1976) and pregnant mice (Chemoff and Carver 1976) may be more sensitive to the toxic effects of the pesticide because the approximate lethal dose appears to be one-half to one-tenth of the lethal doses reported for nonpregnant female rats and mice. No treatment-related deaths were observed in pregnant rats administered 6 mg/kg/day by gavage from gestational day 7 to parturition (Crowder et al. 1980). The vehicle used to deliver toxaphene may influence its toxicity (Lackey 1949). Death was observed in dogs administered a single gavage dose of toxaphene in corn oil at 15 mg/kg; however, when toxaphene was administered in kerosene, a poorly absorbed solvent, death was not seen until the dose reached 200 mg/kg. Furthermore, this study demonstrates that dogs may be more susceptible to the acute lethal effects of toxaphene, since the estimated oral LD<sub>50</sub> (25 mg/kg/day) is lower than that seen for other species. The acute gavage administration of 50 mg/kg toxaphene to heifers (136-232 kg) was fatal in 2 of 8 animals; doses of 100 and 150 mg/kg toxaphene were fatal in 6 of 7 and 5 of 6 animals, respectively (Steele et al. 1980).

The nutritional status of an animal influences its susceptibility to the lethal effects of ingested toxaphene. Boyd and Taylor (1971) found that the oral LD<sub>50</sub> for rats fed a protein-deficient diet was 80 mg/kg/day, whereas the oral LD<sub>50</sub> for rats fed a control diet was 220 mg/kg/day. This has important implications for the possible increased susceptibility of humans who ingest a protein-deficient diet and live in areas of potential exposure to toxaphene.

## 2. HEALTH EFFECTS

In rats, the intermediate exposure to 63 mg/kg/day toxaphene in feed did not increase mortality (Chu et al. 1988). The apparent low toxicity of a near LD<sub>50</sub> dose (see above) may be due to the fact that dosing occurred throughout the day (since the toxaphene was administered in feed), as opposed to one bolus administration as used for the LD<sub>50</sub> studies. Thus, lethal circulating levels of toxaphene may not have been reached in the feed study. Treatment-related mortality was not observed in rats following gavage administration of 6 mg/kg/day for 21 days (Crowder et al. 1980). Studies of intermediate exposure to toxaphene administered in feed to rats and mice indicate that mice are more sensitive than rats to the toxic effects of the pesticides (NCI 1977). A dose of 41.6 mg/kg/day caused 100% mortality in mice, but 128 mg/kg/day toxaphene caused only 40% mortality in female rats. The intermediate (39-42 weeks) exposure to 5 mg/kg/day toxaphene did not cause any treatment-related mortality in rats (Kennedy et al. 1973). Less than 10% mortality was observed in rats or mice chronically exposed to approximately 25-28 mg/kg/day toxaphene (NCI 1977).

The LD<sub>50</sub> values and doses associated with death in each species after acute and intermediate oral exposure are recorded in Table 2-2 and plotted in Figure 2-2.

### 2.2.2.2 Systemic Effects

No studies regarding the musculoskeletal or ocular effects of oral exposure to toxaphene in humans or animals were found. The systemic effects of oral toxaphene exposure are described below.

The highest NOAEL values and all reliable LOAEL values for each species and duration of exposure for each effect can be found in Table 2-2 and plotted in Figure 2-2.

**Respiratory Effects.** A 2-year-old boy ingested an unspecified but lethal amount of toxaphene. Congestion and edema of the lungs were noted upon autopsy (McGee et al. 1952). No further information was located.

In rats, the acute oral administration of toxaphene has been shown to cause congestion and parenchymal hemorrhage, indicative of a generalized inflammatory response (Boyd and Taylor 1971). The study was limited by the fact that the dose was not specified. The chronic administration of toxaphene in feed to rats or mice at doses of 27 and 12.9 mg/kg/day, respectively, has been shown to cause dyspnea (NCI 1977)

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat (Wistar)	once (GO)				80 M (LD <sub>50</sub> low protein diet)	Boyd and Taylor 1971
2	Rat (CD)	Gd 7-16 1x/d (GO)				35 F (31% maternal mortality)	Chernoff and Carver 1976
3	Rat (Sprague- Dawley)	Gd 6-15 1x/d (GO)				32 F (50% maternal lethality without weight loss)	Chernoff et al. 1990
4	Rat (Sherman)	once (GO)				90 M (LD <sub>50</sub> ) 80 F (LD <sub>50</sub> )	Gaines 1969
5	Mouse (ICR/Ha Swiss)	5 d 1x/d (G)				40 M (death; 2/12)	Epstein et al. 1972
6	Dog (NS)	once (GO)				15 (death; 25%)	Lackey 1949
7	Dog (NS)	once (GO)				200 (death; 20%)	Lackey 1949
<b>Systemic</b>							
8	Rat (CD)	Gd 7-16 1x/d (GO)	Bd Wt			15 F (22% reduced maternal weight gain)	Chernoff and Carver 1976

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
9	Rat (Sprague- Dawley)	Gd 6-15 1x/d (GO)	Endocr		32 F (transient increase in adrenal weight gain)		Chernoff et al. 1990
			Bd Wt			32 F (50% reduction in maternal weight gain)	
10	Rat (Wistar)	once (GO)	Hepatic		110M (increased GGTP activity)		Garcia and Mourelle 1984
11	Rat (Sprague- Dawley)	8 d ad lib (F)	Hepatic		5 <sup>b</sup> M (decr. hepatic uptake, metabolism, and biliary excretion of imipramine)		Mehendale 1978
12	Rat (NS)	once (C)	Hepatic		120M (8.6 % increased liver weight, increased microsomal enzyme activity)		Peakall 1976
13	Rat (Sprague- Dawley)	14 d ad lib (F)	Cardio	10M			Trottman and Desaiah 1980
			Hepatic		10M (20% increased liver weight)		
			Renal Bd Wt	10M 10M			
14	Gn Pig (NS)	once (GO)	Hepatic		300 M (13% increased liver weight)		Chandra and Durairaj 1992
			Renal		300M (14% decreased kidney weight)		

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Immunological/Lymphoreticular</b>							
15	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GO)				32 F (positive correlation between maternal thymus weight and fetal death; unspecified decrease in thymus and spleen weights)	Chernoff et al. 1990
16	Rat (Sprague-Dawley)	14 d ad lib (F)			7.5M (31% decreased thymus weight)		Trottman and Desaiah 1980
<b>Neurological</b>							
17	Rat (Sprague-Dawley)	3 d 1x/d (GO)			25M (mild tremors, nervousness)		Rao et al. 1986
18	Gn Pig (NS)	once (GO)			300M (10% decreased brain weight)		Chandra and Durairaj 1992
19	Dog (Beagle)	2 d (C)				10 (convulsions, salivation, and vomiting)	Chu et al. 1986
20	Dog (NS)	once (GO)		5		10 (convulsions)	Lackey 1949
<b>Reproductive</b>							
21	Rat (NS)	once (C)		120M			Peakall 1976
22	Rat (Sprague-Dawley)	14 d ad lib (F)		10M			Trottman and Desaiah 1980

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Developmental</b>							
23	Rat (CD)	Gd 7-16 1x/d (GO)			15	(reduced ossification)	Chernoff and Carver 1976
24	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GO)			32	(significantly increased incidence of fetal supernumerary ribs)	Chernoff et al. 1990
25	Rat (CD)	Gd 7-16 1x/d (GO)			12.5	(decrease in fetal renal protein)	Kavlock et al. 1982
26	Mouse (CD-1)	Gd 7-16 1x/d (GO)		35			Chernoff and Carver 1976
<b>INTERMEDIATE EXPOSURE</b>							
<b>Death</b>							
27	Rat (Osborne-Mendel)	6 wk ad lib (F)				128 F (death: 40%)	NCI 1977
28	Rat (Osborne-Mendel)	6 wk ad lib (F)				128 (death; 100%)	NCI 1977
29	Mouse (B6C3F1)	6 wk ad lib (F)				41.6 (death; 100%)	NCI 1977

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
30	Rat (Sprague-Dawley)	13 wk ad lib (F)	Hemato	45.9 M 63 F			Chu et al. 1986
			Hepatic	0.35 <sup>c</sup> M 0.5 F	1.8 M (mild anisokaryosis) 2.6 F (mild vesiculation of biliary nuclei)	45.9 M (mild basophilia, severe anisokaryosis) 63 F (severe vesiculation of biliary nuclei, severe anisokaryosis)	
			Renal	1.8 M 2.6 F		8.6 M (tubular necrosis and interstitial sclerosis) 12.6 F (tubular, mild anisokaryosis)	
			Endocr	0.35 M  12.6 F	1.8 M (angular collapse of follicles, increased epithelial height and reduced colloid density in the thyroid)  63 F (cytoplasmic vacuolation, decreased colloid density, decreased follicular size, follicular collapse, increased epithelial height in the thyroid)		
			Bd Wt	45.9 M 63 F			



Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
31	Rat (Sprague- Dawley)	26 wk ad lib (F)	Hemato	45 M			Chu et al. 1988
				46 F			
			Hepatic	9.2 M	45 M (15% increased liver weight; increased hepatic microsomal enzyme activity)		
				0.36 F	1.9 F (16% increased liver weight)		
				Renal	0.36 M	45 M (15% increased kidney weight)	
			46 F				
			Endocr	1.8 M	45 M (decreased colloid density in thyroid goiter)		
				1.9 F	8.5 F (decreased colloid density in thyroid)		
Bd Wt	45 M						
	46 F						
32	Rat (Sprague- Dawley)	21 d 1x/d (GO)	Bd Wt	6			Crowder et al. 1980
33	Rat (Wistar)	≤120 d 1x/d (GO)	Hepatic		16.5 M (increased GGTP activity)		Garcia and Mourelle 1984

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
34	Rat (Sprague-Dawley)	39-42 wk ad lib (F)	Cardio	5			Kennedy et al. 1973
			Hepatic	1.25	5	(cytoplasmic vacuolization of hepatocytes)	
			Renal	5			
			Endocr	5			
			Bd Wt	5			
35	Rat (Sprague-Dawley)	9 wk ad lib (F)	Hepatic		15M	(24% liver weight increase and hepatic degeneration)	Koller et al. 1983
			Bd Wt	15M			
36	Rat (Osborne-Mendel)	6 wk ad lib (F)	Bd Wt	128			NCI 1977
37	Rat (Sherman)	2, 4, 6, or 9 mo ad lib (F)	Hepatic		2.5	(centrolobular cellular hypertrophy, peripheral migration of basophilic cytoplasmic granules, fatty infiltration)	Ortega et al. 1957
			Renal	10			
			Bd Wt	10			
38	Rat (NS)	1, 3, 6 mo ad lib (F)	Hepatic		2.4 M	(increased organ weight and enzyme activity)	Peakall 1976

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
39	Mouse (Swiss Webster)	8 wk ad lib (F)	Hepatic	1.3 F	13 F (increased relative liver weight, variation in cell size with some fatty infiltration)		Allen et al. 1983
			Bd Wt	26 F			
40	Mouse (B6C3F1)	6 wk ad lib (F)	Bd Wt	41.6			NCI 1977
41	Dog (Beagle)	13 wk 7 d/wk 1x/d (C)	Hemato	5			Chu et al. 1986
			Hepatic	0.2	2M (hepatocellular cytoplasmic vacuolation)		
					F (biliary lymphoid reaction, increased relative liver weight)		
			Renal	0.2 M	2M (cytoplasmic granularity/basophilia)		
				2 F	5 F (cytoplasmic granularity/basophilia)		
			Endocr	0.2	2 (increased follicular collapse, increased epithelial height, decreased colloid density)		
			Bd Wt	5.0			
<b>Immunological/Lymphoreticular</b>							
42	Rat (Sprague-Dawley)	9 wk ad lib (F)				1.5 M (46% decreased IgG secondary antibody response)	Koller et al. 1983

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
43	Mouse (Swiss Webster)	8 wk ad lib (F)		1.3 F	13 F (decreased antibody response)		Allen et al. 1983
<b>Neurological</b>							
44	Rat (Sprague- Dawley)	21 d 1x/d (GO)		6			Crowder et al. 1980
45	Dog (NS)	44, 106 d 1x/d (C)				4 (convulsions)	Lackey 1949
<b>Reproductive</b>							
46	Rat (Sprague- Dawley)	48 wk ad lib (F)		46			Chu et al. 1988
47	Rat (Sprague- Dawley)	39-42 wk ad lib (F)		5			Kennedy et al. 1973
48	Rat (NS)	1, 3, 6 mo ad lib (F)		2.4 M			Peakall 1976
<b>Developmental</b>							
49	Rat (Holtzman)	62 d ad lib (F)			0.05 (inferior swimming & righting ability in developing rats)		Olson et al. 1980

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
50	Mouse (Swiss Webster)	9.5 wk ad lib (F)			13.0	(suppression of macrophage phagocytic function)	Allen et al. 1983
<b>CHRONIC EXPOSURE</b>							
<b>Death</b>							
51	Rat (Osborne-Mendel)	80 wk ad lib (F)				27.8 M (death; 6%) 27 F (death; 8%)	NCI 1977
52	Mouse (B6C3F1)	80 wk ad lib (F)			25.7	(trend toward increased mortality but individual significance not reached)	NCI 1977
<b>Systemic</b>							
53	Rat (Osborne-Mendel)	80 wk ad lib (F)	Resp		27	(dyspnea, epistaxis)	NCI 1977
			Gastro		27	(abdominal distension, diarrhea)	
			Hepatic	55.6			
			Renal		27	(hematuria)	
			Dermal		27	(alopecia, dermatitis, rough hair coats)	
			Bd Wt	54M	27 F	(unspecified decrease in body weight)	

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
54	Mouse (B6C3F1)	80 wk ad lib (F)	Resp		12.9	(dyspnea)	NCI 1977
			Gastro		12.9	(abdominal distension, diarrhea)	
			Dermal		12.9	(alopecia, rough hair coat)	
			Bd Wt	12.9 M 25.7 F	25.7 M	(unspecified decreased body weight)	
<b>Neurological</b>							
55	Rat (Osborne-Mendel)	80 wk ad lib (F)				27.8 M (leg paralysis, ataxia)	NCI 1977
						27 F (leg paralysis, ataxia)	
56	Mouse (B6C3F1)	80 wk ad lib (F)		25.7 F	12.9 M	(hyperexcitability)	NCI 1977
<b>Reproductive</b>							
57	Rat (Osborne-Mendel)	80 wk ad lib (F)			27 F	(vaginal bleeding)	NCI 1977
<b>Cancer</b>							
58	Rat (Osborne-Mendel)	80 wk ad lib (F)				55.6 M (CEL: follicular-cell carcinomas, thyroid adenomas)	NCI 1977
						54 F (CEL: thyroid adenomas)	

Table 2-2. Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
59	Mouse (B6C3F1)	80 wk ad lib (F)				12.9 M (CEL: hepatocellular carcinoma) 25.7 F (CEL: hepatocellular carcinoma)	NCI 1977

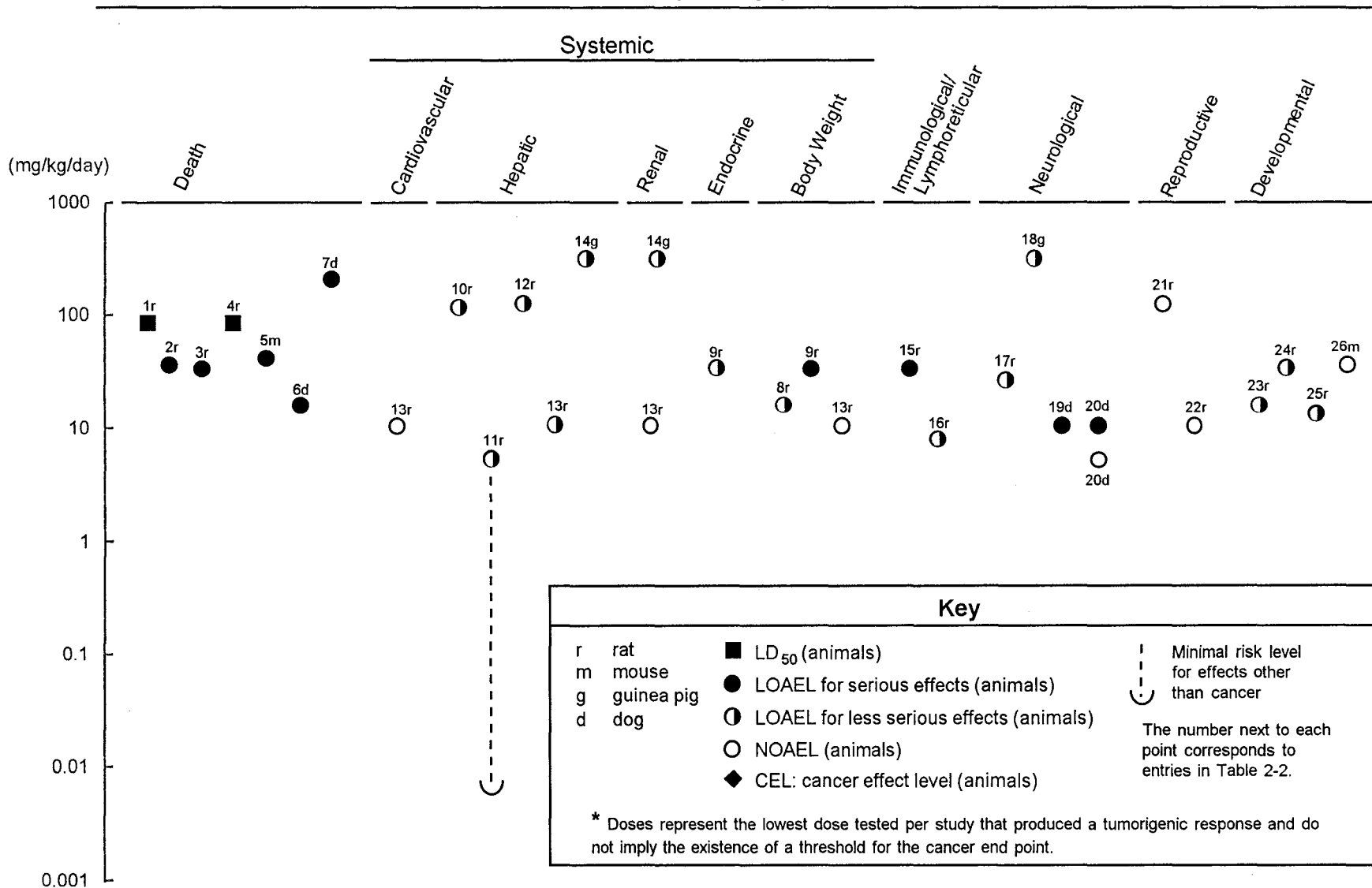
<sup>a</sup>The number corresponds to entries in Figure 2-2.

<sup>b</sup>Used to derive an acute oral minimal risk level (MRL) of 0.005 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability)

<sup>c</sup>Used to derive an intermediate oral MRL of 0.001 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), and an additional modifying factor of 3 because toxaphene may alter offspring behavioral and functional development.

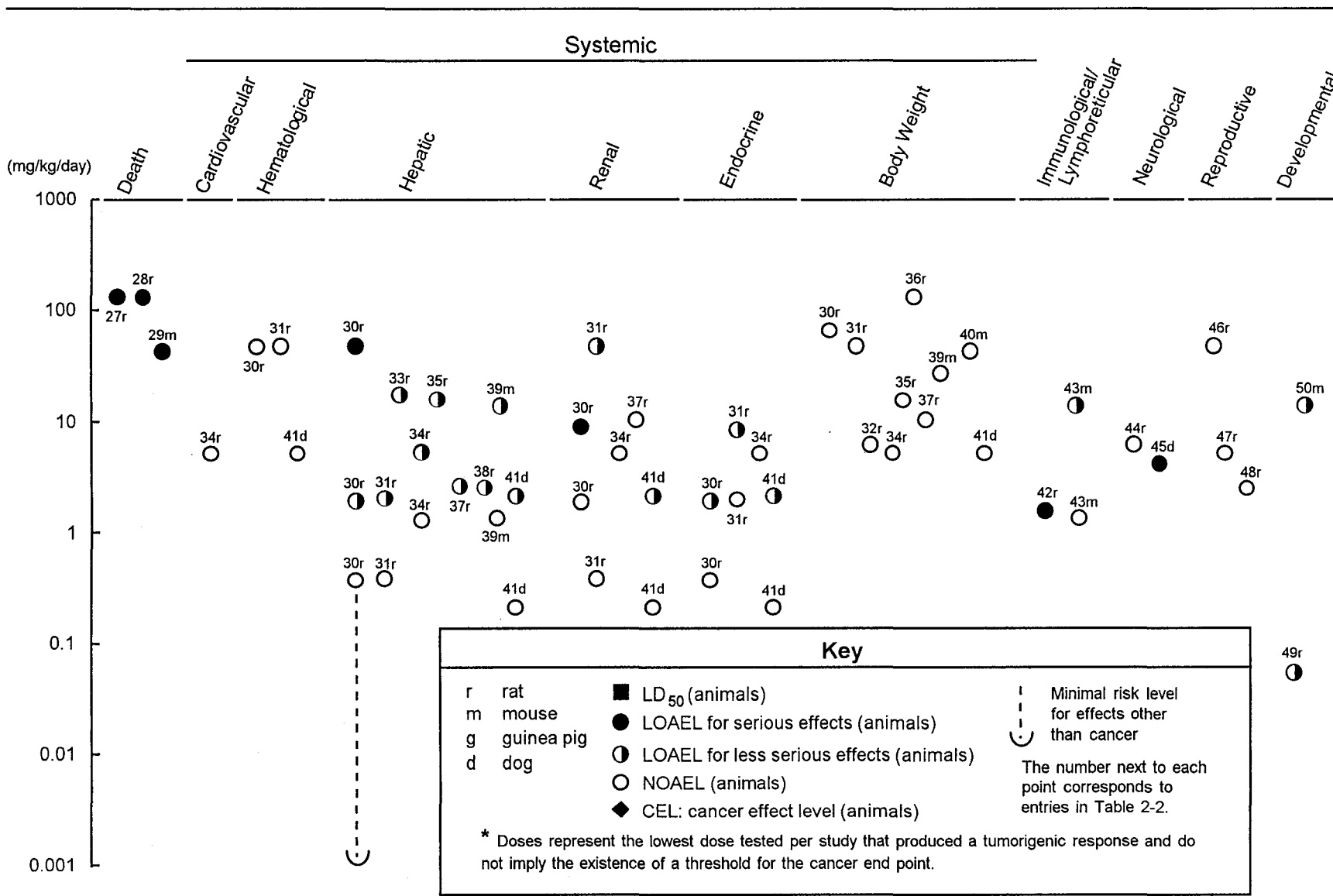
ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day; Endocr = endocrinal; (F) = feed; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; GGTP = gamma glutamyl transpeptidase; Hemato = hematological; LD<sub>50</sub> = lethal dose, 50% kill; M = male; LOAEL = lowest-observable-adverse-effect level; mo = month; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week; x = times

**Figure 2-2. Levels of Significant Exposure to Toxaphene - Oral**  
**Acute ( $\leq 14$  days)**

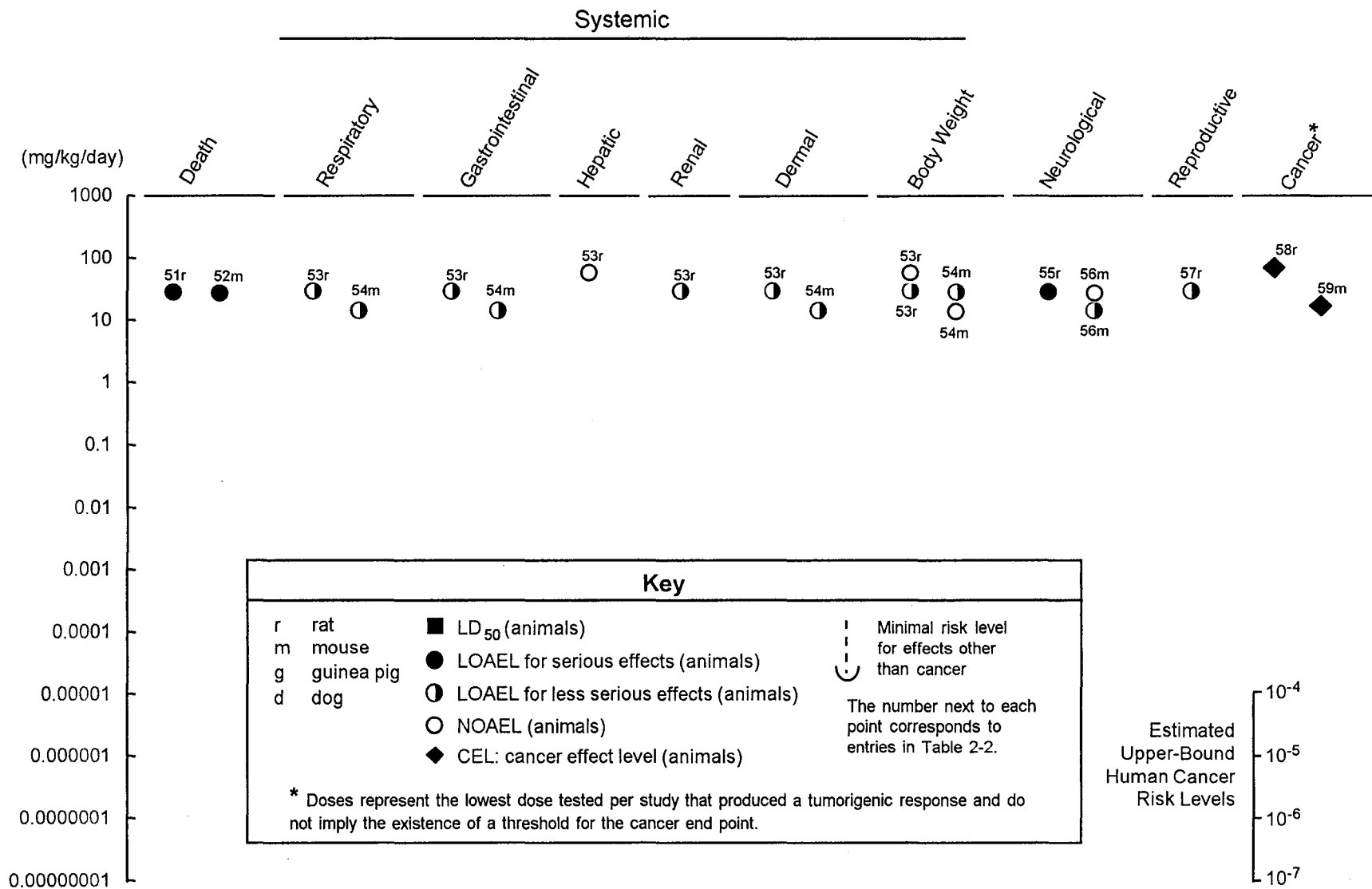




**Figure 2-2. Levels of Significant Exposure to Toxaphene - Oral (cont.)**  
Intermediate (15-364 days)



**Figure 2-2. Levels of Significant Exposure to Toxaphene - Oral (cont.)**  
 Chronic ( $\geq 365$  days)



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**Cardiovascular Effects.** A 2-year-old boy ingested an unspecified but lethal amount of toxaphene. Dilation of the heart was observed upon autopsy (McGee et al. 1952.) No further information was located.

In rats, the acute administration of an unspecified dose of toxaphene by gavage has been shown to cause capillary congestion and capillary hemorrhage in the hearts of rats that died following treatment (Boyd and Taylor 1971). These effects are indicative of a generalized inflammatory response. In dogs, the acute oral administration of 10 mg/kg toxaphene has been reported to increase heart rate but to have no effect on the vascular system (Lackey 1949), and progressive neural degeneration has been identified in the hearts of pregnant rats following daily treatment with 12 mg/kg/day toxaphene by gavage during pregnancy (Badaeva 1976). However, the methods used to identify the lesions in this study are not well described and the effects were not quantitatively evaluated; therefore, these results may not be reliable.

No adverse effects on the heart were observed in rats following acute or intermediate exposure to toxaphene in the diet. Male rats fed diets containing up to 10 mg/kg/day toxaphene for 14 days had reduced thymus weights. The toxicological significance of this effect is unclear. No other cardiovascular effects were noted (Trottman and Desai 1980). Similarly, no effect on heart weight was observed in an intermediate-duration multigenerational study in which male and female rats were fed diets containing up to 5 mg/kg/day toxaphene (Kennedy et al. 1973).

**Gastrointestinal Effects.** No studies were located regarding gastrointestinal effects in humans following oral exposure to toxaphene.

Gastric ulcers and local gastroenteritis (an inflammatory reaction) were observed in rats administered a single unspecified oral dose of toxaphene (Boyd and Taylor 1971). In this study, animals fed a low protein (3.5%) diet had a greater incidence of toxaphene-induced gastritis than rats fed normal chow or a test diet with a normal protein content, in keeping with the apparent “diet-dependency” of toxaphene toxicity. The chronic administration of toxaphene to rats or mice has been shown to cause abdominal distension and diarrhea (NCI 1977).

**Hematological Effects.** No studies were located regarding hematologic effects in humans following oral exposure to toxaphene.

No adverse effects on standard hematological parameters were noted in dogs dosed with up to 5 mg/kg/day by capsule for 13 weeks (Chu et al. 1986); dogs dosed with 4 mg/kg/day by capsule for 44 or

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106 days (Lackey 1949); male and female rats fed diets containing 45.9 or 63 mg/kg/day, respectively, for 13 weeks (Chu et al. 1986); or male rats fed 45 mg/kg/day for 26 weeks (Chu et al. 1988). Abnormalities in the blood-forming elements were observed in the spleens of rats that died following the oral administration of a single unspecified dose of toxaphene (Boyd and Taylor 1971). The authors attributed this to a generalized stress reaction. Based on the available information, it would appear that ingested toxaphene does not adversely affect the hematological status of laboratory animals.

**Hepatic Effects.** Little information was located regarding hepatic effects in humans following oral exposure to toxaphene. Transiently elevated liver lactate dehydrogenase and serum glutamic oxaloacetic transaminase indicative of reversible liver injury were observed in a 26-year-old man who attempted suicide by ingesting the insecticide Tox-Sol, which contains toxaphene as the active ingredient (Wells and Milhom 1983).

Adverse liver effects noted in animals following acute gavage exposure to 300 mg/kg toxaphene include increased fresh liver weight in guinea pigs (Chandra and Durairaj 1992), inhibition of hepatobiliary function in male rats exposed to 5 mg/kg/day toxaphene in feed for 8 days (Mehendale 1978), and induction of hepatic microsomal enzymes with subsequent increased liver weight in male rats given 120 mg/kg/day by capsule or 10 mg/kg/day in feed for 14 days (Peakall 1976; Trotman and Desai 1980). Increased gamma-glutamyl transpeptidase (GGTP) activity was observed in male rat liver plasma membranes and blood serum after a single gavage exposure to 110 mg/kg toxaphene (Garcia and Mourelle 1984). However, the majority of these studies did not report any other evidence of hepatic toxicity. Therefore, enzyme induction in the absence of other signs of liver toxicity cannot be considered adverse, but enzyme induction may precede the onset of more serious hepatic effects. Based on the liver toxicosis observed in rats given 5 mg/kg toxaphene in feed for 8 days (Mehendale 1978), an acute oral MRL of 0.005 mg/kg/day was calculated as described in the footnote to Table 2-2 and Appendix A. This study was chosen because it reported the lowest reliable LOAEL for toxic effects of toxaphene in a target organ.

Morphological and degenerative changes have been observed in the livers of dogs (Chu et al. 1986; Lackey 1949), rats (Chu et al. 1988; Kennedy et al. 1973; Koller et al. 1983; Ortega et al. 1957), and mice (Allen et al. 1983) following intermediate-duration exposure to 4, 5-45, and 13 mg/kg toxaphene, respectively. These changes included generalized hydropic degenerative changes, cytoplasmic vacuolization, centrilobular cell hypertrophy, peripheral migration of basophilic cytoplasmic granules, and the presence of lipospheres. Hepatic enzyme induction has also been observed in rats following intermediate exposure to 2.4 mg/kg/day (Peakall 1976) or 16.5 mg/kg/day (Garcia and Mourelle 1984)

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toxaphene. Toxaphene may also induce hypoxia and alter hepatic energy metabolism because it has been shown to decrease lactate dehydrogenase activity (Gertig and Nowaczynski 1975; Kuz'minskaya and Alekhina 1976).

In keeping with toxaphene-induced induction of hepatic enzymes, 2.4-45 mg/kg/day toxaphene caused increased liver weight in rats (Chu et al. 1988; Koller et al. 1983; Peakall 1976) and mice (Allen et al. 1983). In rats, intermediate exposure duration NOAELs for hepatic toxicity are generally 10-20% of the corresponding LOAELs (Chu et al. 1986, 1988). An intermediate-duration exposure MRL of 0.001 mg/kg/day was derived based on the NOAEL of 0.35 mg/kg/day for hepatic toxicity in rats reported by Chu et al. (1986) and supported by Chu et al. (1988). A description of the derivation of the MRL can be found in the footnote to Table 2-2 and in Appendix A. The intermediate oral administration of 2 mg/kg/day toxaphene to dogs caused increased relative liver weight, hepatomegaly, and hepatocellular cytoplasmic vacuolation (Chu et al. 1986). This study is limited by the fact that the high-dose dogs were inadvertently fed the wrong dose for part of the study period. In rats, biochemical and histological evidence of toxaphene-induced liver toxicosis was observed in F<sub>0</sub> male and female rats fed 45 mg/kg/day toxaphene for at least 26 weeks (Chu et al. 1988).

Mild to severe liver pathology was observed in rats and dogs chronically administered 5 mg/kg/day toxaphene in the feed (Boots Hercules Agrochemicals n.d.). In contrast, no hepatic toxicity was observed in rats exposed to approximately 55 mg/kg/day toxaphene (NCI 1977).

**Renal Effects.** Little information was available regarding renal effects in humans following oral exposure to toxaphene. Renal function was temporarily compromised in a 26-year-old man who attempted suicide by ingesting an unknown quantity of a toxaphene-containing pesticide (Wells and Milhom 1983). Swelling of the kidney was observed in a 2-year-old boy following acute exposure to a lethal amount of toxaphene (McGee et al. 1952).

Toxaphene has been shown to be nephrotoxic in laboratory animals. Guinea pigs given a single oral dose of 300 mg/kg toxaphene were found to have decreased kidney weights 72 hours after treatment (Chandra and Durairaj 1992), but minor ultrastructural changes were found. A single unspecified, but lethal, oral dose of toxaphene induced cloudy swelling of the proximal and distal convoluted tubules and congestion of the loop of Henle in rats (Boyd and Taylor 1971). However, no renal effects were seen in male rats exposed to up to 10 mg/kg/day of toxaphene in feed for 14 days (Trottman and Desai 1980). Renal tubular injury has also been reported to occur following intermediate exposure to toxaphene. Dose-

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dependent injuries of the proximal convoluted tubules that were focally severe were observed in rats fed 8.6 and 12.6 mg/kg/day toxaphene for 13 weeks (Chu et al. 1986), and increased kidney weight was observed after 26 weeks of exposure at a similar dose (Chu et al. 1988). No renal toxicosis was observed in rats at doses 0.35-0.36 mg/kg/day (Chu et al. 1988). Intermediate-duration doses of toxaphene ranging from 1.8 to 9.2 mg/kg/day are reported to cause pathological changes in the rat kidney (Chu et al. 1986, 1988). In contrast, 10 mg/kg/day was not nephrotoxic to rats (Ortega et al. 1957). Hematuria has also been observed in rats chronically administered 27 mg/kg/day toxaphene (NCI 1977), which is in keeping with the above toxaphene-related pathological changes in the kidney.

Marked degenerative fatty changes of the kidney tubular epithelium were observed in dogs following intermediate-duration exposure to 4 mg/kg/day toxaphene (Lackey 1949). Eosinophilic inclusions that were occasionally accompanied by focal necrosis have also been observed in dogs after intermediate exposure to 2 mg/kg/day toxaphene (Chu et al. 1986). These data suggest that the kidney is a target of toxaphene toxicity.

**Endocrine Effects.** No information was available regarding endocrine effects in humans following oral exposure to toxaphene.

The administration of 0.06 mg/kg/day toxaphene in feed for 5 weeks to female rats decreased ACTH-stimulated corticosterone synthesis in isolated or cultured adrenal cells (Mohammed et al. 1985). This effect was not seen after a single dose, suggesting that there are two mechanisms of action for toxaphene-induced depression of adrenal function, or that the effect may take time to develop. These results suggest that toxaphene, by interfering with adrenal gland function, may compromise the ability of animals or humans to respond adequately to stress. The authors suggest that *in vitro* stimulated corticosterone synthesis may be a more sensitive end point of toxaphene-induced injury than liver toxicity, but since no correlation was made between the physiological condition of those animals and the *in vitro* test results, the usefulness of the information for risk assessment is questionable. Adverse effects (decreased coloidal density in the thyroid gland) have been noted in the thyroid gland of rats following the intermediate oral administration of toxaphene at 1.8 mg/kg/day (Chu et al. 1986). The NOAEL for this effect under similar conditions has been reported to be 1.8 mg/kg/day for male and 1.9 mg/kg/day for female rats (Chu et al. 1988). The morphological changes (follicular collapse, increased epithelial height with multifocal papillary proliferation, and reduced colloid density) were dose-dependent, considered mild to moderate in severity, and adaptive in nature. The toxicological significance of the reduced colloid density is not known, but reductions in thyroid hormone levels in humans may cause goiters because the negative

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feedback of thyroid hormone on TSH secretion is reduced, leading to TSH oversecretion, and stimulation of thyroid gland growth. Thus, toxaphene has the potential to be goitrogenic.

**Dermal Effects.** No information was available regarding dermal effects in humans following oral exposure to toxaphene.

The chronic (80 weeks) administration of toxaphene caused alopecia and rough hair coats in rats and mice fed diets containing 27 and 13 mg/kg/day, respectively (NCI 1977).

**Body Weight Effects.** No information was available regarding body weight effects in humans following oral exposure to toxaphene.

Body weight was not affected in male rats fed diets containing up to 10 mg/kg/day toxaphene (Trottman and Desaiiah 1980). The acute administration of 15 mg/kg/day (Chemoff and Carver 1976) or 32 mg/kg/day (Chemoff et al. 1990) toxaphene to pregnant rats or mice from gestational day 6-15 or 7-16, respectively, caused decreased body weight gain. Toxaphene administered to pregnant rats at 6 mg/kg/day from gestational day 7 to parturition did not cause body weight reductions (Crowder et al. 1980). The intermediate-duration oral administration of 6 mg/kg/day toxaphene to male and nonpregnant female rats did not affect body weight (Crowder et al. 1980). However, higher doses orally administered to male rats have been shown to decrease body weight (Thunberg et al. 1984). Intermediate exposure to 4 mg/kg/day toxaphene caused reduced body weight in dogs (Lackey 1949), and the chronic administration of the pesticide in feed to male mice at dose of 26 mg/kg/day caused sex-specific decreases in body weight (NCI 1977).

### 2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects of toxaphene in humans following oral exposure.

The acute administration of 7.5 mg/kg/day toxaphene to rats has also been reported to decrease thymus weight (Trottman and Desaiiah 1980). Additionally, thymus weight has been reported to decrease in pregnant rats following oral administration of 32 mg/kg/day toxaphene from gestational days 6 to 15 (Chemoff et al. 1990). However, the data were reported only as a change from control, and the control values were not given. Thus, the relative magnitude of the changes and their biological significance could not be determined. The administration of 5 mg/kg/day toxaphene to rats for intermediate durations

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(39-42 weeks) did not affect spleen or thymus weights (Kennedy et al. 1973). Toxaphene has been reported to induce immunosuppressive effects (primarily humoral) in laboratory animals. Toxaphene impaired antibody (IgG) production at some, but not all, stages of the IgG response in male rats exposed to 1.5 mg/kg/day toxaphene in feed for 9 weeks (Koller et al. 1983). Similar results were obtained in female mice orally exposed to 26 mg/kg/day toxaphene (Allen et al. 1983). However, the delayed hypersensitivity response was unaffected by toxaphene. These results suggest that toxaphene suppressed only certain components of the immune system, and therefore, the immunotoxic actions of this chemical are specific rather than general.

All reliable LOAEL values for these effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

#### 2.2.2.4 Neurological Effects

Signs of central nervous system stimulation are the hallmark of acute toxaphene intoxication in both humans and animals. Case reports of accidental or intentional toxaphene ingestion indicate that toxaphene poisoning is usually accompanied by convulsive seizures that can be controlled with barbiturates or diazepam (McGee et al. 1952; Wells and Milhom 1983). The dose necessary to induce non-fatal convulsions in humans has been estimated to be approximately 10 mg/kg (Hayes 1963). Contaminated collard greens coated with toxaphene, eaten on empty stomachs, caused convulsive seizures followed by periods of memory loss in three females between the ages of 12 and 20, as well as nausea in a 49-year-old woman (McGee et al. 1952).

Toxaphene-related decreases in brain weight have been observed following the single oral administration of 300 mg/kg toxaphene to guinea pigs (Chandra and Durairaj 1992). Convulsions have also been observed in dogs exposed acutely to 10 mg/kg toxaphene (Lackey 1949). The acute administration of toxaphene is known to cause tremors in rats exposed to 50 mg/kg, while mild tremors were observed at 25 mg/kg (Rao et al. 1986). Hyperreflexia has also been observed in rats at an unspecified dose (Boyd and Taylor 1971) and in dogs following acute oral exposure to 10 mg/kg toxaphene (Lackey 1949). Intermediate (106 days) exposure to 4 mg/kg/day toxaphene caused intermittent convulsions in dogs (Lackey 1949). In mice, chronic exposure to 12.9 mg/kg/day toxaphene caused hyperexcitability in males (NCI 1977). In that same study, no adverse neurological effects were observed in females exposed to as much as 25.7 mg/kg/day toxaphene. Chronic administration of the pesticide has also been shown to cause tremors, leg paralysis, and ataxia in rats exposed to 27 mg/kg/day (females) or 27.8 mg/kg/day



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(males) (NCI 1977). In heifer calves, the oral administration of toxaphene caused hyperexcitability, nystagmus, convulsions, and seizures (Steele et al. 1980).

The neurologic effects of toxaphene can also be manifested as functional (electroencephalographic, behavioral), biochemical (neurotransmitter), and morphological alterations. No effect on learning and learning transfer abilities was observed in young adult rats exposed to 6 mg/kg toxaphene (Crowder et al. 1980). Dogs administered 10 mg/kg for 2 days exhibited convulsions, salivation, and vomiting (Chu et al. 1986). The electroencephalographic (EEG) pattern of squirrel monkeys is also altered by exposure to 1 mg/kg toxaphene (Santolucito 1975). In addition to affecting behavior, a dose of 120 mg/kg toxaphene has also been shown to alter brain catecholamine metabolism in rats (Kuz'minskaya and Ivanitskii 1979). Histopathological examination of the brains of toxaphene-treated rats indicates that a dose of 12 mg/kg/day of the pesticide can also cause central nervous system cell death (Badaeva 1976). However, the methods used to identify the lesions are not well described in this study and the effects were not quantitatively evaluated; therefore, these results may not be reliable. Doses as high as 10 mg/kg/day did not affect whole brain weight in rats (Trottman and Desaiyah 1980), but this is a gross measure and effects on specific neuronal populations would not be detected by this measure.

The highest NOAEL values and all reliable LOAEL values for neurologic effects for each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

#### 2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to toxaphene.

The acute administration of 10 mg/kg/day toxaphene did not affect rat testicular weight (Trottman and Desaiyah 1980). Reproductive effects following oral exposure to toxaphene have been evaluated in multigeneration studies conducted in rats and mice. In rats, the chronic administration of 27 mg/kg/day toxaphene in the diet for 80 weeks was associated with vaginal bleeding (NCI 1977). A three-generation study was conducted in which male and female rats were fed diets containing up to 5 mg/kg/day toxaphene for 3942 weeks (Kennedy et al. 1973). There were no effects on litter sizes, pup survival, or weanling body weights, indicating that toxaphene did not affect reproduction. No treatment-related teratogenic effects occurred. Toxaphene caused slight cytoplasmic vacuolization in the livers of parental animals. However, no accompanying adverse effects were noted on the growth, survival, clinical parameters, and organ weights of the parents. Fertility and offspring growth and viability in rats were unaffected by

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exposure to 46 mg/kg/day toxaphene in the diet for 48 weeks (Chu et al. 1988). In male rats, the acute oral administration of 120 mg/kg and the intermediate exposures to 2.4 mg/kg/day toxaphene in feed for up to 6 months did not affect circulating levels of testosterone (Peakall 1976).

A multigeneration study in which 2.5 mg/kg/day toxaphene was fed in the daily diet to Swiss mice during mating, gestation, and lactation and to pups after weaning indicated that toxaphene did not adversely affect lactation, reproduction, average litter size, and offspring growth and viability through five generations of mice (Keplinger et al. 1970). Histological examination of the livers of parental animals revealed fatty changes.

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

### 2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to toxaphene.

Studies were located that provided data on the developmental effects of toxaphene in laboratory animals. The results of these studies indicate that toxaphene produces fetal toxicity in rats at a dose of 1.5 mg/kg/day (Chernoff and Carver 1976). Although no major anatomical defects in rat or mouse fetuses were reported at doses ranging from 0.05 to 75 mg/kg/day (Allen et al. 1983; Chernoff and Carver 1976; Chernoff and Kavlock 1982; Crowder et al. 1980; Kavlock et al. 1982; Kennedy et al. 1973; Olson et al. 1980), behavioral effects were reported in the offspring of rats at doses as low as 0.05 mg/kg/day (Olson et al. 1980). In mice, immunosuppression (depressed IgG antibody formation) was reported in offspring at doses of 13 mg/kg/day (Allen et al. 1983).

In rats, the gestational administration of toxaphene (0, 15, 25, or 35 mg/kg/day) caused dose-related reductions in maternal weight gain and in the average number of sternal ossification centers in fetuses (Chernoff and Carver 1976). Toxaphene (32 mg/kg/day) administered to pregnant rats on gestational days 6-15 caused 50% maternal mortality without affecting maternal weight gain (Chernoff et al. 1990). The offspring of the surviving animals were found to have an increase in supernumerary ribs, indicating only slight developmental toxicity. Additionally, Chernoff et al. (1990) noted a positive correlation between fetal death and decreased maternal thymus weight. However, the decreases in maternal thymus weight were transient, and fetal deaths were only minimally increased in the toxaphene-treated animals.

Moreover, this study was limited by the fact that 50% of the treated dams died, resulting in the teratological evaluation of the offspring from the least-affected dams. Additionally, decreases in rat fetal alkaline phosphatase activity, and reductions in total protein in fetal kidneys have been observed following prenatal exposure to 12.5 mg/kg/day toxaphene (Kavlock et al. 1982). These effects suggest that toxaphene targets the developing kidney.

Exposure to toxaphene may also alter normal behavioral development. Delayed righting reflex development has been reported for rats following prenatal exposure to 6 mg/kg/day toxaphene (Crowder et al. 1980). Behavioral alternations have been described for juvenile rats after perinatal exposure to 0.05 mg/kg/day toxaphene (Olson et al. 1980). During early development, pups from all three treatment groups showed retarded maturation in the swimming test compared to controls. However, all groups displayed mature swimming behavior by postnatal day 16.

Toxaphene (35 mg/kg/day) administered to mice by gavage from gestational days 7-16 produced no adverse effects on fetal growth, viability, or gross morphology even though the toxaphene-treated dams displayed dose-dependent reductions in weight gain (Chemoff and Carver 1976). However, 75 mg/kg toxaphene administered on gestational days 8-12 caused transient decreases in offspring body weight on postnatal day 1 (Chemoff and Kavlock 1982).

No adverse effects were reported on the growth and survival of offspring in mice exposed to 3.25 mg/kg/day in the diet during mating, gestation, and lactation in a multigeneration reproduction study (Keplinger et al. 1970).

Immunosuppression in mouse offspring was reported by Allen et al. (1983) following daily dietary exposure to concentrations of  $\geq 13$  mg/kg/day toxaphene before breeding, during pregnancy, and during the lactation period. At 8 weeks of age, reductions in the phagocytic ability of macrophages was observed in offspring. At dietary levels of 13 mg/kg/day, delayed hypersensitivity and humoral antibody responses were also suppressed in the offspring. However, no dose-response effect was observed in these assays. The relative degree of immunosuppression was greatest in macrophages, followed by humoral immunity; cell-mediated immunity was least affected. Since the offspring received toxaphene transplacentally, through lactation, and possibly even in the feed, the actual doses of toxaphene cannot be accurately estimated. The results of the study, however, suggest that the neonates can be at risk for immunotoxicity following exposure to prolonged high dietary dosages of toxaphene, and it would be prudent to consider

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that potential adverse maternal and developmental effects from exposure to prolonged high dietary dosages of toxaphene could occur in humans.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

### 2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to toxaphene.

In experimental animals, toxaphene has been found to be negative for mutagenicity using the dominant lethal test in mice (Epstein et al. 1972). No significant decrease in the number of fetal implants or increase in early fetal deaths was observed in female mice mated to male mice that had been treated with single daily oral doses of toxaphene at 40 or 80 mg/kg for 5 days prior to mating. A high mortality rate in the exposed male mice (2 of 12 and 9 of 12 for the 40 and 80 mg/kg/day groups, respectively) indicates that the doses used were sufficient to have adequately tested for mutagenicity using this assay. The potential for toxaphene to cause liver DNA damage was assessed in 90-day old female Sprague-Dawley rats (Kitchin and Brown 1994). Rats were dosed with 12 or 36 mg/kg toxaphene. Other, not specified, doses were also used. Toxaphene did not damage rodent hepatic DNA. Other genotoxicity studies are discussed in Section 2.5.

### 2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to toxaphene.

Bioassays were conducted in male and female rats and mice incorporating up to 56 mg/kg/day toxaphene into the feed for 80 weeks (NCI 1977). Survival was not significantly affected by toxaphene treatment in rats. An increased incidence of follicular cell adenomas was observed in male and female rats in the highdose group when compared to matched and pooled (males and females) controls. These thyroid tumors occurred at a relatively low incidence and the control group was small. Therefore, the evidence that toxaphene was carcinogenic to rats was inconclusive. In mice, however, there was a significant trend toward decreased survival for both males and females exposed to toxaphene. Nevertheless, there were sufficient mice in the treated groups to permit a carcinogenicity evaluation. The results indicated that toxaphene caused a dose-related increase in the incidence of follicular-cell carcinomas or adenomas of the

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thyroid gland in male rats when compared with pooled (but not matched) controls. In the NCI (1977) bioassay, a statistically significant increase in the incidence of hepatocellular carcinomas was observed in mice, using either matched or pooled controls, indicating that toxaphene was carcinogenic. Reanalysis of the liver tissue sections from this study in light of newer criteria for classification of hepatocellular alterations revealed that while the number of diagnosed hepatocellular carcinomas was decreased compared to the original report, hepatocellular carcinomas were still found (unpublished report Brown 1995).

One oral carcinogenicity bioassay conducted with toxaphene concluded that the pesticide was not carcinogenic; however, the study was flawed by the small number of animals used and the fact that the histological evaluations were incomplete (Triolo et al. 1982). Nevertheless, most of the available evidence suggests that toxaphene is carcinogenic in laboratory animals when administered over long periods at maximum tolerated doses.

The water concentrations associated with an individual, lifetime upper-bound risk of  $10^{-4}$  to  $10^{-7}$  are  $9.1 \times 10^{-5}$  to  $9.1 \times 10^{-8}$  mg/kg/day, assuming that a 70-kg human ingests 2 L water per day. The  $10^{-4}$  to  $10^{-7}$  levels are indicated in Figure 2-2.

### 2.2.3 Dermal Exposure

#### 2.2.3.1 Death

No studies were located regarding lethal effects in humans following dermal exposure to toxaphene.

The dermal LD<sub>50</sub> values obtained in laboratory animals range from 780 to 4,556 mg/kg (Gaines 1969; Johnston and Eden 1953; Jones et al. 1968; Industrial Biotest 1973). Toxaphene is thus an order of magnitude less toxic by this route of exposure as compared to oral exposure. All of these studies except Gaines (1969) have design and/or reporting limitations that preclude their inclusion in Table 2-3. The LD<sub>50</sub> from the Gaines (1969) study is plotted in Table 2-3.

Table 2-3. Levels of Significant Exposure to Toxaphene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
<b>ACUTE EXPOSURE</b>						
<b>Death</b>						
Rat (Sherman)	once				1075 M (LD <sub>50</sub> ) 780 F (LD <sub>50</sub> ) mg/kg	Gaines 1969
<b>Systemic</b>						
Rabbit (New Zealand)	4 hr	Dermal	500 mg	(erythema and edema)		International Research and Development Corporation 1973
Pig (NS)	once	Resp	13.5 g/kg	(lung congestion and presence of peribronchial lymphoid follicles)		Dipietro and Haliburton 1979
		Renal	13.5 g/kg	(cystic kidney cortex)		
<b>Neurological</b>						
Pig (NS)	once				13.5 (convulsions) g/kg	Dipietro and Haliburton 1979

F = female; hr = hour; LOAEL = lowest-observable-adverse-effect level; M = male; LD<sub>50</sub> = lethal dose, 50% kill; M = male; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory

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**2.2.3.2 Systemic Effects**

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hepatic, endocrine, ocular, or body weight effects in humans following dermal exposure to toxaphene. No studies were located regarding cardiovascular, hematological, musculoskeletal, endocrine, or body weight effects in animals following dermal exposure to toxaphene. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3.

**Respiratory Effects.** In humans, fluoroscopic examination of the lungs following acute dermal exposure to 500 mg/m<sup>3</sup> toxaphene did not reveal abnormalities (Keplinger 1963).

Toxicosis was observed in a herd of pigs that had been treated with a 61% toxaphene solution (equivalent to 13.5 g/kg). The symptoms generally subsided when the animals were sprayed with warm water (DiPietro and Haliburton 1979). Various lung lesions were observed in three affected pigs that were not treated for toxicosis by spraying with warm water. These lesions differed in the three affected pigs examined and included congested cranial lung lobes, numerous peribronchial lymphoid follicles, and moderate congestion of the lungs. Hyperemic lungs also were observed in rabbits that died following a 24-hour dermal application of 3,038 mg/kg toxaphene (Industrial Biotest 1973). It should be noted that some studies performed by Industrial Biotest have been found to be less than reliable; thus, the accuracy of the above data cannot be assured.

**Gastrointestinal Effects.** No studies were located regarding gastrointestinal effects in humans following dermal exposure to toxaphene.

Dilation of veins and intestinal hemorrhage were observed in rabbits dipped in an unspecified dose suspension of a wettable powder of toxaphene for 2 minutes (Johnston et al. 1953).

**Hematological Effects.** In humans, blood tests conducted after acute dermal exposure to 500 mg/m<sup>3</sup> toxaphene did not reveal any abnormalities (Keplinger 1963).

No studies were located regarding hematological effects in animals following dermal exposure to toxaphene.

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**Hepatic Effects.** No studies were located regarding hepatic effects in humans following dermal exposure to toxaphene.

Rabbits dipped in an unspecified dose suspension of a wetttable powder of toxaphene for 2 minutes had pale and mottled livers (Johnston et al. 1953). Up to 10,250 mg/kg/day technical grade toxaphene applied to intact or burned skin of rabbits for 24 hours caused enlarged gall bladders in both the intact and burned groups at doses as low as 3,038 mg/kg/day (Industrial Biotest 1973).

**Renal Effects.** In humans, urinalysis conducted after acute dermal exposure to 500 mg/m<sup>3</sup> toxaphene did not reveal any abnormalities (Keplinger 1963).

In pigs, cysts were found in the renal cortex after acute dermal exposure to 13.5 mg/kg/day toxaphene (DiPietro and Haliburton 1979).

**Dermal Effects.** In humans, acute dermal exposure to 500 mg/m<sup>3</sup> toxaphene did not produce dermal irritation (Keplinger 1963).

Dermal application of 3,038 mg/kg toxaphene (90% weight to volume [w/v] ratio in xylene) to the skin of rabbits caused moderate to severe edema and erythema followed by severe desquamation following a 24-hour exposure (Industrial Biotest 1973). The skin irritation may have been caused by xylene which has been reported to cause dermal irritation in guinea pigs (Anderson et al. 1986). Exposure to toxaphene (500 mg) for 4 hours caused rabbit skin to be only mildly irritated (International Research and Development Corp. 1973).

**Ocular Effects.** No studies were located regarding ocular effects in humans following dermal exposure to toxaphene.

Mild irritation to the eyelids and loss of eyelid hair were observed after 14 applications of a 20% toxaphene solution in kerosene to the eyes of guinea pigs. The eye was not affected, and the lids cleared completely in 10 days (Boots Hercules Agrochemicals n.d.). This study is limited in that only unpublished summary data were available for evaluation, thereby precluding an assessment of the adequacy of the study design and execution, and the data generated.



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### 2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals following dermal exposure to toxaphene.

### 2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to toxaphene.

Signs of central nervous system toxicity were observed in 40 of 150 pigs 36 hours after being sprayed with 300 mL of a 61% toxaphene solution in water (equivalent to 13.5 g/kg). This dose is about 10 times the recommended dose for treatment of sarcoptic mange (DiPietro and Haliburton 1979). The possibility that inhalation or oral exposure may have also occurred cannot be ruled out. Clinical signs included headpressing, ataxia, depression, lethargy, diarrhea, and convulsive seizures. Within a day after spraying with warm water, the animals were much improved, and complete recovery was seen within 5 days. Muscular weakness, paralysis, and convulsions were observed in rabbits exposed to a 90% w/v solution of toxaphene in xylene for 24 hours (Industrial Biotest 1973); however, this study was limited in that the solvent, xylene, was not tested alone. In the same study, the NOAEL for muscular weakness was 4,556 mg/kg/day. The NOAEL dropped to 2,025 mg/kg/day when the epidermis was damaged by burning.

### 2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to toxaphene.

### 2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to toxaphene.

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### 2.2.3.7 Genotoxic Effects

A higher incidence of chromosomal aberrations was observed in cultured lymphocytes taken from the blood of eight women exposed to toxaphene (Samosh 1974). The exposed women had entered a field that had recently been sprayed with toxaphene and were described as presenting “mild to moderate” clinical symptoms. The nature of the symptoms was not reported by Samosh. The women were likely to have been exposed by both the inhalation and dermal routes. The degree of exposure was not known. Other genotoxicity studies are discussed in Section 2.5.

### 2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals following dermal exposure to toxaphene.

## 2.3 TOXICOKINETICS

Studies in laboratory animals indicate that toxaphene is well absorbed by the intestinal tract and probably well absorbed by the lungs. Dermal absorption is low, relative to the other exposure routes. Once absorbed, toxaphene distributes throughout the body. Studies using radiolabeled toxaphene indicate that distribution to fat predominates over distribution to other organs, and levels are detectable in fat tissue for several months following exposure. Toxaphene is rapidly and extensively degraded in mammals following oral administration. *In vivo* and *in vitro* studies indicated that the principal metabolic pathways involved dechlorination, dehydrodechlorination, and oxidation. Conjugation is also likely, but it is not a major route of metabolism. The primary route of excretion is via the feces (70% of an administered dose), but toxaphene is also excreted in the urine.

### 2.3.1 Absorption

#### 2.3.1.1 Inhalation Exposure

Inhalation studies in humans and animals were located, but did not provide reliable data regarding the absorption of toxaphene in humans or animals following inhalation exposure, but limited inhalation data indicate that it is absorbed (Keplinger 1963; Warraki 1963).

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### 2.3.1.2 Oral Exposure

No studies were located regarding the oral absorption of toxaphene in humans. However, there is strong evidence to suggest that gastrointestinal absorption occurs in humans because deaths and poisonings have resulted from the accidental ingestion of toxaphene-contaminated food (McGee et al. 1952).

The presence of toxaphene residues in the fat of rats (Mohammed et al. 1985; Pollock and Kilgore 1980b; Saleh and Casida 1978; Saleh et al. 1979), mice (Crowder and Whitson 1980; Saleh et al. 1979), guinea pigs, hamsters, rabbits, monkeys and chickens (Saleh et al. 1979) following ingestion indicates that absorption occurred. The identification of toxaphene in the milk of cows following ingestion is also evidence of its absorption (Clabom et al. 1963; Zweig et al. 1963).

Although there are no direct studies regarding the extent of toxaphene absorption, 56.5% of an orally administered dose was present in the feces and 9% of the dose was present in the urine of rats, mostly as metabolites. Very little was present as the parent compound, indicating that considerable metabolism had occurred and thus absorption had taken place (Chandurkhar and Matsumara 1979). Less than 10% of the administered dose was detected in tissues 1 day after oral administration of radiolabeled toxaphene to rats, suggesting that absorption and redistribution may have occurred over the 24 hours following administration (Crowder and Dindal 1974). The proportion of the administered dose that was not redistributed may have been metabolized and eliminated.

The data presented above suggest that toxaphene would be absorbed by humans following the consumption of drinking water or food contaminated with the chemical. Its absorption appears to be extensive and is enhanced when it is dissolved in a vehicle that is readily absorbed. The bioavailability of toxaphene is increased when it is administered in or with vegetable oils like corn oil or peanut oil, and the toxicity of toxaphene is potentiated (EPA 1980a). Thus, toxaphene may be more toxic when ingested in oily foods than when ingested in contaminated water.

### 2.3.1.3 Dermal Exposure

No studies were located in humans regarding the dermal absorption of toxaphene.

However, the detection of high toxaphene levels in cow's milk (21-45 ppm) after dipping the cattle in a toxaphene solution (0.25% w/w toxaphene plus 0.03% w/v dioxathion) indicates that toxaphene was

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absorbed following dermal exposure (Keating 1979). Toxaphene toxicosis was reported in swine 36 hours after the dermal application of this insecticide in a 6 1% solution (equivalent to 13.5 g/kg) (DiPietro and Haliburton 1979).

Under conditions of high dosage, dermal absorption of toxaphene may be efficient enough to cause toxicosis or to produce detectable residues in cow's milk. Toxaphene appears to be well absorbed following dermal exposure in animals, but the extent of absorption has not been quantified. Other evidence suggests that absorption in humans may also be substantial following dermal exposure (Keplinger 1963).

### 2.3.2 Distribution

#### 2.3.2.1 Inhalation Exposure

No studies were available in humans or animals regarding the distribution of toxaphene following inhalation exposure. Although cases of inhalation exposure have been reported, there were no data that detailed distribution of toxaphene residues in various tissues.

#### 2.3.2.2 Oral Exposure

No studies were located regarding the distribution of toxaphene following oral exposure in humans.

Results of tissue sample analysis following the oral administration of radiolabeled toxaphene to rats showed that fat is the principal storage tissue (Ohsawa et al. 1975; Pollock and Kilgore 1980b). Other evidence in animals indicates that muscle may also be a storage site for toxaphene as suggested by the observation of a high distribution of toxaphene in muscle following an oral dose in rats, and by evidence that toxaphene residues persist in muscle for up to 20 days post-administration (Crowder and Dindal 1974). The oral administration of  $^{14}\text{C}$ -toxaphene in olive oil to rats at a dose of 10 mg/kg resulted in toxaphene residue levels of 6.4 mg/kg toxaphene and its metabolites in fat 7 days following administration. Residue levels in all other tissues were less than 0.2 mg/kg (Pollock and Kilgore 1980b). The oral administration of  $^{14}\text{C}$ -toxaphene in corn oil to rats at doses of 19 and 8.5 mg/kg resulted in residue levels of 0.78 and 0.52 mg/kg, respectively, of toxaphene and its metabolites in fat 7 days after administration. Residue levels in all other tissues were less than 0.3 mg/kg (Ohsawa et al. 1975). Although the levels detected in fat by Pollock and Kilgore (1980b) are higher than those detected by

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Ohsawa et al. (1975), a direct comparison cannot be made because the two studies used different sized rats, analyzed their tissues at different times after administration, and used different vehicles. Regardless of these quantitative differences, the available evidence still indicates that fat is the principal storage site for toxaphene and its metabolites.

The highest concentration of activity, except for the gastrointestinal tract, was in the brown fat following administration of 16 mg/kg  $^{14}\text{C}$ -toxaphene in peanut oil to rats (Mohammed et al. 1985). High concentrations of toxaphene residues were also detected in the adrenal cortex, bone marrow, liver, and kidney. Levels of radioactive residues peaked at 3 hours. At 24 hours after administration, most radioactivity was found in the white fat. Lesser amounts of the radiolabel were detected in liver and kidney.

Mice that received an oral dose of 25 mg/kg  $^{36}\text{Cl}$ -toxaphene in corn oil were observed to retain  $^{36}\text{Cl}$  activity in fat, brain, kidney, liver, muscle, and testes. Levels were highest in fat (10.6 ppm) when tissues were analyzed 8 days after administration (Crowder and Whitson 1980).

Toxaphene and its metabolites have been detected in the liver, kidney, bone, brain, heart, lung, muscle, spleen, and testes of rats 7 days after the oral administration of 8.5 and 19 mg/kg  $^{14}\text{C}$ -toxaphene (Ohsawa et al. 1975). After the oral administration of a single dose of 20 mg/kg  $^{36}\text{Cl}$ -toxaphene to rats, the greatest levels of radioactivity were seen at 12 hours in almost all tissues. Levels in blood cells peaked after 3 days. The total fat content after 12 hours was only 0.86% of the total dose, but this exceeded the fraction of the dose found in the kidney (0.43%), testes (0.28%), and brain (0.23%) (Crowder and Dindal 1974). Approximately 77% of the dose was detected in the stomach at 12 hours, and less than 10% of the dose remained in the body after one day. At 12 hours after administration, 5.3% of the dose was present in the muscle. Although this was significantly more than the amount seen in fat and other tissues, the concentration of activity in muscle is low due to the large amount of muscle in the body. Crowder and Dindal (1974) only determined the fraction of the dose based on proportions of radioactivity found in each tissue that may have been derived from a component of the original mixture or a metabolite.

Heifer calves receiving toxaphene at oral bolus doses of 50, 100, or 150 mg/kg  $^{14}\text{C}$ -toxaphene were found to have measurable toxaphene residues in the liver, kidney, and brain 7 days after administration. These tissues were the only ones sampled, so it is not possible to assess the amount of toxaphene that distributed to fat (Steele et al. 1980). This study found that liver residues varied exponentially with dosage, as shown in Table 2-4.

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**Table 2-4. Mean Toxaphene Residues in Cows Following Oral Exposure to Toxaphene**

Dose (mg/kg)	Toxaphene residue		
	Liver (ppm)	Kidney (ppm)	Brain (ppm)
50 <sup>a</sup>	2.88	3.45	2.67
100 <sup>b</sup>	7.66	2.75	4.02
150 <sup>a</sup>	22.26	5.50	3.88

<sup>a</sup>Values represent mean of 6 animals.

<sup>b</sup>Values represent mean of 7 animals.

Source: Steele et al. 1980

Furthermore, liver residue levels correlated with predicted fatality with an accuracy of about 80%. Based upon these tissue distribution results, the authors concluded that liver residue values could serve as a biomarker of toxaphene poisoning. Kidney and brain levels of toxaphene could not be used as biomarkers, because residue levels of the pesticide in these organs did not correlate with observed mortality. Additionally, brain levels are not as consistent as liver values.

In investigations of effects on the adrenal gland, oral administration of 16 mg/kg <sup>14</sup>C-toxaphene to rats resulted in its distribution to the adrenal cortex. Radioactivity was primarily localized in the *zona fasciculata*. Only low levels of radioactivity were detected in the *zona glomerulosa* and the *zona reticularis*, and no radioactivity was found in the medulla (Mohammed et al. 1985). The *zona fasciculata* is responsible for glucocorticoid synthesis. A toxaphene-induced 50% inhibition of ACTH-stimulated adrenal corticosterone synthesis *in vitro* is supported by this pattern of toxaphene distribution *in vivo*. Pretreatment of rats with toxaphene in their diet for 5 weeks also resulted in a significant inhibition of corticosteroid synthesis when compared to controls. Hence, the distribution of toxaphene to the *zona fasciculata* was correlated with an adverse physiological effect.

Administration of <sup>14</sup>C-toxaphene in olive oil at a dose of 2.6 mg/kg to pregnant rats resulted in its distribution to the fat. Fetuses contained the lowest levels of radioactivity relative to other tissues analyzed (Pollock and Hillstrand 1982). After 1 day, the residue level in the fetus was 84 ppb; the residue level after 3 days averaged 28 ppb. Residue levels in the fat of the mothers exceeded 7,000 ppb. The authors reported that the overall amount of placental transfer was similar to that of polychlorinated biphenyls (PCBs), of which much less than 1% of the dose was transferred.

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All studies reviewed consistently demonstrated that toxaphene was distributed throughout the body, but it was preferentially stored in the fat. Although toxaphene has been identified in the fat up to 30 days after administration, the overall tissue activity level was very low. Apparently, toxaphene was rapidly metabolized, and its metabolites and components were not persistent. However, it is not known whether the toxaphene metabolites or the original components that persist in fat are toxic. Therefore, these persistent residues could theoretically reenter the circulation from the fat stores and cause additional delayed toxicity. In addition to its affinity for lipid tissue, it specifically localized in the *zona fasciculata* of the adrenal cortex. Although its transplacental transfer was minimal, the radioactivity that crossed the placenta also localized in the fetal adrenal. Based on the findings in all animals (Saleh et al. 1979), it would seem likely that fat would also be a principal storage site for toxaphene in humans following its ingestion. Toxaphene localizes in the liver after initial exposure but then redistributes to fat over a longer period of time. Tissue samples obtained from a chronic dog study demonstrated that after 2 years exposure, toxaphene (as estimated from tissue chlorine levels) was measurable only in fat (Hercules Research Center 1966). The levels in liver, kidney, and brain were negligible. Fat samples obtained at the interim periods of 6 and 12 months had toxaphene levels comparable to those seen at 24 months, indicating that accumulation of toxaphene in adipose tissue may reach a saturation point, resulting in steady-state levels, with uptake being equal to excretion.

### 2.3.2.3 Dermal Exposure

No studies were available in humans or animals regarding the distribution of toxaphene following dermal exposure. Although cases of dermal exposure have been reported, there were no data that listed the resulting toxaphene levels in tissues.

### 2.3.2.4 Other Routes of Exposure

Intravenous administration of  $^{14}\text{C}$ -toxaphene to mice at a dose of 16 mg/kg resulted in the appearance of radioactivity in the liver, fat, bile, adrenal glands, kidneys, and ovaries within 20 minutes of administration. The distribution significantly changed after 4 hours, with an increase in radioactivity in the abdominal fat and the intestinal contents. There were decreases in other tissues after 4 hours. Highest levels of radioactivity were still localized in the fat 16 days after administration (Mohammed et al. 1983). In autoradiographic studies of pregnant albino mice intravenously injected with  $^{14}\text{C}$ -toxaphene (16 mg/kg), Mohammed et al. (1983) found low levels of activity in fetal tissues. This activity was highly concentrated in the fetal liver and adrenal gland. These results, as after oral administration, suggest that

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the transplacental transfer of toxaphene after intravenous administration is relatively low. The tissue accumulation of intravenously administered  $^{14}\text{C}$ -toxaphene was also examined in normolipidemic and hypolipidemic female NMRI mice (Mohammed et al. 1990b). In normolipidemic mice, the radiolabel first distributed to the liver and adrenal glands 20 minutes after administration of the labeled toxaphene. After 4 hours, the label was primarily found in the abdominal fat. The distribution of the radiolabel in the hypolipidemic mice was different from the controls. After 20 minutes, the labeled toxaphene was found in the liver, adrenal gland, heart, and kidneys. After 4 hours, nearly all the label was found in the liver. The results of the study indicate that lipid metabolism may play an important role in the tissue distribution of toxaphene and thus its toxicity.

### 2.3.3 Metabolism

#### 2.3.3.1 Inhalation Exposure

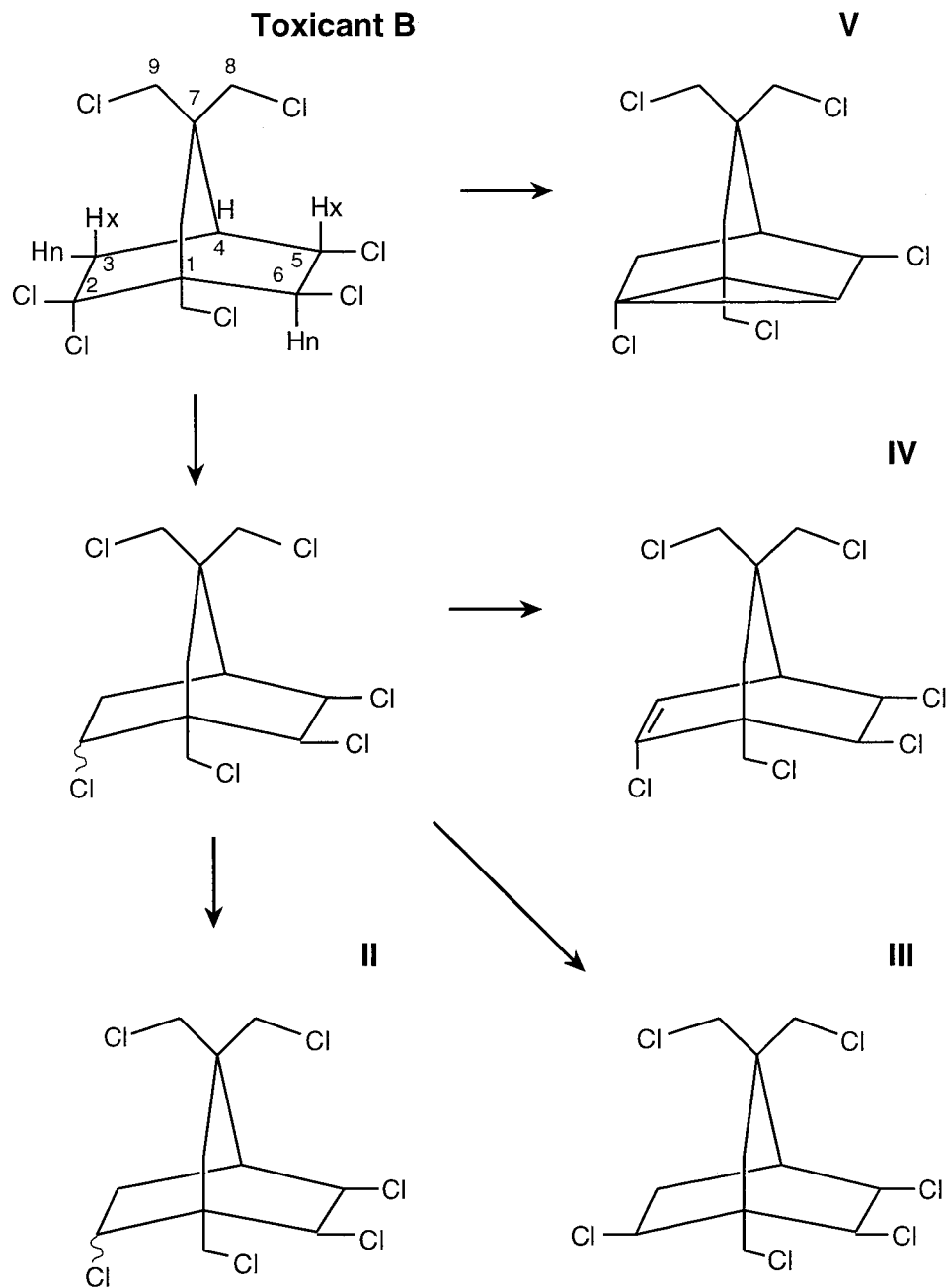
No studies were available in humans or animals regarding the metabolism of toxaphene following inhalation exposure.

#### 2.3.3.2 Oral Exposure

Toxaphene is rapidly and extensively degraded in mammals following oral administration (Figure 2-3). This was clearly evident after analyzing solvent extracts from urine, feces, and tissues. *In vivo* and *in vitro* studies indicated that the principal metabolic pathways involved dechlorination, dehydrodechlorination, and oxidation. Conjugation is also likely, but it is not a major route of metabolism. Administration of  $^{36}\text{Cl}$ -toxaphene to rats at a dose of 13 mg/kg resulted in the excretion of  $^{36}\text{Cl}$ -chloride ion in the urine. This was the only metabolite identified in the urine by Ohsawa et al. (1975), and it accounted for 50% of the administered radioactivity. Results obtained with  $^{36}\text{Cl}$ - and  $^{14}\text{C}$ -toxaphene differed. With either label, the hexane extracts of urine and feces contained some unmetabolized material. The percentage of administered activity was negligible in urine and approximately 8-12% in feces. Hence, most excreted material consisted of metabolites from toxaphene components. The combined chloroform extracts of urine and feces contained a much higher proportion of the administered  $^{14}\text{C}$ - activity (27%) than of the  $^{36}\text{Cl}$ -activity (11.2%). These results indicated that the chloroform fraction consisted of partially dechlorinated metabolites, and a predominance of these products were found in the urine. The aqueous fraction contained 11.4% of the  $^{14}\text{C}$ -dose and 0.5% of the  $^{36}\text{Cl}$  dose. The low amount of  $^{36}\text{Cl}$  activity in the aqueous extracts indicated that this fraction contained metabolites (5-10%) that had been completely



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**Figure 2-3. Proposed Metabolic Scheme for a Toxicant Isolated from Toxaphene**

Note: Toxicant B = 2,2,5-endo-6-exo-8,9,10-heptachlorobornane  
 Metabolite II = 2,5-endo-6-exo-8,9,10-hexachlorobornane  
 Metabolite III = 2,-exo-5-endo-6-exo-8,9,10-hexachlorogornane  
 Metabolite IV = 2,5-endo-6-exo-8,9,10-hexachlorogornene  
 Metabolite V = 2,5-endo-8,9,10-pentachlorotricyclene

Source: Saleh and Casida 1978

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dechlorinated (Ohsawa et al. 1975). About 2% of the  $^{14}\text{C}$ -activity appeared as expired products, probably  $^{14}\text{C}$ -carbon dioxide. Thus, these results indicate that toxaphene was metabolized mostly to partially dechlorinated products, with a small proportion being completely dechlorinated and a small proportion unmetabolized.

Pollock and Kilgore (1980b) confirmed the observations of Ohsawa et al. (1975). Less than 5% of the total activity from an orally-administered dose of 10 mg/kg  $^{14}\text{C}$ -toxaphene was extractable from urine into hexane. Thin-layer chromatography of the urine extract indicated that the components in the urine were more polar than toxaphene. No parent compounds were found in the urine. These results provide additional evidence that most of the toxaphene absorbed is metabolized, since the hexane fraction contained a low percentage of parent compound.

The complexity of toxaphene makes it difficult to understand its metabolism fully. It appears that all of its components undergo rapid metabolism, yet each component has its own rate of biotransformation. A small fraction of fecal radioactivity that was extractable into hexane indicated that some toxaphene components could be excreted unchanged. However, it is possible that some metabolite residues may share chromatographic properties similar to the original component of toxaphene.

Pollock and Kilgore (1980b) also extracted the lipid tissue of rats treated with either  $^{14}\text{C}$ -labeled toxaphene, Fraction 2, or Fraction 7. Fractions 2 and 7 are nonpolar and polar components, respectively, of toxaphene obtained from chromatographic separation of the toxaphene mixture. When compared to the chromatograms of extracts from fat fortified with  $^{14}\text{C}$ -toxaphene, the fat of treated rats had 12% more activity in its polar region. Chromatograms of fat extracts from rats treated with each fraction indicated that two additional compounds were generated that accounted for 11% of the administered activity. With Fraction 2, the additional compounds were of greater polarity. In contrast, the additional compounds generated from Fraction 7 were less polar. The decreased polarity of these metabolites may result in their persistence in the fat and decrease the excretion of Fraction 7. The study does not indicate whether these new compounds were identical.

Metabolism of toxicant B (2,2,5-endo-6-exo-8,9,10-heptachlorobomane), a toxic component of toxaphene, yielded several fecal metabolites when administered orally to mice, rats, hamsters, guinea pigs, rabbits, monkeys, and chickens (Saleh et al. 1979). The greatest amount of fecal metabolites was seen in monkeys and rabbits (20%), with 3-9% in other species, indicating that species differ with respect to metabolic rate

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and/or pathway (Saleh et al. 1979). The extensive metabolism seen in monkeys suggests that similar findings may result in humans; however, urinary metabolites were not monitored.

The chromatographic pattern of these fecal metabolites was characterized by short retention times, which suggested that dechlorination occurred (Ohsawa et al. 1975; Saleh and Casida 1978; Saleh et al. 1979). In several *in vitro* systems, especially in rat microsomes under anaerobic conditions with NADPH, and in rats under *in vivo* conditions, toxicant B is dechlorinated at the germinal dichloro group to yield 3,5-endo-6-exo-8,9,10-hexachlorobornane (II) and 2-exo-5-endo-6-exo-8,9,10-hexachlorobomane (III) (Figure 2-3). Toxicant B is also dehydrodechlorinated to 2,5-endo-6-exo-8,9,10-hexachlorobom-2,3-ene (IV) and 2,5-endo-8,9,10-pentachlorotricyclene (V) in rats *in vivo* and in other *in vitro* systems (Saleh and Casida 1978). There is no evidence that humans either do or do not metabolize toxaphene via this pathway.

Rat liver microsomes did not transform metabolite I unless they were fortified with NADPH, indicating that cytochrome P-450 was required. Furthermore, the direction of metabolism was dependent upon the oxidative conditions. Only under anaerobic conditions did dechlorination of toxicant B occur, yielding metabolites II and III. Since most gastrointestinal reactions are anaerobic, it follows that metabolites II and III would also be present in the feces (Saleh and Casida 1978). The hexachlorobomane ratio (III/II) was relatively equivalent in the feces, fat, and liver of rats treated with toxicant B, in addition to the microsomal system. The consistency of this ratio suggested that the mechanism involved in this reaction was similar among tissues (Saleh and Casida 1978). An alternative (and perhaps more likely) explanation is that most of the metabolism occurs in the anaerobic conditions of the intestine. Then compounds II and III are absorbed and distributed to the various tissues, thus keeping the original ratio found in the intestines.

Dechlorination of toxicant B resulted under aerobic conditions in the generation of five nonhydroxyl compounds in rat microsomes fortified with NADPH (Chandurkhar and Matsumara 1979). As reported by Saleh and Casida (1978), toxicant B was metabolized to a greater extent under anaerobic conditions than under aerobic conditions. It is possible that this dechlorination reaction was representative of reductive reactions that would be more favorably executed under anaerobic conditions.

Metabolites II and III were not produced under aerobic conditions. However, other unidentified products were generated. The requirement of NADPH and anaerobic conditions for production of metabolites II and III suggests the involvement of the mixed function oxidase systems (Chandurkhar and Matsumara 1979; Saleh and Casida 1978).

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Acetonitrile extracts of feces and urine from rats receiving a single oral dose of  $^{14}\text{C}$ -toxaphene at 15 mg/kg confirmed previously discussed findings that most of the toxaphene was metabolized. Gas-liquid chromatography/electron capture (GLC/EC) analysis of thin-layer chromatography (TLC) fractions from urine and feces revealed the presence of methylation products. This showed that fecal and urinary metabolites included acidic and other hydroxyl compounds (Chandurkhar and Matsumara 1979). Further analysis indicated that approximately 9% and 1% of the urinary and fecal metabolites, respectively, were sulfate conjugates. Glucuronide conjugates comprised 9.5% and 7.5% of the urinary and fecal metabolites, respectively. The presence of sulfate and glucuronide conjugates supported the conclusion that oxidative metabolism occurred.

### 2.3.3.3 Dermal Exposure

No studies were located in humans or animals regarding the metabolism of toxaphene following dermal exposure.

### 2.3.3.4 Other Exposure

Gas chromatographic results of bovine liver perfusion showed that the bovine liver can metabolize toxaphene to partially dechlorinated products. These reactions occurred under aerobic conditions in a manner similar to *in vivo* conditions (Maiorino et al. 1984).

## 2.3.4 Excretion

### 2.3.4.1 Inhalation Exposure

Organochlorine pesticides, including toxaphene, were analyzed in 183 human milk samples obtained from women living in different parts of Finland. The signals of toxaphene were detected but could not be quantitatively determined in the milk samples. According to semiquantitative analysis, the residue level of toxaphene in Finnish human milk was estimated to be ~10 mg/kg fat. The route of exposure was not known. The use of toxaphene in Nordic countries is negligible, and the source of toxaphene may be airborne fallout, chlorination processes of the pulp and cellulose industry, or metabolism from other chlorinated compounds (Mussalo-Rauhamaa et al. 1988).

No studies were available in animals regarding the excretion of toxaphene following inhalation exposure.

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**2.3.4.2 Oral Exposure**

It is evident from distribution studies that toxaphene and its metabolites are not persistent in tissues; <sup>36</sup>Cl-labeled metabolites remained for 9 days and <sup>14</sup>C-labeled metabolites remained 16 days in the fat of animals. Metabolism studies indicated that it is rapidly and extensively biodegraded. Consequently, the rate of toxaphene elimination is very high. Table 2-5 summarizes excretion results from studies in which rats were orally administered radiolabeled toxaphene and its components.

The average percentage of an orally administered 20 mg/kg <sup>36</sup>Cl-toxaphene dose excreted over 9 days (approximate half-life of excretion) was 52.6%. Approximately 30% of this amount was excreted in the urine and 70% was excreted in the feces. Fecal excretion reached a plateau 2-3 days after administration. The cumulative urinary excretion steadily increased over the 9 days. Much of the activity in the urine and feces was attributable to <sup>36</sup>Cl-chloride ion. Therefore, dechlorination is a principal metabolic route of toxaphene that facilitates its elimination (Crowder and Dindal 1974). In an excretion study conducted by Ohsawa et al. (1975) in rats with <sup>36</sup>Cl-toxaphene, a 13 mg/kg dose resulted in the excretion of 76% of the radioactivity after 14 days. Approximately 50% of the activity was detected in the urine. The amount of activity excreted in the urine apparently followed the pattern established by Crowder and Dindal (1974) where the cumulative urinary excretion of the dose steadily increased and eventually equalled the fecal elimination. Ohsawa et al. (1975) also found that <sup>36</sup>Cl-chloride ion appeared almost entirely in the urine. The half-time for the elimination of <sup>36</sup>Cl was 2-3 days, a rate equivalent to the excretion of <sup>36</sup>Cl-sodium chloride.

Rats treated orally with 8.5 mg/kg and 19 mg/kg of <sup>14</sup>C-toxaphene showed no dose-related differences with respect to the excretion of radioactivity (Ohsawa et al. 1975). After 14 days, more than 50% of the total activity was excreted in urine. Only 8-12% of the dose detected in the feces was suspected of being parent compound. The remainder of the activity in the urine and the feces was thought to be partially or completely dechlorinated products.

Radiolabeled toxicants A and B, obtained by chromatographic separation of <sup>14</sup>C-toxaphene, were orally administered to rats at doses of 0.84 and 2.6 mg/kg, respectively. Radioactivity from the <sup>14</sup>C-radiolabeled toxicants was excreted rapidly and to a slightly greater extent than toxaphene (Ohsawa et al. 1975). Parent compounds constituted only 8.6% and 2.6% of the fecal residues of toxicants A and B, respectively. However, the dosages used were lower than for toxaphene, and only one animal was tested.

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**Table 2-5. Summary of Excretion Data: Percentage of Dose Excreted in Urine and Feces Following Oral Administration to Rats of Radiolabeled Toxaphene and its Components**

Chemical	Dose (mg/kg)	Vehicle	Days after administration	% Dose		Reference
				Urine	Feces	
<sup>36</sup> Cl-Toxaphene	20	Peanut oil/ gum acacia	1	1.5	23.4	Crowder and Dindal 1974
<sup>36</sup> Cl-Toxaphene	20	Peanut oil/ gum acacia	9	15.3	37.3	Crowder and Dindal 1974
<sup>36</sup> Cl-Toxaphene	14	Corn oil	14	49.1	26.9	Ohsawa et al. 1975
<sup>14</sup> C-Toxaphene	8.5	Corn oil	14	21.3	34.7	Ohsawa et al. 1975
<sup>14</sup> C-Toxaphene	19	Corn oil	14	31.8	27.8	Ohsawa et al. 1975
<sup>14</sup> C-Toxaphene	2.6	Olive oil	5	22.0	28.3	Pollock and Hillstrand 1982
<sup>14</sup> C-Toxaphene	10	Olive oil	7	22.5	35.7	Pollock and Kilgore 1980b
<sup>14</sup> C-Fraction 2	1	Olive oil	7	30.8	38.6	Pollock and Kilgore 1980b
<sup>14</sup> C-Fraction 7	0.6	Olive oil	7	23.5	32.6	Pollock and Kilgore 1980b
<sup>14</sup> C-Toxicant A	0.84	Corn oil	14	28.3	38.4	Oshawa et al. 1975
<sup>14</sup> C-Toxicant B	2.6	Corn oil	9	26.7	47.8	Ohsawa et al. 1975

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Rats orally administered 10 mg/kg  $^{14}\text{C}$ -toxaphene in olive oil excreted 58% of the total activity in urine and feces within 7 days after administration (Pollock and Kilgore 1980b). This agreed closely with the excretion pattern reported by Ohsawa et al. (1975). Rats were also orally administered the  $^{14}\text{C}$ -labeled isolated fractions of toxaphene, Fraction 2 and Fraction 7, which are nonpolar and polar, respectively. Of these three compound mixtures, the greatest percentage of excreted dose was seen with Fraction 2; the least was seen with Fraction 7. The metabolites derived from polar Fraction 7 were less polar, which resulted in their greater persistence in fat and reduced their rate of excretion. In contrast, the nonpolar Fraction 2-derived polar metabolites were more rapidly excreted. Radioactivity measured in the urine of rats receiving Fraction 2 was significantly higher than from those administered Fraction 7 or toxaphene.

Another possible explanation for the unexpected order of excretion is the unexplained contribution of methanol-insoluble activity in the feces. Only the methanol-extractable activity was reported. Ohsawa et al. (1975) reported that some fecal radioactivity was methanol-insoluble and was not detected. Consequently, this may have significantly altered the measurements of total excreted activity. Less polar metabolites from Fraction 7 may be present in the methanol-insoluble extract from feces.

Excretion of radioactivity derived from  $^{14}\text{C}$ -toxaphene in pregnant rats was found to be similar to that of virgin female rats (Pollock and Hillstrand 1982). Although there was a weight difference between the pregnant and nonpregnant rats, approximately 50% of the total activity was excreted in the urine and feces over 5 days after the oral administration of 2.6 mg/kg in olive oil. The increased amount of fatty tissue had no effect on the excretion of  $^{14}\text{C}$ -toxaphene.

Toxaphene fed to cows in their feed at levels of 20, 60, 100, and 140 ppm for 8 weeks was excreted at all dosage levels. Residues in milk increased rapidly and reached a maximum within 4 weeks after feeding commenced. The levels of toxaphene found in milk were dose-dependent. Upon the cessation of toxaphene administration, there was a rapid decrease in toxaphene residues in the milk. The rate of decrease was the same at all dosage levels during the 1st week. Decreases in milk levels after the first week were slower for animals fed toxaphene at levels greater than 20 ppm (Clabom et al. 1963) as shown in Table 2-6. Detectable amounts of toxaphene were found in the milk of cows 7-9 days after feeding of toxaphene at levels of 2.5-20 ppm commenced (Zweig et al. 1963). As with the higher feeding levels discussed above (Clabom et al. 1963), plateaus were achieved after the fourth week, except at the lowest dose of 2.5 ppm, where a maximum was achieved at 9 days. The animals were fed toxaphene for 1-2.5 months. Toxaphene was no longer detected in the milk within 14 days after cessation of toxaphene administration (Zweig et al. 1963)

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**Table 2-6. Toxaphene Levels in Milk from Cows Fed Toxaphene in Their Diet**

Diet concentration (ppm)	Concentration of milk (ppm) <sup>a</sup>				
	Weeks of feeding			Weeks after cessation of toxaphene feeding	
	1	4	8	1	3
20	0.20	0.36	0.23	0.07	—
60	0.56	0.68	0.48	0.13	0.07
100	0.87	1.15	0.91	0.15	0.12
140	1.44	1.89	1.82	0.32	0.20

<sup>a</sup>Values represent means of 3 samples.

Source: Claborn et al. 1963.

The high concentration of radioactivity in the gall bladder from <sup>14</sup>C-toxaphene orally administered to quail confirmed the likelihood that the biliary pathway plays an important role in toxaphene excretion (Biesmann et al. 1983).

### 2.3.4.3 Dermal Exposure

No studies were found regarding the excretion of toxaphene in humans following dermal exposure.

Information regarding the excretion of toxaphene in animals following dermal absorption is limited. Evidence for the excretion of toxaphene in milk is found in a study conducted with cows that were sprayed twice daily with 1 ounce of 2.0% toxaphene oil solution or sprayed twice at 3-week intervals with 0.5% sprays of toxaphene. Residues of toxaphene in milk resulting from daily oil sprays reached a maximum after the third day of spraying. When cows were sprayed twice at 3-week intervals, maximum residues in milk were detected 1 or 2 days after spraying (Claborn et al. 1963). Cows that were dipped in a solution containing 0.25% toxaphene also excreted toxaphene in the milk at levels of 21–45 ppm 1 day after dipping. Toxaphene levels fell to 5 ppm 19 days after exposure ceased (Keating 1979). The absorption, distribution, and excretion of toxaphene were evident from these studies, but insufficient information regarding the dose of toxaphene precludes any estimation of the extent and rate of excretion.



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### 2.3.4.4 Other Routes of Exposure

Mohammed et al. (1983) reported that  $^{14}\text{C}$ -toxaphene was rapidly distributed to most tissues and organs following intravenous administration in mice. Between 20 minutes and 4 hours after injection, there was a significant increase in the radioactivity observed in the intestinal contents. The presence of radioactivity in the intestine probably represented the biliary excretion of  $^{14}\text{C}$ -toxaphene and its metabolites. Sixteen days after administration, the tissues showing the highest concentration of  $^{14}\text{C}$  toxaphene was abdominal fat, which had concentrations about 10% of those found 4 hours after administration.

Based on the rapid and extensive metabolism seen in all animals, the fate of toxaphene in humans is probably similar. The negligible quantities of parent compound in the excreta and the lack of persistence of metabolites in the tissues indicate that toxaphene and its components are readily removed from the body. Low-level exposure is not expected to cause significant harm to humans. Theoretically, however, acute high-level exposure may saturate metabolic pathways and consequently allow toxaphene to accumulate in the tissues for a longer period of time (>16 days).

## 2.4 MECHANISMS OF ACTION

Toxaphene is rapidly absorbed by the gastrointestinal tract and lungs; absorption through the skin can also occur, but it is much less efficient. For that reason, the dermal doses that cause overt toxicity in laboratory animals are an order of magnitude higher than those causing similar toxicity following oral exposure. Toxaphene is more rapidly absorbed if it is mixed in oily (lipophilic) solvents, probably because interactions with polar areas on the cell membrane are reduced. Once absorbed, toxaphene rapidly distributes to all organs of the body; however, the pesticide tends to concentrate in fatty tissues and muscle from which it is slowly released over a period of weeks. Circulating toxaphene is primarily metabolized by hepatic mixed-function oxidases. Toxaphene and its metabolites are excreted in the feces and urine, and most of it is eliminated from the body within a few days.

Toxaphene-induced toxicosis results from a combination of factors, but the most severe effects appear to be associated with a general stimulation of the central nervous system that is manifested after acute highdose exposure to the compound (see Neurological Effects in Section 2.5). The stimulation is proposed to be the result of the noncompetitive inhibition of  $\gamma$ -aminobutyric acid-dependent chloride ion channels.  $\gamma$ -Aminobutyric acid is believed to be an inhibitory neurotransmitter. Thus, blocking its action leads to

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over-activity of those neurons whose activity is modulated by  $\gamma$ -aminobutyric acid. The net result is a global increase in central nervous system activity that can result in tremors, ataxia, convulsions, and death.

### 2.5 RELEVANCE TO PUBLIC HEALTH

Humans living in areas surrounding hazardous waste sites may be exposed to toxaphene via ingestion of contaminated water or even ingestion of soil, particularly by children. Inhalation exposure to toxaphene via volatilization from contaminated water or soil may also occur. Acute exposures to high levels may be extremely unlikely at hazardous waste sites, but would be of particular concern. The clinical signs common to both humans and animals following acute intoxication with toxaphene (e.g., hypersalivation, hyperexcitability, behavioral changes, muscle spasms, convulsions, and death) point to the nervous system as the major target of acute toxicity. This system also appears to be affected, though to a lesser extent, following longer-term exposure in humans and animals. Other toxic manifestations of toxaphene exposure observed in humans and animals include adverse respiratory effects following inhalation exposure. Target organs of toxaphene toxicity identified in experimental animals but not humans include the liver and kidney, and, to a lesser extent, the heart and immune system.

Based on the toxicological data presented in this chapter, minimum risk levels (MRLs) have been established for acute and intermediate oral exposure to toxaphene because sufficient good quality data exist for that route of exposure and those exposure periods. The MRL is considered to be a level of human exposure that is without appreciable risk to health. The MRL is often derived from animal data because adequate human data do not exist. That does not preclude the calculation of an MRL because the calculation takes into account the greater sensitivity of the human response (relative to animals) to toxic insult and the fact that there is great individual variability in the human response to toxic insult.

Using standardized methods for calculating MRLs, the acute oral exposure MRL for toxaphene is 0.005 mg/kg/day and the intermediate oral exposure MRL is 0.001 mg/kg/day. The following paragraphs summarize the information that is pertinent to public health. Appendix A contains a detailed explanation of the derivation of these MRLs.

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**Minimum Risk Levels for Toxaphene.*****Inhalation MRLs.***

MRLs for inhalation could not be derived because of the absence of reliable data following inhalation exposure. The available data regarding inhaled toxaphene are limited because the information is derived from summaries of unpublished reports or from less than reliable studies.

***Oral MRLs.***

- An MRL of 0.005 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to toxaphene.

The MRL is based on a LOAEL of 5.0 mg/kg/day for decreased hepato-biliary function in rats treated with 0 or 5.0 mg/kg/day toxaphene in the diet for 8 days (Mehendale 1978). Livers of treated animals were used in an isolated liver perfusion preparation. Liver function was assessed by monitoring the metabolism and biliary excretion of <sup>14</sup>C-imipramine. Both metabolism and biliary excretion of imipramine were decreased in toxaphene-treated rats. The choice of this end point is supported by data from other studies that showed adverse effects on the liver following acute exposure to toxaphene (Chandra and Durairaj 1992; Garcia and Mourelle 1984; Mehendale 1978; Peakall 1976). The Mehendale (1978) study was used to derive the MRL because it reported the lowest reliable LOAEL for hepatic toxicity.

- An MRL of 0.001 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to toxaphene.

This MRL was based on a study by Chu et al. (1986) that examined Sprague-Dawley rats (1 O/sex/dose group) exposed for 13 weeks to 0, 4, 20, 100, or 500 ppm toxaphene in the feed. The authors calculated that those toxaphene concentrations delivered 0, 0.35, 1.8, 8.6, or 45.9 mg/kg/day toxaphene, respectively, for males, and 0, 0.50, 2.6, 12.6, or 63 mg/kg/day toxaphene, respectively, for females. At the conclusion of the study, the brain, heart, spleen, liver, and kidneys were removed and weighed. Those and a variety of other tissues were analyzed histopathologically. Hematological evaluations were also conducted.

Toxaphene did not cause any clinical signs of toxicity, and food consumption and body weight gain were similar to controls across all treatment groups. Relative liver weight was increased at 500 ppm in both

## 2. HEALTH EFFECTS

sexes; male relative kidney weight was also elevated at 500 ppm. Induction of the hepatic microsomal enzymes aniline hydroxylase and aminopyrine demethylase was observed at that dose in both sexes. The serological findings were negative for all doses of toxaphene. Histopathological evaluation of the tissues from all dose groups indicated that toxaphene targeted the liver, kidney, and thyroid organs. Dosedependent histological changes were observed in hepatic tissues from both sexes and consisted primarily of peripheralized basophilia and anisokaryosis. In the kidneys of both sexes, dose-dependent structural alterations in the proximal tubules were seen. Those consisted primarily of proximal tubule inclusions which were, in severe cases, associated with casts and focal tubular necrosis. The severe renal effects were confined to the males in the 500 ppm group. Toxaphene treatment caused mild to moderate thyroid cytoarchitectural changes. These changes were characterized by reduced colloid density, angular collapse of follicles, and increased epithelial height with multifocal papillary proliferation. The results of this study identified a rat NOAEL of 0.35 mg/kg/day for toxaphene. That NOAEL was supported by a similar study conducted in rats by Chu et al. (1988) that reported a NOAEL of 0.36 mg/kg/day for the same toxicity end points.

Additionally, perinatal exposure to toxaphene in Holtzman rats for 47 days (approximately gestational day 17 through postnatal day 40) impaired swimming ability on postnatal days 10, 11, and 12 (Olson et al. 1980). The results of that study indicate that toxaphene has the potential to alter offspring functional and behavioral development. For that reason, an additional modifying factor of 3 was included in the MRL derivation to take into account the potential for toxaphene to affect the developing nervous system.

An MRL for chronic-duration oral exposure to toxaphene was not derived because a suitable NOAEL or LOAEL value could not be identified in the available literature.

**Death.** Toxaphene can be fatal both to humans and animals following ingestion. Death has also been observed in animals following inhalation and dermal exposure to toxaphene, but no such cases have been reported in humans. Death in humans and animals is due to respiratory arrest following convulsive seizures. The doses required to produce death are relatively large, and case reports describing the occurrence of death were found only in instances of accidental or intentional ingestion of large quantities of toxaphene-containing insecticides and in cases of ingestion of heavily contaminated foods (McGee et al. 1952). Therefore, it is likely that the risk of death is very small under conditions of long-term, lowlevel exposure either from ingestion of contaminated food or water, or from inhalation of toxaphene dusts or mists. However, Boyd and Taylor (1971) found that protein deficiency enhances the lethality of

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ingested toxaphene in rats, so humans consuming protein-deficient diets may represent a sensitive subpopulation (see Section 2.8).

Toxaphene is a complex mixture of at least 670 chlorinated camphenes (Jansson and Wideqvist 1983). Several of the components have been identified and, as indicated below, several are more toxic than technical grade toxaphene (Casida et al. 1974; Matsumura et al. 1975; Nelson and Matsumura 1975; Turner et al. 1975). More than a three-fold difference in toxicity was observed for LD<sub>50</sub> values in mice after the intraperitoneal administration of various toxaphene fractions or components that differed in chemical composition, polarity, and solubility (Pollock and Kilgore 1980b). Identified toxic components of toxaphene are listed in Table 2-7. Toxaphene components A and B have been isolated and found to possess toxicity that is 6 and 14 times greater, respectively, than the technical toxaphene mixture as measured by comparing intraperitoneal LD<sub>50</sub> values in mice (Casida et al. 1974). Toxicant A has been identified as a mixture of 2,2,5-endo,6-exo,8,8,9, 10-octachlorobomane and 2,2,5-endo,6-exo,8,9,9,10-octachlorobomane (Matsumura et al. 1975; Turner et al. 1975) and toxicant B has been identified as 2,2,5-endo,6-exo,8,9, 10-heptachlorobomane (Casida et al. 1974). It has further been determined that toxicant B and four of its derivatives, each with an additional chlorine atom at position 3-exo,8,9, or 10, may be responsible for the bulk of toxaphene's acute toxicity (Saleh et al. 1977). Also, animal studies suggest that detoxification of the toxaphene mixture may be more inefficient in immature animals and possibly also in children than the metabolism and detoxification of the single components such as toxicant A or B.

**Systemic Effects.**

***Respiratory Effects.*** Cases of suspected pulmonary hypersensitivity following exposure to insecticides (containing toxaphene) in aerial applicators have been reported (Warraki 1963). The available data on adverse respiratory effects associated with toxaphene exposure in animals are not conclusive (Boyd and Taylor 1971). The effects observed in humans cannot be definitively attributed to toxaphene, and they were reversible. Because there is no clear evidence that toxaphene is the causative agent and since these effects are not corroborated by animal data, their relevance to public health is not known.

Table 2-7. Identified Toxic Components of Toxaphene

CAS Registry No./ Molecular Formula	Chemical Abstracts Name (Ninth Collective Index)	Synonyms	Reference
51775-36-1/ C <sub>10</sub> H <sub>11</sub> Cl <sub>7</sub>	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7,7-tris(chloromethyl)-,(5-endo,6-exo)-	2,2,5-endo,6-exo,8,9,10-heptachlorobornane; toxaphene toxicant B	Clark and Matsumura 1979; Saleh and Casida 1978; Saleh et al. 1979; Chandurker and Matsumura 1979
52819-39-3/ C <sub>10</sub> H <sub>9</sub> Cl <sub>9</sub>	Bicyclo[2.2.1]heptane,2,3,3,5,6-pentachloro-7,7-bis(chloromethyl)-1-(dichloromethyl)-(2-endo,5-exo,6-exo)	Toxaphene toxicant C*; 2-endo,3,3,5,6-exo,8,9,10,10-nonachlorobornane	Chandurkar and Matsumura 1979
57208-55-4/ C <sub>10</sub> H <sub>10</sub> Cl <sub>8</sub>	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl)-7-(dichloromethyl)-	Toxic fraction A: 2,2,5-endo,6-exo,8,9,9,10-octachlorobornane	Clark and Matsumura 1979
57981-30-3/ C <sub>10</sub> H <sub>11</sub> Cl <sub>7</sub>	Bicyclo[2.2.1]heptane,2,5,6-trichloro-3,3-bis(chloromethyl)-2-(dichloromethyl)-(exo,exo,exo)-	2,5,6-exo,8,8,9,10-heptachloro-dihydrocamphene	Swanson et al. 1978
58002-18-9/ C <sub>10</sub> H <sub>10</sub> Cl <sub>8</sub>	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl)-7-(dichloromethyl)-5-endo,6-exo,7-anti)-	2,2,5-endo,6-exo,8,8,9,10-octachlorobornane; toxaphene toxicant A-1	Pollock and Kilgore 1980b
58002-19-0/ C <sub>10</sub> H <sub>10</sub> Cl <sub>8</sub>	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl)-7-(dichloromethyl)-(5-endo,6-exo,7-syn)-	2,2,5-endo,6-exo,8,9,9,10-octachlorobornane; toxaphene toxicant A-2	Pollock and Kilgore 1980b
66860-80-8/ C <sub>10</sub> H <sub>9</sub> Cl <sub>9</sub>	Bicyclo[2.2.1]heptane,2,3,5,6-tetrachloro-7-(chloromethyl)-1-7-bis(dichloromethyl)-(2-endo,3-exo,5-endo,6-exo,7-syn)-	Toxaphene toxicant Ac	Chandurker et al. 1978
70940-13-5/ C <sub>10</sub> H <sub>9</sub> Cl <sub>9</sub>	Bicyclo[2.2.1]heptane,2,3,3,5,6-pentachloro-1,7-bis(chloromethyl)-7-(dichloromethyl)-	Toxaphene toxicant C*; 2,3,3-endo,5,6-exo,8,9,10,10-nonachlorobornane	Clark and Matsumura 1979

\*Prepared structures have not been confirmed.

Source: EPA 1987f

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**Cardiovascular Effects.** Adverse cardiovascular effects associated with toxaphene exposure have not been reported in humans. Animal studies have shown that acute toxaphene exposure can damage the myocardium (Boyd and Taylor 1971) as well as alter chronotropic control of the heart (Lackey 1949). Degeneration of cardiac nerve terminals has also been observed in rats exposed to toxaphene (Badaeva 1976). Nevertheless, no cardiovascular toxicity has been observed in humans exposed to toxaphene, so is unlikely that this organ system is significantly adversely affected by the pesticide.

**Hepatic Effects.** Biochemical evidence of transient, reversible liver injury in a 26-year-old man who attempted suicide by drinking a toxaphene-containing insecticide was reported by Wells and Milhom (1983). No other information regarding adverse hepatic effects in humans associated with toxaphene exposure was found. Following both short- and long-term ingestion of toxaphene by animals, hepatic hypertrophy with increased microsomal enzyme activity, inhibition of biliary excretion and function, and mild-to-moderate hepatocellular histological changes (fatty degeneration, vesiculation, vacuolation, focal necrosis) have been observed. Because the liver appears to be a target of toxaphene toxicity, hepatotoxicity was the end point used to derive toxaphene MRLs. The acute and intermediate oral exposure MRLs for toxaphene are 0.005 and 0.001 mg/kg/day, respectively.

It should be noted that some authors have speculated that the hepatotoxicity represents adaptive responses to underlying events and not direct toxic effects on the liver (Chu et al. 1986). Some of the possible mechanisms triggering these adaptive responses are as follows:

- (1) As discussed in Section 2.2.2.2, toxaphene, like other chlorinated hydrocarbon insecticides, induces hepatic microsomal enzyme activity. This could result in hepatic cell hypertrophy and liver enlargement. When separated into polar and nonpolar fractions, no difference in the extent of enzyme induction by fraction was noted (Pollock et al. 1983). Microsomal enzyme induction has important implications with regard to altering the apparent toxicity of other xenobiotics in individuals concurrently exposed to several chemicals or drugs (see Sections 2.7 and 2.8).
- (2) Kuz'minskaya and Alekhina (1976) and Gertig and Nowaczyk (1975) reported that both short- and long-term oral administration of toxaphene to rats caused disturbances in energy metabolism as evidenced by changes in hepatic lactate dehydrogenase activity. However, Peakall (1979) demonstrated that these changes are not severe enough to have definite physiological consequences (measured as serum lactate and pyruvate levels) under nonstress conditions.

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The results of these two studies suggest that toxaphene exposure, coupled with stress, could result in detrimental effects on hepatic energy utilization and, ultimately, in hepatic injury.

- (3) Several investigators have demonstrated both *in vivo* and *in vitro* that short- and long-term toxaphene exposure is associated with inhibition of various ATPases in liver (e.g., Fattah and Crowder 1980; Mourelle et al. 1985; Trottman and Desaiyah 1979; Trottman et al. 1985). These enzymes are involved in all aspects of cellular activity, and their inhibition can ultimately result in disturbances in hepatic function, which could trigger injury responses.

Though only one case report of toxaphene-induced hepatotoxicity in humans was found in the literature, animal studies indicate that both short- and long-term exposure to toxaphene can alter hepatic function. Thus, individuals exposed to large amounts toxaphene may be at risk for compromised hepatic function and possible injury.

**Renal Effects.** Clinical chemistry tests indicated that renal function was temporarily compromised in a 26-year-old man who attempted suicide by ingesting a toxaphene-containing insecticide (Wells and Milhom 1983). No other information regarding adverse renal effects in humans associated with toxaphene exposure was found. The kidney is a target organ of toxaphene toxicity following short- and long-term ingestion by animals. Toxaphene-induced adverse renal effects include cloudy swelling, congestion, tubular degeneration, focal necrosis, and kidney enlargement. Though generally more severe than the hepatic effects usually observed, these kidney lesions may also be a response to underlying changes in renal function. Several investigators have demonstrated that various ATPases in the kidney are inhibited by toxaphene (Fattah and Crowder 1980; Trottman and Desaiyah 1979; Trottman et al. 1985). As discussed above, these enzymes are involved in all aspects of cellular activity, and their inhibition can ultimately result in disturbances of renal function, which could trigger injury responses.

Though only one case report of toxaphene-induced nephrotoxicity in humans was found in the literature, animal studies indicate that both short- and long-term exposure to toxaphene can alter renal function. Thus, individuals exposed to toxaphene may be at risk for compromised renal function.

**Endocrine Effects.** The adrenal gland appears to be adversely affected by toxaphene. One animal study has demonstrated that repeated exposure to 1.2 ppm (0.06 mg/kg/day) for 5 weeks (but not a single exposure to 16 mg/kg toxaphene) results in a decrease in ACTH-stimulated corticosterone synthesis in isolated or cultured adrenal cells (Mohammed et al. 1985). Thus, it is possible that prolonged or repeated



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exposure is required to affect the function of this organ. Positive results obtained following continuous (0-24 hours) exposure *in vitro* support such a conclusion. Based on these results, it is possible that adverse effects on corticosterone synthesis in humans may occur after prolonged high-level exposure to toxaphene. However, although animal data suggest that toxaphene has a potential effect on glucocorticoid activity which could alter effective energy utilization in the body, limited evidence in humans occupationally exposed to toxaphene in combination with other pesticides indicates that adrenal function is not adversely affected (Embry et al. 1972; Morgan and Roan 1973).

Results from animal studies suggest that prolonged oral exposure to toxaphene may induce thyroid injury (Chu et al. 1986, 1988; NCI 1977). The thyroid gland is essential to maintaining an organism's metabolic homeostasis, so any substance that may adversely affect the proper functioning of this organ is of concern to the health of those highly exposed on a prolonged basis.

***Dermal Effects.*** In humans, exposure to a toxaphene aerosol containing 500 mg/m<sup>3</sup> (30 minutes/day for 10 days) did not cause dermal irritation (Keplinger 1963). However, 500 mg toxaphene applied to the skin of rabbits caused erythema and edema (International Research and Development Corp. 1973). Thus, exposure to high levels of toxaphene may cause dermal irritation.

***Ocular Effects.*** Information on the potential for toxaphene to injure the eye is limited. However, one animal study indicated that toxaphene did not cause ocular irritation (Boots Hercules Agrochemicals n.d.).

***Body Weight Effects.*** Effects of toxaphene on body weight after acute exposure are not common because changes in body weight usually take several days to appear and by then most of the acute toxic effects have disappeared. Gestational exposure to toxaphene has been reported to decrease maternal body weight gain (Chemoff and Carver 1976; Chemoff et al. 1990). Chronic exposure to low levels of toxaphene does not affect body weight in male rats, but unspecified decreases in the body weight of female rats were seen with chronic exposure. However, body weight for males was unaffected (NCI 1977). The data suggest that pregnant animals may be more sensitive to toxaphene toxicity, suggesting pregnant women may represent a population at risk for toxaphene exposure.

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**Immunological and Lymphoreticular Effects.** No evidence was found to indicate that toxaphene affects the immune system in humans. However, ingestion of toxaphene by laboratory animals results in specific suppression of humoral antibody (IgG) production at doses lower than those necessary to induce adverse effects in other systems (Allen et al. 1983; Koller et al. 1983). These findings could be interpreted to suggest that individuals exposed to toxaphene at levels that may not induce any other evidence of toxicity may be at risk for developing compromised immune function. However, much more data would be needed to confirm such a possibility. The oral administration of toxaphene to pregnant rats has been shown to decrease maternal thymus weight (Chemoff et al. 1990; Trottmann and Desai 1980).

**Neurological Effects.** Signs of central nervous system stimulation are the hallmark of acute toxaphene intoxication in both humans and animals. The dose estimated to induce non-fatal convulsions in humans is approximately 10 mg/kg (Hayes 1963). The same dose has been observed to cause convulsions in dogs, a species considered to be sensitive to the toxic effects of toxaphene (Lackey 1949). Longer-term exposure to toxaphene can also result in less dramatic neurological effects in humans and animals. The neurologic effects of toxaphene can also be manifested as functional (EEG, behavioral), biochemical (neurotransmitter), and morphological alterations. No effect on learning and learning transfer abilities was observed in animals postnatally exposed to toxaphene. However, slight changes in motor function and behavior were observed in rats exposed perinatally (Crowder et al. 1980, see Section 2.2.2.4). Santolucito (1975) reported that the EEG pattern of squirrel monkeys was altered by chronic exposure to toxaphene.

Toxaphene-induced nervous system toxicity may result from a general disruption of nervous system function. Toxaphene has been shown to inhibit brain ATPases (Fattah and Crowder 1980; Moorthy et al. 1987; Morrow et al. 1986; Rao et al. 1986; Trottmann and Desai 1979; Trottmann et al. 1985). Morrow et al. (1986) observed that polar toxaphene fractions were more potent inhibitors of rat brain ATPase than other non-polar or intermediate polar fractions or even toxaphene itself. However, Pollock and Kilgore (1980a) reported that non-polar fractions of toxaphene are more toxic to houseflies and mice than polar fractions, which is opposite to the relationship observed by Morrow et al. (1986). Morrow et al. (1986) proposed that this discrepancy may be explained by the fact that *in vivo* the ATPases are membrane-bound in a hydrophobic environment, whereas in the *in vitro* preparation used in this study, these enzymes may have become disoriented, resulting in exposure of polar groups. Diminished ATPase activity in nervous tissue could have a profound effect on neural transmission because of the tissue's high metabolic rate.

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In addition to interfering with metabolism, toxaphene has the potential to alter central nervous system neurotransmitter activity. Toxaphene acts as a noncompetitive  $\gamma$ -aminobutyric acid (GABA) antagonist at the chloride channel (also known as the picrotoxin binding site) in brain synaptosomes (Lawrence and Casida 1984; Matsumura and Tanaka 1984). Antagonism of GABAergic neurons within the central nervous system leads to generalized central nervous system stimulation by inhibiting chloride influx leading to hyperpolarization and increased neuronal activity. Moreover, the ability of toxaphene to induce convulsions is closely related to its affinity for the picrotoxin binding site. Toxaphene has also been shown to alter catecholamine metabolism in the brain (Kuz'minskaya and Ivanitskii 1979). Thus, toxaphene has the potential to disrupt nervous system function by several mechanisms.

**Reproductive Effects.** Multigeneration studies conducted in rats (Chu et al. 1988; Kennedy et al. 1973; Peakall 1976) or mice (Keplinger et al. 1970) indicated that orally administered toxaphene does not adversely affect male or female reproductive processes. Thus, these systems would not be expected to be at risk following human toxaphene exposure.

**Developmental Effects.** Adverse developmental effects have been observed in laboratory animals following toxaphene ingestion at doses below those required to induce maternal toxicity. The most sensitive end points of fetal toxicity appear to be behavioral effects and immunosuppression (Allen et al. 1983; Olson et al. 1980). Thus, the human fetus may be at risk for toxaphene exposure.

**Genotoxic Effects.** Tables 2-8 and 2-9 present the results of *in vivo* and *in vitro* genotoxicity studies, respectively. Cells in lymphocyte cultures taken from toxaphene-exposed individuals have a higher incidence of chromosomal aberrations than cultures from individuals who have not been exposed (Samosh 1974). These data suggest that toxaphene is capable of inducing genotoxic effects in humans. However, it is not known whether the genotoxic effects will be observed in human germ cells—that is, in cells capable of passing genotoxic effects on to offspring. The one study that used the dominant lethal test did not show an increase in the number of dead implants or a decrease in the number of live implants in female mice that had been mated to toxaphene-exposed males (Epstein et al. 1972). The males were exposed to toxaphene either by gavage or by intraperitoneal injection. The doses used caused death in 9 of 12 of the high-dose orally exposed mice (daily doses of 80 mg/kg for 5 days) and 2 of 9 of the high-dose intraperitoneally exposed mice (180 mg/kg single dose). Therefore, it is likely that a sufficiently high dose was tested by Epstein et al. (1972). Toxaphene has been found to be genotoxic with the Ames test for mutagenicity in the bacteria *Salmonella typhimurium* (Hooper et al. 1979; Mortelmans et al. 1986).

Table 2-8. Genotoxicity of Toxaphene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian systems:			
Human lymphocytes/occupational exposure	Chromosomal aberrations	-	Samosh 1974
Mouse dominant lethal test	Gene mutation	-	Epstein et al. 1972

+ = positive; - = negative

Table 2-9. Genotoxicity of Toxaphene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
EI plasmid DNA isolated from <i>Escherichia coli</i>	DNA damage	ND	-	Griffin et al. 1978
<i>Salmonella typhimurium</i> strain TA98	Gene mutation	ND	+	Hooper et al. 1979
<i>S. typhimurium</i> strain TA100		+	-	Hooper et al. 1979
<i>S. typhimurium</i> strain TA98		(+)	+	Mortelmans et al. 1986
<i>S. typhimurium</i> strain TA100		+	+	Mortelmans et al. 1986
<i>S. typhimurium</i> strain TA1535		-	-	Mortelmans et al. 1986
<i>S. typhimurium</i> strain TA1537		-	(+)	Mortelmans et al. 1986
Fungi and plant systems:				
<i>Neurospora crassa</i>	Gene mutation	ND	+	Mortelmans et al. 1986
Mammalian cells:				
Human lymphoid cells LAZ-007	Sister chromatid exchange	+	+	Sobti et al. 1983

ND = no data; - = negative; + = positive; (+) = weakly positive

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Toxaphene increases the frequency of sister-chromatid exchanges of chromosomes in a cultured cell line derived from human lymphoid cells (Sobti et al. 1983).

Toxaphene does not require metabolic activation to cause mutagenic effects in bacteria (Mortelmans et al. 1986) or to increase sister chromatid exchange in human lymphoid cell lines (Sobti et al. 1983). In fact, the addition of liver S9 fractions from Aroclor 1254-stimulated livers of rats and hamsters decreases the number of reversions in *S. typhimurium* and the incidence of sister-chromatid exchanges in the human lymphoid cell line. The findings suggest that mammalian metabolism of toxaphene may reduce the overall genotoxic effect of the mixture. The findings of Hooper et al. (1979) are of potential relevance to public health. These authors determined that certain components of the mixture of chemicals making up technical toxaphene were much less mutagenic than the mixture as a whole. Specifically, the components that Hooper et al. (1979) identified as having high insecticidal or acute mammalian toxicity activity (e.g., heptachlorobomane, gem-dichloro components, and nonpolar fractions) were less mutagenic using the Ames test with *S. typhimurium* strain TA100 than was the complete toxaphene mixture (or the polar fraction). These findings may have relevance to public health in that the components of complex mixtures such as toxaphene may distribute unevenly in the environment (see Chapter 5). The evidence discussed above suggests that toxaphene may pose a genotoxic threat to humans although it is not known whether these effects are inheritable.

**Cancer.** No conclusive evidence is available to link cancer with toxaphene exposure in humans. However, a conclusive positive cancer bioassay was found for toxaphene administered to rodents in feed. A statistically-increased incidence of thyroid tumors was observed in rats and the incidence of hepatocellular tumors was significantly increased in mice (NCI 1977). Based on these findings, EPA (IRIS 1995) has classified toxaphene as a B2, probable human carcinogen. They derived a cancer slope factor of 1.1 mg/kg/day for oral exposure.

It has been proposed that organochlorines induce their carcinogenic effects via an epigenetic mechanism rather than a genotoxic mechanism (Williams 1981). One of the theories proposed to explain cancer promotion is that substances acting by this mechanism are believed to produce an effect on cell surface membranes that results in decreased intercellular communication. Without proper intercellular communication, abnormal (neoplastic) cells are allowed to proliferate unregulated.

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The basis for assigning this mechanism to organochlorine pesticides includes the following observations:

- The organochlorine pesticides are generally not genotoxic.
- Often, carcinogenic effects induced by organochlorine pesticides are observed only after high and sustained levels of exposure and are sometimes reversible. This is consistent with a mechanism involving reversibly altered membranes. In contrast, genotoxic carcinogens may exert their effects even after a single exposure, at low levels of exposure, and the effects are irreversible.
- In *in vivo* carcinogenicity tests using rodents, organochlorine pesticides generally induce cancer only in the liver, whereas genotoxic carcinogens cause cancer in many organs.

While toxaphene is an organochlorine pesticide, it does not meet all the criteria of an epigenetic carcinogen. For example, toxaphene has been demonstrated to cause genotoxic effects such as microbial mutations. Furthermore, while toxaphene exposure does result in an increased incidence of hepatocellular tumors, it also has been shown to induce thyroid tumors. In conclusion, toxaphene may induce carcinogenicity via an epigenetic and a genotoxic mechanism. Furthermore, though there is no evidence to link cancer with toxaphene exposure in humans, animal evidence suggests that it may cause cancer in humans.

### 2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on

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the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium).

Biomarkers of exposure to toxaphene are discussed in Section 2.6.1. Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by toxaphene are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

### **2.6.1 Biomarkers Used to Identify or Quantify Exposure to Toxaphene**

Following acute exposure to high doses, toxaphene can be readily detected in human blood (Griffith and Blanke 1974; Taylor et al. 1979; Tewari and Sharma 1977). If exposure is via inhalation, however, absorption is probably not sufficient to yield quantifiable levels in the blood (EPA 1980a). Other body fluids in which this insecticide has been detected include breast milk, urine, and stomach washings (Munn et al. 1985; Tewari and Sharma 1977; Vaz and Blomkvist 1985). Trace amounts were found in breast milk from Swedish women (0.1 mg/kg milk fat) (Vaz and Blomkvist 1985). Only one study was found quantifying levels of toxaphene in human tissues, and none were found relating levels in the environment to levels in human fluids or tissues. Tissue samples taken from dogs sacrificed at intervals in a 2-year study demonstrated that levels of toxaphene in fat were proportional to the levels in the feed, and that tissue levels were essentially stable over the period of 2 years (Hercules Research 1966). Levels detected in tissues generally reflect only very recent exposures (less than 1 week) because toxaphene is rapidly



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cleared from the body. Metabolites of toxaphene are excreted predominantly in the urine and feces; however, analytic procedures for detecting toxaphene metabolites are not sensitive or reliable enough to allow for screening for metabolites in the blood or excreta.

### 2.6.2 Biomarkers Used to Characterize Effects Caused by Toxaphene

Toxaphene causes a number of physiological effects including central nervous system excitation, liver enzyme induction, renal tubular degeneration, immune suppression, and chromosomal aberrations. However, none of these effects is specific to toxaphene exposure.

The following changes are potential biomarkers of effect for toxaphene. However, none of the observed changes is unique to toxaphene exposure. Depression of ACTH-stimulated corticosterone synthesis was observed in adrenal cells exposed to toxaphene (Mohammed et al. 1985). Also, changes in catecholamine levels are associated with adrenal toxicity (Kuz'minskaya and Ivanitskii 1979). Changes of electroencephalographic (EEG) activity may be associated with the central nervous system excitation produced by toxaphene (Santolucito 1975). Hepatic effects of toxaphene include increased microsomal enzyme activity (Chu et al. 1986) and decreased biliary excretion (Mehendale 1978). Depressed IgG production is associated with the immunosuppression caused by toxaphene in adults (Koller et al. 1983), and reduced phagocytic activity is associated with the immunosuppression observed in the newborn. Chromosomal aberrations in lymphocytes may be indicative of the genotoxic effects produced by toxaphene (Samosh 1974). Further study may indicate that one, or a combination, of the above effects may be a more specific biomarker of the effects of toxaphene.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

## 2.7 INTERACTIONS WITH OTHER SUBSTANCES

Toxaphene is likely to interact with other chemicals, such as other pesticides, that also induce hepatic microsomal mixed-function oxidase systems. For example, Deichmann and Keplinger (1970) observed that the toxaphene 96-hour LD<sub>50</sub> values were increased by about 2 times in rats pretreated with aldrin and dieldrin, and these values were increased by about 3 times in rats pretreated with DDT. Aldrin, dieldrin, and DDT are all known to induce microsomal enzymes. Equitoxic concentrations of toxaphene plus

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parathion, diazinon, or trithion yielded LD<sub>50</sub> values that were higher than expected based on an assumption of additivity, indicating that toxaphene antagonized the lethal effects of these three pesticides (Keplinger and Deichmann 1967).

Another example of microsomal enzyme induction by toxaphene resulting in altered activity of other chemicals was reported by Jeffery et al. (1976). They described the case of a farmer who was being treated with warfarin for thrombophlebitis and was observed to have a loss of warfarin effect that coincided with exposures to a toxaphene-lindane insecticide. The authors concluded that the toxaphene mixture induced the hepatic microsomal enzymes (for up to 3 months), thereby increasing the metabolism of warfarin.

Triolo et al. (1982) investigated the effects of toxaphene administered in the diet on benzo(a)pyrene (BP)-induced lung tumors in mice (BP was administered by oral intubation). There was no increase in the incidence of these tumors when toxaphene was administered alone, but toxaphene did significantly reduce the incidence of BP-induced lung tumors when given in combination. This reduction correlated with a toxaphene-induced reduction in BP hydroxylase activity in the lung. The results of this study suggest that toxaphene antagonizes the tumorigenic effect of BP, possibly by inhibiting the biotransformation of BP to a reactive metabolite or by promoting degradative metabolism of BP to nonactive forms in the target tissue. By this mechanism, toxaphene may have anticarcinogenic properties in mammals.

### **2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

A susceptible population will exhibit a different or enhanced response to toxaphene than will most persons exposed to the same level of toxaphene in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects on clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

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Subsets of the human population that may be unusually susceptible to the toxic effects of toxaphene include pregnant women, their fetuses, nursing babies, young children, people with neurologic diseases (particularly convulsive disorders), and individuals with protein-deficient diets. Others at increased risk include people with hepatic, cardiac, renal, or respiratory diseases, those with immune system suppression, and those ingesting alcohol or consuming therapeutic or illicit drugs.

Pregnant women, fetuses, nursing infants, and very young children may be at greater risk of adverse health effects from pesticide exposure than the general population (Calabrese 1978). Exposure to organochlorine insecticides, such as toxaphene, may adversely affect reproductive physiology (i.e., hormonal balance) in certain women (Calabrese 1978). Embryos, fetuses, and neonates up to age 2-3 months may be at increased risk of adverse effects following pesticide exposure because their enzyme detoxification systems are immature (Calabrese 1978). Animal studies suggest that detoxification of the toxaphene mixture may be less efficient in the immature human than the metabolism and detoxification of the single components such as toxicant A or B (Olson et al. 1980). Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10-12 years of age (Calabrese 1978).

Placental transfer of toxaphene has been documented in animals (Pollock and Hillstrand 1982).

Toxaphene residues have also been detected in the milk of exposed cows (Clabom et al. 1963; Zweig et al. 1963). Adverse effects have been observed in the offspring of experimental animals exposed to toxaphene during gestation and nursing. Results of experimental studies indicate that maternal toxaphene exposure may induce behavioral effects in neonates and in nursing babies (Crowder et al. 1980; Olson et al. 1980).

Toxaphene exposure during gestation and nursing has been suggested to be associated with immunosuppression in offspring (Allen et al. 1983). Other effects of maternal toxaphene exposure observed in the offspring were histologic changes in fetal liver, thyroid, and kidney tissues (Chu et al. 1988).

Toxaphene exposure by inhalation, ingestion, or dermal application has induced neurotoxic effects manifested in part by seizures and other functional, biochemical, and morphological alterations (Badaeva 1976; Dille and Smith 1964; DiPietro and Halibut-ton 1979; Kuz'minskaya and Ivanitskii 1979; Lawrence and Casida 1984; McGee et al. 1952; Wells and Milhom 1983). Persons with latent or clinical neurologic diseases, such as epilepsy or behavioral disorders, may be at an increased risk of adverse effects following toxaphene exposure.

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Persons consuming diets deficient in protein may also be at increased risk of adverse effects from exposure to toxaphene. It has been estimated that 30% of women and 10% of men aged 30-60 ingest less than two-thirds of the required daily allowance (RDA) for protein (Calabrese 1978). An experimental study showed that central nervous system effects occurred sooner and at lower doses in rats ingesting toxaphene and diets deficient in protein (Boyd and Taylor 1971).

People with liver disease of a genetic origin (i.e., Gilbert's syndrome) and viral infections are at increased risk of developing toxic effects due to insecticide exposure (Calabrese 1978). Liver effects have been observed in both humans and animals following acute exposure to toxaphene. Liver enzymes were transiently elevated in a young man who attempted suicide by ingesting toxaphene (Wells and Milhorn 1983). Liver effects were observed in experimental studies with animals following acute, intermediate, or chronic exposure to toxaphene (Boyd and Taylor 1971; Chu et al. 1986; Gertig and Nowaczyk 1975; Kennedy et al. 1973; Koller et al. 1983; Kuz'minskaya and Alekhina 1976; Lackey 1949; Mehendale 1978).

Persons with diseases that affect cardiac, renal, adrenal gland, or respiratory function may be at increased risk of adverse effects due to toxaphene exposure. Renal function was temporarily affected in a young man who attempted suicide by ingesting toxaphene (Wells and Milhorn 1983). Respiratory function was adversely affected in two men occupationally exposed to toxaphene (War&i 1963). The heart (Kuz'minskaya and Ivanitskii 1979; Trottmann et al. 1985), kidney (Boyd and Taylor 1971; Chu et al. 1986; Fattah and Crowder 1980; Trottmann and Desaiyah 1979; Trottmann et al. 1985), and adrenal gland (Kuz'minskaya and Ivanitskii 1979; Mohammed et al. 1985) are recognized as target organs of toxaphene toxicity in experimental animals.

People susceptible to the toxic effects of toxaphene may develop compromised immune function. People with suppressed immune systems, such as found in acquired immune deficiency syndrome (AIDS), may also be at increased risk of developing more severe effects from toxaphene exposure. Toxaphene has produced primarily humoral immunosuppressive effects in experimental animals (Allen et al. 1983; Koller et al. 1983).

The induction of hepatic microsomal enzymes, such as mixed function oxidases, by pesticides such as toxaphene may also affect the metabolism of some drugs and alcohol (Calabrese 1978). The efficacy of prescription drugs may be reduced because of the increased rate of metabolism. For example, Jeffery et al. (1976) observed a decrease in the effectiveness of warfarin in a farmer who had been exposed to a

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toxaphene-lindane insecticide. Furthermore, because toxaphene is a neurotoxic agent, neurological effects associated with other agents or drugs may be exacerbated in persons exposed concomitantly to toxaphene.

### 2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to toxaphene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to toxaphene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

#### 2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to toxaphene may occur by inhalation, ingestion, or by dermal contact. Toxaphene and other chlorinated hydrocarbons are efficiently absorbed from the gastrointestinal tract, particularly in the presence of dietary lipids. Although relatively non-volatile, absorption following inhalation exposure to dusts and sprays probably occurs through mucocilliary trapping and transport followed by gastrointestinal absorption. Dermal absorption can also be significant.

Decontamination is the first step in reducing absorption. It is recommended that decontamination begin immediately after the exposure, that contaminated clothing be removed, and that the skin, hair, and nails be washed copiously with a mild detergent and water. Leather clothing absorbs pesticides and should be discarded. Decontamination includes irrigation of the eyes with copious amounts of room-temperature water, or saline if available, for at least 15 minutes. If irritation, lacrimation, or especially pain, swelling, and photophobia persist after 15 minutes of irrigation, it is recommended that expert ophthalmologic treatment be provided.

For inhalation exposure, treatment commonly includes moving the exposed individual to fresh air, then monitoring for respiratory distress. Injuries to the airways and lungs are likely to be manifested as severe respiratory irritation and persistent cough. Emergency airway support and 100% humidified supplemental oxygen with assisted ventilation may be needed.

Induced emesis may be indicated following acute ingestion unless the patient is obtunded, comatose, or convulsing. It is most effective if initiated within 30 minutes of exposure. Administration of castor oil

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cathartics are ill-advised because they tend to increase peristaltic activity, resulting in increased intestinal absorption of toxaphene. Adrenergic amines (decongestants, bronchodilators, or caffeine) are not recommended because they may increase myocardial irritability and produce refractory ventricular arrhythmias (Bryson 1986; Dreisbach 1983).

Gastric lavage with subsequent administration of activated charcoal and sorbitol cathartic or administration of activated charcoal and sorbitol alone have been recommended in acute management to reduce gastrointestinal absorption. Repeated dosing with activated charcoal or cholestyramine resin may be administered to enhance elimination by interrupting enterohepatic circulation as has been demonstrated for chlordane and kepone (Cohn et al. 1978; Garretson et al. 1984, 1985).

Exchange transfusion, peritoneal dialysis, hemodialysis, and hemoperfusion are not likely to be beneficial because of the large volume of distribution of toxaphene, resulting in a small proportion of removable toxin.

### 2.9.2 Reducing Body Burden

Once absorbed, toxaphene bioaccumulates in adipose tissue and is metabolized and excreted over several days to a few weeks following exposure. Prolonged treatment with cholestyramine resin beyond the initial acute exposure may be beneficial in increasing excretion by disrupting the enterohepatic recirculation and significantly reducing the total body half-life as has been demonstrated for chlordane (Cohn 1982).

### 2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The most serious toxicological effects of exposure to chlorinated hydrocarbon pesticides are central nervous system excitability. Organochlorine compounds are thought to interfere with the normal flux of sodium and potassium ions across the axon membrane, disrupting central nervous system activity and resulting in generalized central nervous system excitation, which may lead to convulsions and seizures in severe cases. Toxaphene-induced central nervous system stimulation is believed to result from the noncompetitive inhibition of  $\gamma$ -aminobutyric acid-dependent chloride ion channels that are found on the neuron. The putative role of  $\gamma$ -aminobutyric acid in the central nervous system is to suppress neuronal activity. Thus, if its actions are blocked, neuronal activity increases. Unchecked neuronal excitation can lead to tremors, convulsions, seizures, and death.

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Toxaphene is considered to be a moderately toxic chlorinated hydrocarbon in the same toxicity category (animal LD<sub>50</sub> > 50 mg/kg) as DDT, chlordane, lindane, heptachlor, kepone, and mirex. Several cases of toxaphene-induced seizures in humans have been reported (McGee et al. 1952; Wells 1983). The acute management of seizures with anticonvulsants such as diazepam (a  $\gamma$ -aminobutyric acid agonist), phenobarbital, and phenytoin has been recommended (Schenker et al. 1992). These drugs tend to suppress neuronal activity, thus counteracting the stimulatory effects of toxaphene. High exposures to organochlorines can lead to stimulation of the peripheral nervous system. An important result of this is cardiac arrhythmias, possibly due to increased myocardial sensitivity to catecholamines (Olson 1990). The stimulatory effects on the cardiovascular system can be reduced by the administration of propranolol, a beta-adrenergic receptor blocker (Olson 1990).

### 2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of toxaphene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of toxaphene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 2.10.1 Existing Information on Health Effects of Toxaphene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to toxaphene are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of toxaphene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying*

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Figure 2-4. Existing Information on Health Effects of Toxaphene

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●	●			●			●	
Oral		●				●				
Dermal		●							●	

**Human**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●				●				
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●				●				●

**Animal**

● Existing Studies



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*Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

The data describing the toxic effects of toxaphene in humans are generally limited to a small number of case reports of toxicity following ingestion, inhalation, or dermal contact. Some controlled studies in humans exist, but the data are incomplete or unreliable. Thus, although human toxicity information exists, animal data must be considered in order to adequately assess the risk of toxaphene exposure. The database for the health effects of toxaphene following ingestion in experimental animals is substantial. However, as can be seen in Figure 2-4, very little information is available on the effects of inhalation and dermal exposure to toxaphene in animals. Furthermore, the health effects associated with acute-duration exposure are more fully characterized than those associated with intermediate or chronic-duration exposure.

### 2.10.2 Identification of Data Needs

**Acute-Duration Exposure.** Data on the acute effects of inhaled toxaphene are probably not needed because all uses have been banned in the United States and its territories (EPA 1990). Sufficient data exists to calculate an acute oral exposure MRL of 0.005 mg/kg/day. The MRL was based on a study by Mehendale (1978) who found defects in hepatobiliary function in rats following exposure to 5 mg/kg toxaphene for 8 days. This study represented the lowest LOAEL for hepatic toxicity. Since the liver has been identified as a target of toxaphene toxicity, the LOAEL from this study was used to calculate the acute oral exposure MRL. The greatest chance of exposure to toxaphene is at hazardous waste sites; therefore, it would be helpful to gather additional information in animals or humans concerning toxicity following acute dermal exposure. Data from animal studies indicate that dermal exposure to toxaphene can be lethal, but at doses that are an order of magnitude higher than those for oral administration of the pesticide (Gaines 1969; Johnston and Eden 1953; Jones et al. 1968) because absorption through the skin is much less efficient. Nevertheless, toxicity data regarding distribution and toxicity needs to be gathered so a realistic estimate of the potential health risks can be determined.

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**Intermediate-Duration Exposure.** Limited information is available on the effects of repeated-dose exposures in both humans (inhalation and oral) and experimental animals (oral only). The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from case reports rather than controlled studies. Most of the information on human exposure is from combinations of pesticides; only one study was located in which oral exposure to toxaphene alone was clearly linked with adverse effects in humans (McGee et al. 1952). The animal studies described predominantly neurological, hepatic, renal, developmental, and immunological end points. Sufficient data were available to calculate an oral intermediate-duration MRL of 0.001 mg/kg/day. The MRL was based on a study by Chu et al. (1986). In that study, rats were exposed to 0.35, 1.8, 8.6, or 49.5 mg/kg/day toxaphene for 13 weeks. No hepatic toxicity was observed at the 0.35 mg/kg/day dose. Since the liver has been identified as a target of toxaphene toxicity, the NOAEL from this study was used to calculate the intermediate oral exposure MRL.

Little or no reliable information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, dermal, or ocular effects in animals is available. The health effects data available on inhalation and dermal exposure to toxaphene in animals come primarily from secondary unpublished sources and, therefore, do not have sufficient details for evaluation. Since waste-site toxaphene may leak into surrounding areas or evaporate, both the inhalation and dermal routes are possible means of exposure for individuals living near hazardous waste sites. Thus, more information on the health effects (specifically neurological, hepatic, and renal toxicity) associated with intermediate-duration low-level inhalation and dermal exposure to toxaphene would be useful. Because the use of toxaphene diminished considerably after the registration for most uses was canceled in 1982, and has presumably ceased since the EPA banned all registered use in 1990 (EPA 1990b), there is little potential for long-term exposure in the United States.

**Chronic-Duration Exposure and Cancer.** Few controlled epidemiological studies that examine the effects of chronic exposure to toxaphene have been conducted. Chronic toxicity/carcinogenicity bioassays have been conducted in animals (NCI 1977; Brown 1995). These studies have found predominantly hepatic, renal, and neurological effects. The health effects data available on chronic inhalation exposure to toxaphene in animals come primarily from secondary unpublished sources, and therefore, do not have sufficient details for evaluation. No information is available on the health effects of chronic dermal exposure to toxaphene. Since waste-site toxaphene may leak into surrounding areas or evaporate, both the inhalation and dermal routes are possible means of exposure for individuals living near

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hazardous waste sites. Additionally, more information on the chronic health effects associated with chronic low-level inhalation and dermal exposure to toxaphene would be useful.

Although studies on the relationship between chronic exposure to toxaphene and cancer in humans are lacking, studies in rats and mice indicate that toxaphene causes cancer in rodents. Increased incidences of thyroid and hepatic carcinomas were observed in animals chronically exposed to high doses of toxaphene (EPA 1990b; NCI 1977). No information is available for either humans or animals on the potential cancer risk following inhalation or dermal exposure to toxaphene. Because the use of toxaphene diminished considerably since its registration for most uses was canceled in 1982 and all registered uses were banned in 1990 (EPA 1990b), the potential for additional long-term exposure is low. However, some populations may be exposed to higher amounts of toxaphene because a large portion of their diet is composed of game animals that bioaccumulate toxaphene. For these populations, epidemiological studies of persons exposed to toxaphene and bioassay data from chronic inhalation and dermal studies in animals would be helpful in estimating the cancer risk for persons exposed to toxaphene by these routes. There appears to be little need for additional oral exposure studies since the existing database well describes the potential health effects from chronic oral exposure to toxaphene.

**Genotoxicity.** Two studies are available on the genotoxic effects of toxaphene in mammals: one in humans (Samosh 1974) and one in mice (Epstein et al. 1972). The results suggested that toxaphene is genotoxic in lymphocytes of humans, but no information was available on the possible genotoxic effects of toxaphene on the germ cells of humans. With the exception of these two studies, all information on the genotoxic effects of toxaphene comes from *in vitro* studies, predominantly microbial assays (Hooper et al. 1979). More information on the genotoxic effects of toxaphene in somatic and germ cells in humans and animals would be useful because *in vitro* tests indicate that toxaphene is potentially genotoxic. Because the effects of toxaphene on mammalian germ cells are not known, it would be useful to determine whether the genotoxic effects induced by toxaphene are inheritable. This could be determined through the conduct of multigeneration reproductive/developmental toxicity studies in rodents.

**Reproductive Toxicity.** No information on the reproductive effects of toxaphene in humans is available. The available information from multigeneration studies in rats indicates that toxaphene does not adversely affect reproductive end points (Kennedy et al. 1973; Keplinger et al. 1970). The available studies were well-conducted and there appears to be no need for additional oral exposure studies. Since it is likely that the distribution of dermally and orally administered toxaphene is similar, dermally absorbed

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toxaphene should not be expected to cause reproductive toxicity. Thus, further studies in that area are not warranted. Inhalation studies are also not necessary because toxaphene use is banned in the United States.

**Developmental Toxicity.** Information on the developmental effects of toxaphene in humans resulting from ingestion was not found. Data in experimental animals indicate that toxaphene can cause offspring behavioral toxicity (Olson et al. 1980) and immunosuppression (Allen et al. 1983) at doses that are not maternally toxic. However, only one dose was used in these studies that demonstrated behavioral effects, no NOAEL was identified, and the effect was no longer apparent after 16 weeks. Therefore, a comprehensive developmental neurobehavioral toxicity test battery may be useful in determining the potential for toxaphene to disrupt brain development. Moreover, the tests could be used to assess which central nervous system effects predominate and whether they are transient or long-lasting. Because dermal exposure is a potential means of exposure to toxaphene at hazardous waste sites, examination of developmental effects by this route is also desirable. Additionally, little is known about the kinetics of toxaphene exposure in pregnant animals, the transfer of toxaphene across the placenta, or its persistence in the fetus. That information could be used to determine if the fetus is potentially at greater risk from the effects of toxaphene.

**Immunotoxicity.** No information on the immunologic effects of toxaphene in humans is available. Toxaphene-related depressed IgG production has been observed in adult rats (Koller et al. 1983), and reduced phagocytic activity, which is associated with the immunosuppression, has been seen in neonates (Allen et al. 1983). A comprehensive immunological test battery in adult and neonatal animals exposed to toxaphene would help determine the potential for toxaphene to alter immunological function. Furthermore, since it is not known if the immunosuppression observed in response to toxaphene in animals is reversible, further research into this area could be helpful in determining if there are populations at higher risk because of pre-existing permanent immunosuppression (e.g., people with AIDS). In addition, studies on the effects on the immune system following dermal exposure would provide useful information for persons exposed in areas near hazardous waste sites.

**Neurotoxicity.** The available information describes neurological involvement in humans (McGee et al. 1952) and animals (Boyd and Taylor 1971; Lackey 1949; Rao et al. 1986) following short- and long-term high-level inhalation and oral exposure to toxaphene. Two mechanisms have been proposed to explain the neurotoxic effects of toxaphene: the noncompetitive inhibition of  $\gamma$ -aminobutyric acid-dependent chloride ion channels, and the inhibitory effect on ATPases (Fattah and Crowder 1980; Rao et al. 1986). Very little information is available on the long-term neurotoxic effects of low-level exposure to toxaphene in humans

## 2. HEALTH EFFECTS

and animals. A comprehensive adult and developmental neurobehavioral toxicity test battery may be useful in determining the potential for toxaphene to disrupt brain development. Moreover, the tests could be used to assess which central nervous system effects predominate and whether they are transient or longlasting. Toxicity via oral and dermal routes of exposure should be assessed.

**Epidemiological and Human Dosimetry Studies.** Most of the available information on the effects of toxaphene in humans comes from cases of acute poisoning following the accidental or intentional ingestion of toxaphene and from occupational exposures in agricultural industries. Limitations inherent in these studies include unquantified exposure concentrations and durations, and concomitant exposure to other pesticides. Despite their inadequacies, those studies suggest that toxaphene can adversely affect the liver, kidneys, lungs, and central nervous system (McGee et al. 1952; Warraki 1963). Children may be more susceptible to the toxic effects of toxaphene since most of the toxaphene-related deaths have occurred in children (McGee et al. 1952). However, it may be that those children merely ingested proportionately (relative to body weight) higher doses than those reported for adults. Well-controlled epidemiological studies of people living in close proximity to areas where toxaphene has been detected at hazardous waste sites and of people exposed in the workplace could add to and clarify the existing database on toxaphene-induced human health effects. A common problem in epidemiological studies is acquisition of reliable dosimetry data on the exposed populations. For this reason, efforts to more accurately define past and current levels of exposure to toxaphene would be valuable. Follow-up of workers exposed to toxaphene may also be helpful.

### **Biomarkers of Exposure and Effect.**

**Exposure.** Toxaphene levels have been measured in blood, fat, urine, and feces (Ohsawa et al. 1975; Pollack and Kilgore 1980b). No studies demonstrate a reliable correlation between blood levels and levels of exposure. Fat samples have been shown to have toxaphene levels proportional to treatment levels (Pollack and Kilgore 1980b), but fat samples are difficult to obtain from humans. Levels of toxaphene in milk fat may provide a more accurate estimate of exposure than body fat or blood (Keating 1979), but these samples can only be obtained from a small portion of the population. Because toxaphene is rapidly eliminated from the body, tissue levels are a poor estimate of any but the most immediate exposure to toxaphene. An alternate biomarker of exposure to toxaphene would be especially helpful in estimating human exposure levels. Although toxaphene is rapidly eliminated from the body via the feces and urine, persistent metabolites of toxaphene could be identified and their elimination constants determined so that urine or fecal samples could be used to determine whether or not someone has been exposed to toxaphene.

## 2. HEALTH EFFECTS

One study in animals has shown that ACTH-stimulated corticosterone synthesis is depressed following repeated exposure to toxaphene at a dose lower than that required to produce adverse liver effects (Mohammed et al. 1985). This test is probably of little use since psychological state and many other factors greatly influence cortisol levels.

**Effect.** No specific biomarkers of effects have been identified for toxaphene. Toxaphene has been demonstrated to cause a number of adverse health effects including central nervous system excitation, liver and kidney damage, and developmental and immunosuppressive effects. None of these effects is specific for toxaphene and no studies exist which demonstrate good correlation of toxaphene levels with human health effects. Neurological tests such as electroencephalographic monitoring can record levels of central nervous system activity. Liver and kidney function tests exist which detect hepatic and renal impairment. Microsomal enzyme activity may indicate early effects in the liver. Effects on the immune system can be measured by measuring immunoglobulin levels. Although each of these tests can indicate the presence of disease in the systems affected by toxaphene, the effects can be caused by a number of other disease states. This fact emphasizes the need to develop an early indicator of biological effect.

**Absorption, Distribution, Metabolism, and Excretion.** Quantitative evidence on the absorption of toxaphene in humans and animals following all routes of exposure is very limited. Animals dipped in toxaphene excrete the substance in the milk and also sometimes experience toxicosis (Claborn et al. 1963). Humans and animals have become seriously ill following accidental or intentional ingestion of toxaphene. The evidence clearly indicates that toxaphene is absorbed. Reports that specifically evaluate its rate or extent of absorption as a result of inhalation, oral, and dermal exposure would be useful.

No studies were located regarding the distribution of toxaphene in humans or animals following inhalation or dermal exposures. No evidence is available regarding the distribution of toxaphene in humans following ingestion. However, animal studies conducted in several species indicate that distribution following oral absorption is similar across species (Mohammed et al. 1983; Ohsawa et al. 1975; Pollock and Kilgore 1980b) and it is assumed that distribution of the pesticide in humans would be similar. Once absorbed, toxaphene and its components are distributed initially throughout the blood compartment and then to fat. Studies that investigate the distribution of toxaphene following inhalation or dermal exposure would be helpful in order to evaluate whether toxaphene behaves similarly across all routes of exposure.

Information was not available regarding the metabolism of toxaphene following dermal or inhalation exposure in animals or humans. This information would be useful for estimating health effects by these

## 2. HEALTH EFFECTS

routes. Moreover, no information was available regarding the metabolites formed by humans following ingestion. Evidence from animals receiving toxaphene orally indicates that dechlorination, dehydrodechlorination, and oxidation are principal metabolic pathways (Crowder and Dindal 1974; Ohsawa et al. 1975). Although several metabolites have been isolated and identified (Ohsawa et al. 1975), several others remain unknown. Their identification will help elucidate the toxaphene metabolic pathway(s).

Quantitative information regarding the metabolites produced would suggest which biodegradation pathways are favored and provide insight into the enzyme kinetics. Information regarding the overall rate of metabolism and the rates of specific reactions would be useful. In addition, such studies might also provide information to help facilitate the metabolism of the toxaphene mixture in accidentally exposed humans.

No studies in humans were found regarding the excretion of toxaphene. Animal studies regarding the excretion of toxaphene following inhalation exposure are unavailable, but information is available for toxaphene excretion following oral and dermal exposures. Mice that received toxaphene intravenously were found to have toxaphene present in the intestinal content, suggesting biliary excretion (Mohammed et al. 1983). The presence of several metabolites in the urine and feces suggests that toxaphene degradation is extensive and complex (Ohsawa et al. 1975; Pollock and Kilgore 1980b). Though metabolism of toxaphene facilitates its excretion, and the kinetics of toxaphene metabolism are related to the kinetics of excretion, they are not the same. Since metabolites may also contribute to the toxic effects attributed to toxaphene, it would also be beneficial to conduct studies that would establish elimination rates for each toxaphene metabolite or for similar metabolic products. In addition, such studies may also provide information to facilitate the rapid removal of toxaphene and its metabolites in exposed people.

Virtually all toxicokinetic properties reported in this profile were based on results from acute-duration exposure studies. Very limited information was available regarding intermediate-duration or chronic exposure to toxaphene. Since toxaphene is known to induce hepatic enzymes, the kinetics of metabolism during chronic exposure probably differ from those seen during acute exposure. Thus, additional studies on the metabolism of toxaphene during intermediate-duration or chronic exposure would be useful to assess the potential for toxicity following longer duration exposures.

## 2. HEALTH EFFECTS

**Comparative Toxicokinetics.** The absorption, distribution, metabolism, and excretion of toxaphene have been studied in animals, but only information on absorption is available in humans. In several mammalian species it is evident that toxaphene is absorbed, metabolized in the liver (with some elimination probably occurring at this point via the hepatobiliary system), and then possibly some parent compound and metabolites are distributed to fat (Ohsawa et al. 1975; Pollock and Kilgore 1980b). Very little is excreted unchanged. In studies of mammals, the extent of metabolism increased with the physiological complexity of the species. Based on this trend, humans would be expected to metabolize toxaphene extensively in a manner qualitatively similar to animals. A comprehensive investigation of metabolic pathways in lower animals would aid in the understanding of possible human kinetics.

**Methods for Reducing Toxic Effects.** The medical procedures used to reduce the toxic effects of toxaphene are well established and are the same as those used to treat organochlorine poisoning or poisoning due to other chemicals with central nervous system stimulatory properties. However, data on how to best reduce body burden and also on how to prevent the inhibition of  $\gamma$ -aminobutyric acid-dependent chloride ion channels would be useful.

### 2.10.3 Ongoing Studies

No ongoing studies were identified that explored the health effects or toxicokinetics of toxaphene or that attempted to associate toxaphene levels in human tissues with effects (FEDRIP 1995).



### **3. CHEMICAL AND PHYSICAL INFORMATION**

#### **3.1 CHEMICAL IDENTITY**

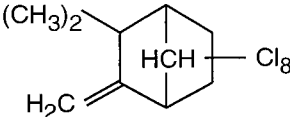
Information regarding the chemical identity of toxaphene is located in Table 3- 1.

#### **3.2 PHYSICAL AND CHEMICAL PROPERTIES**

Information regarding the physical and chemical properties of toxaphene is located in Table 3-2.

## 3. CHEMICAL AND PHYSICAL INFORMATION

**Table 3-1. Chemical Identity of Toxaphene**

Characteristic	Information	Reference
Chemical name	Toxaphene	HSDB 1995
Synonym(s)	Campheclor; chlorinated camphene; polychlorocamphene; Chlorocamphene; octachlorocamphene; toxafeen (Dutch); polychlorocanthene (USSR)	Merck 1989 HSDB 1995
Registered trade name(s)	Agricide Maggot Killer; Alltox; Camphofene Huilex; Geniphene; Hercules 3956; Hercules Toxaphene; Motox; Penphene; Phenicide; Phenatox; Strobane-T; Synthetic 3956; Toxakil	IARC 1979
Chemical formula	C <sub>10</sub> H <sub>10</sub> Cl <sub>8</sub> (approx)	Merck 1989
Chemical structure <sup>a</sup>		Paris and Lewis 1973
Identification numbers:		
CAS Registry	8001-35-2	HSDB 1995
NIOSH RTECS	XW5250000	HSDB 1995
EPA Hazardous Waste	P123	HSDB 1995
OHM-TADS	7216561	HSDB 1995
DOT/UN/NA/IMCO	NA 2761/toxaphene	HSDB 1995
HSDB	1616	HSDB 1995

<sup>a</sup> Structure representative of the predominant chlorinated camphene compounds present in technical toxaphene

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM-TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances; STCC = Standard Transport Commodity Code

## 3. CHEMICAL AND PHYSICAL INFORMATION

**Table 3-2. Physical and Chemical Properties of Toxaphene<sup>a</sup>**

Property	Information	Reference
Molecular weight	414 (average)	DOT 1978; Worthing 1979
Color/form	Yellow, waxy, Amber	Merck 1989 DOT 1978
Physical state	Solid	Merck 1989
Melting point	65–90 °C	Merck 1989
Boiling point	Not applicable (dechlorinates at 155 °C)	Merck 1989
Density at 25 °C	1.65 g/cm <sup>3</sup>	Worthing 1979
Odor	Mild turpentine-like odor Pleasant piney odor Mild odor of chlorine and camphor	HSDB 1995 Merck 1989 HSDB 1995
Odor threshold:		
Air	0.14 ppm (detection) 2.4 mg/m <sup>3</sup>	Sigworth et al. 1965 Ruth 1986
Water	0.14 mg/kg (detection)	Verschueren 1983; HSDB 1995
Solubility:		
Water	0.0003 g/100 cc	Wauchope et al. 1992 Worthing 1979 Mackison et al. 1981 HSDB 1995
Organic solvent(s)	Freely soluble in aromatic hydrocarbons Readily soluble in organic solvents, including petroleum oils	Merck 1989; HSDB 1995 Worthing 1979; HSDB 1995
Partition coefficients:		
Log K <sub>ow</sub>	3.3±0.4 3.30	HSDB 1995 EPA 1981a
Log K <sub>oc</sub>	2.474 5.00 3.69	EPA 1981a Wauchope et al. 1992 ASTER 1995
Vapor pressure <sup>b</sup>	0.2–0.4 mm Hg at 20 °C 0.4 mm Hg at 25 °C 4x10 <sup>-6</sup> mm Hg at 20 °C 3x10 <sup>-7</sup> mm Hg at 10 °C 5x10 <sup>-6</sup> mm Hg at 20 °C	Mackinson et al. 1981 Sunshine 1969 Wauchope et al. 1992 Suntio et al. 1988 Bidleman et al. 1981 Agrochemicals Handbook 1983
Henry's law constant	0.21 atm-m <sup>3</sup> /mol 0.063 atm-m <sup>3</sup> /mol 0.0050 atm-m <sup>3</sup> /mol	EPA 1981a HSDB 1995 Shen 1982

## 3. CHEMICAL AND PHYSICAL INFORMATION

**Table 3-2. Physical and Chemical Properties of Toxaphene (continued)**

Property	Information	Reference
Autoignition temperature	No data	
Flashpoint	34.4 °C 135 °C (closed cup)	DOT 1978 Mackison et al. 1981 HSDB 1995
Flammability limits in air	1.1–6.4% in air Solid is not flammable but is usually dissolved in combustible liquid	DOT 1978 HSDB 1995
Conversion factors (25 °C)	1 ppm x 16.89 (average) = 1 mg/m <sup>3</sup> ;  1 mg/m <sup>3</sup> x 0.059 (average) = 1 ppm	Calculated
Explosive limits	No data	

<sup>a</sup> Technical toxaphene is a complex mixture of at least 670 polychlorinated bicyclic terpenes consisting predominantly of chlorinated camphenes (Jansson and Wideqvist 1983; Paris and Lewis 1973). Toxaphene contains 67–69% chlorine by weight (Windholz 1983).

<sup>b</sup> Disagreement was found among sources for the values of vapor pressure. Four values were found and two were at the 0.2 to 0.4 level and three were at the 10<sup>-6</sup> to 10<sup>-7</sup> level. From these data it cannot be ascertained which values are correct. Measurements made on mixtures containing different distributions of compounds could explain part of the discrepancy.

## 4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

### 4.1 PRODUCTION

Toxaphene does not occur naturally (Canada, Department of National Health and Welfare 1978; EPA 1976a; IARC 1979). It is a complex mixture of at least 670 chlorinated terpenes (Jansson and Wideqvist 1983). Technical toxaphene can be produced commercially by reacting chlorine gas with technical camphene in the presence of ultraviolet radiation and catalysts, yielding chlorinated camphene containing 67-69% chlorine by weight (EPA 1976a; Korte et al. 1979). It has been available in various forms: a solid containing 100% technical toxaphene; a 90% solution in xylene or oil; a 40% wettable powder; 5-20% and 40% dusts; 10% and 20% granules; 4%, 6%, and 9% emulsifiable concentrates; 1% baits; a 2: 1 toxaphene; DDT emulsion; and a 14% dust containing 7% DDT (IARC 1979; IUPAC 1979; Penumarthi et al. 1976).

In 1982, EPA canceled the registrations of toxaphene for most uses as a pesticide or pesticide ingredient, except for certain uses under specific terms and conditions (EPA 1982a, 1993a; USDA 1995). All registered uses were banned in 1990 (EPA 1990b), and existing stocks were not allowed to be sold or used in the United States after March 1, 1990 (USDA 1995). In 1976, toxaphene was produced primarily by Hercules Incorporated, Wilmington, Delaware (Penumarthi et al. 1976). Production by a total of three U.S. companies (Hercules Incorporated, Tenneco, and Vicksburg Chemical Co., a division of Vertac) during 1976 totaled 19 million kg, which was a 29% decline from the production level of 27 million kg in 1975 (IARC 1979). More recently, Montgomery and Welkom (1990) listed Hercules Incorporated, Brunswick, Georgia, and Sonford Chemical Company, Port Neches, Texas, as selected manufacturers of toxaphene; however, no production estimates were provided. Total U.S. production in 1977 was estimated to be 18.1 million kg (HSDB 1995). The most recent production volumes found in the available literature are from 1982, when it was estimated that 3.7 million pounds (less than 2 million kg) were produced in the United States (EPA 1987a). This represents a decline of more than 90% from 1972, when toxaphene was the most heavily manufactured insecticide in the United States, with a production volume of 23,000 tons (21 million kg) (Grayson 1981).

Especially in the United States, the definition of “technical toxaphene” was patterned after the Hercules Incorporated product (Hercules Code Number 3956) marketed under the trademark name of “Toxaphene.” In recent years, Hercules Incorporated has essentially let the name of toxaphene lapse into the public

## 4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

domain so that many products with similar properties are referred to as toxaphene (Worthing and Walker 1987). Other companies used slightly different manufacturing processes, leading to a chlorinated camphene mixture with degrees of total chlorination and a distribution of specific congeners that are not the same as the Hercules Incorporated product. For instance, the toxaphene-like product commonly marketed under names like “Stroban(e)” had a slightly lowered degree of chlorination and used slightly different camphene or pinene feedstocks (Walter and Ballschmiter 1991).

Toxaphene-like pesticide agents are still produced and are widely used in many countries. While it is impossible to quantify production figures or usage rates, India and many countries in Latin America, Eastern Europe, the former Soviet Union, and Africa still use various toxaphene products as pesticides (Bidleman et al. 1989; Stem et al. 1993). It has been recently estimated that total global toxaphene use from 1950 to 1993 was greater than 1.3 million tons (1.2 billion kg) (Voldner and Li 1993); however, this is likely to be a significant underestimation (Swackhamer et al. 1993). Since toxaphene is a complex mixture, continued reliance on the use of “technical toxaphene” as a reference may actually complicate the task of identifying toxaphene signatures for contaminants transported via global atmospheric pathways.

While most attention has been focused on the intentional production of polychlorinated camphenes (PCCs) as pesticide agents, there is growing evidence that PCC congeners may be an unintentional byproduct of manufacturing processes that use chlorination, such as those for paper and pulp (Rantio et al. 1993). Studies from places as far-flung as New Zealand, Japan, the Great Lakes region of the United States, and Scandinavia suggest that PCCs can be found in many parts of the world where toxaphene mixtures were never used as pesticide agents (EPA 1993a; Jamuzi et al. 1992; Paasivirta and Rantio 1991).

Because toxaphene is a Priority Pollutant under the Clean Water Act, it is required to be included in the Toxics Release Inventory (TRI) (EPA 1995a). Since all registered uses of toxaphene on food commodities were canceled by 1990 (EPA 1982a, 1990b, 1993b), and the sale and use of existing stocks in the United States were prohibited after March 1, 1990 (USDA 1995), production of toxaphene for all domestic uses in the United States has ceased. However, U.S. chemical manufacturers can legally produce pesticides for export that are currently banned or not registered for use in the United States (FASE 1996). Toxaphene currently has no entries associated with its production in 1993, the most recent production year for which data are available (TR193 1995). However, the TRI is not an exhaustive list. If toxaphene is being produced in the United States for export, production information would not necessarily appear on the TRI database.

## 4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

**4.2 IMPORT/EXPORT**

No current information was found regarding the import of toxaphene into or the export of toxaphene from the United States (HSDB 1995). In 1972, a total of 8,000 tons (7.25 million kg) of toxaphene, or 35% of the annual production, was exported (SRI International 1993; USITC 1991; von Rumker et al. 1974).

**4.3 USE**

Toxaphene was formerly used as a nonsystemic stomach and contact insecticide with some acaricidal activity. Being nonphytotoxic (except to cucurbitus), it was used to control many insects thriving on cotton, corn, fruit, vegetables, and small grains and to control the *Cussia obtusifolia* soybean pest.

Toxaphene was also used to control livestock ectoparasites such as lice, flies, ticks, mange, and scab mites (Knipling and Westlake 1966; Meister 1988; Worthing 1979). Its relatively low toxicity to bees and its long-persisting insecticidal effect made it particularly useful in the treatment of flowering plants.

Toxaphene was not used to control cockroaches because its action on them is weaker than chlordane (IARC 1979). Toxaphene was used at one time in the United States to eradicate fish (Muirhead-Thomson 1971). The principal use was for pest control on cotton crops (IUPAC 1979; Verschueren 1983). In 1974, an estimated 20 million kg used in the United States was distributed as follows: 85% on cotton; 7% on livestock and poultry; 5% on other field crops; 3% on soybeans; and less than 1% on sorghum (IARC 1979). Based on estimates of von Rumker et al. (1974) for 1972, 75% of the toxaphene production for that year was for agricultural use; 24% was exported; and 1% was used for industrial and commercial applications.

Toxaphene solutions were often mixed with other pesticides partly because toxaphene solutions appear to help solubilize other insecticides with low water solubility. Toxaphene was frequently applied with methyl or ethyl parathion, DDT, and lindane (IARC 1979; WHO 1974).

Through the early 1970s toxaphene or mixtures of toxaphene with rotenone were used widely in lakes and streams by fish and game agencies to eliminate biologic communities that were considered undesirable for sport fishing (Lockhart et al. 1992; Stern et al. 1993). This practice was especially prominent in parts of Canada and the northern United States for fish restocking experiments on smaller glacial lakes. Because the toxic effects of toxaphene may persist for many years in an aquatic system, difficulties in establishing the desired sports fisheries were among the first strong indications that toxaphene was a persistent and

## 4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

bioaccumulative material. Such uses of toxaphene by fish and game agencies have apparently been discontinued in the United States and Canada.

Toxaphene use in this country has declined drastically since 1975, when it was reported to be the most heavily used pesticide (Sanders 1975). The total used was estimated at only 9,360 tons (8.5 million kg) in 1980 and 5,400 tons (4.9 million kg) in 1982 (WHO 1984). In November 1982, EPA canceled the registrations of toxaphene for most uses as a pesticide or pesticide ingredient (EPA 1982a). In the period following November 1982, its use was restricted to controlling scabies on sheep and cattle; controlling grasshopper and army worm infestations on cotton, corn, and small grains; controlling specific insects on banana and pineapple crops in Puerto Rico and the U.S. Virgin Islands; and for emergency use only (to be determined on a case-by-case basis by EPA) (EPA 1982a; WHO 1984). Formulations suitable for other purposes could be sold or distributed until December 31, 1983, for use only on registered sites (EPA 1982a). The distribution or sale of remaining stocks of toxaphene formulations were permitted until December 31, 1986, for use on no-till corn, soybeans, and peanuts (to control sicklepod), and dry and southern peas, and to control emergency infestations. All registered uses of toxaphene mixtures in the United States and any of its territories were canceled in 1990 (EPA 1990b). On September 1, 1993, all tolerances, interim tolerances, and food additive regulations for toxaphene on all agricultural commodities were revoked (EPA 1993b).

#### 4.4 DISPOSAL

Four types of toxaphene hazardous wastes have been defined under the Resource Conservation and Recovery Act (RCRA) (EPA 1980b). Only one type (waste exhibiting a "toxicity characteristic" for toxaphene) has a technology-based standard under the RCRA land disposal restrictions. A solid waste is said to exhibit a toxicity characteristic for toxaphene, and is classified as a RCRA toxic, if an aqueous extract performed by the legally defined procedure from a representative sample of the waste contains toxaphene in a concentration equal to or greater than 0.5 mg/L (ppm) (EPA 1980b). It must be treated by biodegradation or incineration (waste waters only) to comply with the restrictions. The three remaining wastes are: waste water treatment sludge from the production of toxaphene; untreated process waste water from the production of toxaphene; and off-specification toxaphene (does not meet the desired chemical purity). These three wastes have concentration-based standards that must be achieved before the waste can be land-disposed in a RCRA permitted facility (EPA 1988c).



## 4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Toxaphene may not be disposed of by water or ocean dumping or by burning in the open air. The recommended disposal method is incineration in a pesticide incinerator at a temperature and residence time combination that will result in complete destruction of the chemical (EPA 1974, 1980b, 1988c). Any emissions generated by incineration must meet the requirements of the Clean Air Act Amendments, Title III, and any liquids, sludges, or solid residues produced should be disposed of in accordance with federal, state, and local pollution control requirements. Municipal solid waste incinerators may be used, providing that they meet the criterion of a new pesticide incinerator and are operated under supervision (EPA 1974). Landfill has also been identified as a recommendable method of disposal of toxaphene (IRPTC 1985). Recent research has shown that thermal desorption is an effective technology for treating soils contaminated with toxaphene (Troxler et al. 1993). Federal, state, and local regulations governing the treatment and disposal of wastes containing toxaphene are presented in Chapter 7.

No information was found in the available literature on the amounts of toxaphene disposed of in the United States by any disposal method.



## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.1 OVERVIEW

Toxaphene is a complex mixture of at least 670 polychlorinated bicyclic terpenes consisting predominantly of polychlorinated camphenes (PCCs) (Jansson and Wideqvist 1983; Paris and Lewis 1973). The transport and transformation of each of these components is influenced by its individual physical/chemical properties, in addition to those of the mixture as a whole. Although some data in the available literature indicate selective volatilization and metabolism of individual fractions of the mixture, the environmental fate of the mixture rather than of individual components has been studied by most investigators.

At present, information on the toxicities of specific toxaphene congeners is very limited. In addition, the qualitative identification and quantitative estimation of the levels of toxaphene in environmental or biological samples presents many challenges. A major difficulty in quantifying toxaphene is that, because of factors such as environmental and metabolic transformation and selective volatilization and atmospheric transport of some congeners, there is a difference in congener composition between the standard technical toxaphene and that found in environmental or biological samples (Andrews et al. 1993; Bidleman et al. 1993; Bruns and Birkholz 1993; de Boer and Wester 1993; Muir and de Boer 1995; Vetter et al. 1993; Zhu et al. 1994). At present, very few reference standards are readily available to determine the relative responses of individual congeners or to match the profiles detected in environmental or biological samples. Therefore, almost all estimates of toxaphene concentration are semi-quantitative. Without readily available, well-characterized standards for the individual components in toxaphene, accurate determination of concentrations in environmental or biological samples is impossible. This situation is analogous to that of PCBs in the early 1970s. In addition, the amount of substance identified by analysis would not necessarily indicate the level that is toxicologically available. Until additional knowledge of the relative toxicities of toxaphene congeners is gained, and improved capabilities for analysis are developed, it will be very difficult to develop quantitative estimates of the potential toxic effects of toxaphene contaminants found in the environment (Bidleman et al. 1993).

Toxaphene has been widely released to the environment mainly as a result of its past use as an insecticide. The mixture partitions to the atmosphere, surface water and groundwater, soil and sediment particulates, and adipose tissue. As a result of its volatility and resistance to photolytic transformation, toxaphene has

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been transported over long distances in the atmosphere (Andersson et al. 1988; Bidleman and Olney 1975; Muir et al. 1988c; Swackhamer and Hites 1988; Zell and Ballschmeir 1980). The half-life (first-order kinetics) for reaction of atmospheric toxaphene with photochemically produced hydroxyl radicals has been estimated to be at least 4-5 days (Howard 1991; Kelly et al. 1994). Toxaphene strongly adsorbs to particles and is relatively immobile in soils (ASTER 1995; EPA 1981a; Swann et al. 1983; Wauchope et al. 1992). In water, toxaphene is strongly adsorbed to suspended particulates and sediments and is bioconcentrated by aquatic organisms to fairly high levels, with bioconcentration factors (BCFs) on the order of 10,000 (ASTER 1995). Toxaphene also appears to be biomagnified in aquatic food chains. Toxaphene is biotransformed relatively rapidly in soils and sediments under anaerobic conditions, with a half-life or half-disappearance time in the range of weeks to months (EPA 1979a). However, the mixture appears to be relatively resistant to biotransformation in these media under aerobic conditions (half-life = years) (EPA 1979a; Nash and Woolson 1967; Parr and Smith 1976; Smith and Willis 1978).

Human exposure to toxaphene currently appears to be limited to ingestion of low concentrations of the mixture in food, particularly fish, and possibly to inhalation of ambient air. The most probable populations potentially exposed to relatively high concentrations of the mixture are individuals residing in the vicinity of hazardous waste disposal sites contaminated with toxaphene. Other subpopulations with potentially higher exposure rates may be northern Native American groups that eat aquatic mammals, which may contain residues of toxaphene (Muir et al. 1992) and recreational or subsistence hunters in the southern United States that consume significant amounts of game animals (especially species like raccoons) (Ford and Hill 1990). An additional subpopulation that could experience slightly higher levels of exposure are infants and young children who receive vitamin supplements from cod liver oil. This is of some concern in Europe where fish oil products may involve catches taken in polluted areas (Walter and Ballschmitter 1991). While no recent literature was identified on fish oil products entering U.S. markets, studies conducted in the early 1980s did detect toxaphene residues in food products that would be part of typical toddler and infant diets (Gartrell et al. 1986a, 1986b). Cod liver samples taken from the east coast of Canada have also shown measurable concentrations of toxaphene (Musial and Uthe 1983).

Toxaphene has been identified in at least 58 of the 1,430 current or former hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1996). However, the number of sites evaluated for toxaphene is not known. The frequency of these sites can be seen in Figure 5-1.



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**5.2 RELEASES TO THE ENVIRONMENT**

Toxaphene has been detected in the atmosphere, soils, surface waters and sediments, rainwater, aquatic organisms, and foodstuffs. Historically, toxaphene has been released to the environment mainly as a result of its use as an agricultural insecticide (EPA 1979f). Toxaphene-like mixtures of PCC congeners may also be released to the environment as unintentional by-products from manufacturing processes involving chlorination, such as those used for paper and pulp (EPA 1995c; Rantio et al. 1993). There are no known natural sources of the mixture.

Because toxaphene is a Priority Pollutant under the Clean Water Act, it is required to be included in the Toxic Release Inventory (TRI) (EPA 1995a). However, since most registered uses of toxaphene as a pesticide were canceled in 1982 (EPA 1982a) and all registered uses were canceled in the United States and its territories after 1990 (EPA 1990b), production of toxaphene for domestic use in the United States has ceased. Consequently, toxaphene has no entries for producers associated with it for the 1993 production year (TR193 1995).

Current sources of toxaphene in the environment that may result in exposure for the U.S. population include atmospheric emissions from countries currently producing or using toxaphene (e.g., Mexico and countries in Central America, eastern Europe, the former Soviet Union, and parts of Asia) (Swackhamer et al. 1993; Voldner and Li 1993) and continued releases from previously contaminated U.S. soils and waters.

**5.2.1 Air**

As a result of its use as an insecticide on cotton in the southern United States, toxaphene was released directly to the atmosphere by aerial and ground application (EPA 1979f). Volatilization of the mixture from treated crop and soil surfaces following application also introduced substantial amounts of toxaphene to the atmosphere. For example, Willis et al. (1980, 1983) reported volatilization losses from treated cotton canopies of up to 80% of applied toxaphene within 11 days after treatment. Seiber et al. (1979) also reported that volatilization from leaf and soil surfaces was the major removal mechanism for toxaphene applied to cotton crops under field conditions. These investigators reported differential vaporization of the mixture (i.e., selectively greater loss of the more volatile components from soil and leaf surfaces) which was matched by a corresponding enrichment of these components in ambient air samples.

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Toxaphene shows a strong tendency to sorb to particulates, and there has been a tendency to believe that toxaphene residuals in older hazardous waste sites would be relatively inert. Recent studies, based primarily on theoretical considerations and computer screening models, suggest that the PCCs could volatilize to the atmosphere unless a waste site has a clay cap thicker than approximately 0.3 meters. The potential for volatilization increases if the soil matrix in which the toxaphene is buried has a significant sand fraction (Jury et al. 1990). These theoretical findings seem compatible with field measurements on several pesticides that showed the volatilization rates for toxaphene applied to soils were significantly higher than rates for triazine herbicides or alachlor (Glotfelty et al. 1989a). Toxaphene was detected in air samples collected at 1 of 58 NPL hazardous waste site where it was detected in some environmental media (HazDat 1996).

**5.2.2 Water**

Toxaphene has been released to surface waters as a result of its direct application to lakes as a piscicide (EPA 1979f), in waste water releases from manufacturing and formulation plants (Durant and Reimold 1972), and in activities associated with the disposition of residual pesticides. For example, Mirsatari et al. (1987) described the release of aircraft rinse water to drainage ditches following aerial application of toxaphene, and the compound has been detected in surface water samples taken from disposal ponds at a Superfund site (EPA 1986a). Reimold (1974) reported that concentrations in the effluent of a manufacturing plant decreased over a 4-year period from an average maximum monthly concentration of 2,332 ppb in August 1970 to 6 ppb in July 1974.

Because neat technical toxaphene sorbs to particulates and is markedly hydrophobic, it has been argued that toxaphene would not be able to migrate more than about 10 cm down a soil profile and, therefore, would not be of concern as a groundwater contaminant. Such arguments tend to overlook the fact that technical toxaphene used as a pesticide was usually mixed with a hydrocarbon solvent (e.g., xylene) as a carrier. Recent analysis of data compiled by the EPA on pesticides in groundwater indicates that toxaphene was found in groundwater in one state as a result of normal agricultural use (Ritter 1990). Also, when such pesticide preparations have been introduced at old waste disposal sites, the toxaphene may be able to move into groundwater with the carrier-solvent. This scenario has been documented at a waste disposal site in California (Jaquess et al. 1989). The authors see this as a possibility at many waste disposal sites containing solvent materials, with toxaphene detections in groundwater at NPL sites, in the Mississippi Delta, and near Houston, Texas, supporting similar pollution pathways. Toxaphene has also been detected in surface water samples from 12 of 58 NPL sites, in groundwater samples from 20 of

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58 NPL sites, and in leachate samples from 1 of 58 NPL sites where toxaphene has been detected in some environmental media (HazDat 1996). For most groundwater supplies, however, any significant residence time in poorly oxygenated or anaerobic subsoil vadose zones would be expected to allow for anaerobic biochemical degradation of toxaphene.

### 5.2.3 Soil

Toxaphene has been released directly to soils primarily as a result of its past use as an insecticide on agricultural crops (EPA 1979f). Disposal of spent livestock-dipping solutions (McLean et al. 1988) and wastes from manufacturing and formulation processes (EPA 1979f) were other significant sources of soil contamination. Mirsatari et al. (1987) reported that toxaphene has been found as a contaminant at pesticide disposal sites at concentrations in soils or sediment approaching or exceeding 100 ppm. Toxaphene was listed as a chemical of concern at the Crystal City Airport Super-fund site in Crystal City, Texas. The mixture was detected in surface soil samples taken at the airport following abandonment of agricultural chemicals at the site by defunct aerial application operators (EPA 1987b). Toxaphene was also found in pesticide contaminated soils at four other Super-fund sites in Litchfield, Arizona; Albany, Georgia; Marianna, Florida; and Malone, Florida; concentrations in these soils ranged from 18 to 1,505 mg/kg (ppm) (Troxler et al. 1993). More recently, toxaphene has been detected in soil samples from 33 of 58 NPL sites and in sediment samples from 15 of 58 NPL sites where toxaphene has been detected in some environmental media (HazDat 1996).

## 5.3 ENVIRONMENTAL FATE

### 5.3.1 Transport and Partitioning

A combination of monitoring and modeling efforts during the 1980s has firmly established the importance of atmospheric pathways as a major source of PCC inputs to regions in the upper latitudes far removed from regions where it was heavily used as an agricultural pesticide. Adaptations to regional transport models initially developed to study acid rain phenomena show the physical possibility for atmospheric transport of toxaphene from locations in the southern United States to the Great Lakes Region of the northern United States and Canada (Voldner and Schroedere 1989, 1990).

An ongoing series of studies by Canadian researchers has gathered detailed information on levels of toxaphene in various environmental compartments in regions ranging from Lake Baikal in Russia, to the



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Sargasso Sea, to the southeastern United States, to various areas in Canada and the Canadian Arctic (Barrie et al. 1993; Bidleman et al. 1989, 1992, 1993; Cotham and Bidleman 1991; Lockhart et al. 1992; McConnell et al. 1993; Muir et al. 1990, 1992). These studies help provide at least partial validation for the predictions from regional transport models and document the continued supply of PCC materials to areas in the northern hemisphere far removed from areas of former significant toxaphene use.

With continued inputs of PCCs from atmospheric pathways, there is the potential for bioaccumulation in food chains. While this does not always pose an exposure risk for human populations, it can be a significant stressor to aquatic organisms and wildlife. Toxaphene, in conjunction with several other organochlorine contaminants, may adversely impact wildlife hormone systems and other reproductive end points (Lundholm 1991). This threat is especially pronounced for aquatic mammals that may lack hepatic enzymes found in most terrestrial mammals and enzymes that help metabolize PCC toxicants (Muir et al. 1992). For Native American groups in Canada (and possibly Alaska) that hunt aquatic mammals, there are genuine human health concerns.

Researchers working with the atmospheric transport of toxaphene have assembled useful time series observations for sites along the southern Atlantic coast in the United States, in the Canadian Maritime provinces, and at stations in the Canadian Arctic (Bidleman et al. 1989, 1992). Comparisons of recent levels in environmental media with baseline concentrations in the 1970s and early 1980s do not suggest declines in toxaphene contaminants, with ambient air concentrations in particular remaining about the same or even increasing. Especially in high latitude areas, impacts from toxaphene are still a matter of concern nearly a decade after the United States began phasing out the use of toxaphene as a pesticide agent.

Reported values for the vapor pressure of toxaphene vary widely, ranging from  $3 \times 10^{-7}$  mm Hg at 20 °C to 0.4 mm Hg at 20-25 °C (Agrochemicals Handbook 1983; Bidleman et al. 1981; Mackinson et al. 1981; Sunshine 1969; Suntio et al. 1988). The disparities in these values may be due to the different methods used to determine vapor pressure and/or to the varying compositions (degree of total chlorination and distribution of specific congeners) of the toxaphene mixtures used. The higher vapor pressure values (0.2-0.4 mm Hg at 20 °C) and Henry's law constant values ranging from 0.005 to 0.21 atm·m<sup>3</sup>/mol (EPA 1981a; HSDB 1995; Shen 1992) for toxaphene suggest that the mixture readily partitions to the atmosphere following release to surface waters and surface soils. A half-life (first-order kinetics) of 6 hours has been estimated for the vaporization of toxaphene from a model river, one meter deep, with a flow rate of one meter/second and a wind velocity of 3 meters/second (Howard 1991). The results of

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numerous field dissipation and atmospheric monitoring studies indicate that the atmosphere is indeed the most important environmental medium for transport of the mixture. In addition to the field dissipation studies cited in Section 5.2.1 (Seiber et al. 1979; Willis et al. 1980, 1983), significant partitioning of toxaphene to the atmosphere has been reported in a model agroecosystem study (Nash et al. 1977) and from fallow field soils (Glotfelty et al. 1989a).

The persistence of toxaphene in the atmosphere allows the mixture to be transported long distances from the application sites. The presence of toxaphene in surface waters of the Great Lakes has been attributed to aerial transport of the mixture from application sites in the southern United States (EPA 1984b). Detection of toxaphene in the tissues of fish taken from a remote lake on Isle Royale in Lake Superior was also cited as evidence of long-range atmospheric transport (Swackhamer and Hites 1988).

Numerous other investigations have reported long-range atmospheric transport of toxaphene to remote locations. Toxaphene was detected in ambient air samples taken over the western North Atlantic Ocean and Bermuda. The source of the contamination was attributed to cotton-growing areas in the southern United States 1,200 km away (Bidleman and Olney 1975). Maximum concentrations of toxaphene found in North American peat bogs corresponded to the period of maximum production and use of the compound in the United States in the mid-1970s (Rapaport and Eisenreich 1986). The composition of the toxaphene residues in the peat cores indicated that they were delivered to the peat surface by atmospheric transport and deposition with the dominant wind circulation patterns from primary source regions in the southern and southeastern United States. The presence of toxaphene in the following sources has also been attributed to its long-range atmospheric transport: fish taken from remote lakes in northern Canada (Muir et al. 1988~); fish from pristine areas in the North Atlantic Ocean, North Pacific Ocean, and Antarctic Ocean (Zell and Ballschmier 1980); and fish, birds, and seals from the western North Atlantic Ocean, Arctic Ocean, Greenland, Canada, and Sweden (Andersson et al. 1988). Evidence of regional-scale transport of the mixture in the drainage basin of the Chesapeake Bay has also been reported (Glotfelty et al. 1989b).

Atmospheric toxaphene is transported back to soil and water surfaces by wet and dry deposition processes (Glotfelty et al. 1989b; Hoff et al. 1993a; Villeneuve and Cattini 1986). Several investigators have reported that washout in rain appears to be more important than the dry deposition of toxaphene (Bidleman et al. 1981; EPA 1984b). Hoff et al. (1993a) cited an unpublished 1992 report from the Great Lakes Protection Fund/ Environment Canada in which the wet and dry deposition fluxes of PCCs to the Great Lakes were estimated to be 3.5-12.5 and 1.5-6.3 kg/year, respectively. Dry deposition accounted

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for only 15% of the input of atmospheric toxaphene into a rural estuary in South Carolina (Harder et al. 1980). Based on a range of assumptions about the concentration of PCCs in the Great Lakes, Hoff et al. (1993a) estimated that the annual loading of toxaphene by gas exchange may be more than an order of magnitude higher than the input by wet or dry deposition. The authors noted that even though potential errors in the assumptions for the gas transfer of PCCs were very large, they were not large enough to make wet and dry deposition fluxes comparable to the estimates of the gas phase mass transfer of toxaphene across the air/water interface.

For higher latitude regions, there is more uncertainty about the importance of specific deposition mechanisms. Especially in Arctic areas, model estimates and available monitoring data suggest that dry particle deposition may be more important than scavenging through snowfall (Cotham and Bidleman 1991). The mechanisms for toxaphene show many similarities with fate and transport processes for hexachlorobenzene (HCB) and perhaps several other organochlorine toxicants. The hydrophobic properties of these organochlorines encourage partitioning in either a volatile or semi-volatile phase or in forms sorbed to particulates. These properties then facilitate the incorporation of the contaminants into food chains starting with algae, zooplankton, and macroinvertebrates. This in turn encourages biomagnification at higher trophic levels (Cotham and Bidleman 1991; Hargrave et al. 1992).

Toxaphene released to soils will persist for long periods of time. The high  $K_{OC}$  (soil organic carbon partition coefficient) values for toxaphene ( $\log K_{OC}=2.47-5.00$ ) (ASTER 1995; EPA 1981a; Wauchope et al. 1992) suggest that the mixture should be strongly sorbed to soil particulates and, therefore, should be relatively immobile to leaching and inhibited from volatilizing from subsurface soils (Swann et al. 1983). Field studies have verified this behavior. Half-lives (first-order kinetics) ranging from approximately 1 year (Adams 1967 as cited in Howard 1991) to 14 years (Nash and Woolson 1967) have been reported for toxaphene in soils. In surface soils, where volatilization will be a significant partitioning process, half-lives of 2 months and 4 months have been reported for samples taken at the top 2.5 cm and top 7.5 cm, respectively (Sieber et al. 1979). Between 85 and 90% of the total toxaphene residues were found in the upper 23 cm (cultivated layer) of a sandy loam test soil 13 years after the last foliar application of the mixture (Nash and Woolson 1968). Following multiple annual applications of toxaphene to cotton crops grown in a clay soil, Swoboda et al. (1971) detected 90-95% of toxaphene residues in the top foot of the 5-foot profile sampled; toxaphene was not detected in any of the drainage water samples taken from the site. About 93% of the toxaphene found in runoff from a treated cotton field on a silty clay soil was bound to the sediment fraction; only 7% was found in the aqueous fraction of the runoff (McDowell et al. 1981). Toxaphene concentrations in runoff varied seasonally, and losses in two of the years studied totaled only

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0.5-1 % of the amount applied. Runoff losses from a cotton crop grown in the Mississippi Delta were found to be 0.4% of applied toxaphene (Lorber and Mulkey 1982). According to the simulation models Foliar Washoff of Pesticides (FWOP), Chemical Runoff and Erosion from Agricultural Management Systems (CREAMS), and Pesticide Runoff Simulator (PRS), up to 3% of applied toxaphene may be lost in runoff from treated agricultural fields; all of the toxaphene would be associated with the sediment fractions (Smith and Carsel 1984). To evaluate the effects of toxaphene on groundwater and surface water quality under different land management practices, Donigian and Carsel(1987) used three models: the Pesticide Root Zone Model (PRZM); the Analytical Transient One-, Two-, and Three-Dimensional Simulation of Waste Transport in the Aquifer System (AT123D); and the Stream Transport and Agricultural Runoff of Pesticides for Exposure Assessment (STREAM). The dissolved mean toxaphene concentration in surface water predicted by the STREAM model for a 1.0 kg/ha application rate was 11.6 ppb for conventional-till, 4.9 ppb for reduced-till, and 3.4 ppb for no-till practices. Surface water runoff loadings and concentrations of toxaphene and several other pesticides typically decreased under the conservation tillage scenarios, but groundwater loadings and concentrations generally increased as a result of decreased runoff and increased groundwater recharge. The authors did not provide estimates of groundwater concentrations for toxaphene because this pesticide did not demonstrate mean annual loadings high enough to require estimation of groundwater concentrations.

The mobility of toxaphene in soils also is influenced by soil moisture status and the presence of other organic solvating materials (Jaquess et al. 1989). Toxaphene did leach from laboratory columns of sand and sandy loam soils treated with organic solvents and emulsifiers when the columns were allowed to dry completely between wetting cycles. The mixture did not leach from the amended columns when a similar amount of water was applied on a continuous basis. Drying of the soil allowed crevices to form in the columns which expedited movement of the mixture. Toxaphene dissolved in the organic solvent or contained in the emulsifier amendment could leach through the macropores.

There is also evidence that vaporization is the primary route of loss from toxaphene-treated foliage. In a study by Seiber et al. (1979), residues of toxaphene were analyzed in cotton leaves and associated air samples up to 58 days after a 9 kg/ha application of toxaphene to a cotton field in the San Joaquin Valley, California. Analyses of the cotton leaf samples indicated a 59% loss of toxaphene at 28 days postapplication. Leaf residues declined from 661 ppm on the day of application to 135 ppm on day 50 postapplication, with an observed trend toward greater loss of the more highly volatile components. A corresponding enrichment of volatile toxaphene components was observed in air samples. There was no

indication of chemical degradation in these samples in spite of the presence of abundant sunlight, oxygen, and atmospheric oxidant throughout the study.

Toxaphene is highly insoluble in water (3 mg/L) (Mackinson et al. 1981; Wauchope et al. 1992; Worthing 1979). Toxaphene in surface waters that is not volatilized to the atmosphere is sorbed to sediments or suspended particulates, which are ultimately deposited in sediments (EPA 1979a). The lower-solubility, more-chlorinated components of the mixture are preferentially sorbed to particulates and sediments. Paris et al. (1977) reported that the less soluble, more highly chlorinated fractions of toxaphene also appear to be selectively sorbed to aquatic microorganisms and, consequently, would be expected to bioaccumulate up the food chain. At very low concentrations, sorption of toxaphene to aquatic microorganisms may be described adequately by the following relationship:

$$C_d = C_m/C_w$$

Where

$C_d$  = distribution coefficient (unitless)

$C_m$  = mg toxaphene sorbed/mg microorganism

$C_w$  = concentration of toxaphene in the medium (mg/mg) at equilibrium.

$C_d$  values ranged from  $3.4 \times 10^3$  to  $1.7 \times 10^4$  for a variety of bacteria, fungi and algae (*Bacillus subtilis*, *Flavobacterium harrisonii*, *Aspergillus sp.*, *Chlorella pyrenoidosa*) (Paris et al. 1977). Direct sorption of toxaphene onto sediment, plankton, and other suspended solids deposited in the sediment has also been reported in three lakes in Wisconsin where the mixture was applied for the control of nongame fish. Toxaphene sorbed to sediments was not found to be readily desorbed (Veith and Lee 1971).

Toxaphene is bioconcentrated in the tissues of aquatic organisms. The major toxaphene congeners found in fish from pristine environments in the Canadian Rocky Mountains have been found to be the Cl<sub>7</sub>-Cl<sub>9</sub> camphenes (i.e., hepta-, octa-, and nonachlorobomenes) (Bruns and Birkholz 1993). Experimentally determined bioconcentration factors (BCFs) for several freshwater and marine organisms have been found to range from 4,200-90,000 (ASTER 1995). Freshwater species and their respective BCF ranges include: 4,200-18,000 for brook trout (*Salvelinus fontinalis*); 7,900-90,000 for fathead minnows (*Pimephales promelas*); and 11,000-39,000 for channel catfish (*Ictalurus punctatus*) (ASTER 1995). Marine species and their respective BCF ranges include: 13,350 for Eastern oyster (*Crassostrea virginica*); 9,380 for juvenile, 21,950-26,550 for juvenile (first and second generation), and 64,750-70,140 for adult sheepshead minnow (*Cyprinodon variegatus*); 22,640-31,550 for embryo and fry, and 34,440 for juvenile longnose killfish (*Fundulus similis*) (ASTER 1995). Additional experimental data located in the available literature are consistent with this compilation.

In a flow-through bioassay conducted with the longnose killfish (*F. similis*), BCFs of up to 33,300 in fry and 60,000 in juvenile fish after 28 days of exposure were reported; BCFs in adults ranged from 4,200 to 6,800 after 14 days of exposure (Schimmel et al. 1977). Oysters (*C. virginica*) exposed to 1 ppb toxaphene have been found to accumulate up to 23 ppm in tissue after 24 weeks exposure; tissue concentrations decreased to nondetectable levels at the end of a 12-week depuration period (Lowe et al. 1971). In a model ecosystem study using radiolabeled toxaphene, BCFs of 6,902 for algae, 9,600 for snails, 890 for mosquitoes, and 4,247 for fish (*Gambusia affinis*) were reported (Sanbom et al. 1976). Toxaphene has also been detected in the tissues of aquatic organisms in numerous field studies (see Section 5.4.4). For example, mean toxaphene concentrations of 11 ppm in lipid tissue for lake trout (*Salvelinus namaycush*) and 7 ppm in lipid tissue for whitefish (*Coregonus clupeaformis*) taken from a remote lake on Isle Royale in Lake Superior have been reported (Swackhamer and Hites 1988). Studies conducted in a natural ecosystem in northwestern Ontario on the fate of toxaphene in lake trout (*S. namaycush*) and white suckers (*Catostomus commersoni*) indicated depuration half-lives for total toxaphene ranging from 232 days (lake trout, initial intraperitoneal dose 7.0 µg/g) to 524 days (white suckers, initial intraperitoneal dose 3.5 µg/g), with first-order kinetics assumed (Delorme et al. 1993). Depuration half-lives for two of the more persistent toxaphene congeners, octachlorobomane T2 and nonachlorobomane T12, ranged from 294 days (lake trout; T2, initial intraperitoneal dose 7.0 µg/g) to 716 days (white suckers; T2, initial intraperitoneal dose 3.5 µg/g) with first-order kinetics assumed. The overall results of this study indicated significant interspecies differences in the ability to eliminate toxaphene, as well as possible intraspecies differences in the ability to eliminate different toxaphene congeners.

Toxaphene also appears to be biomagnified in aquatic food chains, although not to the extent of other chlorinated insecticides, such as DDT. Evans et al. (1991) reported trophic biomagnification of toxaphene, with toxaphene concentration increasing by an average factor of 4.7 from plankton (mean concentration = 0.55 ppm) to fish (deepwater sculpin: mean concentration = 2.57 ppm). DDE and PCBs were found to be more strongly biomagnified, increasing 28.7 and 12.9 times, respectively, in average concentration from plankton to sculpin. In a study that included analyses of tissue residue levels in 16 species of fish, birds, amphibians, and reptiles, biomagnification of toxaphene was reported in three oxbow lakes in northeastern Louisiana (Neithammer et al. 1984). Tissue residue concentrations were highest in tertiary consumers (carnivores) and lowest in primary consumers (herbivores); toxaphene was not detected in the limited number of surface water or sediment samples taken from the lakes. The source of the toxaphene was apparently the surrounding cotton and soybean cropland, which had historically

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analyses of tissue residue levels in 8 species of fish and water snakes in the area of the Yazoo National Wildlife Refuge, Mississippi (Ford and Hill 1991). Biomagnification of several organochlorine pesticides, including toxaphene, was apparent from soil sediments (geometric mean concentration approximately 0.1 ppm) to mosquito fish, a larger secondary consumer and forage fish (geometric mean concentration = 0.25 ppm), to the spotted gar, a tertiary consumer (geometric mean concentration = 2.71 ppm) (Table 5-1). There was, however, no clear pattern of biomagnification in larger secondary consumers such as smallmouth buffalo and carp, or in tertiary consumers such as water snakes.

Biomagnification of toxaphene in marine ecosystems appears to be species dependent (de Boer and Wester 1993). The two main toxaphene congeners found in marine mammals such as seals and beluga whales are an octa- and a nonachlorobomane, which are present only as minor constituents in technical toxaphene (Vetter et al. 1993, 1994). No biomagnification of toxaphene in a Canadian arctic marine food chain was reported in a study conducted by Muir et al. (1988a). Toxaphene was detected in the muscle tissue of the arctic cod (*Boreogadus saida*) at a mean concentration of 0.018 ppm, but not in the blubber and liver of the ringed seal (*Phoca hispida*), which preys on the cod, or the fat of the polar bear (*Ursus maritimus*), which preys on the seal. Similar results were found by Andersson et al. (1988), who performed limited sampling of biota from various trophic levels in marine food chains in the western North Atlantic Ocean, Greenland, Sweden, and Canada. They reported that toxaphene concentrations in fish, bird, and seal tissues ranged from 0.33 to 17 ppm in fat tissue for all trophic levels versus 0.14-990 ppm for DDT and PCB residues. These results were interpreted as being indicative of less biomagnification and/or more effective metabolism of toxaphene at higher trophic levels, as compared with DDT and PCB.

In another study, however, toxaphene was found in the tissues of white-beaked dolphins (*Lagenorhynchus albirostris*) and pilot whales (*Globicephalu melaeu*) taken off the coast of Newfoundland in 1980 and 1982 (Muir et al. 1988b). The toxaphene peaks from the gas liquid chromatography (GLC) analyses of the dolphin blubber indicated considerable metabolism of the mixture, as compared with toxaphene residues detected in the local fish populations preyed upon by the dolphins. Other studies in the area of Baffin Bay, Canada, have found cetacean blubber with an average toxaphene congener concentration of 9.2 ppm for male narwhals. Tissue concentrations in individual males ranged up to 13.2 ppm (Muir et al. 1992). De Boer and Wester (1993) also found evidence of biomagnification of toxaphene in the marine food chain from fish to fish predators, and reported biomagnification factors (BMFs) of approximately 40 for harbor porpoise/fish and 100 for whitebeaked dolphin/fish. Comparison of the chromatograms from whitebeaked dolphin (blubber) and fish (hake liver) indicated similar metabolism of toxaphene for both species.

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**Table 5-1. Toxaphene Levels Detected in Tissue Samples of Aquatic Animals from the Yazoo National Wildlife Refuge, Mississippi, in 1988**

Species	Number of Samples	Geometric Mean Concentration (ppm wet weight)	Concentration Range (ppm wet weight)
Mosquitofish	25	0.25	ND - 0.25 (17) <sup>a</sup>
Carp	8	3.06	0.51 - 6.20 (8)
Smallmouth buffalo	6	5.77	0.75 - 15.00 (6)
Bowfin	5	2.70	0.27 - 8.60 (5)
Spotted gar	10	2.71	ND - 16.00 (9)
Water snake	20	0.33	ND - 27.00 (17)
Cottonmouth	10	0.03	ND - 1.30 (5)

Source: Ford and Hill 1991

<sup>a</sup>Numbers in parentheses indicate numbers of samples containing toxaphene.

ND = not detected (minimum detection limit 0.01 ppm)



## 5. POTENTIAL FOR HUMAN EXPOSURE

Recent tissue residue data from marine ecosystems have been used by Hargrave et al. (1993) to calculate the following ranges of BMFs (ng PCC/g lipid predator per ng PCC/g lipid prey) for various predator-prey links among arctic marine organisms. In a hypothetical food web the following ranges in BMF values were reported: arctic cod and char/zooplankton (19.7-36.7); ringed seal/arctic cod and char (0.1-0.2); beluga/arctic cod and char (2.0-2.3); narwhal/arctic cod and char (3.3-3.4); small lysianassid amphipods/arctic cod and char (0.7-2.7); small lysianassid amphipods/ringed seal (4.7-15.5); small lysianassid amphipods/sibeluga (0.4-1.1); *Eurythenes gyrillus*/arctic cod and char (9.1-11.1); *E. gyrillus*/narwhal (2.8-3.2); *E. gyrillus*/beluga (4.664.8); *E. gyrillus*/ringed seal (55.3-65.3); *E. gyrillus*/eelpout (4.4-19.2); eelpout/small lysianassid amphipods (0.2-2.7).

### 5.3.2 Transformation and Degradation

#### 5.3.2.1 Air

The worldwide, long-range atmospheric transport of the mixture suggests that toxaphene is relatively resistant to transformation in the atmosphere. Since the production of toxaphene involves exposing chlorinated camphenes to ultraviolet radiation, the congeners in the final mixture are resistant to degradation from direct photolysis (EPA 1976a; Korte et al. 1979). Consequently, toxaphene in the atmosphere is not expected to degrade readily by direct photolysis when attached to particulates. However, a half-life of approximately 4-5 days (first-order kinetics) has been estimated for the reaction of vapor phase toxaphene with photochemically produced hydroxyl radicals (Howard 1991; Kelly et al. 1994). Rapaport and Eisenreich (1986) cited an atmospheric residence time of 46-70 days for the mixture. They noted that the toxaphene found in peat cores taken from remote regions in the northern United States and Canada was deposited from the atmosphere in a relatively untransformed state.

#### 5.3.2.2 Water

Little information was found in the available literature on the biodegradation of toxaphene in aquatic systems. Toxaphene is resistant to chemical and biological transformation in aerobic surface waters. It is not expected to undergo direct photolysis or photooxidation (EPA 1979a). Hydrolysis is also not an important fate process; a hydrolytic half-life (first-order kinetics) of greater than 10 years for pH 5 to 8 at 25 °C has been estimated (EPA 1976d, 1979a). Detoxification of toxaphene in eight Wisconsin lakes was reported to be due to adsorption rather than biodegradation (Sanbom et al. 1977 as cited in Howard 1991).

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**5.3.2.3 Sediment and Soil**

Toxaphene has been reported to be quite persistent in aerobic surface soils. Nash and Woolson (1967) reported a half-life of 11 years (first-order kinetics) in an aerobic sand loam soil that had received high application rates (112 and 224 kg/ha, corresponding to approximately 50 and 100 ppm) of toxaphene. Seiber et al. (1979) reported half-lives of approximately 2 months (top 2.5 cm) and 4 months (top 7.5 cm) in aerated topsoil that had been treated with toxaphene at an application rate of 9 kg/ha. While the observed declines in toxaphene concentrations were primarily due to vaporization, at least one toxaphene component was reported to be significantly degraded. The mechanism of degradation was postulated to be dehydrochlorination or reductive chlorination, but this was not investigated further. Studies by Parr and Smith (1976) and Smith and Willis (1978) in a silty loam soil indicated no transformation of toxaphene in moist amended (i.e., alfalfa meal added) or unamended samples incubated under aerobic conditions, but rapid transformation (65-96% over 4 weeks) in amended and unamended samples incubated under anaerobic conditions. The transformation was reported to be a dechlorination reaction. No transformation was observed in autoclaved samples. A 50% loss of toxaphene in 6 weeks due to biodegradation in anaerobic, flooded soils was reported; however, no biodegradation was found in aerobic sediments (EPA 1979a).

There is conflicting information in the literature regarding the transformation of toxaphene in sediments. Seiber et al. (1979) found that in sediment samples taken from the bottom of a drainage ditch a year or more after application of toxaphene to an adjacent field (13.5 kg/ha), several major components of toxaphene, including toxicant B, were significantly degraded. Reductive dechlorination appeared to be a major mechanism of degradation. This mechanism results in lower weight products than occur in technical toxaphene, at least some of which are relatively stable in the environment. As a consequence, the authors emphasized that the environmental and toxicological significance of these products needs to be determined. Using a microcosm system, Williams and Bidleman (1978) reported that toxaphene transformation in an anaerobic salt marsh sediment was mediated chemically, rather than biologically. The transformation, believed to be a reductive dechlorination, was rapid, occurring within 2-6 days even in sterilized samples. In contrast, Mirsatari et al. (1987) found no transformation of toxaphene in autoclaved (i.e., sterile) sediment and soil samples over a 60-day test period. In addition, no transformation was observed in unsterile sediment samples incubated under aerobic conditions for 6 weeks. Rapid transformation (half-life = 1 week) was observed only in unsterile sediment samples amended with organic matter and incubated under anaerobic conditions. The microbially mediated transformation was apparently a reductive dechlorination. Clark and Matsumura (1979) added

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radiolabeled toxaphene to sediments and incubated them for 30 days under aerobic and anaerobic conditions. As in the Mirsatari et al. (1987) study, no transformation was observed in autoclaved samples. However, toxaphene was transformed in the aerobically incubated samples by the bacterium *Pseudomonas putida*. Clark and Matsumura (1979) stated that toxaphene biotransformation is likely to proceed initially as a dechlorination reaction under anaerobic conditions followed by oxidative transformation of the less chlorinated products under aerobic conditions. Thus, toxaphene apparently undergoes some biotransformation in the sediment layers of rivers and lakes under both anaerobic and aerobic conditions.

**5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT**

As a result of past widespread use as an insecticide and its persistence, toxaphene has been detected in ambient air, surface water and groundwater, soils and sediments, rainwater, and food. Data reported in this section have been obtained largely from national surveys in an attempt to present a representative national perspective of toxaphene contamination of various environmental media. However, toxaphene contamination of certain media may be a more serious problem on a regional basis than indicated by these national averages. For example, higher soil concentration levels can be expected in cotton growing areas of the South, and higher tissue residue levels have been found in fish taken from the Great Lakes.

A factor complicating the analysis of toxaphene in various environmental media is the difficulty in making trend comparisons for monitoring information collected before the early 1980s. Reliable detection of low levels of PCCs became possible only with the adoption of capillary column gas chromatography technology in the early 1980s. The prevailing earlier packed-column methods were usually unable to provide reliable total toxaphene readings for the large numbers of congeners (each present in minute amounts) encountered in most samples (Schmitt et al. 1990). For instance, U.S. Fish and Wildlife Service programs like the National Pesticide Monitoring Program (now the National Contaminant Biomonitoring Program) started in the 1970s; however, due to problems in quantification with the older technologies, results of these programs cannot be compared with more recent toxaphene sampling results (Schmitt et al. 1990). These problems seriously interfere with drawing conclusions for such media as sediments or tissue samples, and make it almost impossible to make trend determinations for ambient water.

Another complicating factor is the mounting evidence that wastes from paper and pulp operations may be a source of toxaphene-like materials. Much of this research comes from countries where toxaphene was never used as a pesticide agent, but where anomalous findings of PCC materials were encountered. There is a tendency in such cases to conclude that all the PCC congeners are the result of hemispheric or global

## 5. POTENTIAL FOR HUMAN EXPOSURE

atmospheric transport pathways, but in some cases, PCC from paper and pulp wastes may help explain localized hotspots. While most of this research has come from other countries (Jamuzi et al. 1992; Rantio et al. 1993), the State of Michigan (EPA 1995c) is confident that PCC congeners from paper industry wastes are found in the Great Lakes region.

Reliable evaluation of the potential for human exposure to toxaphene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on toxaphene levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

#### 5.4.1 Air

Toxaphene has been detected in ambient air and rainwater samples collected at a number of sites in the United States; however, the available data are not current. No information was found in the available literature regarding ambient indoor exposure levels of toxaphene.

Toxaphene has also been detected in ambient air samples taken at remote locations. Toxaphene concentrations of less than 0.04-1.6 ng/m<sup>3</sup> in ambient air samples taken over the western North Atlantic Ocean from 1973 to 1974 have been reported (Bidleman and Olney 1975). Mean concentrations in ambient air samples from Bermuda were 0.81 ng/m<sup>3</sup> ( $\pm 0.45$  ng/m<sup>3</sup> S.D.) and 0.72 ng/m<sup>3</sup> ( $\pm 0.09$  ng/m<sup>3</sup> SD.).

In an ambient air monitoring study conducted at four urban sites (Baltimore, Maryland; Fresno, California; Riverside, California; and Salt Lake City, Utah) and at five rural sites (Buffalo, New York; Dothan, Alabama; Iowa City, Iowa; Orlando, Florida; and Stoneville, Mississippi) in the United States in 1967-1968, toxaphene was detected only in samples taken from the three agricultural areas in southern states. Maximum concentrations detected were 68 ng/m<sup>3</sup> (detected in 11 of 90 samples), 2,520 ng/m<sup>3</sup> (9 of 99 samples), and 1,340 ng/m<sup>3</sup> (55 of 98 samples) in Dothan, Alabama; Orlando, Florida; and Stoneville, Mississippi, respectively (Stanley et al. 1971). Toxaphene was included in the ambient air sampling of agricultural and urban areas conducted in 14-16 states as part of the National Air Pesticide Monitoring Program. For the years 1970-72, toxaphene was detected in 3.5% of the 2,479 samples collected at mean and maximum concentrations of 17 ng/m<sup>3</sup> and 8,700 ng/m<sup>3</sup>, respectively; and the mean of the positive samples was 1,890 ng/m<sup>3</sup> (Kutz et al. 1976). In 1981, toxaphene was detected at maximum concentrations

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of 9.05 ng/m<sup>3</sup>, 1.73 ng/m<sup>3</sup>, 0.44 ng/m<sup>3</sup>, and 0.14 ng/m<sup>3</sup> in Greenville, Mississippi; Saint Louis, Missouri; Bridgeman, Michigan; and Beaver Island, Michigan; respectively (EPA 1984b; Rice et al. 1986).

A seasonal variation in toxaphene concentrations in ambient air samples collected in Stoneville, Mississippi, from 1972 to 1974 was noted in a study by Arthur et al. (1976). The highest concentrations were observed in summer months, corresponding to the growing season, and the lowest in winter months. The sampling site was located in the middle of the most intensive cotton-growing area in Mississippi. The maximum concentration detected in weekly air samples was 1,747 ng/m<sup>3</sup>. Average monthly levels were 258, 82, and 160 ng/m<sup>3</sup> for 1972, 1973, and 1974, respectively. A similar seasonal variation was found in atmospheric toxaphene concentrations in southern Ontario, which was attributed to increased volatilization of PCCs during the warmer summer months (Hoff et al. 1993b). During this 1988-1989 study, average monthly concentrations ranged from 0.08 pg/m<sup>3</sup> in February to 110 pg/m<sup>3</sup> in July; the overall maximum and mean concentrations (n=114) were 580 and 26 pg/m<sup>3</sup>, respectively.

Toxaphene has also been detected in air samples collected at 1 of 58 NPL hazardous waste sites where toxaphene was detected in some environmental media; however, concentrations were not reported (HazDat 1996).

Toxaphene has been detected in rainwater samples taken in southern France near the Mediterranean Sea at mean concentrations of 7.2 ppt (range: not detected to 53 ppt) and 25.2 ppt (range: not detected to 81 ppt) in solution and sorbed to particulates, respectively (Villeneuve and Cattini 1986). No information was found in the literature for concentrations of toxaphene in rainwater samples collected in the United States.

#### 5.4.2 Water

Toxaphene has been detected very rarely in drinking water supplies. Toxaphene concentrations ranged from 5 to 410 ppt (0.005 to 0.410 ppb) in drinking water samples collected in Flint Creek, Alabama, between 1959 and 1963 (Faust and Suffet 1966). More recently, in an extensive water quality monitoring program conducted by the California Department of Health Services, toxaphene was detected (detection limit not specified) in only 2 of 5,279 public drinking water sources sampled from 1984-1992, at mean and maximum concentrations of 0.30 and 0.50 ppb, respectively (Storm 1994). Concentrations did not exceed the Maximum Concentration Level (MCL) of 5.0 ppb.

## 5. POTENTIAL FOR HUMAN EXPOSURE

The median toxaphene concentration detected in ambient surface waters in the United States in 1980-1982, according to analyses of EPA's STORET water quality database, was 0.05 ppb (Staples et al. 1985). The mixture was detected in 32% of the 7,325 samples collected over that period. Toxaphene was detected in only 3.4% of the 708 effluent samples taken during 1980-1983 at a median concentration of less than 0.2 ppb.

In a study of toxaphene concentrations in surface water and runoff from the Bear Creek, Mississippi, watershed conducted in 1976-79, toxaphene concentrations in surface water were found to be measurable only after major runoff events (Cooper et al. 1987). At other times, only trace amounts of the compound (<0.01-1.07 ppb) were detected. However, runoff from two fields historically cultivated in cotton and soybeans contained toxaphene residues of 0.04-4.18 ppb and 289-2,964 ppm in the aqueous and particulate fractions, respectively. Petty et al. (1995) recently conducted studies using semipermeable membrane devices to determine bioavailable organochlorine pesticide residues in streams receiving irrigation drainwater from agricultural activity in the Lugert Altus Watershed in southwestern Oklahoma. Among the pesticides monitored, toxaphene was predominant, with calculated bioavailable (dissolved) water concentrations at six sampling sites ranging from 0.3 to 7 µg/L (ppb). In general, concentrations were higher in summer than in spring. The authors noted that the  $K_{ow}$  used in these calculations was an average for the toxaphene mixture and that, because  $K_{ow}$  values for individual congeners may vary by an order of magnitude, water concentrations of toxaphene congeners could range from 0.9 to 9 ppb. There is an additional uncertainty in these estimates because they were derived from the dialysate data using models and preliminary data on uptake kinetics. The results do indicate, however, that significant concentrations of bioavailable toxaphene may still be present in this aquatic ecosystem several years after discontinuation of its use.

In contrast to agricultural areas, municipal areas do not show evidence of toxaphene in water samples. Toxaphene was not detected in 86 samples of municipal runoff collected from 15 cities in the United States in 1982 as part of the Nationwide Urban Runoff Program (Cole et al. 1984). More recently, toxaphene was not detected (detection limits 0.06-0.2 ppb) in surface water samples collected in 1990-1993 from 13 sites in the Potomac River and Upper Chesapeake Bay areas (Hall et al. 1993, 1995). Sampling sites included both clean reference areas and suspected polluted areas.

Toxaphene has also been detected at hazardous waste sites in surface water, groundwater, and leachates. Toxaphene was detected at a maximum concentration of 17 ppb in surface water samples taken from 2 of 9 disposal ponds at a Super-fund site (EPA 1986a). In a study of the chemical composition of leachates

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within existing landfills, toxaphene was not detected in any of the municipal landfill leachates examined (Brown and Donnelly 1988). However, the mixture was detected in industrial landfill leachates at a concentration of  $\leq 10$  ppb. In a review of groundwater monitoring data collected in 1981-1984 from more than 500 wells at 334 hazardous waste disposal sites (RCRA and CERCLA sites) located in all 10 EPA regions and 42 states, Plumb (1987) reported that toxaphene was detected at 0.2% frequency at the 178 CERCLA sites examined and at 1.1% frequency at the 156 RCRA sites examined. Concentration data were not provided. More recently, toxaphene has been detected in surface water samples from 12 of 58 NPL sites, in groundwater samples from 20 of 58 NPL sites, and in leachate samples from 1 of 58 NPL sites where toxaphene has been detected in some environmental media; however, concentrations were not reported (HazDat 1996).

#### 5.4.3 Sediment and Soil

Toxaphene has been detected in some samples of urban and agricultural soils from throughout the United States. Wiersma et al. (1972a) detected the mixture in concentrations that ranged from 0.11 to 52.7 ppm in samples of surface soils from 3 of 8 U.S. cities in 1969. In another study of 14 cities conducted in 1970, toxaphene was detected at 3 of 28 sites (10.7%) at mean and geometric mean concentrations of 1.94 and 0.012 ppm, respectively; concentrations in the positive samples ranged from 7.73 to 33.4 ppm. In Sikeston, Missouri, toxaphene was detected at 1 of 27 sites at a concentration of 0.60 ppm. Carey et al. (1979a) monitored soils in 5 U.S. cities in 1971 and found toxaphene only in 11 of 43 samples (25.6%) taken from Macon, Georgia, at a mean concentration of 0.24 ppm (range, 0.23-4.95 ppm; geometric mean, 0.02 ppm).

Toxaphene residues in domestic cropland soils were surveyed in the National Soils Monitoring Program (Carey et al. 1978, 1979b; Wiersma et al. 1972b). Rapaport and Eisenreich (1986) found toxaphene in samples of peat from bogs located in remote regions of the northern United States and Canada at concentrations ranging from less than 1 ppb (detection limit) to 30 ppb. More recently, toxaphene was not detected (detection limit 0.5 ppm wet weight) in surface core samples (0-15 cm depth) of soils derived from dredged materials from 9 confined disposal facilities in the Great Lakes region (Beyer and Stafford 1993).

Toxaphene has also been detected in sediment samples, primarily in the southern United States. Toxaphene was detected in 2.2% of 548 sediment samples collected in the lower Mississippi River and its tributaries in 1964 and from 1966 to 1967. Concentrations in the positive samples ranged from 0.1 to

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13.18 ppm, the mean concentration was 6.5 ppm (Barthel et al. 1969). In southern Florida, toxaphene was detected, but not quantified, in 3.2% of 126 sediment samples collected from 1969 to 1972 (Matraw 1975). Toxaphene was not detected in 27 sediment samples collected in Delaware and in the Raritan Canal, New Jersey, from 1979 to 1980 (Granshrom et al. 1984), or in sediment samples collected in Casco Bay, Maine, in 1991 (Kennicutt et al. 1994). At a site 1.4 miles from the outfall of a toxaphene plant on Terry Creek in Brunswick, Georgia, toxaphene was found at a concentration of 5.27 ppm in a 70-80 cm deep sediment sample collected in 1971 (IARC 1979). According to analyses of EPA's STORET water quality database, the median toxaphene concentration in sediment was 2.0 ppb; the compound was detected in 25% of the 1,603 samples taken during 1980-1983 (Staples et al. 1985). More recently, toxaphene was found at maximum concentrations of 1,600 and 500 ng/g (ppb) in sediments from two different Canadian lakes that had been treated with toxaphene at concentrations of 0.0184 and 0.0075 ppm, respectively, almost 30 years earlier (Miskimmin and Schindler 1994).

In a recent investigation of organochlorine pesticides in soil sediments in the upper Steele Bayou watershed of Mississippi, toxaphene was found in 41% of 56 samples collected at two depths (2.54-7.62 cm and 25.4-30.48 cm) along 8 different drainages (Ford and Hill 1991). The geometric mean and maximum wet weight toxaphene concentrations were 0.12 ppm and 2.80 ppm for the shallow samples, and 0.07 ppm and 4.60 ppm for the deeper samples, respectively. There was no significant difference in toxaphene concentrations between corresponding shallow and deep samples.

Ongoing studies in agricultural areas of the Mississippi Delta provide indications of the persistence of toxaphene in soils and sediments under what might be construed as a worst case scenario. Results of investigations at Moon Lake and sites within its watershed just to the east of the main levees on the Mississippi River in Coahoma County, Mississippi, have been reported (Cooper 1991). In soils, which provide a generally aerobic redox environment, the average total toxaphene level based on 69 samples collected in the period 1983-1984 was 734 ppb. The toxaphene concentration in lake sediments averaged 12.4 ppb. In core samples from wetland flats displaying marked signs of anaerobic conditions, there was no detectable toxaphene. These findings underscore the fact that it is only in media providing appreciable residence times in biologically active anoxic conditions that one can expect significant biodegradation of toxaphene. In even moderately aerobic environments, and especially in soil or sediments rich in clay colloids, the pesticide agent is persistent for many years.

Toxaphene has also been found in soils and sediments at hazardous waste disposal sites. Mirsatari et al. (1987) reported that toxaphene has been found as a contaminant at pesticide disposal sites at



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concentrations in soils or sediment approaching or exceeding 100 ppm. Toxaphene was also detected at a maximum concentration of 2,900 ppb (2.9 ppm) in sediment samples taken from 2 of 9 disposal ponds at a Superfund site (EPA 1986a). Toxaphene was found at concentrations ranging from 18 to 1,505 mg/kg (ppm) in pesticide contaminated soils at four other Superfund sites in Litchfield, Arizona; Albany, Georgia; Marianna, Florida; and Malone, Florida (Troxler et al. 1993). More recently, toxaphene was detected in soil samples from 33 of 58 NPL sites and in sediment samples from 15 of 58 NPL sites where toxaphene has been detected in some environmental media; however, concentrations were not reported (HazDat 1996).

#### 5.4.4 Other Environmental Media

Several studies conducted to determine the levels of toxaphene in food indicate that this substance is found only infrequently in the U.S. food supply, generally at very low residue concentrations which have decreased significantly since the restriction of its use in 1982 (EPA 1982a) and its total ban in 1990 (EPA 1990b). Except for fish and wild game animals from some areas of the United States (EPA 1995b; Ford and Hill 1990), the current U.S. food supply does not appear to contain levels of toxaphene that are of concern for human health.

Levels of toxaphene in food have been determined as part of the Federal Drug Administration's (FDA) Total Diet Studies. In a 1980-82 survey of pesticides, toxaphene was detected in samples of food groups that comprised typical infant and toddler diets. Concentrations ranging from 0.1 to 0.2 ppm (number positive samples = 3) and from 0.7 to 0.12 ppm (number positive samples = 6) were found in the oils and fats food groups of infants' and toddlers' diets, respectively. The samples were collected in 13 U.S. cities. Toxaphene was not detected in drinking water or the other foods examined in the diet of either group. Other food groups examined included: whole milk; other dairy and dairy substitutes; meat, fish, and poultry; grain and cereal products; potatoes; vegetables; fruit and fruit juices; sugar and adjuncts; and beverages (Gartrell et al. 1986a, 1986b). In a recent summary of data from 1985-1991 FDA Total Diet Studies on pesticide residues in infant foods and adult foods eaten by infants and children, toxaphene was found only in peanut butter at a maximum concentration of 0.16 ppm (number of positive samples = 27 of 27) (Yess et al. 1993).

Toxaphene was detected each year in regulatory monitoring of domestic and imported foods conducted by the FDA from 1988 to 1994 as part of its Pesticide Residue Monitoring Program (FDA 1989, 1990, 1991, 1992, 1993, 1994, 1995). Concentrations were not reported; however, <1% of the surveillance samples

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had any pesticide residue levels that were above established tolerances. Toxaphene was also detected in the FDA Total Diet Studies in 1987, 1988, 1989, 1990, and 1991 (FDA 1988, 1990, 1991, 1992). From 1987-1990, it was listed among the most commonly found pesticides, with frequencies of detection of 1-2% (FDA 1988, 1989, 1990, 1991). Reports of 1992-1994 FDA Total Diet Studies indicated that the types of pesticide residues found and their frequencies of occurrence were consistent with those in previous years; however, there was no explicit statement that toxaphene was detected in the years 1992-1994 (FDA 1993, 1994, 1995). Concentrations of toxaphene found in the FDA Total Diet Studies were not reported. However, in an overall summary for the 5-year period 1986-1991, average dietary intakes of toxaphene, in  $\mu\text{g}/\text{kg}$  body weight/day, for eight age/sex groups were reported to range from 0.0057 (25-30-year-old females) to 0.0224 (2-year-old children) (FDA 1993).

Overall, in 234 ready-to-eat foods tested 37 times each from 1982 to 1991 as part of the FDA Total Diet Studies, toxaphene was found 138 times at an average concentration of 0.04  $\mu\text{g}/\text{g}$  (ppm) in 18 different foods: cantaloupe, raw carrots, boiled collards, corn chips, cucumbers, cooked frankfurters, dry-roasted peanuts, creamy peanut butter, dill pickles, cured ham, potato chips, radishes, boiled spinach, boiled summer squash, boiled winter squash, strawberries, tomato sauce, and cooked veal cutlet (KAN-DO Office and Pesticides Team 1995). Concentrations ranged from 0.0050  $\mu\text{g}/\text{g}$  (ppm) (strawberries) to 0.12  $\mu\text{g}/\text{g}$  (ppm) (dry-roasted peanuts). During the period 1989-1991, estimated toxaphene intakes were less than 0.01  $\mu\text{g}/\text{kg}$  body weight/day for 6-11-month-old infants, 14-16-year-old males, and 60-65-year-old females, with a noticeable downward trend in all age categories (FDA 1990, 1991, 1992). (See Section 5.5 for more detailed information on estimated daily toxaphene intakes.) While progressive improvements in analytical technologies complicate comparisons of older values with more recent collections, the FDA Total Diet Studies clearly suggest that toxaphene residue levels in food and general population intake levels have fallen dramatically over the last decade.

Other studies further indicate that the occurrence of toxaphene in the U.S. food supply is very low. Toxaphene was not detected as a violative residue in a 1992-1993 statistically based FDA study of pesticide residues in more than 3,000 samples of domestic and imported pears and tomatoes (Roy et al. 1995). A regional food basket study conducted in San Antonio, Texas, in the period from 1989 to 1991 screened 6,970 produce items for a suite of 111 pesticide analytes. Toxaphene was not detected in any produce items at levels above FDA violation thresholds (Schattenberg and Hsu 1992). A summary of results from the FOODCONTAM database (Minyard and Roberts 1991) for the period 1988-1989 showed no detectable toxaphene residues in food samples. This database involves 10 states that follow quality

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assurance/quality control (QA/QC) protocols consistent with those of such federal counterpart agencies as the USDA, EPA and the FDA.

Toxaphene has been found in fish and shellfish in some areas of the United States at levels of concern for human health and, at present, there are four fish consumption advisories in effect for this compound (see Section 5.6) (EPA 1995b). Toxaphene was found at maximum concentrations of 11 ppm in shellfish samples from California (4 positives in 85 samples) and 54 ppm in shellfish samples from Georgia (128 positives in 211 samples) in a National Pesticide Monitoring Program survey of estuarine molluscs conducted from 1965-1972, a period when toxaphene was heavily used (Butler 1973). More recently, toxaphene was detected at concentrations <0.10 ppm wet weight in eggs, ovary, liver, and muscle tissue of three pallid sturgeon (*Scaphirhynchus albus*) samples from the Missouri River in North Dakota and Nebraska (Ruelle and Keenlyne 1993).

Toxaphene is of particular concern as a major contaminant of Great Lakes fish. Residues of toxaphene and other pesticides in fish were examined as part of the National Contaminant Biomonitoring Program (NCBP), formerly a part of the National Pesticide Monitoring Program conducted in 1984. Composite samples (n=321) of bottom-feeding and predatory fish were taken from 112 stations located along the major domestic rivers and in the Great Lakes. Toxaphene residues were detected in fish tissue samples collected at 69% of the stations. In earlier sampling periods, the percentage of stations where detectable residues were present was approximately 60% (1976-1977 and 1978-1979) and 88% (1980-1981). The maximum and geometric mean wet weight concentrations of the mixture in the 1984 samples were 8.2 ppm and 0.14 ppm, respectively, the lowest values found in any NCBP sampling period. Maximum and geometric mean wet weight concentration data for earlier sampling periods were 12.7 and 0.34 ppm (1976-1977), 18.7 and 0.28 ppm (1978-1979), and 21.0 and 0.28 ppm (1980-1981) respectively (Schmitt et al. 1985, 1990).

Fillets of Great Lakes coho salmon collected from the 5 lakes in 1980 had mean concentrations of 0.19-1.53 ppm of "apparent toxaphene" (Clark et al. 1984). Lake trout collected from Lake Michigan have been found to contain residues of toxicant congeners A and B that were approximately one-tenth or less of the estimated total toxaphene residues (Gooch and Matsumura 1985, 1987). The percentages of toxicant A and toxicant B in the fish residues were, however, similar to those in the technical toxaphene, indicating that in the environment the rates of degradation of these congeners are roughly the same as those of other toxaphene components.

Toxaphene concentrations in nearshore fish collected from the mouths of rivers and embayments around Lake Michigan in 1983 were determined in a study conducted by Camanzo et al. (1987). In 28 composite whole-fish samples collected from 14 sites, toxaphene was detected at a mean concentration of 0.04-3.46 ppm in samples of rock bass, northern pike, common carp, smallmouth bass, lake trout, bowfin, pumpkinseed, channel catfish, and largemouth bass. The investigators noted that bottom-feeding species (e.g., common carp, channel catfish) had higher residue levels than top predatory fish (e.g., northern pike), possibly as a result of the bottom-feeders being older, having more fat tissue, and living in proximity to contaminated sediments. Most of the residues differed from the GLC peaks for the toxaphene standard, indicating that some metabolism/transformation of the compound had taken place. In 1982, toxaphene (reported as a toxaphene-like compound) was detected (detection limit 1 mg/kg [ppm] wet weight) in all of 10 samples of lake trout collected in Lake Michigan (mean concentration  $4.7 \pm 0.5$  ppm), and in 9 of 10 samples of lake trout collected in Lake Superior (mean concentration  $1.6 \pm 0.2$  ppm) (Miller 1993). In this same study, toxaphene was detected in all of 10 samples of chinook salmon collected in Lake Michigan in 1982 (mean concentration  $2.0 \pm 0.2$  ppm), and in 4 of 8 samples of chinook salmon collected in Lake Michigan in 1983 (mean concentration  $1.0 \pm 0.0$  ppm). In a more recent study, fish fillet samples from 11 species of Great Lakes fish were found to have toxaphene levels ranging from not detected (detection limit 10 ppb [0.01 ppm] wet weight) in bass and bullhead, to 936 ppb (0.936 ppm) wet weight in trout (Andrews et al. 1993; Newsome and Andrews 1993). The levels appeared to be species specific, with higher levels found in fish having higher fat content (trout, herring) than in fish having lower fat content (bass, bullhead, perch, pickerel, smelt, menominee).

Levels of toxaphene in fish to which consumers are actually exposed are dependent on the type of sample and the method of preparation, with higher concentrations generally found in the higher fat content skinon fillets. Zabik et al. (1995a, 1995b) recently investigated the levels of pesticides in Great Lakes fish and the effects of processing and selected cooking methods on residue levels. Toxaphene was not detected (detection limit 0.050 ppm wet weight) in skin-on or skin-off fillets of carp from Lake Huron and Lake Michigan (Zabik et al. 1995a); however, in skin-on fillets of walleye and white bass from these lakes, concentrations ranged from not detected to 0.09 ppm (Zabik et al. 1995b). In chinook salmon, toxaphene was found in skin-on fillets at average concentrations of 0.41 and 0.34 ppm in Lake Huron and Lake Michigan, respectively; corresponding concentrations in skin-off fillets were 0.23 and 0.22 ppm (Zabik et al. 1995a). Baking and charbroiling significantly reduced toxaphene concentrations in both skin-on and skin-off fillets of salmon (38-56% reduction), while canning skin-off fillets resulted in a 77% reduction of toxaphene concentration. Toxaphene was not found in any samples from Lake Erie (Zabik et al. 1995a, 1995b).

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Toxaphene was also detected in fish tissue samples collected at 1 of 58 NPL hazardous waste sites where toxaphene was detected in some environmental media (HazDat 1996).

Toxaphene was also detected in tissue samples from seven species of aquatic animals in the area of the Yazoo National Wildlife Refuge, Mississippi, collected during 1988 (Ford and Hill 1991). Results of this study are summarized in Table 5-1. The authors noted that the occurrence of toxaphene levels above the FDA limit of 5.0 ppm in fish was a cause for public health concern.

Toxaphene concentrations of 1.1 ppm on a wet weight basis (24 ppm fat weight basis) in cod liver samples and 0.4-1.0 ppm wet weight basis (4.4-12 ppm fat weight basis) in herring fillets collected from the east coast of Canada were reported by Musial and Uthe (1983). Toxaphene was not detected in samples of deep sea scallops.

The chief regions where bioaccumulation or biomagnification in fish or wildlife might pose a serious public health concern are in high latitude areas outside the contiguous United States. Studies on marine mammals in eastern Canada (Muir et al. 1992) suggest risks to native Inuit groups that eat blubber or visceral tissues such as liver. While no comparable work has been done in Alaska, this is an area of the United States where there could be genuine concern for Native American Inuit groups that hunt and consume marine mammals.

Within the contiguous United States, there is concern for populations that regularly consume meat from omnivores or carnivores, such as raccoons. Studies reported in Ford and Hill (1990) on the Upper Steele Bayou near the Yazoo National Wildlife Refuge in Mississippi show wildlife still displaying toxaphene residues in adipose tissues in collections made in 1988. The residues were most pronounced for raccoons, where adipose concentrations of total toxaphene up to 31 ppm (weight mass basis) were observed. The Upper Steel Bayou region in Washington County was close to another area on the Big Sunflower River previously studied in 1980. Due to radical changes in the GC methods for analyzing toxaphene, researchers are hesitant to make quantitative comparisons (Ford and Hill 1990). Nevertheless, in the late 1970s the U.S. Fish and Wildlife Service was concerned enough to issue advisories on human consumption of wildlife in the Mississippi Delta region. Many members of this region's rural subsistencelevel population eat significant amounts of game meat, including raccoons.

Toxaphene was also reported to be a contaminant of tobacco crops and products. Gibson et al. (1974) reported that toxaphene was a sporadic contaminant of Kentucky Burley tobacco crops during the period

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1963-1972. Toxaphene was detected in about 4% of the samples at maximum concentrations exceeding 100 ppm. Toxaphene was also detected in 6 brands of cigar tobacco sampled in 1972 at an average concentration of 0.92 ppm; 4 of the 6 samples had toxaphene concentrations of less than 0.5 ppm.

Toxaphene has also been found as a contaminant in anhydrous lanolin, which is used as a moisturizer in cosmetics and as a vehicle compound in pharmaceutical preparations (Heikes and Craun 1992).

Toxaphene was detected (detection limit not reported) in 2 of 10 samples of anhydrous lanolin analyzed in 1989 at concentrations of 2.8 and 5.8 mg/kg (ppm), but not in any of 10 samples analyzed in 1991.

### 5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Current human exposure to toxaphene in the United States appears to be very limited. Members of the general population may be exposed to low levels of the mixture through ingestion of contaminated foodstuffs and possibly through inhalation of ambient air (Kutz et al. 1991). Populations consuming large quantities of fish and shellfish potentially contaminated with toxaphene may be exposed to higher levels than the general public. Exposure to higher concentrations of toxaphene may also result from contact with contaminated media in the vicinity of waste disposal sites containing toxaphene-contaminated wastes. No information was found in the available literature regarding the size of the human population potentially exposed to toxaphene in the vicinity of hazardous waste sites.

Based on the toxaphene levels in their 1980-1982 food survey, the FDA estimated average dietary intakes, in  $\mu\text{g}/\text{kg}$  body weight/day of 0.080, 0.036, and 0.023 for infants, toddlers, and adults, respectively (Gartrell et al. 1986a, 1986b). However, actual intakes must be lower than the estimates because other reported average dietary intakes were based on the mean concentration of the positive samples. More recently, toxaphene intakes, in  $\mu\text{g}/\text{kg}$  body weight/day, estimated for the total diet analyses were 0.0059, 0.0087, and 0.0046 in 1989 (FDA 1990); 0.0071, 0.0085, and 0.0093 in 1990 (FDA 1991); and 0.0033, 0.0059, and 0.0024 in 1991 (FDA 1992); for 6-11-month-old infants, 14-16-year-old males, and 60-65-year-old females, respectively. An overall summary for the 5-year period 1986-1991 of average dietary intakes of toxaphene, in  $\mu\text{g}/\text{kg}$  body weight/day, by eight age/sex groups was recently reported: 6-11-month-old infants, 0.0071; 2-year-old children, 0.0224; 14-16-year-old females, 0.0062; 14-16-year-old males, 0.0089; 25-30-year-old females, 0.0057; 25-30-year-old males, 0.0067; 60-65-year-old females, 0.0078; 60-65-year-old males, 0.0077 (FDA 1993). These dietary intake estimates suggest a decreasing trend following the cancellation of most registered uses of toxaphene as an agricultural pesticide in the United States in 1982 (EPA 1982a) and a cancellation of all registered uses in 1990 (EPA 1990b).

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Average daily inhalation exposures are likely to be much less than dietary exposures. Inhalation exposure to the toxaphene mixture has been estimated to be 0.0004-0.0033  $\mu\text{g}/\text{day}$ , based on an estimated average daily air intake of ambient air with concentrations in the range of 0.02-3.3  $\text{ng}/\text{m}^3$  (HSDB 1995).

Toxaphene has not been detected in human adipose tissue in the United States. However, it has been detected at a concentration of 0.1  $\text{mg}/\text{kg}$  on a milk fat basis in pooled human breast milk samples collected in Uppsala, Sweden (Vaz and Blomkvist 1985), and at an average concentration ( $n=16$ ) of 2.0  $\text{mg}/\text{kg}$  lipid weight in human breast milk samples from Nicaragua, where toxaphene is still being produced and used (de Boer and Wester 1993). Similar data on U.S. populations are not available.

When toxaphene was being manufactured and used as an insecticide, occupational exposure to toxaphene, particularly via the dermal and inhalation routes, may have been significant. Dermal exposures of 22.72 and 16.56  $\mu\text{g}/\text{hour}$  were reported by Munn et al. (1985) for adults and youths, respectively, harvesting a toxaphene-treated onion crop in the Platte River Valley of Colorado in 1982. Any farmers, farm workers, or pesticide applicators who formerly used the mixture to control insects on livestock and crops may have been exposed to relatively high concentrations via these exposure routes.

According to OSHA (1974), the current 8-hour time-weighted average (TWA) permissible exposure level (PEL) for toxaphene is 0.5  $\text{mg}/\text{m}^3$  (skin) in workplace air. The use of the skin designator indicates that air sampling alone is insufficient to accurately quantitate exposure, and that measures to prevent significant cutaneous absorption may be required. The American Conference of Governmental Hygienists (ACGIH) recommended threshold limit value (TLV) for occupational exposure is also 0.5  $\text{mg}/\text{m}^3$  (skin) (ACGIH 1994). The exposure limit recommended by NIOSH is the lowest feasible concentration (NIOSH 1992).

### 5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Members of the general population currently having potentially higher intakes of toxaphene include residents living near the 58 NPL sites and other hazardous waste sites contaminated with toxaphene; populations that consume large quantities of fish and shellfish from waterbodies where fish consumption advisories for toxaphene contamination are in effect; and Native American and subsistence hunter groups that consume large quantities of wild game animals in their diet. No information was found in the available literature regarding the size of these populations. The concentrations of toxaphene in all of the contaminated media to which these populations might be exposed have not been adequately characterized.

## 5. POTENTIAL FOR HUMAN EXPOSURE

As of September 1994, toxaphene was cited as the causative pollutant in three fish consumption advisories in Arizona and one in Michigan (EPA 1995b). The advisories are summarized below.

<u>State</u>	<u>Waterbody</u>	<u>Extent</u>
Arizona	Gila River	From above confluence with Salt River and SW to Painted Rocks Barrow Pit lake near Gila Bend
Arizona	Hassayampa River	From Buckeye Canal to the Gila River
Arizona	Salt River	Below or west of 59th Avenue in Phoenix
Michigan	Lake Superior	Including tributaries into which migratory species enter

EPA has identified toxaphene as a target analyte and recommended that this chemical be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. Residue data obtained from these monitoring programs should be used by states to conduct risk assessments to determine the need for issuing fish and shellfish consumption advisories (EPA 1995c).

In much of the contiguous United States where toxaphene was once used as a pesticide agent, the incidence of toxaphene residues in freshwater fish appears to be declining. While changes in GC analysis technologies make it very hard to compare post-1980 records with analyses conducted in the 1970s, results from two sampling periods in the 1980s from the U.S. Fish and Wildlife Service National Contaminant Biomonitoring Program show that the number of sites with detectable levels of total toxaphene in fish tissue samples dropped from 88% in 1980-1981 to 69% in samples collected in 1984. This is interpreted as an indication of a declining trend in toxaphene contamination levels in fish in the contiguous United States (Schmitt et al. 1990). There may still be the potential for localized contamination of fish in the vicinity of hazardous waste sites. Toxaphene was detected in fish samples from 1 of 58 NPL sites where this compound has been detected in some environmental medium; however, concentrations were not reported (HazDat 1996).

As noted in Section 5.4.4, there could also be risks of high exposures for two U.S. subpopulations that consume large amounts of marine mammals or game animals. The first includes Native American groups in Alaska, although any quantification of the risks would have to be based on data collected from such groups as the Inuit in the Baffin Bay area of Canada (Muir et al. 1992). The second includes people such as recreational or subsistence hunters in rural areas of the Southeast where historically heavy use of



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toxaphene as a pesticide agent occurred. People in this area who eat large amounts of wild game animals, particularly such species as raccoons, could be at risk of higher exposures (Ford and Hill 1990).

Nursing infants may also be at risk for potentially high exposure to toxaphene; however, no data on levels of toxaphene congeners in breast milk from U.S. women could be located in the available literature. In high latitude Scandinavian countries, there are documented cases of toxaphene congeners in fats from human breast milk (Mussalo-Rauhamaa et al. 1988; Vaz and Blomkvist 1985). Toxaphene congeners were also found in the fats in human breast milk in Nicaragua, where toxaphene is still being produced and used (de Boers and Wester 1993). The high concentrations found, and the lack of correlation between the number of children a woman had and the toxaphene concentration in her breast milk, were cited as evidence that elimination of toxaphene via transfer to the infant was fully compensated for by a regular intake of toxaphene. Consequently, nursing infants of mothers who incur regular and potentially high exposures to toxaphene (e.g., from the consumption of contaminated fish or game) may be at a potentially high risk for exposure to toxaphene. Estimates of risks to nursing infants are complicated because the identified congeners are usually partially metabolized and there is little information on the toxicities of such congeners (Mussalo-Rauhamaa et al. 1988; Vaz and Blomkvist 1985).

### 5.7 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of toxaphene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of toxaphene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

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**5.7.1 Identification of Data Needs**

**Physical and Chemical Properties.** In general, physical and chemical properties of toxaphene have been sufficiently well characterized to permit estimation of its potential environmental fate (Bidleman et al. 1981; Mabey 1981; Mackison et al. 1981; Merck 1989; Worthing 1979). However, reported values for the vapor pressure of toxaphene vary widely, ranging from  $3 \times 10^{-7}$  mm Hg at 20 °C to 0.4 mm Hg at 20-25 °C (Agrochemicals Handbook 1983; Bidleman et al. 1981; Mackison et al. 1981; Sunshine 1969; Suntio et al. 1988). These disparities may be due to the different methods used to determine vapor pressure and/or to the varying compositions of the toxaphene mixtures used. Reliable vapor pressure estimates for well-characterized toxaphene mixtures are needed. Since toxaphene is a complex mixture, the environmental fates of specific congeners in original product formulations will vary. Information on the physical and chemical properties of specific congeners is needed for more reliable prediction of environmental fate and transport processes for toxaphene mixtures. This information, in combination with additional information on the toxicities of toxaphene congeners and their degradation products, is necessary to permit more quantitative estimation of exposure risks and analysis of environmental exposures to toxaphene. Unfortunately, information on the toxicities of components in the original mixtures is limited to perhaps 10 congeners, the most familiar being the appreciably toxic and persistent toxicant A and toxicant B. Once in the environment, however, the toxic properties of congener degradation or transformation products are usually unknown (Bidleman et al. 1993). This situation seriously complicates efforts to quantify risks.

**Production, Import/Export, Use, Release, and Disposal.** Toxaphene is no longer being produced in the United State for domestic use since all registered uses were canceled in 1990 (EPA 1990b; USDA 1995). U.S. manufacturers, however, can legally produce pesticides for export that are currently banned or not registered for domestic use (FASE 1996). It is not known whether toxaphene is still being produced for export purposes. The most recent estimate of U.S. production levels was in 1982, the year that EPA first restricted the use of toxaphene (EPA 1982a). Production levels that year were less than 2 million kg (EPA 1987a), substantially lower than in 1972 (21 million kg) when toxaphene was the most widely manufactured pesticide in the United States (Grayson 1981). It is estimated that production levels between 1982 and 1990 continued to be low; however, information on production during that period, as well as between 1990 and the present time, would be helpful in estimating current human exposure to toxaphene.

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In other parts of the world, toxaphene use continues at very high levels (Bidleman et al. 1989; Stem et al. 1993). Although reliable information on use levels outside western European countries is almost impossible to obtain, many researchers feel that global use levels are quite substantial (Lahaniatis et al. 1992; Stem et al. 1993). It has been estimated that total global usage of toxaphene from 1950 to 1993 exceeded 1.3 million tons (Voldner and Li 1993); however, this may be a significant underestimation (Swackhamer et al. 1993). Since toxaphene, once volatilized, can be transported atmospherically over very long distances, all terrestrial and aquatic ecosystems, including those in the United States, are still subject to low levels of exposure. Especially in terms of atmospheric inputs, the best available monitoring information shows no demonstrable downward trends (Bidleman et al. 1992). More reliable information on global usage and atmospheric emissions of toxaphene would be useful in estimating potential human exposures in the United States. Additional information on the amounts of PCCs released to the environment as by-products of the chlorinated pulp processes involving pine oils (pinene) (EPA 1995c; Rantio et al. 1993; Swackhamer et al. 1993) would also be useful in developing estimates of global production and emissions for toxaphene.

No current information on import and export quantities of toxaphene was identified. Even though toxaphene is no longer produced for domestic use in the United States, current export volumes could be high (FASE 1996). A recent report by the Foundation for the Advancement of Science and Education reported that the majority of pesticides (74%) produced for export in 1992-1994 could not be definitively identified. Several organochlorine pesticides that were banned in the United States are still being produced for export. Although toxaphene was not identified as currently being exported, the authors caution that only 25% of the exported pesticides could be specifically identified by name (FASE 1996). It is also likely that toxaphene is currently not being imported into the United States since all registered uses of toxaphene were canceled in July 1990 (EPA 1990b). Quantitative information confirming current import and export volumes of toxaphene would be useful to more reliably estimate potential human exposure to toxaphene.

In 1982, the use of toxaphene was restricted by EPA to its use as a pesticide on livestock; to control grasshopper and army worm infestation on cotton, corn, and small grains (in emergency situations only); and on banana and pineapple crops in Puerto Rico and the Virgin Islands (EPA 1982a). After July 1990, the pesticide registrations for all toxaphene formulations were canceled in the United States and in all U.S. territories (EPA 1990b). Because of its historic use as a pesticide, toxaphene has been widely distributed in the air, soil, surface water and sediments, aquatic organisms, and foodstuffs. Information on the current

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distributional patterns, which may involve localized hotspots, would be helpful in estimating human exposure.

Incineration in a pesticide incinerator is the preferred method of disposal for toxaphene (EPA 1974, 1980b, 1988c). Additional information on the amount of toxaphene disposed of by this method, as well as the amount of toxaphene disposed of or abandoned at hazardous waste sites, would be helpful for estimating the potential for human exposure.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. Toxaphene is included under TRI because it is one of a very small number of pesticides identified under the Clean Water Act as Priority Pollutants. The TRI database, however, contains no listings for toxaphene (TR193 1995). While TRI does not constitute an exhaustive inventory, the absence of listings in TRI indicates that it is unlikely that there are significant releases of toxaphene from production or processing facilities to any environmental media in the United States.

**Environmental Fate.** Information on the environmental fate of toxaphene congeners (as a chemical group) is only sufficient to permit a general understanding of the partitioning and widespread transport, of toxaphene mixtures in the environment. The composition of toxaphene mixtures varies among producers (Walter and Ballschmiter 1991; Worthing and Walker 1987), and only limited data are available on the transport and transformation of individual toxaphene congeners in these mixtures. Additional information on the identity, physical/chemical properties, and environmental fate of toxic fractions of toxaphene mixtures would be useful. However, the sampling and analytical methodology limitations that have contributed to the lack of availability of this type of data in the past have not been completely overcome (Andrews et al. 1993; Bidleman et al. 1993; Bruns and Birkholz 1993; de Boer and Wester 1993; Muir and de Boer 1995; Vetter et al. 1993; Zhu et al. 1994). Therefore, the development of this information may be difficult. More information on the rates of biotransformation and abiotic reduction of toxaphene in soils and sediments under anaerobic conditions would improve the current understanding of toxaphene's environmental fate. The role of biotic transformations in aerobic environments following initial reductive dechlorination needs to be clarified. In addition, the identity, toxicity, and environmental fate of the major transformation products need to be discerned. This information will be useful in making a more critical assessment of potential human exposure to the mixture.

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**Bioavailability from Environmental Media.** Animal studies and case reports of human exposure indicate that toxaphene is absorbed following inhalation, oral, and dermal exposure (Kutz et al. 1991; Munn et al. 1985). Pharmacokinetics data indicate that toxaphene present in water or food is extensively absorbed; however, the degree to which toxaphene is absorbed as a result of inhalation of contaminated air or dermal contact with contaminated environmental media has not been well studied. The high  $K_{oc}$  for toxaphene indicates that it is adsorbed relatively strongly to soil, but it is not possible to estimate the extent to which toxaphene present on ingested soil would be absorbed from the gastrointestinal tract. Toxaphene is not expected to be available to humans via ingestion of plants unless they have been recently treated with the mixture. Since all registered uses of toxaphene as a pesticide were canceled in the United States and U.S. Territories in July 1990; ingestion of domestically grown agricultural commodities should no longer be a source for toxaphene. In addition, with the revocation of tolerances of toxaphene (September 1993) in all agricultural commodities; detection of any toxaphene residues will result in seizure of these products and removal from the marketplace (EPA 1993b). More information on the extent of absorption of components of the mixture following contact with contaminated air, water, or soil would be helpful in determining the potential health effects resulting from human exposure.

**Food Chain Bioaccumulation.** Laboratory bioassay and field monitoring data clearly indicate that toxaphene components are bioconcentrated by aquatic organisms. Available model ecosystem and field monitoring studies of aquatic food chains are sufficient to indicate that toxaphene bioaccumulates in aquatic organisms (Lowe et al. 1971; Sanborn et al. 1976; Schimmel et al. 1977; Swackhamer and Hites 1988). However, as the result of metabolism, toxaphene is not biomagnified to the same degree as other chlorinated compounds, such as DDT and PCBs (Evans et al. 1991; Ford and Hill 1991; Neithammer et al. 1984). While several studies show toxaphene is biomagnified in some ecosystems, several other studies show that little or no biomagnification of toxaphene occurs in other ecosystems because of effective metabolism of toxaphene by higher trophic level mammalian species (Andersson et al. 1988; Muir et al. 1988a, 1988b, 1992). Further congener-specific information on the bioaccumulation and biomagnification potential of toxaphene in both terrestrial and aquatic food chains would be desirable to resolve differences observed in different ecosystems. These data will be helpful in assessing the potential for human exposure as a result of ingestion of contaminated food.

**Exposure Levels in Environmental Media.** Although a large amount of monitoring data is available for toxaphene, most of the data were collected 10 to 20 years ago when the mixture was widely used as a pesticide. Historic monitoring data exist for air (Kutz et al. 1976; EPA 1984b; Stanley et al. 1971), surface water (Cole et al. 1984; Cooper et al. 1987; Staples et al. 1985), drinking water (Faust and Suffet 1966), and groundwater (Plumb 1987). Additional information on current levels in environmental media would be helpful in characterizing current concentrations to which humans could be exposed. This is particularly important for concentrations of toxaphene in air, soils, and surface waters in the vicinity of hazardous waste sites. The data currently available are too limited to be useful in estimating the exposure of populations coming into contact with the mixture through inhalation of contaminated air, consumption of contaminated surface water, groundwater, or foodstuffs, and/or contact with contaminated soil. Reliable information is needed on current exposure levels in all environmental matrices and food sources (fish, shellfish, and terrestrial wildlife) in the vicinity of hazardous waste sites. Additional biomonitoring studies of both aquatic and terrestrial wildlife populations near hazardous waste sites, near water bodies where fish consumption advisories are currently in force (EPA 1995b), and in areas where toxaphene was historically used in agriculture applications (Ford and Hill 1991) are needed. This information on levels of toxaphene in the environment would be useful in assessing the potential risk of adverse health effects in populations living in these areas.

**Exposure Levels in Humans.** Exposure levels for the populations with either short- or long-term contact with hazardous waste sites are unknown. These levels currently cannot be estimated because of the lack of toxaphene concentration data for contaminated media in the vicinity of hazardous waste sites. Exposure of the general population has been estimated from levels in air (HSDB 1995) and foodstuffs (FDA 1990, 1991, 1992, 1993). Estimates of average dietary intakes for several age/sex categories are based on data obtained subsequent to the restriction of most uses of toxaphene in 1982 (EPA 1982a) and appear to be adequate. Inhalation is not a major exposure route for the general public; consequently, additional data are not necessary. Pharmacokinetic data indicate that toxaphene rapidly redistributes to body fat and toxaphene has been identified in human breast milk fat from non-U.S. nursing mothers (de Boer and Wester 1993; Mussalo-Rauhamaa et al. 1988; Vaz and Blomkvist 1985). Tissue levels have not been obtained from persons exposed to toxaphene as a result of contact with a hazardous waste site. This information would be useful in assessing the risk to human health for populations living in the vicinity of hazardous waste sites. If it can be verified that toxaphene is still being produced for export, information on tissue levels for persons who are occupationally exposed to toxaphene would also be useful in assessing the risk to human health in these populations. This information is necessary for assessing the need to conduct health studies on these populations.

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**Exposure Registries.** No exposure registries for toxaphene were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

### 5.7.2 Ongoing Studies

A search of the Federal Research in Progress database (FEDRIP 1995) indicates that the following research studies are in progress to fill the data needs identified in Section 5.7.1.

The U.S. Department of Agriculture is sponsoring a study at Pennsylvania State University to define pathways of microbial degradation of toxaphene and chlordane, to develop a protocol for using compost as a process environment, to develop the methodology for using compost for bioremediation of toxaphenecontaminated soils, and to evaluate the use of dissected plant materials as catalytic agents for decontamination.

The U.S. Department of Agriculture is sponsoring a study at the University of California-Davis to integrate field and laboratory studies of bioremediation treatments of a pesticide waste disposal site. Toxaphene is one of several pesticides and organochlorine compounds included in this study.





## 6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring toxaphene, its metabolites, and other biomarkers of exposure and effect to toxaphene. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

This chapter summarizes the methods available for the analysis of toxaphene in biological and environmental media. In designing a study and choosing a method, it is very important that adequate attention be paid to the extent of validation and field applicability. Some of the EPA methods have been validated, while some of the literature methods have not. It is the analyst's responsibility to determine the data quality needed before initiating the application of a particular method.

The analytical methods used to quantify toxaphene in biological and environmental samples are summarized below.

### 6.1 BIOLOGICAL SAMPLES

Table 6-1 lists the applicable analytical methods for determining toxaphene in biological samples. The analysis and chemical characterization of toxaphene is difficult because of the extreme complexity of the compound. Commercial toxaphene is a complex mixture of chlorinated camphene derivatives containing more than 670 components (Jansson and Wideqvist 1983). Furthermore, widespread contamination from ubiquitous polychlorinated biphenyls (PCB s), 1,1 -dichloro-2,2-bis (chlorophenyl)-ethane (DDE), and other organochlorine pesticides, which are also complex multi-isomeric chemicals, often interferes with toxaphene's analysis. Hence, identification of toxaphene in biological and environmental samples almost invariably involves rigorous sample preparation and clean-up procedures prior to chromatographic analysis (Gooch and Matsumura 1985; Matsumura et al. 1975; Nelson and Matsumura 1975).

Table 6-1. Analytical Methods for Determining Toxaphene in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human tissues (toxaphene and some metabolites)	Maceration of tissue into a fine slurry; addition of anhydrous Na <sub>2</sub> SO <sub>4</sub> and acetone; filtration of solution and addition of water and saturated Na <sub>2</sub> SO <sub>4</sub> solution to extract; extraction with chloroform; addition of 5% KOH to chloroform extract; extraction with water; water removal (Na <sub>2</sub> SO <sub>4</sub> ); evaporation and dissolution of residue in acetone	TLC	1 µg/sample	94	Tewari and Sharma 1977
Tissues	Grinding of sample (20 g, wet weight) containing internal standards anhydrous sodium sulfate followed by extraction with 1:1 dichloromethane:hexane, volume reduction; clean-up using GPC and Florisil	GC/NCIMS	~10 ppb	77–107 at 40–50 ppb	Fowler et al. 1993
Human breast milk	Centrifugation of milk sample; freeze-drying of fat concentrate; dissolution in acetone and cooling to -60 °C; re-dissolution of residue in hexane and shaking with concentrated H <sub>2</sub> SO <sub>4</sub> ; clean-up using silica gel column	GC/ECD and GC/NCIMS	100 ng/g	No data	Vaz and Blomkvist 1985
Human breast fat	Homogenization and extraction with petroleum ether; removal of water from extract with anhydrous Na <sub>2</sub> SO <sub>4</sub> ; volume reduction	GC/ECD	No data	No data	Head and Burse 1987
Stomach washings and urine (toxaphene and some metabolites)	Filtration of sample and wash of residue with water; addition of saturated solution of Na <sub>2</sub> SO <sub>4</sub> and extraction with hexane; filtration of extract through anhydrous Na <sub>2</sub> SO <sub>4</sub> and evaporation to dryness; dissolution of residue in acetone	TLC	1 µg/sample	94	Tewari and Sharma 1977
Human blood	Addition of 60% H <sub>2</sub> SO <sub>4</sub> to blood sample; extraction with hexane:acetone (9:1); centrifugation and evaporation to dryness; dissolution of residue in hexane	GC/ECD GC/MC	No data 10–40 ppb	100 100	Griffith and Blanke 1974

Table 6-1. Analytical Methods for Determining Toxaphene in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Addition of sample to a solution of dilute H <sub>2</sub> SO <sub>4</sub> and 10% sodium tungstate; filtration of solution and wash of residue with water; water removal with (Na <sub>2</sub> SO <sub>4</sub> ) and extraction with hexane; filtration of extract through anhydrous Na <sub>2</sub> SO <sub>4</sub> and evaporation to dryness; dissolution of residue in acetone	TLC	1 µg/sample	94	Tewari and Sharma 1977

ECD = electron capture detector; GC = gas chromatography; GPC = gel permeation chromatography; MC = microcoulometry; NCIMS = negative chemical ionization mass spectrometry; TLC = thin-layer chromatography

## 6. ANALYTICAL METHODS

Cautions regarding potential transformations of toxaphene components during sample clean-up operations are described below in Section 6.2. The determination of trace amounts of toxaphene in human tissues and fluids has been restricted to a limited number of analytical techniques. These include gas chromatography equipped with either an electron capture detector (GC/ECD), or a microcoulometric detector (GCNC), or negative ion chemical ionization mass spectrometry (GC/NCIMS), and thin-layer chromatography (TLC).

The most prevalent analytical technique employed to determine trace amounts of toxaphene in biological and environmental samples is GC/ECD because ECD offers a uniquely high sensitivity for substituents such as halogens. Griffith and Blanke (1974) and Head and Burse (1987) employed GC/ECD for analysis of toxaphene in human blood and breast fat, respectively. Identification of low ppb levels of toxaphene in human blood was achieved by GC/MC (Griffith and Blanke 1974). The advantages of GC/MC are that the system is linear, more specific, and a lower temperature is generally required to vaporize the compound in the GC column. A GC method that uses electron capture NCIMS for detection has been developed by Vaz and Blomkvist (1985) to quantitatively and selectively detect components of toxaphene at ppb (ng/g) levels in human breast milk. Vaz and Blomkvist (1985) demonstrated that several mass (*M*) fragments containing mainly (*M*-35)<sup>-</sup> ions can be identified, thereby giving relatively simple mass spectra. More important, however, fragmented ions from contamination by other organochlorine compounds were not detected because they gave weak NCIMS spectra.

A radioreceptor assay has been described for the determination of toxaphene in whole blood (Saleh and Blancato 1993). The method is based on the ability of toxaphene to displace <sup>35</sup>S tertiary butylbicyclopophosphorothioate from the chloride channel of isolated gamma-aminobutyric acid receptor ionophore complexes. Unlike chromatographic methods, this approach requires no sample clean-up, needs only 0.1 mL of blood, and is sensitive to toxaphene concentrations in blood of 2 ppb. An advantage of this method is that it assays those toxaphene isomers that are toxic to the nervous system by exploiting the known receptor-based mechanism of that toxicity.

In addition to direct measurement of toxaphene in biological media, it is also possible to determine the level of metabolites in biological tissues and fluids. Tewari and Sharma (1977) developed a TLC method for determination of toxaphene and its metabolites (dechlorinated and dehydrochlorinated toxaphene) in urine, stomach washings, and blood. A detection limit of  $1 \times 10^{-6}$  g of toxaphene per sample was achieved. The authors employed a series of solvent systems and chromogenic reagents on silica gel plates impregnated with silver reagents and copper sulfate for separation of the pesticides. The TLC technique

## 6. ANALYTICAL METHODS

is, however, laborious and time consuming. Becker et al. (1989) used GC/ECD and GC/NCIMS for the determination of dechlorinated toxaphene residues.

Despite the availability of advanced instrumental methods, the accurate quantitative determination of the level of toxaphene is difficult because of inherent differences between the GC fingerprint pattern of the technical toxaphene standard and the pattern found in human fluid extracts containing toxaphene. These differences reflect changes caused by metabolism and degradation of the original compound.

## 6.2 ENVIRONMENTAL SAMPLES

Table 6-2 lists the methods used for determining toxaphene in environmental samples. Residues of toxaphene are detectable in the environment because of its use as a piscicide and its use as a pesticide on field crops, fruits, vegetables, and uncultivated lands. The identification and quantification of toxaphene in environmental samples is complicated by changes in the numbers and relative sizes of constituent peaks (components) due to the difference in their rates of degradation, sorption, and volatilization in the environment. In addition, quantitative analysis can be further hindered by the lack of purified, individual congeners, although improvements in this area are being made (Muir and de Boer 1993). This is important because of the differing detector response factors of the different congeners, a problem of particular relevance to mass spectrometric detection methods (Xu et al. 1994).

A number of potential problems in the procedures used to isolate toxaphene components (chlorobornanes) have been noted and compiled after a workshop on the analytical chemistry of toxaphene (Muir and de Boer 1993). Extraction/clean-up procedures that include treatments with sulfuric or nitric acid modify the toxaphene peak profile. Gel permeation chromatography (GPC) or column chromatography on alumina were judged suitable for the isolation of lipids from toxaphene and related organochlorines. The use of base hydrolysis for the removal of lipids would degrade chlorobornanes and is not recommended. It has also been reported that oxygen in the chemical ionization (CI) source during mass spectrometric detection can produce fragment ions from PCBs that appear to be derived from chlorobornanes and this can lead to errors in quantitation (Andrews et al. 1993; Muir and de Boer 1993). Other researchers claim that the problem of residual oxygen in the ion source does not present a major problem (Fowler et al. 1993). In order to minimize problems with interferences during analysis, it is recommended that toxaphene components be isolated as completely as possible from PCBs and that the presence of oxygen in the ion source be minimized.

**Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Trapping on chromasorb 102; extraction with hexane	GC/ECD	0.234–0.926 ng/m <sup>3</sup>	100	Thomas and Nishioko 1985
Air	Collection of air sample in an air sampling train equipped with prefilter and ethylene glycol; dilution of ethylene glycol with water and extraction with hexane; extraction of prefilter with hexane; pooling of extracts before drying and concentration	GC/ECD	1–10 ng/m <sup>3</sup>	No data	Kutz et al. 1976
Air	Adsorption onto PUF using a high volume sampling pump; extraction with hexane and volume reduction	GC/ECD;GC/MS	0.10 pg/m <sup>3</sup> (10,000 m <sup>3</sup> sample)	No data	Barrie et al. 1993
Ambient air	High volume sampler consisting of glass fiber filter with PUF backup adsorbent and flow rate approximately 200–280 L/minute for 24 hours; Extraction of filter and PUF in soxhlet with 5% ether in hexane. Clean-up using alumina column chromatography and concentration using K-D. (EPA Method TO4)	GC/ECD (EPA Method 608)	Generally >1 ng/m <sup>3</sup>	No data	EPA 1984a

Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water	Extraction of sample with 15% dichloromethane in hexane; water removal using anhydrous Na <sub>2</sub> SO <sub>4</sub> ; extract volume reduction	GC/ECD or GC/MC or GC/electrolytic conductivity and GC/MS	0.001–0.01 µg/L (single component pesticide sample) 0.050–1.0 µg/L (multiple component pesticide sample)	No data	EPA 1987a
Drinking water	Extraction of sample with dichloromethane, water removal and solvent exchange to methyl-t-butyl ether (EPA Method 508)	GC/ECD (capillary column)	No data	No data	EPA 1989
Drinking water, groundwater, soil, sludges, wastes	Extraction of sample with organic solvent and clean-up using Florisil column.	GC/ECD	0.24 µg/L (drinking water) to 24 mg/L (non-water miscible waste)	No data	EPA 1986f
Drinking water	Extraction of sample with acetone on a water sampling apparatus equipped with porous polyurethane plugs; elution of extract through activated Florisil column with diethyl ether in petroleum ether	GC/ECD and GC/MS	0.01 ng/L	100	EPA 1976b
Tap water, groundwater, river water	Isolation of compounds from water using C <sub>18</sub> SPE followed by recovery of adsorbed analytes with supercritical carbon dioxide containing acetone.	GC/ion trap MS	7.4 µg/L (ppb, w:v)	105 (18% RSD) at 25 µg/L	Ho et al. 1995

Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water	Extraction with dichloromethane	Tandem MS	5 µg/sample		Hunt et al. 1985
Waste water	Extraction with dichloromethane, solvent exchange to hexane; Florisil clean-up	GC/ECD (packed column)	0.24 µg/L	96	EPA 1984c
Waste water	Extraction with 15% dichloromethane in hexane followed by water removal with sodium sulfate and concentration with K-D. Additional clean-up, if needed, by partition with acetonitrile to remove fats and oils or fractionation using a Florisil column	GC/ECD	No data	96	EPA 1992c
Municipal and industrial discharge water	Adjustment to pH=11 and extraction with dichloromethane. Concentration using K-D after drying.	GC/MS	No data	No data	APHA 1989a
Municipal and industrial discharges	Extraction with dichloromethane (no pH adjustment) and solvent exchange to hexane during concentration; magnesia-silica gel clean-up and concentration	GC/ECD	0.24 µg/L	80	APHA 1989b



Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Municipal and industrial waste water, sludges	(1) If solids <1%, extraction with dichloromethane. (2) For nonsludges with solids 1–30%, dilution to 1% and extraction with methylene chloride. If solids >30% sonication with methylene chloride/acetone. (3) For sludges: if solids <30% treatment as in #2 above. If solids >30%, sonication with acetonitrile then methylene chloride. Back extraction with 2% sodium sulfate. Water removal with sodium sulfate, concentration using K-D, purification using GPC, Florisil and/or SPE.	GC with ECD, MC or electrolytic conductivity	910 ng/L (lower if many interferences)	76–122 at 5,000 ng/L is acceptable	EPA 1992d
Primary sludge	Extraction of sample with hexane: dichloromethane: acetone (83:15:2); extract concentration and clean-up on Florisil column and elution with 20% acetone in hexane	GC/ECD and GC/MS	No data	85–93	EPA 1982b
Soil, water	Extraction of sample with organic solvent or mixture of organic solvents, depending on the sample matrix, followed by open-column, chromatographic clean-up.	GC/ECD or GC/ELCD	0.086 µg/L (0.086 ppb, wt/wt) for water; 5.7 µg/kg (5.7 ppb, wt/wt) for soil	No data	EPA 1995c

Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Addition of water and extract with methanol:toluene (1:1); loading of extract onto chromaflex column containing Florisil; concentration of sample; addition of 43% methanolic KOH solution and refluxing followed by extraction with hexane and Florisil column clean-up	GC/MS and HPLC	0.05 µg/g	76–91	Crist et al. 1980
Soil	Soxhlet extraction using methylene chloride or sonication with methylene chloride: acetone (1:1, v/v). GPC or SPE clean-up	GC/EC-NIMS	100 µg/kg	No data	Brumley et al. 1993
Soil	Extraction of sample (1 g) with dichloromethane:acetone (1:1) using sonication; removal of water with a sodium sulfate column; solvent exchange to isooctane; Florisil clean-up	GC/NCIMS	50 µg/kg (ppb, w:w)	90-109 (10% RSD)	Onuska et al. 1994
Soil	Extraction of soil; introduction of extract with enzyme-toxaphene conjugate into tube containing immobilized toxaphene antibody.	Colorimetric immunoassay	0.5 µg/g (0.5 ppm)	118% over 0.25 to 5.0 µg/g	EPA 1995a
Sediment, and mussel tissue	Extraction of sample with hexane; elution from alumina column and concentration of eluent	HPLC followed by GC/FID or GC/ECD	<1 ng/g	95–100	Petrick et al. 1988
Pesticide formulation	Extraction of sample using 50% methanolic KOH; elution with ether from Florisil	GC/ECD	1 ng/sample	No data	Gomes 1977
Pesticide formulation	Removal of solvent (xylene) from pesticide sample by reduced pressure; extraction with hexane	Open tubular GC column and GC/TLC	No data	No data	Saleh and Casida 1977

Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Pesticide formulation	Extraction of sample with hexane	TLC	1 µg/sample	No data	Ismail and Bonner 1974
Pesticide formulation	Dissolution of sample in hexane and loading onto alumina column; elution with hexane, then 20% methylene chloride in benzene and finally 100% methanol	GC/ECD or GC/FID	No data	No data	Seiber et al. 1975
Cotton leaves	Extraction of sample with water and petroleum ether; addition of methanolic KOH and heat treatment; concentration of extract	TLC followed by GC/ECD	0.16–0.45 µg/cm <sup>2</sup>	No data	Bigley et al. 1981
Non-fatty foods	Extraction of homogenized sample with solvent (acetone, acetonitrile, or acetonitrile/water, depending on moisture and sugar content) followed by water removal and Florisil clean-up	GC/ECD (PAM1 methods 302, 303)	<0.2 ppm	>80%	FDA 1994a
Various produce	50 g homogenized sample extracted with acetonitrile, filtered, and salt added to affect phase separation. Evaporation to near dryness and reconstitution in benzene	GC/ECD	2 ppm	No data	Hsu et al. 1991
Fruits and vegetables	Extraction with acetone in blender; filtration and extraction with petroleum ether/di-chloromethane; solvent evaporation and dissolution of residue in minimum amount of acetone	GC/ECD	No data	No data	WHO 1984

Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cucumber	Blending of sample with acetone folloed by extraction with petroleum ether and dichloromethane (1:1); water removal ( $\text{Na}_2\text{SO}_4$ ) and concentration followed by Florisil column clean-up	GC/ECD or FID	4.34 ppm	113	Luke et al. 1975
Fortified extracts (various foods)	Preparation of sample solution with acetone or hexane; addition of diphenylamine and zinc chloride solution and evaporation to dryness; heating of residue (250 °C) for a few minutes and dissolution of residue complex in acetone	Spectrophotometer (absorbance at 640 nm)	<1 ppm	69–100	Graupner and Dunn 1960
Molasses	Dilution of sample with water; extraction with hexane: isopropanol	GC/ECD	0.03 mg/kg	No data	WHO 1984
Fatty foods	Extraction of fats and residues from homogenized sample by dissolution in an organic solvent followed by isolation of the residues from the fat using Florisil.	GC/ECD	<0.2 ppm	>80%	FDA 1994b
Meat	Blending with ethyl acetate followed by drying ( $\text{Na}_2\text{SO}_4$ ) and filtration; treatment of extract with KOH and heat; extraction with hexane; Florisil column clean-up	GC/ECD	No data	76–79	Boshoff and Pretorius 1979
Bovine defibrinated whole blood	Dilution of blood with water and exatraction with hexane	GC/ECD	0.58 µg/mL	73.4	Maiorino et al. 1980
Bovine defibrinated whole blood	Addition of sample to 88% formic acid and shaking on a vortex mixer; extraction with hexane and extraction of hexane with 5% potassium carbonate; extract volume reduction	GC/ECD	0.465 µg/mL	71.7	Maiorino et al. 1980

Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bovine defibrinated whole blood	Addition of sample to 88% formic acid followed by mixing and loading onto Florisil column; elution with 6% diethyl ether in petroleum ether; volume reduction and washing with hexane	GC/ECD	0.026 µg/mL	103.4	Maiorino et al. 1980
Lard	Extraction with petroleum ether; centrifugation; removal of water from extract with anhydrous Na <sub>2</sub> SO <sub>4</sub> ; volume reduction	GC/ECD	1.37 µg/g	46.5–107.3	Head and Burse 1987
Poultry fat	Rendering of fat followed by direct analysis.	GC/ECD	0.475–0.908 ppm	92.6–96.9	Ault and Spurgelon 1984
Milk fat	Centrifugation and fractionation using Florisil column	GC/ECD and GC/MS	<10 ppb (ECD) 7 ppb (MS)	No data	Cairns et al. 1981
Milk and butter	Addition of sample to KOH followed by heat treatment and extraction with hexane; centrifugation and clean-up using Florisil	GC/ECD	No data	78–88	Boshoff and Pretorius 1979
Human breast milk	Centrifugation of milk sample; freeze-drying of fat concentrate; dissolution in acetone and cooling to -60 °C; re-dissolution of residue in hexane and shaking with concentrated H <sub>2</sub> SO <sub>4</sub> ; clean-up using silica gel column	GC/ECD and GC/NCIMS	100 ng/g	No data	Vaz and Blomkvist 1985
Fish (whole)	Blending of frozen sample with dry ice and anhydrous Na <sub>2</sub> SO <sub>4</sub> ; extraction in a column with hexane: acetone (1:1), followed by methanol	GC/NCIMS	75 pg/sample	98	Swackhamer et al. 1987

Table 6-2. Analytical Methods for Determining Toxaphene in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish tissues	Extraction of tissues with a mixture of hexane and acetone followed by a second extraction with hexane and diethyl ether; evaporation and dissolution of lipid extract in hexane; shaking of extract with H <sub>2</sub> SO <sub>4</sub> to remove lipid	GC/NCIMS	No data	No data	Jansson and Wideqvist 1983
Fish tissue	Homogenization of 10 g sample with hexane:acetone (1:2.5) under acid condition, extraction twice more with 10% diethyl ether in hexane. Treatment with 98% H <sub>2</sub> SO <sub>4</sub> and clean-up using GPC and silica gel chromatography.	GC/NCIMS	No data	94 (RSD = 11%) at 19 ng/g	Jansson et al. 1991
Fish	Homogenization of 20 g sample followed by extraction with hexane/acetone, addition of internal standards ( <sup>13</sup> C-PCBs), and clean-up using GPC and Florisil	GC/HRMS (SIM)	10 ppb (wet weight)	No data	Andrews et al. 1993
Fish tissue	Pulverization of tissue with anhydrous sodium sulfate and extraction with acetone. Solvent exchange to hexane and volume reduction. Clean-up using dry-packed Florisil, wet-packed Florisil and silica gel.	GC/MS (SIM)	0.1 ng/g	90 (RSD = 7%) at 100 ng	Jarnuzi and Wakimoto 1991

ECD = electron capture detector; ELCD = electrolytic conductivity detector; FID = flame ionization detector; FTIR = Fourier transform infrared spectroscopy; GC = gas chromatograph; GPC = gel permeation chromatography; HPLC = high performance liquid chromatography; HRMS = high resolution mass spectrometry; K-D = Kuderna-Danish concentration; MC = microcoulometry; MS = mass spectrometry; NCIMS = negative ion chemical ionization mass spectrometry; PUF = polyurethane foam; SIM = selected ion monitoring; RSD = relative standard deviation; SPE = solid phase extraction; TLC = thin-layer chromatography; v/v = volume/volume; wt/wt = weight/weight

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GC/ECD, sometimes in combination with GC/MS, is the most frequently used analytical method for characterization and quantification of toxaphene in air, drinking water, fish, and other environmental samples (Boshoff and Pretorius 1979; Cairns et al. 1981; EPA 1976c, 1985c, 1995c; Kutz et al. 1976; Luke et al. 1975; Thomas and Nishioka 1985; WHO 1984; Wideqvist et al. 1984). Analysis of the sample includes extraction in organic solvent; a Florisil silica, gel permeation, or TLC clean-up step; and detection by GC (Atuma et al. 1986; Ault and Spurgeon 1984; EPA 1976b; Head and Burse 1987; Ismail and Bonner 1974; Maiorino et al. 1980; Saleh and Casida 1977; Seiber et al. 1975). A typical gas chromatogram contains a series of hills and valleys with three main peaks (EPA 1982b; Gomes 1977). Detection limits of toxaphene residues in fish and drinking water were 50 ng of toxaphene per g of sample and 1 ng of toxaphene per g of sample, respectively (EPA 1976c, 1987a). GC/ECD is the standardized method used by EPA (method 808 1A) for determining toxaphene in water and soil samples (EPA 1995C). Detection limits of 0.086 µg/L of water and 5.7 µg/kg of soil were reported for toxaphene. EPA method 8270c (GC/MS, electron impact ionization) is not recommended for toxaphene because of limitations in sensitivity arising from the multicomponent nature of toxaphene (EPA 1995b).

Archer and Crosby (1966) developed a confirmatory method for toxaphene analysis in environmental samples that involved dehydrohalogenating (in 50% methanolic potassium hydroxide) the residue extract prior to GC analysis. The gas chromatogram indicated one main peak and several minor peaks. Also, the detector response was doubled, thereby increasing the sensitivity of this procedure. While this method was also rapid, its main application was in samples where toxaphene was the major residue. In samples with multiple organochlorine pesticide residues, it would be difficult to measure accurately all the residues and quantify the amount of toxaphene (Archer and Crosby 1966; Bigley et al. 1981; Crist et al. 1980; Gomes 1977). Recoveries from various samples are generally good with detection limits at levels of less than 1 ppm.

The tandem MS method has been used as an alternative to GC/MS. This method employs the technique of collision-activated dissociation on a triple quadrupole mass spectrometer. This facilitates direct and rapid qualitative and semiquantitative analysis of toxaphene samples in both liquid and solid environmental matrices at the 10-100 ppb level (Hunt et al. 1985). Additional features of tandem MS include the elimination of most wet chemical and chromatographic separation steps, detection of both known and unknown compounds by molecular weight and functional group, and a total analysis time per sample of less than 30 minutes. A disadvantage is that tandem MS is somewhat less specific than GC/MS in the identification of some isomeric compounds.

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Techniques developed by Jansson and Wideqvist (1983) and modified by Swackhamer et al. (1987) indicated that toxaphene can be detected at 75 pg per sample (approximately 1.2 ng/g) in fish using methane NCIMS. The authors noted that the NCIMS technique is more specific and 100 times more sensitive than electron impact (EI) or chemical ionization (CI) mass spectrometry and GC/ECD. In combination with a selected ion monitoring program, specific fragment ions can be monitored without any pre-separation column chromatography to eliminate other organochlorine pesticides that coelute with toxaphene (Swackhamer et al. 1987). Furthermore, NCIMS spectra are less complex than EI or CIMS spectra and contain higher mass ions due to successive losses of chloride and hydrochloride from the molecular ion. Jansson et al. (1991) reported a GC/NCIMS method for toxaphene in fish that allowed detection of levels below 19 ng/g. Methods based on GC/NCIMS generally give lower limits of detection than GC/ECD methods and thus are recommended for the best sensitivity (Muir and de Boer 1993).

Shafer et al. (1981) reported that the combined data of a gas chromatograph coupled to a Fourier-transform infrared spectrometer (GC/FT-IR) and GC/MS provide complementary information that leads to a better understanding and identification of the EPA's priority pollutants (including toxaphene) in air. Both GC/FT-IR and GC/MS separations were performed quickly and efficiently on wall-coated open tubular capillary columns.

A semi-specific spectrophotometric method for toxaphene analysis in fortified extracts of various foods was developed by Graupner and Dunn (1960). It was based on measuring the absorbance at 640 nm of a greenish-blue diphenylamine-toxaphene complex that was formed by reacting a sample extract with diphenylamine in the presence of zinc chloride. Several other organochlorine pesticides also reacted under these conditions, but only a few formed complexes that absorbed appreciably at 640 nm, thereby causing some interference with toxaphene analysis. A detection limit of less than 1 ppm of toxaphene was reported (Grauper and Dunn 1960).

The EPA (1995a) has proposed an immunoassay method for screening soils for toxaphene that uses commercially available test kits. It has been shown to be applicable to concentrations as low as 0.5 µg/g. Chemically similar compounds can interfere (e.g., endrin) but the assay was found to be relatively insensitive to other organochlorine pesticides such as Lindane, DDT, and DDE. Positive results should be confirmed using alternate analytical methods such as EPA methods 8081 or 8270.

Recently, Petrick et al. (1988) employed high-performance liquid chromatography (HPLC) as a clean-up technique prior to GC analysis. Petrick and co-workers efficiently separated toxaphene residues from



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other organochlorinated compounds in fat-rich samples with quantitative recovery. A detection limit of less than 1 ng of toxaphene per gram of sample was achieved by GC/ECD. The authors noted that the HPLC technique is highly efficient and reproducible and has a low consumption of solvents and high sample loading capacity.

### 6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of toxaphene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of toxaphene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 6.3.1 Identification of Data Needs.

**Methods for Determining Biomarkers of Exposure and Effect.** Methods are available for detecting and quantifying levels of toxaphene in the blood and milk fat of humans. The precision, accuracy, reliability and specificity of these methods have been reported. These methods are sufficiently sensitive to determine background levels of toxaphene in the general population and levels at which adverse health effects would begin to occur. Pharmacokinetic data indicate that toxaphene rapidly redistributes to fat; therefore, blood levels would be useful for identifying very recent exposures to toxaphene. Levels in milk fat are retained somewhat longer, but these levels decrease within weeks of cessation of exposure.

A highly sensitive and specific NCIMS technique has been employed to detect components of toxaphene at ppb levels in breast milk without the interference of other organochlorine pesticides (Vaz and Blomkvist 1985). GC/ECD and GC/MS can also detect trace amounts of toxaphene in human tissues and fluids

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following an efficient sample preparation and rigorous clean-up procedures. Currently, the only method available for analysis of toxaphene metabolites is TLC (Tewari and Sharma 1977). There is a growing need for research and development of highly sensitive and quantitative methods for determination of toxaphene metabolites. These methods would be useful, since they would allow investigators to assess the risks and health effects of long-term low-level exposure to toxaphene.

Currently, no methods are available to quantitatively correlate monitored levels of toxaphene in tissues or fluids with exposure levels or toxic effects in humans. If methods were available, they would provide valuable information on systemic effects following exposure to trace levels of toxaphene.

No specific biomarkers of effect have been clearly associated with toxaphene poisoning. Some biological parameters have been tentatively linked with toxaphene exposure, but insufficient data exist to adequately assess the analytical methods associated with measurement of these potential biomarkers.

**Methods for Determining Parent Compounds and Degradation Products in Environmental**

**Media.** Human exposure to toxaphene occurs primarily by inhalation of ambient air, ingestion of contaminated foodstuffs, and contact with contaminated soil and surface water. Reliable analytical methods are available to detect background levels of toxaphene in a wide range of environmental matrices. Toxaphene levels of 75 pg/sample (approximately 1.2 ng/g) can be detected in fish using the NCIMS technique (Swackhamer et al. 1987). However, there is a need to implement more refined software to process efficiently the data generated by the NCIMS technique. GC/ECD is the standardized analytical method used by EPA (1995c, method 8081c) to determine toxaphene in soil and water samples at ppb and sub ppb levels, respectively. GC/ECD, GC/MS, and tandem MS can detect and quantify toxaphene in air, soil, plant material, fish, water, milk, fat, and meat at ppb levels. The MRL for intermediate oral exposure to toxaphene is 0.001 mg/kg/day. Assuming a 70-kg individual and oral intakes of either 2 L/day of water or 2 kg/day of food, analytical methods would need to have sensitivities below 35 ppb (35 µg/L or 35 µg/kg) in either medium. The methods reported for drinking water have limits of detection far below this value (EPA 1976b, 1987a, 1989, 1986f; Ho et al. 1995). The needed sensitivities can be achieved for produce (Hsu et al. 1991; Luke et al. 1975), molasses (WHO 1984), and fish (Andrews et al. 1993; Jamuzi and Wakimoto 1991; Swackhamer et al. 1987). Limits of detection in Food and Drug Administration (FDA) methods are reported as “<0.2 ppm” and are thus inadequate for these MRLs. Additional analytical methods for detecting low levels of toxaphene are needed for foods other than produce.

## 6. ANALYTICAL METHODS

Little is known about the toxic properties of toxaphene congener metabolites in the environment (Bidleman et al. 1993). Additional analytical methods specifically targeted at toxaphene metabolites and degradation products are needed to support such investigations.

**6.3.2 Ongoing Studies**

No ongoing studies concerning techniques for measuring and determining toxaphene in biological and environmental samples were reported.



## 7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding toxaphene in air, water, and other media are summarized in Table 7- 1.

ATSDR has derived an acute-duration oral MRL of 0.005 mg/kg/day for toxaphene based on a hepatotoxicity study (Mehendale 1978).

ATSDR has derived an intermediate-duration oral MRL of 0.001 mg/kg/day based on hepatic effects (Chu et al. 1986).

No EPA reference concentration or reference dose exists for the compound.

EPA has classified toxaphene as a B2, probable human carcinogen (IRIS 1995). They derived a cancer potency factor of 1.1 mg/kg/day for oral exposure. IARC classifies toxaphene as 2B, possibly carcinogenic to humans (IARC 1987).

Toxaphene is on the list of chemicals appearing in The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) (EPA 1988a). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to toxaphene to institute engineering controls and work practices to reduce employee exposure to, and maintain employee exposure at, levels at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted level (TWA) of 0.5 mg/m<sup>3</sup>. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1989).

Also, to prevent or reduce skin absorption, an employee's skin exposure to toxaphene must be prevented or reduced to the extent necessary in the circumstances through the use of gloves, coveralls, goggles, or other appropriate personal protective equipment, engineering controls, or work practices.

## 7. REGULATIONS AND ADVISORIES

Toxaphene is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Sections 400-475, of the Code of Federal Regulations. For each point source category, toxaphene may be regulated as one of a group of chemicals controlled as Total Toxic Organics, or may have a specific Regulatory Limitation, or may have a Zero Discharge Limitation. The one point source category for which toxaphene is controlled as a Total Toxic Organic is electroplating (EPA 1981 a). The point source category for which toxaphene has a Zero Discharge Limitation is steam electric power generation (EPA 1982a).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), food tolerance restrictions for toxaphene ranged from 0.1 to 7 ppm (EPA 1971a, 1971b, 1986a). Tolerances for residues of toxaphene in various raw agricultural commodities, milk, and crude soybean oil were revoked in September 1993 (EPA 1993b).

The Resource Conservation and Recovery Act (RCRA) identifies toxaphene as a hazardous waste in three ways: (1) when it exceeds a toxicity characteristic leaching procedure test concentration of 0.5 mg/L (EPA 1990c); (2) when it occurs as a waste from specific sources (EPA 1981b); and (3) when it is discarded as a commercial product, off-spec species, container residue, or spill residue (EPA 1980a). Toxaphene is also designated a hazardous air pollutant under the Clean Air Act Amendments of 1990.

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene**

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
WHO		NA	
IARC	Group (cancer ranking)	2B <sup>a</sup>	IARC 1987
<u>NATIONAL</u>			
Regulations:			
a. Air:			
OSHA	PEL (TWA)	0.5 mg/m <sup>3</sup> (0.030 ppm)	29 CFR 1910.1000 OSHA 1974
	PEL (Ceiling)	skin designation	29 CFR 1910.1000 OSHA 1974
EPA OAR	Hazardous Air Pollutant	Yes	Clean Air Act Amendments Title III, Section 112 (b) U.S. Congress 1990
b. Water			
OW	Effluent Guidelines and Standards: Toxic pollutants	Yes	40 CFR 401.15 EPA 1979a
	Pretreatment Regulations: Appendix B -- 65 Toxic Pollutants	Yes	40 CFR 403 EPA 1986b
	Appendix G - Removal Credits	Yes	40 CFR 403 EPA 1986b
	Effluent Guidelines and Standards: Electroplating Definition of Total Toxic Organic	>0.01 mg/L	40 CFR 413.02 EPA 1981a
	Effluent Guidelines and Standards: Steam Electric Power Generation: Appendix A - 126 Priority Pollutants	Yes	40 CFR 423 EPA 1982a
	Effluent Guidelines and Standards: Metal Finishing - Definition of Total Toxic Organic	>0.01 mg/L	40 CFR 433.11 EPA 1983a
	Applicability; Description of the Organic Pesticide Chemicals Manufacturing Subcategory	Yes	40 CFR 455.20 EPA 1978a
	Designation of Hazardous Substances	Yes	40 CFR 116.4 EPA 1978b
	Reportable Quantities of Hazardous Substances: Section 311 of the Clean Water Act	1 lb	40 CFR 117.3 EPA 1979b
	Appendix D -- NPDES Permit Application Testing Requirements (122.21)	Yes	40 CFR 122 EPA 1983b
	Form 2D	Yes	40 CFR 122 EPA 1983b
Instructions -- Form 2C	NA	40 CFR 125 EPA 1979c	
Toxic Pollutant Effluent Standards	Yes	40 CFR 129.4 EPA 1977b	
Toxaphene Effluent Standard		0 - 1.5 µg/L discharge/ day	40 CFR 129.103 EPA 1977b

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	Identification of Test Procedures	Yes	40 CFR 136.3 EPA 1973
	Method 608 -- Organochlorine Pesticides and PCBs	Yes	40 CFR 136 EPA 1973
	Method 625 -- Base/Neutrals and Acids		40 CFR 136 EPA 1973
	Organic Chemicals Other Than Total Trihalomethanes, Sampling and Analytical Requirements	0.01 mg/L (detection limit)	40 CFR 141.24 EPA 1975
	Public Notification	Yes	40 CFR 141.32 EPA 1975
c. Other EPA OERR/ CEPP	Reportable Quantity	1 lb.	40 CFR 302 EPA 1985a
	Designation of hazardous substances	Yes	40 CFR 302.4 EPA 1985a
	Extremely Hazardous Substances and Their Threshold Planning Quantities (Camphechlor)	500/10,000 lbs.	40 CFR 355, App. A EPA 1987a
	Chemicals and chemical categories to which this part applies (Toxic Release Inventory)	25,000 lb. mfd. or processed 10,000 lb. otherwise used	40 CFR 372.65 EPA 1988a
EPA OSW	Municipal Solid Waste Landfills: Design Criteria - MCL for Upper Aquifer	0.005 mg/L	40 CFR 258.40 EPA 1991a
	Municipal Solid Waste Landfills: Appendix II	2 µg/L (Practical Quantitation Limit)	40 CFR 258 EPA 1991a
	Toxicity characteristic	0.5 mg/L	40 CFR 261.24 EPA 1990c
	Hazardous wastes from specific sources	Yes	40 CFR 261.32 EPA 1981b
	Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof	Yes	40 CFR 261.33 EPA 1980a
	Appendix VII - Basis for Listing Hazardous Waste	Yes	40 CFR 261 EPA 1981c
	Appendix VIII - Hazardous Constituents	Yes	40 CFR 261 EPA 1988b
	Appendix IX - Wastes Excluded Under 260.20 and 260.22	Yes	40 CFR 261 EPA 1984e
	Groundwater concentration limits	0.005 mg/L	40 CFR 264.94 EPA 1982b
	Appendix IX - Groundwater Monitoring List	2 µg/L (practical quantitation limit)	40 CFR 264 EPA 1987b



## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	Appendix III - EPA Interim Primary Drinking Water standards	0.005 mg/L	40 CFR 265 EPA 1980b
	Appendix VII - Health-based Limits for Exclusion of Waste-Derived Residues	$5 \times 10^{-3}$ mg/kg	40 CFR 266 EPA 1991b
	Identification of Wastes to be Evaluated by August 8, 1988	Yes	40 CFR 268.10 EPA 1986c
	Identification of Wastes to be Evaluated by June 8, 1989	Yes	40 CFR 268.11 EPA 1986c
	Treatment Standards - Applicability	Yes	40 CFR 268.40 EPA 1987c
	Treatment Standards Expressed as Specified Technologies	Yes	40 CFR 268.42 EPA 1986c
	Treatment Standards Expressed as Waste Concentrations	Yes	40 CFR 268.43 EPA 1988c
	Appendix III- List of Halogenated Organic Compounds Regulated Under 268.32	Yes	40 CFR 268 EPA 1987d
	Universal Treatment Standards	0.0095 mg/L (wastewater) 2.6 mg/kg (non-wastewater)	40 CFR 268.48 EPA 1995a 60 FR 242
Guidelines:			
a. Air			
ACGIH	Ceiling Limit for Occupational Exposure (TLV-TWA)	0.5 mg/m <sup>3</sup> (0.030 ppm) (skin)	ACGIH 1994
	TLV-STEL	1 mg/m <sup>3</sup> (0.059 ppm)	ACGIH 1994
NIOSH	Recommended Exposure Limit for Occupational Exposure (TWA)	lowest feasible concentration (skin)	NIOSH 1992
	Recommended Exposure Limit for Occupational Exposure (Ceiling)	lowest feasible concentration (skin)	NIOSH 1992
	Immediately Dangerous to Life and Health	200 mg/m <sup>3</sup> (11.81 ppm)	EPA 1987e
EPA	Cancer Unit Risk Factor (inhalation exposure)	$3.2 \times 10^{-4}$ $\mu\text{g}/\text{m}^3$ ( $1.89 \times 10^{-8}$ ppm)	IRIS 1995
b. Water:			
EPA/ODW	10-d Health Advisory	0.04 mg/L (child)	EPA 1995b
	Maximum Contaminant Level	0.003 mg/L	40 CFR 141.61 EPA 1975
	Maximum Contaminant Level Goal	0.0 mg/L	40 CFR 141.50 EPA 1975
	Appendix I to 40 CFR Part 257 -- Maximum Contaminant Levels (MCLs)	0.005 mg/L	40 CFR 257 EPA 1979d

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
	Variances and Exemptions from MCLs for Organic and Inorganic Chemicals	Yes	40 CFR 142.62 EPA 1991c
	q <sub>1</sub> * Cancer Slope Factor (oral exposure)	1.1x10 <sup>0</sup> mg/kg/d	IRIS 1995
c. Other			
EPA	Cancer Classification	B2 <sup>b</sup>	IRIS 1995
NIOSH	Cancer Classification	Potential occupational carcinogen	NIOSH 1992
NTP	Cancer Classification	Positive - mice Equivocal - rats	NTP 1995
<u>STATE:</u>			
a. Air:			
	Acceptable ambient air concentration guidelines or standards		NATICH 1992
AZ	1 hr. avg. time	8.3 µg/m <sup>3</sup> (4.90x10 <sup>-4</sup> ppm)	
	24 hr. avg. time	1.5 µg/m <sup>3</sup> (8.86x10 <sup>-5</sup> ppm)	
	Annual avg. time	4.0x10 <sup>-3</sup> µg/m <sup>3</sup> (2.36x10 <sup>-7</sup> ppm)	
CT	8 hr. avg. time	2.5 µg/m <sup>3</sup> (1.48x10 <sup>-4</sup> ppm)	
FL-FTLDLE	8 hr. avg. time	5.0x10 <sup>-3</sup> mg/m <sup>3</sup> (2.95x10 <sup>-4</sup> ppm)	
FL-PINELLA	8 hr. avg. time	5.0 µg/m <sup>3</sup> (2.95x10 <sup>-4</sup> ppm)	
	24 hr. avg. time	1.2 µg/m <sup>3</sup> (7.09x10 <sup>-5</sup> ppm)	
	Annual avg. time	3.1x10 <sup>-3</sup> µg/m <sup>3</sup> (1.77x10 <sup>-7</sup> ppm)	
FL-TAMPA	8 hr. avg. time	5.0x10 <sup>-3</sup> mg/m <sup>3</sup> (2.95x10 <sup>-4</sup> ppm)	
KS-KC	Annual avg. time	3.13x10 <sup>-3</sup> µg/m <sup>3</sup> (1.85x10 <sup>-7</sup> ppm)	
MI	Annual avg. time	3.0x10 <sup>-3</sup> µg/m <sup>3</sup> (1.77x10 <sup>-7</sup> ppm)	
ND	8 hr. avg. time	5.0x10 <sup>-3</sup> mg/m <sup>3</sup> (2.95x10 <sup>-4</sup> ppm)	
	1 hr. avg. time	1.0x10 <sup>-2</sup> mg/m <sup>3</sup> (5.91x10 <sup>-4</sup> ppm)	
NV	8 hr. avg. time	1.2x10 <sup>-2</sup> mg/m <sup>3</sup> (7.09x10 <sup>-4</sup> ppm)	

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE (cont.)</u>			
NY	1 yr. avg. time	1.67 µg/m <sup>3</sup> (9.86x10 <sup>-5</sup> ppm)	
OK	24 hr. avg. time	5.0 µg/m <sup>3</sup> (2.95x10 <sup>-4</sup> ppm)	
PA-PHIL.	1 yr. avg. time	1.2 µg/m <sup>3</sup> (7.09x10 <sup>-5</sup> ppm)	
	Annual avg. time	1.2 µg/m <sup>3</sup> (7.09x10 <sup>-5</sup> ppm)	
SC	24 hrs. avg. time	2.5 µg/m <sup>3</sup> (1.48x10 <sup>-4</sup> ppm)	
TX	30-min. avg. time	5.0 µg/m <sup>3</sup> (2.95x10 <sup>-4</sup> ppm)	
	Annual avg. time	5.0x10 <sup>-1</sup> µg/m <sup>3</sup> (2.95x10 <sup>-5</sup> ppm)	
VA	24 hr. avg. time	8.3 µg/m <sup>3</sup> (4.90x10 <sup>-4</sup> ppm)	
WA-SWEST	Annual avg. time	3.0x10 <sup>-3</sup> µg/m <sup>3</sup> (1.77x10 <sup>-7</sup> ppm)	
	24-hr. avg. time	1.7 µg/m <sup>3</sup> (1.00x10 <sup>-4</sup> ppm)	
b. Water			
	Water Quality: Human Health		CELDs 1993
AL	Drinking water standard	5.0 µg/L	FSTRAC 1990
AZ	Domestic water source	3.0 µg/L	CELDs 1993
	Fish consumption	0.0008 µg/L	CELDs 1993
	Drinking water guideline	0.03 µg/L	FSTRAC 1990
	Drinking water standard	5.0 µg/L	FSTRAC 1990
CA		0.21 µg/L	CELDs 1993
CT	Organisms only	0.00075	CELDs 1993
	Organisms and water only	0.00073	CELDs 1993
DE	Freshwater fish ingestion	0.93 ng/L	CELDs 1993
	Freshwater fish & water ingestion	0.91 ng/L	CELDs 1993
	Marine/estuarine fish/shellfish ingestion	0.13 ng/L	CELDs 1993
FL	Domestic/Drinking water	5 µg/L	Sittig 1994
HI	Fish consumption	0.00024 µg/L	CELDs 1993
ID	All Classes - Upper value	0.005 mg/L	EPA 1988d
IL	Public and food processing water supply standard	0.005 mg/L	EPA 1988d
IN		0.9973 µg/L	CELDs 1993

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE</u> (cont.)			
KY	Consumption of fish tissue	0.00073 µg/L	CELDs 1993
	Domestic water supply	0.00071 µg/L	CELDs 1993
LA	Drinking water supply	0.24 ng/L	CELDs 1993
	Non-drinking water supply	0.24 ng/L	CELDs 1993
MA	Drinking water standard	5 µg/L	FSTRAC 1990
ME	Drinking water guideline	0.3 µg/L	FSTRAC 1990
MD	Drinking water	5 µg/L	CELDs 1993
	Fish consumption	0.0073 µg/L	CELDs 1993
MI	Domestic/Drinking water	0.032 µg/L	Sittig 1994
MN	Drinking water standard	5 µg/L	FSTRAC 1990
	Drinking water guideline	0.3 µg/L	FSTRAC 1990
MO	Fish consumption	0.000073µg/L	CELDs 1993
	Drinking water	0.000071 µg/L	CELDs 1993
MS	Organisms only	0.00075 µg/L	CELDs 1993
	Water & organisms	0.00073 µg/L	CELDs 1993
NJ	Class FW2	0.013 µg/L	CELDs 1993
	All SE, SC classes	0.005 µg/L	CELDs 1993
	Toxic effluent limitations for potable water	0.71 ng/L	CELDs 1993
	Domestic/Drinking water	3 µg/L	Sittig 1994
NE	MCL	0.005 mg/L	CELDs 1993
NV	Municipal or domestic	0.005 mg/L	CELDs 1993
	Industrial	0.005 mg/L	CELDs 1993
NY	Class GA	Not detectable	CELDs 1993
	Class A, A-S, AA, AA-S, B.C, SA, SB, SC	0.005 µg/L	CELDs 1993
	Class D	1.0 µg/L	CELDs 1993
	Domestic/Drinking water	0.01 µg/L	Sittig 1994
OH	Public water supply	0.00071 µg/L	EPA 1988d
OK	Public and private water supply	0.005 mg/L	EPA 1988d
OR	Water and fish ingestion	0.71 ng/L	CELDs 1993
	Fish consumption only	0.73 ng/L	CELDs 1993
	Drinking water MCL	0.005 mg/L	CELDs 1993
	Domestic/Drinking water	0.08 mg/L	Sittig 1994

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE (cont.)</u>			
RI	Drinking water standard	5 µg/L	FSTRAC 1990
	Drinking water guideline	0.03 µg/L	FSTRAC 1990
	Class A: upper value	1.6 µg/L	EPA 1988d
	ClassA: secondary upper limit	0.013 µg/L	EPA 1988d
	Domestic/Drinking water	0.3-5.0 µg/L	Sittig 1994
SD	Domestic water	0.00071 µg/L	CELDs 1993
	All other sources	0.00073 µg/L	CELDs 1993
TN		5 µg/L	CELDs 1993
	Domestic/Drinking water	3 µg/L	Sittig 1994
TX	Domestic/Drinking water	3 µg/L	Sittig 1994
UT	Domestic source; maximum; Class 1C	5 µg/L	CELDs 1993
VA	Surface public water supply	0.005 mg/L	EPA 1988d
VT	Class A or B waters	0.71 ng/L	CELDs 1993
	Class C waters	0.73 ng/L	CELDs 1993
	Drinking water standard	0.031 µg/L	FSTRAC 1990
WI	Sport fish community-public water supplies	5.6 ng/L	CELDs 1993
	Cold water communities - public water supply	1.7 ng/L	CELDs 1993
	Great Lakes communities - public water supply	1.7 ng/L	CELDs 1993
	Warm water sport fish communities-non-public water supplies	5.7 ng/L	CELDs 1993
	Cold water communities - non-public water supplies	1.7 ng/L	CELDs 1993
	Warm water forage and limited forage fish communities and limited aquatic life - non-public water supplies	62,000 µg/L	CELDs 1993
	MCLG	0.00003 mg/L	CELDs 1993
WV	Criteria based on body burden of 1 µg/L; all water uses	0.71 ng/L	CELDs 1993
	All Classes - upper value	0.005 µg/L	EPA 1988d
	Water Quality: Aquatic Life		
AL	Acute- freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-Marine	0.21 µg/L	CELDs 1993
	Chronic-marine	0.0002	CELDs 1993

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE (cont.)</u>			
AR	Chronic	0.002 µg/L	CELDs 1993
	Acute	0.73 µg/L	CELDs 1993
	All Classes: upper value	2.4 µg/L	EPA 1988d
	All Classes: secondary upper limit	0.013 µg/L	EPA 1988d
AZ	Acute-cold water fishery	0.73	CELDs 1993
	Acute-warm water fishery	0.73	CELDs 1993
	Acute-effluent dominated water	0.73	CELDs 1993
	Acute-ephemeral	1100	CELDs 1993
	Chronic-cold water fishery	0.0002	CELDs 1993
	Chronic-warm water fishery	0.02	CELDs 1993
	Chronic-effluent dominated water	0.02	CELDs 1993
	Chronic-ephemeral	1.5	CELDs 1993
	CT	Acute- freshwater	0.73
Chronic- freshwater		0.002	CELDs 1993
Acute-salt water		0.21	CELDs 1993
Chronic-salt water		0.0002	CELDs 1993
DE	Acute-freshwater	0.78 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-marine	0.21 µg/L	CELDs 1993
	Chronic-marine	0.0002 µg/L	CELDs 1993
HI	Acute-freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-saltwater	0.21 µg/L	CELDs 1993
	Chronic-saltwater	0.0002 µg/L	CELDs 1993
IN	Acute	0.0002 µg/L	CELDs 1993
	Chronic	0.73 µg/L	CELDs 1993
KS	Special aquatic life waters: upper value	0.013 µg/L	EPA 1988d
KY	Chronic	0.0002 µg/L	CELDs 1993
	Acute	0.73 µg/L	CELDs 1993
LA	Acute-freshwater	0.73 µg/L	CELDs 1993
	Acute-marine water	0.21 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Chronic-marine water	0.0002 µg/L	CELDs 1993

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE (cont.)</u>			
MD	Acute-freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-salt water	0.21µg/L	CELDs 1993
	Chronic-salt water	0.0002 µg/L	CELDs 1993
	All Classes - upper value	0.005 µg/L	EPA 1988d
MS	Acute-freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-salt water	0.21 µg/L	CELDs 1993
	Chronic-salt water	0.0002 µg/L	CELDs 1993
NE	All Classes - upper value	0.005 mg/L	EPA 1988d
NC	Freshwater	0.0002 µg/L	CELDs 1993
	Tidal saltwater - upper value	0.07 µg/L	EPA 1988d
ND	Chronic	0.002 µg/L	CELDs 1993
	Acute	0.73 µg/L	CELDs 1993
NJ	Toxic effluent limitations 24-hr avg. - freshwater	0.013 µg/L	CELDs 1993
	Toxic effluent limitations- saltwater	0.070	CELDs 1993
	All saline classes - upper value	0.005 µg/L	EPA 1988d
NV	Aquatic use	0.00001 mg/L	CELDs 1993
OH	Warm water, outside mixing zone, 30-d avg.	0.005 µg/L	CELDs 1993
	Warm water, human health, 30-d avg.	0.0073 µg/L	CELDs 1993
	Aquatic life habitat: limited resource-cold water; outside mixing zone, 30-d avg.	0.005 µg/L	CELDs 1993
	Aquatic life habitat: limited resource-cold and warm water, human health, 30-d avg.	0.0073 µg/L	CELDs 1993
OK	Acute	0.78 µg/L	CELDs 1993
	Chronic	0.0002 µg/L	CELDs 1993
	Fish and Wildlife propagation	1.0 µg/L	EPA 1988d
OR	Acute-freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Marine- acute	0.21 µg/L	CELDs 1993
	Chronic-marine	0.0002 µg/L	CELDs 1993
PR	All coastal water classes - upper value	0.005 µg/L	EPA 1988d

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE (cont.)</u>			
RI	Freshwater Classes D and E		
	Upper level	1.6 µg/L	EPA 1988d
	Secondary upper limit	0.013 µg/L	EPA 1988d
	Saline Classes SA, SB and SC		
	Upper level	0.07 µg/L	EPA 1988d
SD	Acute	0.73 µg/L	CELDs 1993
	Chronic	0.0002 µg/L	CELDs 1993
TN	Continuous	0.002 µg/L	CELDs 1993
	Max	0.73 µg/L	CELDs 1993
TX	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-freshwater	0.78 µg/L	CELDs 1993
	Acute-marine	0.21 µg/L	CELDs 1993
	Chronic-marine	0.0002 µg/L	CELDs 1993
UT	4-d avg.	0.0002 µg/L	CELDs 1993
	1-h avg.	0.73 µg/L	CELDs 1993
	Aquatic life classes 3A-D	0.005 µg/L	EPA 1988d
VA	Chronic- freshwater	0.013 µg/L	CELDs 1993
	Chronic- saltwater	0.0007	CELDs 1993
VT	Acute	0.73 µg/L	CELDs 1993
	Chronic	0.0002 µg/L	CELDs 1993
WI	Acute-Great Lakes	0.61 µg/L	CELDs 1993
	Acute-cold water	0.81 µg/L	CELDs 1993
	Acute-warm water sport fish	0.61 µg/L	CELDs 1993
	Acute-all others	0.81 µg/L	CELDs 1993
	Chronic-Great Lakes	0.01 µg/L	CELDs 1993
	Chronic-cold water	0.01 µg/L	CELDs 1993
	Warm water sport fish	0.01 µg/L	CELDs 1993
	All others	0.01 µg/L	CELDs 1993
	Water Quality: Propagation of Wildlife		
NV		0.005 mg/L	CELDs 1993
	Water Quality: Agricultural Use		
AZ	Irrigation	0.005 mg/L	CELDs 1993
	Livestock watering	0.005 mg/L	CELDs 1993



## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE (cont.)</u>			
NV	Irrigation	0.005 mg/L	CELDs 1993
	Watering of livestock	0.00001 mg/L	CELDs 1993
OH		0.0071 µg/L	CELDs 1993
	Water Quality: Recreational Use		
AZ	Full body contact	3.0 µg/L	CELDs 1993
	Partial body contact	1000 µg/L	CELDs 1993
DC		0.01 µg/L	CELDs 1993
RI	Freshwater Classes B & C - upper value	1.6 µg/L	EPA 1988d
	Freshwater Classes B & C - secondary upper limit	0.013 µg/L	EPA 1988d
TN		0.008 µg/L	CELDs 1993
	Groundwater Quality Standards		CELDs 1993
AZ	Drinking water protected use	0.005 mg/L	
CO		0.005 mg/L	
MA		0.005 mg/L	
MO		0.000071 µg/L	
NJ	GW1 (GW 2 & 3)	0.005 mg/L	
NC	GS waters	0.000031 mg/L	
OR	Human consumption	0.005 mg/L	
TN		0.005 mg/L	
UT		0.005 mg/L	
WI	Public health-enforcement std.	0.0007 µg/L	
	Public health-preventive action	0.00007 µg/L	
	Max. conc. for GW prtxn	0.005 mg/L	
	Groundwater Monitoring Parameters		CELDs 1993
CO		0.005 mg/L	
IN		0.005 mg/L	
IL	Max conc.-hazardous waste facility std.	0.005 mg/L	
	Monitoring constituent	Yes	
LA	Max conc.-hazardous waste facility std.	0.005 mg/L	
	Monitoring constituent	Yes	
MN	Monitoring constituent	Yes	
	Max conc.-hazardous waste facility std.	0.005 mg/L	
MO	Max conc.-hazardous waste facility std.	0.005 mg/L	
NJ	Max level-hazardous waste facility std.	0.005 mg/L	

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE</u> (cont.)			
TN		0.005 mg/L	
VA	Monitoring constituent	Yes	
WI	Monitoring constituent	Yes	
	Max conc.-hazardous waste facility std.	0.005 mg/L	
WV	Monitoring constituent	Yes	
CA	Restricted Pesticides	Yes	
	Discharge Limits	0.21 ng/L	
	Total Threshold Limit Conc. In Extremely Hazardous Wastes	500 mg/kg	
	Persistent and Bioaccumulative Toxic Substances and Their Total Threshold Limit Concentration for Extremely Hazardous Wastes	500 mg/kg (w/w)	
	Prohibition of Net Discharge Associated with Industrial, Toxic and Other Wastes	Yes	
IL	Public and Food Processing Water	0.005 mg/L	
WI	No qty>qty which remains after BATEA treatment or a lesser qty that provides an ample safety margin		
	Toxic Discharge	Yes	
NJ	NPDES Permits: Testing Requirements for Organic Toxic Pollutants	Yes	CELDs 1993
OK	Alert and Concern Levels in Fish Tissue	5.0 mg/kg (alert) 2.5 mg/kg (concern)	CELDs 1993
	Max allow concs for organochlorides & other persistent pesticides (preservation of species dependent on waterbody)		CELDs 1993
PR	Coastal estuarine waters	0.0002 µg/L	
	Surface waters	0.0002 µg/L	
	Ground waters	0.0002 µg/L	
SD	Surface Water Discharge Permit Application Requirements: Test Requirements for Organic Toxic Pollutants	Yes	CELDs 1993
c. Other:			
	Hazardous Waste		CELDs 1993
CA		Yes	
CO		Yes (LDR)	
IL		Yes	
LA		Yes	
MA		Yes (LDR)	
ND		Yes	

## 7. REGULATIONS AND ADVISORIES

**Table 7-1. Regulations and Guidelines Applicable to Toxaphene (continued)**

Agency	Description	Information	Reference
<u>STATE</u> (cont.)			
NH		Yes	
WI		Yes	
WV		Yes	
	Hazardous Waste Toxicity Characteristic		CELDs 1993
CA		0.5 mg/L	
CO		0.5 mg/L	
IL		0.5 mg/L	
LA		0.5 mg/L	
MA		0.5 mg/L	
MN		0.5 mg/L	
ND		0.5 mg/L	
PA		0.5 mg/L	
WI		0.5 mg/L	
WV		0.5 mg/L	
	Hazardous Waste Constituents		CELDs 1993
CO		Yes	
IL		Yes (App. H)	
		Yes (App. G)	
LA		Yes	
MN		Yes	
ND		Yes (App. IV)	
WI		Yes	
WV		Yes (App. VIII)	
		Yes (App. VII)	

NOTE: Update of drinking water guidelines and other areas in progress.

Units in table reflect values and units of measure designated by each agency in its regulations or advisories.

<sup>a</sup>Possibly carcinogenic to humans

<sup>b</sup>Probably carcinogenic to humans

ACGIH = American Conference of Governmental and Industrial Hygienists; CAAA = Clean Air Act; CELDs = Computer-aided Environmental Legislative Database; CEPP = Chemical Emergency Preparedness Program; CPSC = Consumer Product Safety Commission; EPA = Environmental Protection Agency; FSTRAC = Federal State Toxicology and Regulatory Alliance Committee; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; LDR = Land Disposal Restriction; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NA = Not available at the present time; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; NTP = National Toxicology Program; OAR = Office of Air and Radiation; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OPTS = Office of Pesticides and Toxic Substances; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OW = Office of Water; PCB = Polychlorinated Biphenyl; PEL = Permissible Exposure Limit; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TSCA = Toxic Substances Control Act; TWA = Time Weighted Average; WHO = World Health Organization



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## 9. GLOSSARY

**Acute Exposure**-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

**Adsorption Coefficient ( $K_{oc}$ )**--The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio ( $K_d$ )**--The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment, or in mL/g or L/ng.

**Bioconcentration Factor (BCF)**-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Cancer Effect Level (CEL)**-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen**-A chemical capable of inducing cancer.

**Ceiling Value**-A concentration of a substance that should not be exceeded, even instantaneously.

**Chronic Exposure**-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

**Developmental Toxicity**-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Embryotoxicity and Fetotoxicity**-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

**EPA Health Advisory**-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Immediately Dangerous to Life or Health (IDLH)**-The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

**Intermediate Exposure**-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

**Immunologic Toxicity**--The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

***In Vitro***--Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo***--Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**--The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**--A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(LO)</sub> (LD<sub>LO</sub>)**--The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)**--The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**--A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)**--The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Malformations**--Permanent structural changes that may adversely affect survival, development, or function.

**Minimal Risk Level**--An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

**Mutagen**--A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

**Neurotoxicity**--The occurrence of adverse effects on the nervous system following exposure to chemical.

**No-Observed-Adverse-Effect Level (NOAEL)**--The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient (K<sub>OW</sub>)**--The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

**Permissible Exposure Limit (PEL)**--An allowable exposure level in workplace air averaged over an 8-hour shift.



**q<sub>1</sub>\*** -The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q<sub>1</sub>\* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m<sup>3</sup> for air).

**Reference Dose (RfD)**--An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Reportable Quantity (RQ)**--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity**--The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Short-Term Exposure Limit (STEL)**--The maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily TLV-TWA may not be exceeded.

**Target Organ Toxicity**--This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen**--A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)**--A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

**Time-Weighted Average (TWA)**--An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

**Toxic Dose (TD<sub>50</sub>)**--A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Uncertainty Factor (UF)**-- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.



## APPENDIX A

### ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 994991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

### MINIMAL RISK LEVEL (MRL) WORKSHEET(S)

Chemical name: Toxaphene  
 CAS number: 8001-35-2  
 Date: August 1996  
 Profile status: Draft 3 Postpublic comment  
 Route:  Inhalation  Oral  
 Duration:  Acute  Intermediate  Chronic  
 Key to figure: 11  
 Species: Rat

MRL: 0.005  mg/kg/day  ppm  mg/m<sup>3</sup>

Reference: Mehendale HM. 1978. Pesticide-induced modification of hepatobiliary function: hexachlorobenzene, DDT, and toxaphene. *Food. Cosmet. Toxicol.* 16:19-25.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): An unspecified number of rats were administered 100 ppm (5 mg/kg) toxaphene in feed for 8 days. The rats were sacrificed and the livers used in a perfusion apparatus to determine the effects of toxaphene on the hepatic metabolism and biliary secretion of imipramine.

Effects noted in study and corresponding doses: Toxaphene-treated rats had decreased hepatic uptake, metabolism, and biliary excretion of imipramine, indicating that toxaphene compromised hepatic function.

Dose endpoint used for MRL derivation:

NOAEL  LOAEL

Uncertainty factors used in MRL derivation:

1  3  10 (for use of a LOAEL)  
 1  3  10 (for extrapolation from animals to humans)  
 1  3  10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

If so, explain:

Yes. Dose = 100 ppm or 100 mg toxaphene/kg feed. The average rat consumes 0.05 kg of feed per kg body weight per day. Thus, the average daily dose of toxaphene is estimated to be 100 mg/kg x 0.05 kg feed/kg body weight/day = 5 mg/kg/day.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No

If so, explain:

## APPENDIX A

Other additional studies or pertinent information that lend support to this MRL:

The liver appears to be a target organ of toxaphene; therefore, using hepatic effects to calculate the MRL is appropriate.

Agency Contact (Chemical Manager): Ms. Nickolette Roney

## APPENDIX A

## MINIMAL RISK LEVEL WORKSHEET

Chemical name: Toxaphene  
CAS number: 8001-35-2  
Date: September 1996  
Profile status: Draft 3 Postpublic comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 30  
Species: Rat

MRL: 0.001 [] mg/kg/day  ppm  mg/m<sup>3</sup>

Reference: Chu I, Villeneuve DC, Sun C-W, et al. 1986. *Toxicity of toxaphene in the rat and beagle dog*. Fundam. Appl. Toxicol. 7:406-418.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): 10 rats/sex/group were fed toxaphene at 0, 4, 20, 100, or 500 ppm for 13 weeks. This concentration of toxaphene in the feed was calculated by the authors to have delivered 0, 0.35, 1.8, 8.6, or 45.9 mg/kg/day toxaphene, respectively, for males, and 0, 0.50, 2.6, 12.6, or 63 mg/kg/day toxaphene, respectively, for females. At the conclusion of the study, the brain, heart, spleen, liver, and kidneys were removed and weighed. Those and a variety of other tissues were analyzed histopathologically. Hematological evaluations were also conducted

Effects noted in study and corresponding doses: Toxaphene did not cause any clinical signs of toxicity, and food consumption and body weight gain were similar to controls across all treatment groups. Relative liver weight was increased at 500 ppm in both sexes; male relative kidney weight was also elevated at 500 ppm. Induction of the hepatic microsomal enzymes aniline hydroxylase and aminopyrine demethylase was observed at that dose in both sexes. The serological findings were negative for all doses of toxaphene. Histopathological evaluation of the tissues from all dose groups indicated that toxaphene targeted the liver, kidney, and thyroid organs. Dose-dependent histological changes were observed in hepatic tissues from both sexes and consisted primarily of peripheralized basophilia and anisokaryosis. No effect on the liver was observed at 20 ppm toxaphene. In the kidneys of both sexes, dose-dependent structural alterations in the proximal tubules were seen. Those consisted primarily of proximal tubule inclusions which were, in severe cases, associated with casts and focal tubular necrosis. The severe renal effects were confined to the males in the 500 ppm group. Toxaphene treatment caused mild to moderate thyroid cytoarchitectural changes. These changes were characterized by reduced colloid density, angular collapse of follicles, and increased epithelial height with multifocal papillary proliferation.

Dose endpoint used for MRL derivation:

NOAEL  LOAEL No hepatic toxicity observed at 0.35 mg/kg/day toxaphene.

## APPENDIX A

Uncertainty factors used in MRL derivation:

- 1  3  10 (for use of a LOAEL)  
 1  3  10 (for extrapolation from animals to humans)  
 1  3  10 (for human variability)  
 1  3  10 (additional modifying factor because of possible developmental effects)

Was a conversion factor used from nnm in food or water to a mg/body weight dose?

If so, explain: No. The doses in mg/kg/day were derived by the authors using the weight and food consumption data obtained during the study.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No

If so, explain:

Other additional studies or pertinent information that lend support to this MRL:

Chu I, Secours V, Villeneuve DC, et al. 1988. Reproductive study of toxaphene in the rat. *J. Environ Sci Health B23*:101-126. Olson KL, Masamura F, and Boush GM. 1980. Behavioral effects on juvenile rats from perinatal exposure to low levels of toxaphene and its toxic components, toxicant A and toxicant B. *Arch Environ Contam Toxicol* 9:247-257

Agency Contact (Chemical Manager): Ms. Nickolette Roney



## APPENDIX B

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

#### Chapter 2

##### Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

#### LEGEND

##### See LSE Table 2-1

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in chapter 8 of the profile.

- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

## LEGEND

**See Figure 2-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale “y” axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1

**TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

2

3

4

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)		
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5d/wk 6hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)		Nitschke et al. 1981
-----							
CHRONIC EXPOSURE							
						11	
						↓	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

12

<sup>a</sup> The number corresponds to entries in Figure 2-1.

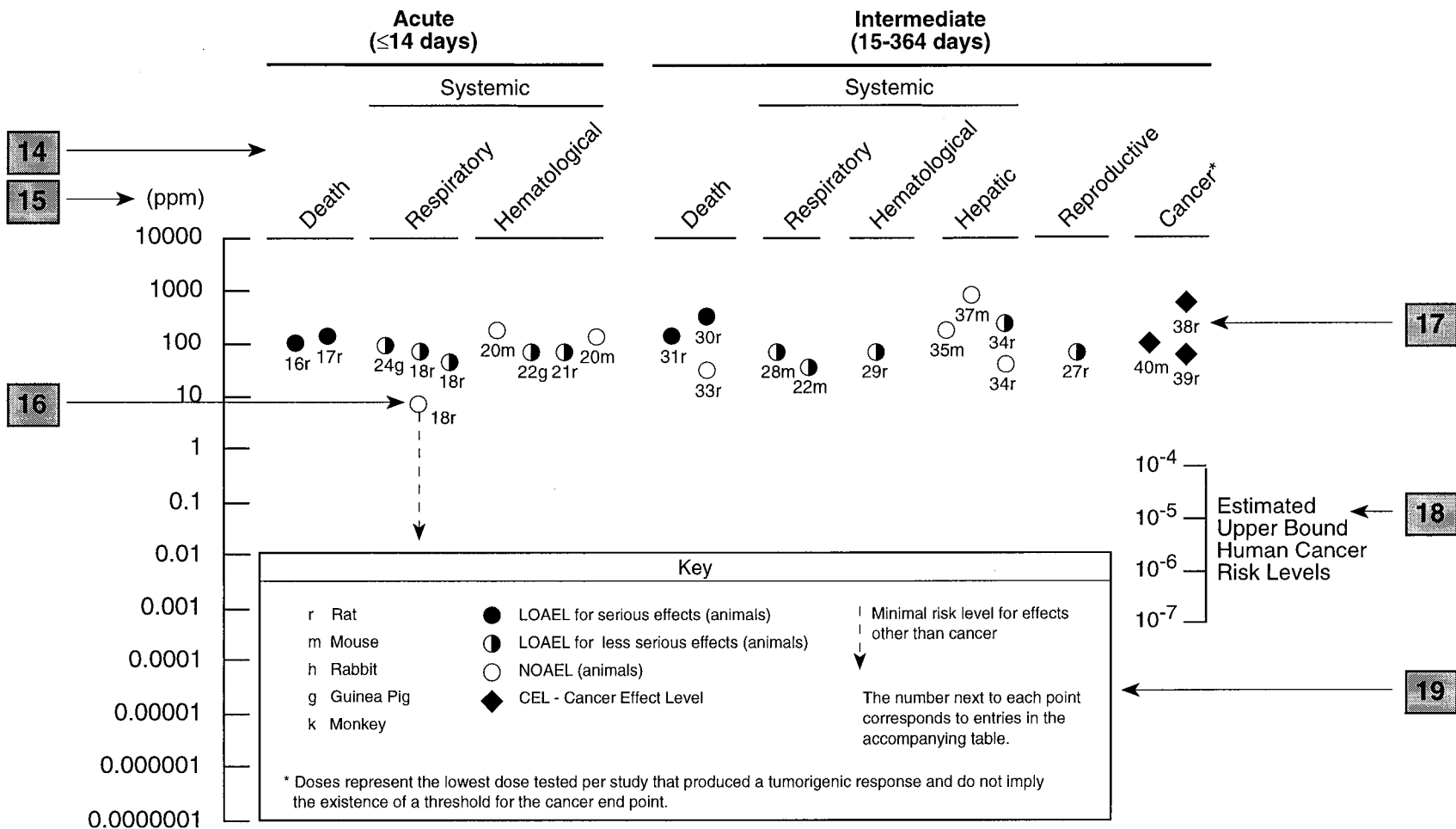
<sup>b</sup>

uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

**SAMPLE**

**13** → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



## APPENDIX B

**Chapter 2 (Section 2.5)****Relevance to Public Health**

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.7, "Interactions with Other Substances," and 2.8, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.





**APPENDIX C****ACRONYMS, ABBREVIATIONS, AND SYMBOLS**

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F <sub>1</sub>	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K <sub>d</sub>	adsorption ratio
kg	kilogram
kkg	metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient

## APPENDIX C

L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit

## APPENDIX C

STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

