DRAFT
TOXICOLOGICAL PROFILE FOR TOXAPHENE

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

September 2010

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UPDATE STATEMENT

A Toxicological Profile for Toxaphene was released in 1996. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology 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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 toxic 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 audiences for the toxicological profiles are health professionals at the federal, state, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

The Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
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Electronic Comments should be sent to: TPPublicComments@cdc.gov

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health-related authorities" of the statute. This includes the preparation of 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. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs 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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Thomas R. Frieden, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. 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 end points.

2. 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 MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. Dr. Laurie H.M. Chan, Professor, Aboriginal Environmental Health, University of Northern British Columbia, Prince George BC V2N 4Z9, Canada;

2. Dr. Lucio G. Costa, Professor, Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington; and

3. Dr. Mark Robson, Professor and Dean of Agricultural and Urban Programs, Rutgers University, New Brunswick, New Jersey.

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.

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 to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Toxaphene has been found in at least 68 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which toxaphene is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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 will determine whether you will 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 any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS TOXAPHENE?

Chlorinated camphene	Toxaphene is made by reacting chlorine gas with a substance called camphene. The resulting product (toxaphene) is a mixture of hundreds of different chlorinated camphenes and related chemicals.
Manufactured insecticide	Toxaphene was one of the most heavily used pesticides in the United States in the 1970s and early 1980s. It was used primarily to control insect pests on cotton and other crops in the southern United States. Other uses included controlling insect pests on livestock and killing unwanted fish in lakes.
Banned for all registered uses in the United States	Toxaphene was banned for all registered uses by 1990.

Form	Toxaphene is usually found as a solid or gas. In its original form, toxaphene is a yellow to amber waxy solid that has a piney odor.

1.2 WHAT HAPPENS TO TOXAPHENE WHEN IT ENTERS THE ENVIRONMENT?

Movement between air, water, soil, and sediment	When toxaphene is released to the environment, it can enter the air (by evaporation), the soil (by sticking to soil particles), and the water (from runoff after rains). Toxaphene 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.
Breaks down slowly	Once toxaphene is in the environment, it can last for many years because it breaks down very slowly.
Transported by air over long distances	Toxaphene has been found in water, soil, sediment, air, and animals in places far from where it has been used. This shows that toxaphene can be carried long distances by the air.
Bioaccumulates	Toxaphene levels may be high in some predatory fish and mammals because toxaphene accumulates in fatty tissues. Even when levels are low or confined to a certain area, they could be high in individual animals.

1.3 HOW MIGHT I BE EXPOSED TO TOXAPHENE?

Hazardous waste sites	People living near a location with heavy toxaphene contamination, such as a hazardous waste sites, may be exposed to higher levels through breathing contaminated air or through direct skin contact with contaminated soil or water.
Eating contaminated soil	Infants and toddlers, who are likely to put things in their mouth, may be exposed to toxaphene by eating contaminated soil.
Eating fish, shellfish, and wild game	People who eat large quantities of fish, shellfish, or wild game animals from areas contaminated by toxaphene may have higher exposure to this substance since these animals tend concentrate toxaphene in their fatty tissues.
Drinking water	Individuals may be exposed to toxaphene through drinking water contaminated with toxaphene runoff from contaminated soils.

1.4 HOW CAN TOXAPHENE ENTER AND LEAVE MY BODY?

May enter your body through food, drinking water, breathing, and skin contact	Toxaphene can enter your body if you eat food contaminated with toxaphene, such as fish caught from water where toxaphene is present. Toxaphene in drinking water can similarly enter your body, although when toxaphene has been detected in drinking water, levels have been generally more than 1,000 times lower than levels measured in toxaphene-contaminated food. Toxaphene could enter your body if it were to come into contact with your skin (for example, by bathing or showering in water contaminated with the chemical) or if you were to breathe air containing toxaphene.
Leaves through bodily fluids	Toxaphene is quickly broken down into other substances in your body. Toxaphene and its breakdown products leave your body mostly in urine and feces. Small amounts may leave through breast milk and exhaled air.

1.5 HOW CAN TOXAPHENE AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Nervous system	Convulsions were experienced by some people who accidentally or intentionally swallowed large amounts of toxaphene, including three women who ate collard greens contaminated with toxaphene. However, since toxaphene is no longer used as a pesticide, you would not likely eat enough toxaphene-contaminated food to affect your nervous system in this way.
Immune system	Effects on the immune system have been observed in laboratory studies of animals that were given toxaphene by mouth in amounts that you would not likely get by eating food or drinking water containing toxaphene.
Liver	Toxaphene temporarily damaged the liver of a man who attempted suicide by drinking a large amount of an insecticide that contained toxaphene. Liver damage was seen in laboratory studies of animals that were given toxaphene by mouth in amounts that you would not likely get by eating food or drinking water containing toxaphene.
Kidneys	Toxaphene temporarily damaged the kidneys of a man who attempted suicide by drinking a large amount of an insecticide that contained toxaphene. Swollen kidneys were seen in a small boy who died after drinking a large amount of toxaphene. Kidney damage was seen in laboratory studies of animals that were given toxaphene by mouth in amounts that you would not likely get by eating food or drinking water containing toxaphene.

Cancer	Toxaphene caused liver cancer in mice and possibly thyroid cancer in rats that were given toxaphene by mouth in large amounts that you would not likely get by eating food or drinking water containing toxaphene. We do not know whether toxaphene would cause cancer in humans. However, based on animal studies, the Department of Health and Human Services has determined that toxaphene may reasonably be anticipated to be a carcinogen. The International Agency for Research on Cancer has determined that toxaphene is possibly carcinogenic to humans. Also, the EPA has determined that toxaphene is a probable human carcinogen.

1.6 HOW CAN TOXAPHENE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	Toxaphene would be expected to affect children in the same manner as adults. It is not known whether children are more susceptible than adults to the effects of toxaphene.
Developmental effects	A few studies in animals have shown minor changes in fetal development. We do not know if toxaphene would cause developmental effects in humans.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO TOXAPHENE?

Reduce consumption of foods and drinking water that contain toxaphene	For people who live in areas where surface waters (lakes) have been contaminated with toxaphene, consumption of toxaphene-contaminated foods such as fish may need to be reduced. Also, do not drink water that has been contaminated with toxaphene.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TOXAPHENE?

Can be measured in blood and urine	Toxaphene and some of its breakdown products can be measured in blood and urine. However, it is not likely that you would be exposed to enough toxaphene to make such measurements that would be meaningful to your health.

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for toxaphene include the following:

Levels in drinking water set by EPA	The EPA has determined that exposure to toxaphene in drinking water at concentrations of 0.004 mg/L for up to 10 days is not expected to cause any adverse effects in a child. The EPA has determined that lifetime exposure to 0.01 mg/L toxaphene in the drinking water is not expected to cause any adverse noncancer effects if the only source of exposure to toxaphene is the drinking water. EPA established a maximum contaminant level (MCL) of 0.003 mg/L for toxaphene in drinking water.

Bottled water	The FDA has determined that the toxaphene concentration in bottled drinking water should not exceed 0.003 mg/L.
Levels in workplace air set by OSHA	OSHA set a legal limit of 0.5 mg/m^3 for toxaphene in air averaged over an 8-hour work day.

1.10 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 contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TOXAPHENE IN THE UNITED STATES

Toxaphene is a manufactured pesticide comprising a complex mixture of hundreds of chlorinated terpenes. After DDT was banned from use in the United States in 1972, toxaphene became the most popular substitute. Control of pests on cotton crops was the principal use of toxaphene in the United States, although the pesticide was used to control a variety of insects on a range of crops and to eradicate undesirable fish species in some aquatic environments. In November of 1982, EPA canceled the registration of toxaphene for most uses as a pesticide or pesticide ingredient. All registered uses of toxaphene mixtures in the United States and its territories were canceled in 1990.

Toxaphene was widely released to the environment mainly as a result of its past use as an insecticide. Toxaphene has been transported over long distances in the atmosphere. 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. Atmospheric toxaphene is transported back to soil and water surfaces by wet and dry deposition processes. Toxaphene strongly adsorbs to particles and is relatively immobile in soils. 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 4,200–60,000. Toxaphene also appears to be biomagnified in aquatic food chains.

The composition of technical toxaphene released to the environment has changed over time since toxaphene congeners degrade at different rates, resulting in what is commonly termed weathered toxaphene. Degradation proceeds mainly through dechlorination and dehydrochlorination resulting in a shift in composition toward lower chlorinated homologs. Presently, exposure to persistent toxaphene congeners and degradation products is the primary health concern for the general population. Toxaphene congeners that have been found to persist in fish, marine mammals, and human serum and breast milk include those identified as Parlars p-26, p-40/41, p-44, p-50, and p-62. Pooled results of studies that assessed levels of these congeners in human serum and/or breast milk indicate that p-26, p-50, and p-62 comprise most of the total toxaphene body burden.

The major source of exposure for the general population appears to be ingestion of low concentrations of persistent toxaphene congeners in food, particularly fish, and toxaphene-contaminated drinking water. Subpopulations with increased potential for significant exposure to persistent toxaphene congeners

include northern Native American groups that eat toxaphene-contaminated aquatic mammals, recreational or subsistence hunters in the southern United States that consume significant amounts of game animals (especially species like raccoons), and people who consume certain types of sport-caught fish (such as trout, salmon, herring, smelt, and walleye) from the Great Lakes.

2.2 SUMMARY OF HEALTH EFFECTS

This toxicological profile for toxaphene summarizes health effects information for toxaphene based on exposure to technical toxaphene that was formerly widely used as a pesticide in the United States. Since being banned for use as a pesticide in the United States in 1990, the greatest present concern for the general population would be exposure to persistent toxaphene congeners and degradation products of technical toxaphene formerly released to the environment.

Limited information is available regarding noncancer health effects in humans or laboratory animals following inhalation exposure to toxaphene. Pulmonary hypersensitivity and hematological alterations were indicated in two Egyptian agricultural pesticide workers involved in spraying a pesticide formulation (68% toxaphene, 35% kerosene, 3% xylol, and 2% emulsifier). One controlled study found no signs of toxicity in a group of 25 volunteers exposed to an aerosol containing a maximum of 500 mg toxaphene/m^3 30 minutes/day for 30 days. The nervous system and the liver have been identified as targets of toxaphene toxicity in limited animal studies that employed the inhalation exposure route.

Ingestion of toxaphene has resulted in death in some cases of acute poisoning. Mortalities have also been observed in animals following single- and repeated-dose oral exposure.

Clinical signs of central nervous system stimulation including convulsions have been reported in humans following accidental or intentional ingestion of toxaphene. Similar effects have been observed in animals following oral exposure to toxaphene. Dogs appear to be particularly sensitive to the neurological effects of toxaphene; convulsions were elicited at oral doses as low as 10 mg/kg/day.

Animal studies provide evidence that toxaphene can also affect the liver, kidney, endocrine system, immunological system, and body weight, as well as the nervous system. Morphological and degenerative changes were observed in the livers of dogs, rats, and mice following repeated oral exposure to toxaphene; doses as low as 1.8 mg/kg/day caused nuclear changes in hepatocytes of rats. Renal tubular injury was reported in the kidneys of rats receiving toxaphene at 8.6 mg/kg/day for 13 weeks.

Histopathological evidence of effects on the thyroid gland of male rats was observed following 13 weeks of oral administration of toxaphene at 1.8 mg/kg/day. Significant reductions in IgM responses (indicative of depressed humoral immunity) were reported in female cynomolgus monkeys administered toxaphene by oral capsule at a dose level of 0.4 mg/kg/day during a 75-week treatment period. Pregnant animals may be particularly sensitive to toxaphene-induced effects on body weight; for example, average body weight gain of rat dams administered toxaphene by gavage at 15 mg/kg/day during pregnancy was 22% lower than that of pregnant control rat dams.

Toxaphene-induced reproductive effects have not been demonstrated in animal studies. Effects such as decreased early postnatal body weight and increased incidences of supernumary ribs were observed in offspring of rat dams that were fed toxic doses of toxaphene. Decreased renal protein was noted in the kidneys of 21-day-old rat fetuses whose mothers had been administered toxaphene by gavage at 12.5 mg/kg/day during gestation. Suppression of macrophage phagocytic function was reported in 8-week-old offspring of mouse dams administered toxaphene at doses ≥2 mg/kg/day during premating and throughout mating, gestation, and lactation. In one developmental toxicity study, slight delays in successful responses to a righting reflex test were observed in nursing pups from rat dams administered toxaphene by gavage at 6 mg/kg/day during mating and throughout gestation. Retarded swimming ability and righting reflex were reported in young pups of rat dams administered toxaphene at 0.05 mg/kg/day during gestation and lactation; however, the effect was transient, observed only during postpartum days 10–12 and of uncertain toxicological significance.

Limited animal data indicate that dermal exposure to high levels of toxaphene can cause clinical signs of neurotoxicity, liver effects, and death at very high doses.

Statistically significant associations between exposure to toxaphene and risk of cancers such as leukemia and certain types of non-Hodgkin's lymphoma have been reported in case-control studies of groups of farm workers. It should be noted that all uses of toxaphene in the United States were canceled in 1990. Increased incidences of thyroid tumors were observed in rats administered toxaphene at approximately 80 mg/kg/day for 80 weeks; in similarly-treated mice, increased incidences of hepatocellular tumors were noted at toxaphene doses of 17 and 34 mg/kg/day. One unpublished study reported increased incidences of hepatocellular tumors in male mice administered toxaphene orally at approximately 8.6 mg/kg/day for 18 months. Available *in vivo* studies and *in vitro* assays provide equivocal evidence for toxaphene-induced genotoxicity. The International Agency for Research on Cancer (IARC) has classified toxaphene as Group 2B (possibly carcinogenic to humans). The National Toxicology Program (NTP) considers

toxaphene as "reasonably anticipated to be a human carcinogen". EPA has given toxaphene a classification of B2 (probable human carcinogen). The cancer classifications are based on the findings of hepatocellular tumors in toxaphene-treated mice, thyroid tumors in toxaphene-treated rats, and evidence of mutagenicity in *in vitro* bacterial assays.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (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 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.

Inhalation MRLs

No inhalation MRLs were derived for toxaphene due to the lack of reliable human and animal data. One controlled human study found no evidence of adverse effects among 25 human subjects exposed to an aerosol containing a maximum of 500 mg toxaphene/m^3 for 30 minutes/day for 10 days (Keplinger 1963). However, exposures were brief, air concentrations were not measured, and assessments were limited to clinical examinations and incomplete blood and urinalysis testing. Acute pulmonary insufficiency was noted in two agricultural workers involved in spraying a formulation consisting of (60% toxaphene, 35% kerosene, 3% xylol, and 2% emulsifier) for 2 months. No other information was located regarding health effects in humans exposed to toxaphene in the air.

Available animal data are limited to summaries of unpublished data cited in a secondary unpublished bulletin and a report of clinical signs of neurotoxicity in several animal species following repeated inhalation exposure to toxaphene dust (Industrial Biotest 1965). Some studies conducted by Industrial Biotest have been shown to be less than reliable.

Oral MRLs

- An MRL of 0.05 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to toxaphene.

Information on effects of acute-duration oral exposure to toxaphene in humans is limited to reports of cardiac dilatation and swelling of the kidneys in a 2-year-old boy who ingested an unspecified lethal amount of toxaphene (McGee et al. 1952), temporarily-compromised hepatic and renal function in a 26-year-old male who attempted suicide by ingesting an insecticide containing toxaphene as the active ingredient (Wells and Milhorn 1983), and signs of neurotoxicity (convulsive seizures, temporary memory loss, nausea) in several females who had ingested collard greens coated with toxaphene (McGee et al. 1952).

Available acute-duration oral toxicity animal studies include single-dose studies in rats (Garcia and Mourelle 1984; Peakall 1976), guinea pigs (Chandra and Durairaj 1992, 1995), and dogs (Chu et al. 1986; Lackey 1949); and multiple-dose studies in rats (Chernoff and Carver 1976; Chernoff et al. 1990; Kavlock et al. 1982; Mehendale 1978; Rao et al. 1986; Trottman and Desaiah 1980; Waritz et al. 1996), mice (Chernoff and Carver 1976; Hedli et al. 1998), and dogs (Chu et al. 1986; Lackey 1949). Targets of acute oral toxaphene toxicity include the nervous system, liver, body weight, immunological system, endocrine system, and development.

Several animal studies include reports of treatment-related liver weight changes following acute-duration oral exposure to toxaphene. Chernoff and Carver (1976) reported 23, 25, and 32% increased mean relative liver weight in mouse dams administered toxaphene by gavage at 15, 25, and 35 mg/kg/day during gestation days 7–16; the 35 mg/kg/day dose level represented a no-observed-adverse-effect level (NOAEL) for liver weight in similarly-treated rat dams. Trottman and Desaiah (1980) reported 20% increased mean liver weight in rats receiving toxaphene from the diet at 18 mg/kg/day for 14 days; the NOAEL for effects on liver weight was 13.5 mg/kg/day. Hedli et al. (1998) reported 48 and 78% increased mean relative liver weights in mice gavaged at 50 and 100 mg/kg/day, respectively, for 7 days;

the NOAEL for effects on liver weight was 25 mg/kg/day. Peakall (1976) reported a 9% increase in relative liver weight and significantly increased microsomal enzyme activity in rats at 5 days following administration of a single 120 mg/kg oral dose of toxaphene. Mehendale (1978) reported decreased biliary excretion of imipramine metabolites from perfused livers of rats that had received toxaphene from the diet at an estimated dose of 10 mg/kg/day for 8 days.

Chu et al. (1986) observed convulsions in dogs following oral administration of toxaphene at 10 mg/kg/day for 2 days; convulsions were not elicited after the dose was reduced to 5 mg/kg/day for the remainder of a 13-week treatment period. Lackey (1949) reported convulsions in dogs administered a single 10 mg/kg dose of toxaphene. Mild tremors and nervousness were noted in rats receiving toxaphene by gavage at 25 mg/kg/day for 3 days (Rao et al. 1986).

Toxaphene-induced effects on maternal body weight were observed in rat and mouse dams administered toxaphene via gavage during organogenesis (Chernoff and Carver 1976; Chernoff et al. 1990). The mouse study identified a NOAEL of 15 mg/kg/day and a serious lowest-observed-adverse-effect level (serious LOAEL) of 25 mg/kg/day for 22% decreased maternal body weight gain (Chernoff and Carver 1976). The rat studies identified serious LOAELs of 32 mg/kg/day (the only dose tested by Chernoff et al. 1990) and 15 mg/kg/day (the lowest dose tested by Chernoff and Carver 1976) for the effect.

Trottman and Desaiah (1980) reported a 36% decrease in mean thymus weight in rats receiving toxaphene from the diet at an estimated dose of 13.5 mg/kg/day for 14 days; this effect was not observed at the lower dose (9 mg/kg/day). The study report made no mention of histopathological evaluations.

A greater than 2-fold increase in serum TSH and histopathologic thyroid lesions were reported in rats administered toxaphene by gavage at 75 mg/kg/day (the only dose tested) for 14 days (Waritz et al. 1996).

Significantly increased incidence of supernumerary ribs (17% greater than controls) was reported in fetuses of rat dams administered toxaphene by gavage at 32 mg/kg/day (the only dose tested) during gestation days 6–15 (Chernoff et al. 1990). Significantly decreased fetal renal protein and slight, but statistically significant retardation in kidney development were reported in fetuses of rat dams administered toxaphene by gavage at 12.5 or 25 mg/kg/day during gestation days 7–16; lower dose levels were not tested (Kavlock et al. 1982).

The most sensitive effects of acute oral toxaphene toxicity were observed at doses in the range of 10–15 mg/kg/day and include increased liver weights, clinical signs of neurotoxicity, depressed maternal body weight gain, and indicators of treatment-related effects on developmental end points. There is some degree of uncertainty regarding the toxicological significance of the reported effects on liver weight, fetal renal protein, thymus weight, and biliary excretion of imipramine metabolites. The reported 22% decreased maternal body weight gain in the toxaphene-treated rat dams of the Chernoff and Carver (1976) study is clearly a serious adverse effect. However, this effect was observed at the lowest dose tested, and the study did not identify a NOAEL. ATSDR does not derive MRLs based on a serious LOAEL in the absence of an identified NOAEL. The dog study of Chu et al. (1986) identified a NOAEL (5 mg/kg/day) and a LOAEL (10 mg/kg/day) for clinical signs of toxaphene-induced neurotoxicity, but did not include histopathological investigations. To derive an acute-duration oral MRL for toxaphene, the dog study of Chu et al. (1986) is selected as the principal study, and the NOAEL of 5 mg/kg/day is selected as the critical effect and point of departure (POD) for MRL derivation. An acute-duration oral MRL derived in this manner is expected to be protective of toxaphene-induced effects on the nervous system, liver, endocrine system, and developmental end points.

In the principal study (Chu et al. 1986), groups of male and female beagle dogs (6/sex/group) were given gelatin capsules containing toxaphene at 0, 0.2, 2.0, or 5.0 mg/kg daily for 13 weeks. During the first 2 treatment days, the high-dose group received toxaphene at 10 mg/kg/day. This dose was reduced to 5 mg/kg/day on treatment day 3 because the 10 mg/kg/day dose level elicited convulsions, salivation, and vomiting in 1/6 males and 2/6 females. These clinical signs were not observed in any of the toxaphene-treated dogs throughout the remainder of the scheduled 13-week treatment period. This study identified a serious LOAEL of 10 mg/kg/day for neurological effects elicited during the first 2 days of oral treatment and a NOAEL of 5 mg/kg/day. Using the NOAEL of 5 mg/kg/day as the POD, application of a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) yields an acute-duration oral MRL of 0.05 mg/kg/day for toxaphene.

- An MRL of 0.002 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to toxaphene.

No human studies were located regarding the effects of intermediate-duration oral exposure to toxaphene.

Intermediate-duration oral toxicity studies are available for rats (Chu et al. 1986, 1988; Crowder et al. 1980; Garcia and Mourelle 1984; Kennedy et al. 1973; Koller et al. 1983; NCI 1979; Olson et al. 1980; Ortega et al. 1957; Peakall 1976; Waritz et al. 1996), mice (Allen et al. 1983; NCI 1979), dogs (Chu et al.

1986; Lackey 1949), and cynomolgus monkeys (Bryce et al. 2001; Tryphonas et al. 2000, 2001). The animal studies identified the nervous system, liver, kidney, thyroid gland, and immunological system as targets of toxaphene toxicity from intermediate-duration oral exposure. Lackey (1949) reported occasional convulsions in groups of dogs (2/group) administered toxaphene by capsule at 4 mg/kg/day for 44 or 106 days, but did not include more specific details. Study limitations preclude the usefulness of this study for quantitative risk assessment. One developmental toxicity study reported inferior swimming ability at postnatal days 10–12 in pups of rat dams receiving toxaphene from the diet at 0.05 mg/kg/day throughout gestation and for 30 days postpartum; however, swimming behavior appeared normal by postnatal day 16 (Olson et al. 1980). No additional studies were located to support the finding of toxaphene-related effects on postnatal development at such low dose levels.

Identified LOAELs for liver, kidney, and thyroid effects range from 0.5 to 45 mg/kg/day. A 13-week dietary study of male and female rats (Chu et al. 1986) identified the lowest LOAELs for these effects. Significantly increased incidences of histopathologic lesions of the liver (anisokaryosis) and kidney (renal tubular injury) were observed in the females at a 0.5 mg/kg/day dose level in the absence of an identified NOAEL. Similar effects were observed in the males at the dose level of 1.8 mg/kg/day; the lowest dose tested in the male rats (0.35 mg/kg/day) represented a NOAEL for liver and kidney effects. The same study identified NOAELs of 0.35 and 12.6 mg/kg/day and LOAELs of 1.8 and 63 mg/kg/day for morphologic lesions in the thyroid (angular collapse of follicles, increased epithelial height with multifocal papillary proliferation, and reduced colloid density) of the males and females, respectively. Chu et al. (1986) also observed hepatomegaly in dogs administered toxaphene by capsule at 5 mg/kg/day for 13 weeks, but no evidence of treatment-related liver effects at a daily 2 mg/kg dose level.

Depressed humoral immune responses have been observed in rats, mice, and cynomolgus monkeys administered toxaphene orally for periods ranging from 8 to 52 weeks. In an enzyme-linked immunosorbent assay (ELISA) performed on female mice that received toxaphene from the diet at doses ≥19 mg/kg/day for up to 8 weeks, Allen et al (1983) reported suppressed antibody production, indicating depressed humoral immunity; the study identified a NOAEL of 2 mg/kg/day for the effect. Koller et al. (1983) reported a 46% decrease in the IgG primary antibody response in male rats receiving toxaphene from the diet at 2.6 mg/kg/day for up to 9 weeks and challenged twice (after 8 and 15 days on test) with keyhole limpet hemocyanin (KLH).

Tryphonas et al. (2001) reported a NOAEL of 0.1 mg/kg/day and a LOAEL of 0.4 mg/kg/day for toxaphene-induced decreased anti-SRBC (IgM) titers as an indicator of depressed humoral immunity. In

the study, groups of 10 female cynomolgus monkeys/dose group received toxaphene via oral capsules at 0, 0.1, 0.4, or 0.8 mg toxaphene/kg/day for up to 75 weeks. Groups of 5 males dosed at 0 or 0.8 mg/kg/day were included in the study. Testing for immune effects was initiated on week 33 and included flow cytometry, lymphocyte transformation, natural killer cell activity and determination of serum cortisol during weeks 33–46 and immunizations with sheep red blood cells (SRBC) treatment at week 44 for a primary response and week 48 for a secondary response (observations made through treatment week 52). Treatment with toxaphene at 0.4 mg/kg/day resulted in significant ($p<0.05$) reductions in mean primary anti-SRBC IgM responses at weeks 1 and 4 following primary immunization (27 and 35% lower than that of controls) and secondary anti-SRBC IgM responses at week 1 following secondary immunization (10% lower than that of controls). The dose level of 0.8 mg/kg/day resulted in significantly reduced mean primary anti-SRBC IgM responses at weeks 1–4 following primary immunization, significantly reduced mean secondary anti SRBC IgM response at weeks 1 and 4 following secondary immunization, and significantly reduced primary anti-SRBC IgG responses at weeks 2 and 3 following primary immunization (51 and 43% lower than that of controls). In males, 0.8 mg/kg/day toxaphene induced a significant reduction in mean primary anti-SRBC IgM response at weeks 1–3 following primary immunization. Flow cytometry tests showed that the only effect on leukocyte and lymphocyte subsets was a reduction in absolute B lymphocytes (CD20) in 0.8 mg/kg/day females (62% lower than controls). There were no detectable treatment-related effects on natural killer cell activity, lymphoproliferative response to mitogens, or serum cortisol levels. This study identified the lowest LOAEL (0.4 mg/kg/day for depressed humoral immunity) among reliable LOAELs for intermediate-duration oral exposure to toxaphene, and is selected as the critical effect for deriving an intermediate-duration oral MRL for toxaphene.

To derive a POD for MRL derivation, BMD modeling was conducted using data for depressed humoral immunity from the female cynomolgus monkeys (Tryphonas et al. 2001). All continuous variable models in the EPA Benchmark Dose Software (Version 2.1.1) were fit to the mean anti-SRBC (IgM) titre data at week 1 post-immunization at treatment week 44; the modeled data are presented in Table A-3 of Appendix A. A default benchmark response (BMR) of 1 standard deviation (1SD) from the control mean was selected in the absence of a toxicological rationale for selecting an alternative BMR. As discussed in detail in Appendix A, the polynomial and power models converged on the linear model and provided identical fit to the data. These models predicted BMD_{1SD} and $BMDL_{1SD}$ values of 0.34 and 0.22 mg/kg/day, respectively. The $BMDL_{1SD}$ of 0.22 mg/kg/day was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability). The resulting intermediate-duration oral MRL is 0.002 mg/kg/day.

A chronic-duration oral MRL was not derived for toxaphene for the following reasons:

1. No human studies were located regarding the effects of chronic-duration oral exposure to toxaphene.

2. A study designed to assess the effect of toxaphene on the immune system of cynomolgus monkeys identified a LOAEL of 0.4 mg/kg/day for decreased anti-SRBC IgM response during intermediate-duration oral exposure (<52 weeks) that is lower than the LOAEL of 0.8 mg/kg/day for decreased anti-TT response to chronic-duration oral exposure (testing initiated after 53 weeks of treatment).

3. Toxaphene doses used in chronic duration oral toxicity studies in rats and mice (NCI 1979) were 2 orders of magnitude higher than doses eliciting immunological effects in cynomolgus monkeys treated for intermediate and chronic durations.

3. HEALTH EFFECTS

3.1 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 on 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 composed of over 670 different constituents; the relative proportions of the major components of the pesticide are essentially the same in different formulations. The production and use of toxaphene have been banned in the United States and all of its territories since 1990 (EPA 1990b). Nevertheless, because of its earlier widespread use, persistence in the environment, and storage in waste sites, exposure to toxaphene and its persistent congeners is still possible.

Following its release to the environment, technical toxaphene undergoes biotic and abiotic "weathering" processes, resulting in congener mixtures that differ from those of technical toxaphene (EPA 2010e; Ruppe et al. 2003, 2004; Simon and Manning 2006). Because toxaphene has not been used as a pesticide in the United States since 1990, exposure to persistent toxaphene congeners from weathered toxaphene is of primary health concern. Major congeners of toxaphene that have been found to persist in fish, marine mammals, and human serum and breast milk include Parlars p-26, p-40/41, p-44, p-50, and p-62 (Simon and Manning 2006). Pooled results of studies that assessed levels of these congeners in human serum and/or breast milk (Gill et al. 1996; Polder et al. 2003; Sandanger et al. 2003; Skopp et al. 2002b; Walker et al. 2003) indicate that p-26, p-50, and p-62 comprise approximately 33, 55, and 6%, respectively, of the total toxaphene body burden (Simon and Manning 2006).

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

3.2 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).

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 Levels of Significant Exposure (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 (LOAELs) 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 3-2 and Figure 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 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.

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.

3.2.1 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.

Limited information is available regarding health effects in animals following inhalation exposure to toxaphene. Secondary sources have cited unpublished results of studies for Hercules Incorporated, a major U.S. producer while toxaphene was registered for use as a pesticide in the United States. Although the primary study reports have not been made available to ATSDR, the results are presented in Section 3.2.1 as summarized in the Drinking Water Criteria Document for Toxaphene (EPA 1985c).

3.2.1.1 Death

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

A 40% toxaphene dust (3,000–4,000 mg/m^3) caused death in about one-half of an exposed group of rats after 1 hour of exposure (EPA 1985c). Unpublished results of repeated inhalation exposure studies cited by EPA (1985c) include the death of all rats (number unspecified) exposed to toxaphene dust at 250 mg/m^3 for up to 1 week, unspecified numbers of deaths among rats, dogs, and guinea pigs exposed at 12 mg/m^3 for up to 3 months (but no deaths at 4 mg/m^3), and no mortality in rats and rabbits exposed at 500 mg/m^3 for 3 weeks.

3.2.1.2 Systemic Effects

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

One controlled human study investigated the general effects of inhaled toxaphene. Keplinger (1963) reported that no toxic effects were seen in 25 human subjects (15 males, 10 females) exposed to an aerosol containing a maximum of 500 mg toxaphene/m^3 for 30 minutes/day for 10 days. The author estimated the absorbed dose to be as much as 60 mg/person/day. After a 3-week period, these same subjects were exposed for three more 30-minute periods. Examinations of these subjects 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 3-1 and plotted in Figure 3-1.

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.

Hematological Effects. No blood abnormalities were observed in a group of volunteers exposed to toxaphene spray 30 minutes/day for 10 days at a maximum nominal concentration of 500 mg/m^3 (Keplinger 1963). Clinical findings in two male Egyptian agricultural pesticide workers involved in the spraying of toxaphene (formulated as 60% toxaphene, 35% kerosene, 3% xylol, and 2% emulsifier) for approximately 2 months included elevated sedimentation rates, the presence of blood eosinophilia, and high serum globulin (Warraki 1963).

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

Slight hepatocellular necrosis was reported in some female rats that survived inhalation exposure to toxaphene dust (4 or 12 mg/m^3) for 3 months (EPA 1985c).

Table 3-1 Levels of Significant Exposure to Toxaphene - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Human	10 d 30 min/d	Resp	500			Keplinger 1963	
			Hemato	500				
			Renal	500				
			Dermal	500				

a The number corresponds to entries in Figure 3-1.

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

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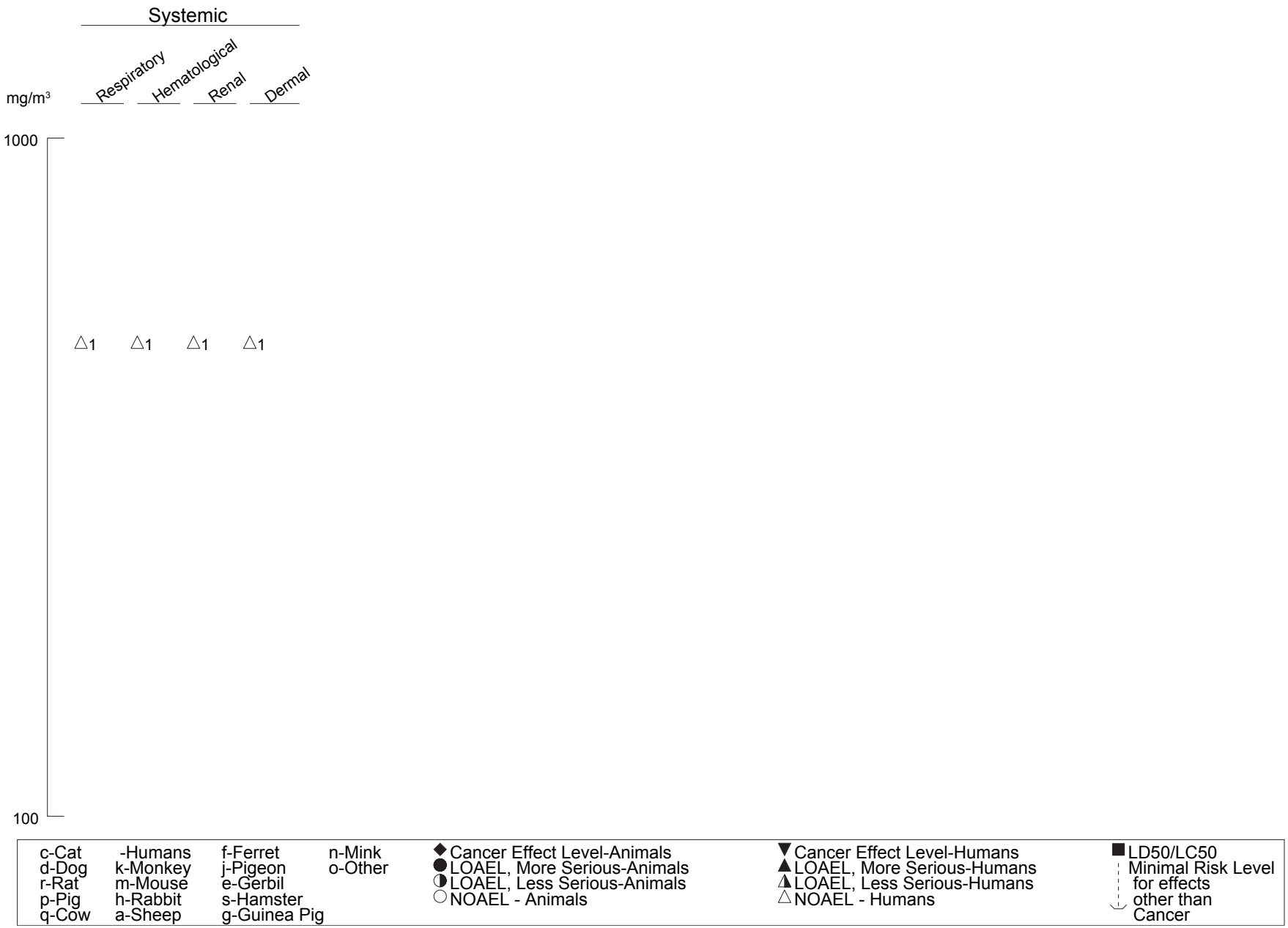
Figure 3-1 Levels of Significant Exposure to Toxaphene - Inhalation

Acute (≤14 days)



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Renal Effects. Urinalyses were normal for a group of volunteers exposed to toxaphene spray 30 minutes/day for 10 days at a maximum nominal concentration of 500 mg/m^3 (Keplinger 1963).

No studies were located regarding renal toxicity in animals following inhalation exposure to toxaphene.

Dermal Effects. There were no signs of exposure-related dermal effects in a group of 25 volunteers exposed to an aerosol containing a maximum nominal concentration of 500 mg/m^3 toxaphene for 30 minutes/day for 10 days (Keplinger 1963).

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

Body Weight Effects. No studies were available regarding body weight effects in humans or animals following inhalation exposure to toxaphene.

No studies were located regarding the following effects in humans or animals following inhalation exposure to toxaphene:

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

Mills et al. (2005) reported a significant association (odds ratio [OR]=2.20, 95% confidence interval [CI] 1.04–4.65) between risk of leukemia and exposure to toxaphene in a nested case-control study of 131 lymphohematopoietic cancer cases (leukemia, multiple myeloma, non-Hodgkin's lymphoma [NHL]) diagnosed between 1988 and 2001 among members of the United Farm Workers (UFW) labor union in California (cohort of 139,000 workers). For each case, five gender- and age-matched members of the UFW without any cancer diagnoses were selected as controls. Crop and pesticide exposures were estimated by linking job history information from union records with California Department of Pesticide Regulation pesticide use reports during the 20-year period prior to cancer diagnosis. There was no significant association between exposure to toxaphene and risk of multiple myeloma or NHL.

Schroeder et al. (2001) reported a significant association (OR=3.7, 95% CI 1.9–7.0) between t(14;18)-positive NHL cases (n=5) and toxaphene exposure. The FARM (Factors Affecting Rural Men) case-control study included 182 NHL cases assayed for the t(14;18) translocation. This translocation is a common somatic mutation associated with B cell CLL/lymphoma-2 gene expression. Controls consisted of 30 participants who did not report use of toxaphene on farms where they worked. The study authors mentioned that chromosomal damage has been reported to be higher in peripheral blood lymphocytes during the peak spraying season (Schroeder et al. 2001). This study is limited by the small numbers of cases and controls.

In an agricultural health study of 22,409 subjects assessed by interview and/or questionnaire for total lifetime exposure days to various pesticides, a statistically significant increased risk for rectal cancer (RR=2.0, 95% CI=1.1–3.5) was noted among those with self-reported exposure to toxaphene; the risk was independent of age (Purdue et al. 2006). However, no statistically significant association was found between toxaphene exposure and risk of leukemia or NHL within this study group.

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

3.2.2 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 animal studies 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, immunological system, and adrenal gland have also been identified as targets of toxaphene toxicity.

3.2.2.1 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. An approximate minimum lethal dose in humans was estimated to be 2–7 g (CDC 1963); however, the available report did not provide a basis for the estimate.

In animals, single-dose gavage administration of toxaphene resulted in estimated oral LD_{50} values of 80–293 mg/kg for rats (Boyd and Taylor 1971; Gaines 1969; Jones et al. 1968) and 25 mg/kg for dogs (Lackey 1949). A 300 mg/kg dose was reported to be lethal to male guinea pigs within 72 hours postdosing; the study authors indicated that the 300 mg/kg dose represented an LD_{50} dose level, but did not provide more detailed dosing information (Chandra and Durairaj 1995). Gavage administration of toxaphene to heifers (136–232 kg) at 50, 100, or 150 mg/kg resulted in 2/8, 6/7, and 5/6 deaths, respectively (Steele et al. 1980).

Mortality was also reported in animals following repeated gavage dosing. Epstein et al. (1972) observed the death of 2/12 and 9/12 male mice administered toxaphene by daily gavage on 5 consecutive days at 40 and 80 mg/kg, respectively. Chernoff and Carver (1976) administered toxaphene to rat and mouse dams on gestation days 7–16 at gavage doses of 0 (vehicle controls), 15, 25, or 35 mg/kg/day. Mortality was noted in 0/33, 2/39, 3/39, and 5/16 of the rat dams (0, 15, 25, and 35 mg/kg/day dose levels, respectively) and 1/75, 0/26, 0/45, and 07/90 of the mouse dams. In a separate study, Chernoff et al. (1990) observed mortality in 50% of the rat dams (n~25) administered toxaphene at 32 mg/kg/day during gestation days 6–15. In a 28-day oral toxicity study, Waritz et al. (1996) administered toxaphene (in corn oil) by daily gavage to a group of 40 male rats. An initial dose level of 100 mg/kg/day was reduced to 75 mg/kg/day after 2/40 of the treated rats died after three doses; no additional unscheduled deaths were observed. 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). Among groups of dogs administered toxaphene once via gavage in corn oil at 15, 20, 25, 30, 40, or 50 mg/kg, mortalities were noted in 2/8, 1/5, 6/7, 4/7, 3/7, and 5/5 animals, respectively. However, when toxaphene was administered in kerosene (a poorly absorbed solvent) at 25–250 mg/kg, mortalities were observed only at doses ≥200 mg/kg.

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_{50} for rats fed a protein-deficient diet was 80 mg/kg/day, whereas the oral LD_{50} 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.

No treatment-related deaths were observed in a one-generational two-litter study of rats administered toxaphene in the diet for 48 weeks at estimated doses up to 46 mg/kg/day (Chu et al. 1988). The lack of lethality at a dietary dose within the range of LD_{50} doses noted previously is likely a reflection of differences in dose rate (i.e., bolus gavage dosing versus a slower dose rate from feeding). Treatment-related mortality was not observed in rats following gavage administration of 6 mg/kg/day for 21 days (Crowder et al. 1980). In a 6-week range-finding study that employed groups of male and female B6C3F1 mice (5/sex/group), estimated toxaphene doses of 58 and 115 mg/kg/day to males resulted in 1/5 and 2/5 deaths, respectively; estimated toxaphene doses of 62 and 125 mg/kg/day to females resulted in 1/5 and 4/5 mortalities, respectively (NCI 1979). In similarly-treated Osborne-Mendel rats, estimated doses of 112 and 224 mg/kg/day to males resulted in 0/5 and 1/5 deaths, respectively; estimated doses of 121 and 242 mg/kg/day to females caused 0/5 and 2/5 deaths, respectively. In a subsequent cancer bioassay in which toxaphene was administered in the diet to Osborne-Mendel rats and B6C3F1 mice for 80 weeks, estimated TWA doses as high as 83 and 34 mg/kg/day, respectively, did not appear to significantly affect survival (NCI 1979). No treatment-related mortality was observed in parental male or female Sprague-Dawley rats administered toxaphene in the diet for up to 42 weeks at estimated doses up to 8.6 mg/kg/day (males) or 9.8 mg/kg/day (females) (Kennedy et al. 1973).

The LD_{50} values and doses associated with death in each species following acute and intermediate oral exposure are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal effects following oral exposure of humans or animals to toxaphene. 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 systemic effect are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Available information regarding respiratory effects in humans following oral exposure to toxaphene is limited to an account of congestion and edema of the lungs at autopsy of a 2-year-old boy who ingested an unspecified but lethal amount of toxaphene (McGee et al. 1952).

Table 3-2 Levels of Significant Exposure to Toxaphene - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	once (GO)				220 M (LD50 for standard laboratory chow diet)	Boyd and Taylor 1971	
2	Rat (Wistar)	once (GO)				80 M (LD50 low protein diet)	Boyd and Taylor 1971	
3	Rat (Wistar)	once (GO)				293 M (LD50 for normal-protein diet)	Boyd and Taylor 1971	
4	Rat (CD)	Gd 7-16 1x/d (GO)				35 F (5/16 maternal deaths)	Chernoff and Carver 1976	
5	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GO)				32 F (50% maternal lethality)	Chernoff et al. 1990	
6	Rat (Sherman)	once (GO)				90 M (LD50) 80 F (LD50)	Gaines 1969	
7	Rat (NS)	once (G)				283 (LD50)	Jones et al. 1968	
8	Mouse (CD-1)	Gd 7-16 1x/d (GO)				35 F (7/90 maternal deaths)	Chernoff and Carver 1976	
9	Mouse (ICR/Ha Swiss)	5 d 1x/d (G)				40 M (death; 2/12)	Epstein et al. 1972	

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Gn Pig (NS)	once (GO)				300 M (death)	Chandra and Durairaj 1995	
11	Dog (NS)	once (GO)				15 (death of 2/8 dogs)	Lackey 1949	
12	Dog (NS)	once (GO)				200 (death in 1/5 dogs)	Lackey 1949	
Systemic								
13	Rat (CD)	Gd 7-16 1x/d (GO)	Hepatic	35 F			Chernoff and Carver 1976	
			Bd Wt			15 F (22% reduced maternal weight gain)		
14	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GO)	Bd Wt			32 F (up to 50% depressed maternal weight gain)	Chernoff et al. 1990	
15	Rat (Sprague-Dawley)	8 d ad lib (F)	Hepatic		10 M (23% decline in biliary excretion of imipramine metabolites)		Mehendale 1978	
16	Rat (Osborne-Mendel)	80 wk ad lib (F)	Bd Wt	147 F	130 M (14% lower mean body weight)		NCI 1979	Body weight results during the first 2 weeks of an 80-week dietary exposure period

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Rat (NS)	once (C)	Hepatic		120 M (9% increased relative liver weight)		Peakall 1976	
18	Rat (Sprague-Dawley)	14 d ad lib (F)	Hepatic	13.5 M	18 M (20% increased relative liver weight)		Trottman and Desaiah 1980	No effects on body, heart, or kidney weights
			Bd Wt	18 M				
19	Rat (Sprague-Dawley)	14 d 1 x/d (GO)	Endocr		75 M (increased TSH; thyroid histopathology)		Waritz et al. 1996	
20	Mouse (CD-1)	Gd 7-16 1x/d (GO)	Hepatic		15 F (23% increased relative liver weight)		Chernoff and Carver 1976	
			Bd Wt	15 F		25 F (22% depressed body weight gain)		
21	Mouse (CD-1)	7 d 1 x/d (GO)	Hepatic	25 M	50 M (48% increased relative liver weight)		Hedli et al. 1998 toxaphene	
			Bd Wt	100 M				
22	Gn Pig (NS)	once (GO)	Hepatic	300 M			Chandra and Durairaj 1992	
			Renal	300 M				

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
23	Rat (Sprague-Dawley)	14 d ad lib (F)		9 M	13.5 M (36% decreased relative thymus weight)		Trottman and Desaiah 1980	
Neurological								
24	Rat (Sprague-Dawley)	3 d 1x/d (GO)			25 M (mild tremors, nervousness)		Rao et al. 1986	
25	Gn Pig (NS)	once (GO)				300 M (sedation, convulsions)	Chandra and Durairaj 1995	
26	Dog (Beagle)	13 wk (C)		5[b]		10 (convulsions, salivation, and vomiting in 1/6 males and 2/6 females)	Chu et al. 1986	Neurological effects observed during the first 2 treatment days at 10 mg/kg/day, but not 5 mg/kg/day from treatment day 3 onward
27	Dog (NS)	once (GO)		5		10 (convulsions)	Lackey 1949	
28	Bovine (Mixed-breed)	once (GW)				50 (convulsions)	Steele et al. 1980	
Developmental								
29	Rat (Sprague-Dawley)	Gd 6-15 1x/d (GO)			32 (significantly increased incidence of fetal supernumerary ribs)		Chernoff et al. 1990	

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Rat (CD)	Gd 7-16 1x/d (GO)			12.5 F (decreased fetal renal protein)		Kavlock et al. 1982	Decreased fetal renal protein may indicate retardation in fetal growth
31	Mouse (CD-1)	Gd 7-16 1x/d (GO)		35 F			Chernoff and Carver 1976	
INTERMEDIATE EXPOSURE								
Death								
32	Rat (Osborne-Mendel)	6 wk ad lib (F)				224 M (death in 1/5 males) 242 F (death of 2/5 females)	NCI 1979	
33	Mouse (B6C3F1)	6 wk ad lib (F)				57.7 M (death of 1/5 males) 31.2 F (death of 1/5 females)	NCI 1979	
Systemic								
34	Monkey (Cynomolgus)	52 wk 1 x/d (C)	Ocular		1 (inflammation and/or enlargement of tarsal glands during treatment weeks 8-13; impacted diverticulae of eyelids during treatment weeks 10-41)		Bryce et al. 2001	

Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Rat (Sprague-Dawley)	13 wk ad lib (F)	Hemato	45.9 M 63 F			Chu et al. 1986	
			Hepatic	0.35 M 0.5 F	1.8 M (nuclear necrosis, anisokaryosis) 2.6 F (nuclear necrosis, anisokaryosis)			
			Renal	0.35 M	1.8 M (tubular injury) 0.5 F (tubular necrosis, anisokaryosis)	8.6 M (focally severe tubular injury) 45.9 M (multiple and relatively severe kidney lesions) 12.6 F (focally severe tubular injury)		
			Endocr	0.35 M 12.6 F	1.8 M (moderate morphological changes in thyroid) 63 F (moderate morphological changes in thyroid)			
			Bd Wt	45.9 M 63 F				

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Sprague-Dawley)	26 wk ad lib (F)	Hemato	45 M 46 F			Chu et al. 1988	
			Hepatic	45 M 46 F				
			Renal	9.2 M 8.5 F	45 M (18% increased kidney weight, increased incidence of tubular injury) 46 F (increased incidence of renal tubular injury)			
			Endocr	9.2 M 8.5 F	45 M (cytoplasmic vacuolation in thyroid) 46 F (cytoplasmic vacuolation in thyroid)			
			Bd Wt	45 M 46 F				
37	Rat (Sprague-Dawley)	21 d 1x/d (GO)	Bd Wt	6			Crowder et al. 1980	

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
38	Rat (Sprague-Dawley)	39-42 wk ad lib (F)	Cardio	8.6 M			Kennedy et al. 1973	
				9.8 F				
			Hepatic	2.2 M	8.6 M (cytoplasmic vacuolation)			
				2.5 F	9.8 F (cytoplasmic vacuolation)			
			Renal	8.6 M				
				9.8 F				
			Endocr	8.6 M				
				9.8 F				
			Bd Wt	8.6 M				
				9.8 F				
39	Rat (Sprague-Dawley)	6-9 wk ad lib (F)	Hepatic	2.6 M	26 M (24% liver weight increase and hepatic degeneration)		Koller et al. 1983	
			Endocr	26 M				
			Bd Wt	26 M				
40	Rat (Osborne-Mendel)	6 wk ad lib (F)	Bd Wt	224 M			NCI 1979	
				242 F				

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
41	Rat (Sherman)	up to 9 mo ad lib (F)	Renal	20 M 22.6 F			Ortega et al. 1957	
			Bd Wt	20 M 22.6 F				
42	Rat (Sprague-Dawley)	28 d 1 x/d (GO)	Endocr		75 M (increased TSH; thyroid histopathology)		Waritz et al. 1996	
43	Mouse (Swiss Webster)	8 wk ad lib (F)	Resp	39 F			Allen et al. 1983	
			Cardio	39 F				
			Gastro	39 F				
			Hepatic	2 F	19.5 F (increased relative liver weight, variation in cell size with some fatty infiltration)			
			Renal	39 F				
			Endocr	39 F				
			Bd Wt	39 F				
44	Mouse (B6C3F1)	6 wk ad lib (F)	Bd Wt	57.7 M			NCI 1979	

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
45	Dog (Beagle)	13 wk 7 d/wk 1x/d (C)	Hemato	5			Chu et al. 1986	
			Hepatic	2	5 (increased liver weight, increased serum alkaline phosphatase, hepatomegaly)			
			Renal	5				
			Bd Wt	5				
Immuno/ Lymphoret								
46	Monkey (Cynomolgus)	52 wk 1 x/d (C)		1			Tryphonas et al. 2000	Antibody response testing was performed during treatment weeks 36-51
47	Monkey (Cynomolgus)	Up to 75 wk 1 x/d (C)		0.1 F	0.4 F[c] (depressed humoral immunity)		Tryphonas et al. 2001	27-35% depressed humoral immunity expressed as reduced anti-SRBC IgM response during treatment weeks 45-49
48	Rat (Sprague-Dawley)	39-42 wk ad lib (F)		8.6 M 9.8 F			Kennedy et al. 1973	

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
49	Rat (Sprague-Dawley)	9 wk ad lib (F)				2.6 M (46% decreased IgG primary antibody response at day 15 postimmunization)	Koller et al. 1983	
50	Mouse (Swiss Webster)	8 wk ad lib (F)		2 F	19.5 F (depressed humoral immunity)		Allen et al. 1983	
Neurological								
51	Rat (Sprague-Dawley)	21 d 1x/d (GO)		6			Crowder et al. 1980	
52	Dog (NS)	44 or 106 d 1x/d (C)				4 (convulsions)	Lackey 1949	
Reproductive								
53	Rat (Sprague-Dawley)	48 wk ad lib (F)		46			Chu et al. 1988	
54	Rat (Sprague-Dawley)	39-42 wk ad lib (F)		8.6 M 9.8 F			Kennedy et al. 1973	
55	Mouse (Swiss)	multigen (F)		4.9 F			Keplinger et al. 1970	

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
56	Rat (Sprague-Dawley)	Gd 7-21 1x/d (GO)			6 (transiently delay in development of righting reflex)		Crowder et al. 1980	
57	Mouse (Swiss Webster)	9.5 wk ad lib (F)		2	19.5 (suppression of macrophage phagocytic function)		Allen et al. 1983	Immune function was tested in 8-week-old mice from dams that had been administered toxaphene in the diet during gestation and lactation
CHRONIC EXPOSURE								
Systemic								
58	Monkey (Cynomolgus)	75 wk 1 x/d (C)	Hemato	0.8 F			Arnold et al. 2001	
			Bd Wt	0.8 F				
59	Monkey (Cynomolgus)	52 wk 1 x/d (C)	Resp	1			Bryce et al. 2001	
			Cardio	1				
			Gastro	1				
			Hemato	1				
			Hepatic	1				
			Renal	1				
			Endocr	1				
			Bd Wt	1				

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
60	Rat (Osborne-Mendel)	80 wk ad lib (F)	Resp		39 M (dyspnea, epistaxis)		NCI 1979	
			Gastro		39 M (abdominal distension, diarrhea)			
			Hepatic	77.9 M 83.3 F				
			Renal		39 M (hematuria)			
			Dermal		39 M (alopecia, dermatitis, rough hair coats)			
			Bd Wt	77.9 M	41.6 F (up to 15% lower mean body weight)			
61	Mouse (B6C3F1)	80 wk ad lib (F)	Resp		17 (dyspnea)		NCI 1979	
			Gastro		17 (abdominal distension, diarrhea)			
			Dermal		17 (alopecia, rough hair coat)			
			Bd Wt	34				

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Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
62	Monkey (Cynomolgus)	Up to 75 wk 1 x/d (C)		0.4 F	0.8 F (depressed humoral immunity)		Tryphonas et al. 2001	Depressed humoral immunity expressed as reduced anti-TT titers during treatment weeks 53-63
Neurological								
63	Monkey (Cynomolgus)	52 wk 1 x/d (C)		1			Bryce et al. 2001	
64	Rat (Osborne-Mendel)	80 wk ad lib (F)				39 M (leg paralysis, ataxia, epistaxis) 41.6 F (leg paralysis, ataxia, epistaxis)	NCI 1979	
65	Mouse (B6C3F1)	80 wk ad lib (F)		34 F	17 M (hyperexcitability)		NCI 1979	
Reproductive								
66	Monkey (Cynomolgus)	75 wk 1 x/d (C)		0.8 F			Arnold et al. 2001	NOAEL is for menstrual status
67	Monkey (Cynomolgus)	52 wk 1 x/d (C)		1			Bryce et al. 2001	

Table 3-2 Levels of Significant Exposure to Toxaphene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Rat (Osborne-Mendel)	80 wk ad lib (F)			41.6 F (vaginal bleeding)		NCI 1979	
Cancer								
69	Rat (Osborne-Mendel)	80 wk ad lib (F)				77.9 M (CEL: follicular -cell carcinomas, thyroid adenomas)	NCI 1979	
						83.3 F (CEL: thyroid adenomas)		
70	Mouse (B6C3F1)	80 wk ad lib (F)				17 M (CEL: hepatocellular carcinoma)	NCI 1979	
						17 F (CEL: hepatocellular carcinoma or neoplastic nodule)		

a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

c Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.002 mg/kg/day; the BMDL1SD of 0.22 mg/kg/day, based on benchmark dose analysis of anti-SRBC (IgM) titers as an indicator of humoral immunity, was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F)= feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; x = time(s); wk = week(s)

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Figure 3-2 Levels of Significant Exposure to Toxaphene - Oral

Acute (≤14 days)

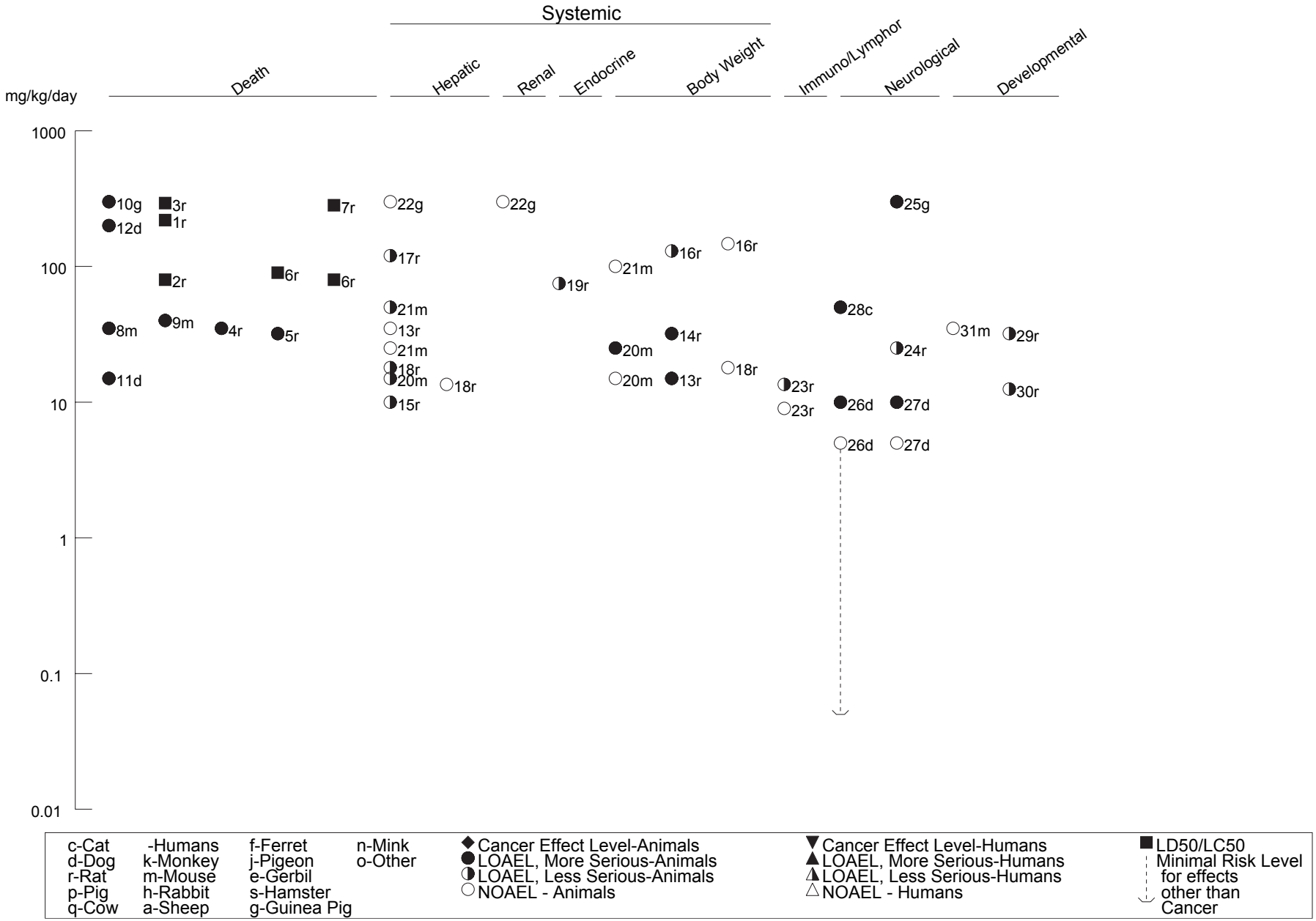

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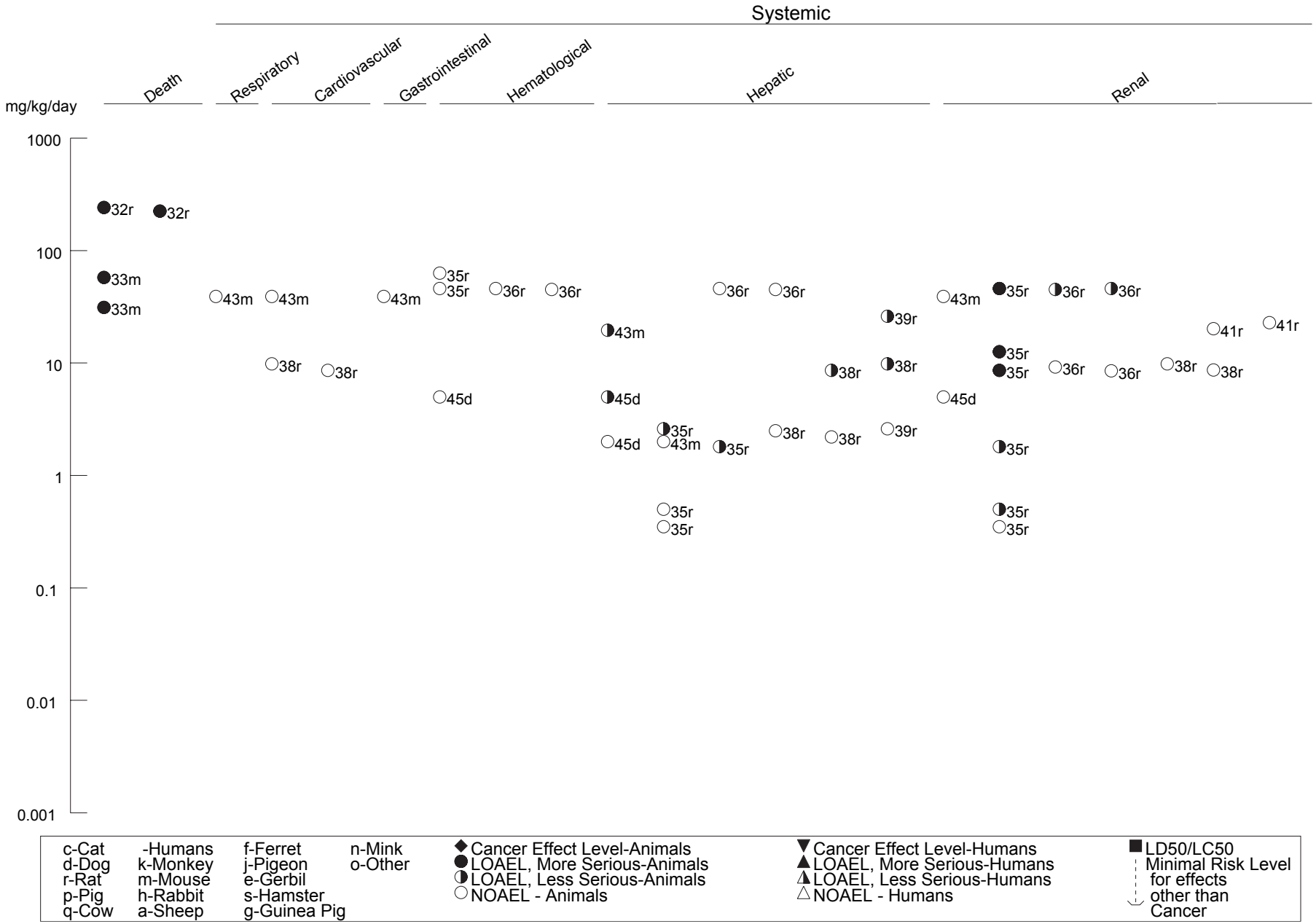
Figure 3-2 Levels of Significant Exposure to Toxaphene - Oral *(Continued)*

Intermediate (15-364 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

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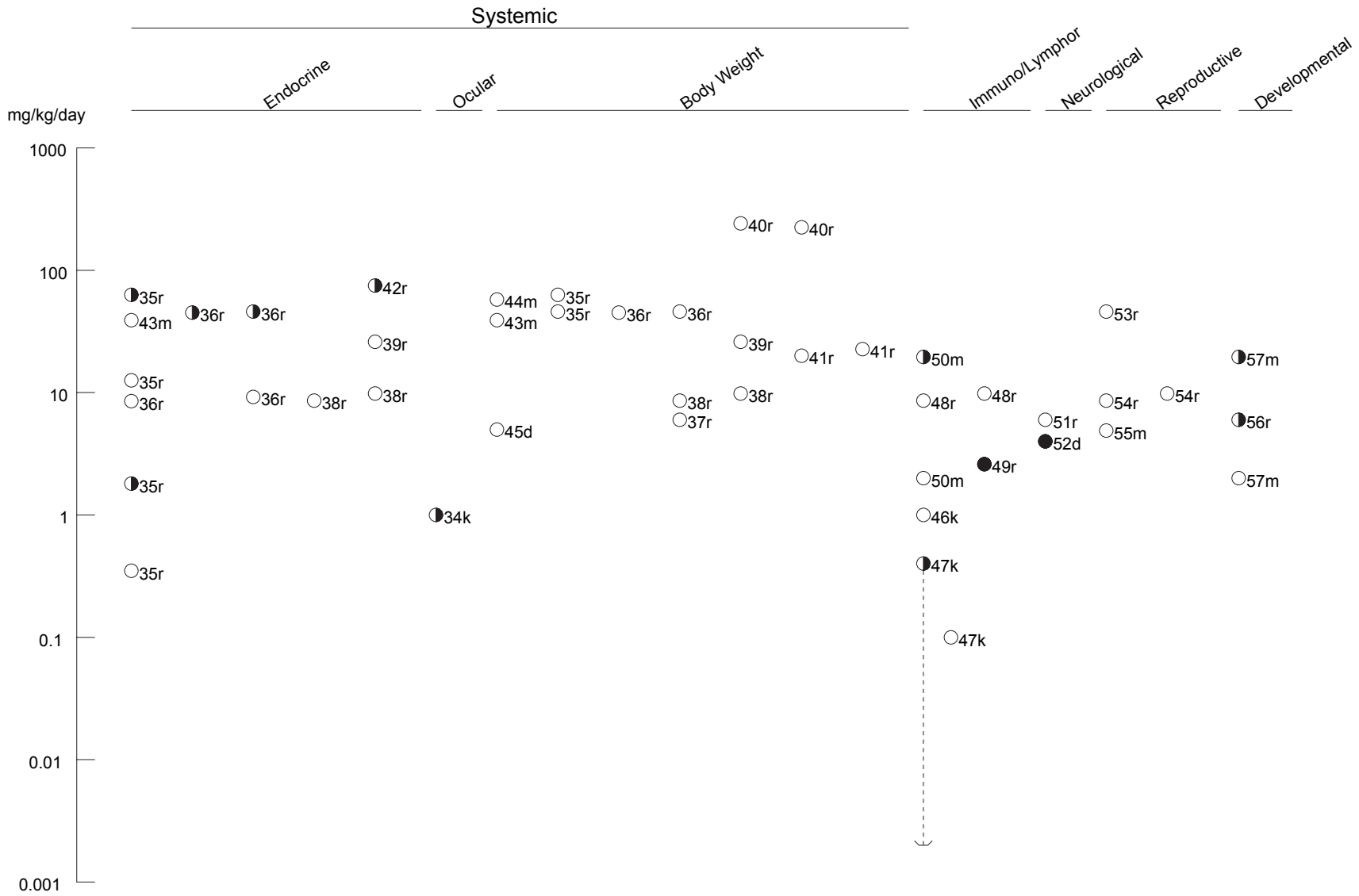
Figure 3-2 Levels of Significant Exposure to Toxaphene - Oral *(Continued)*

Intermediate (15-364 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

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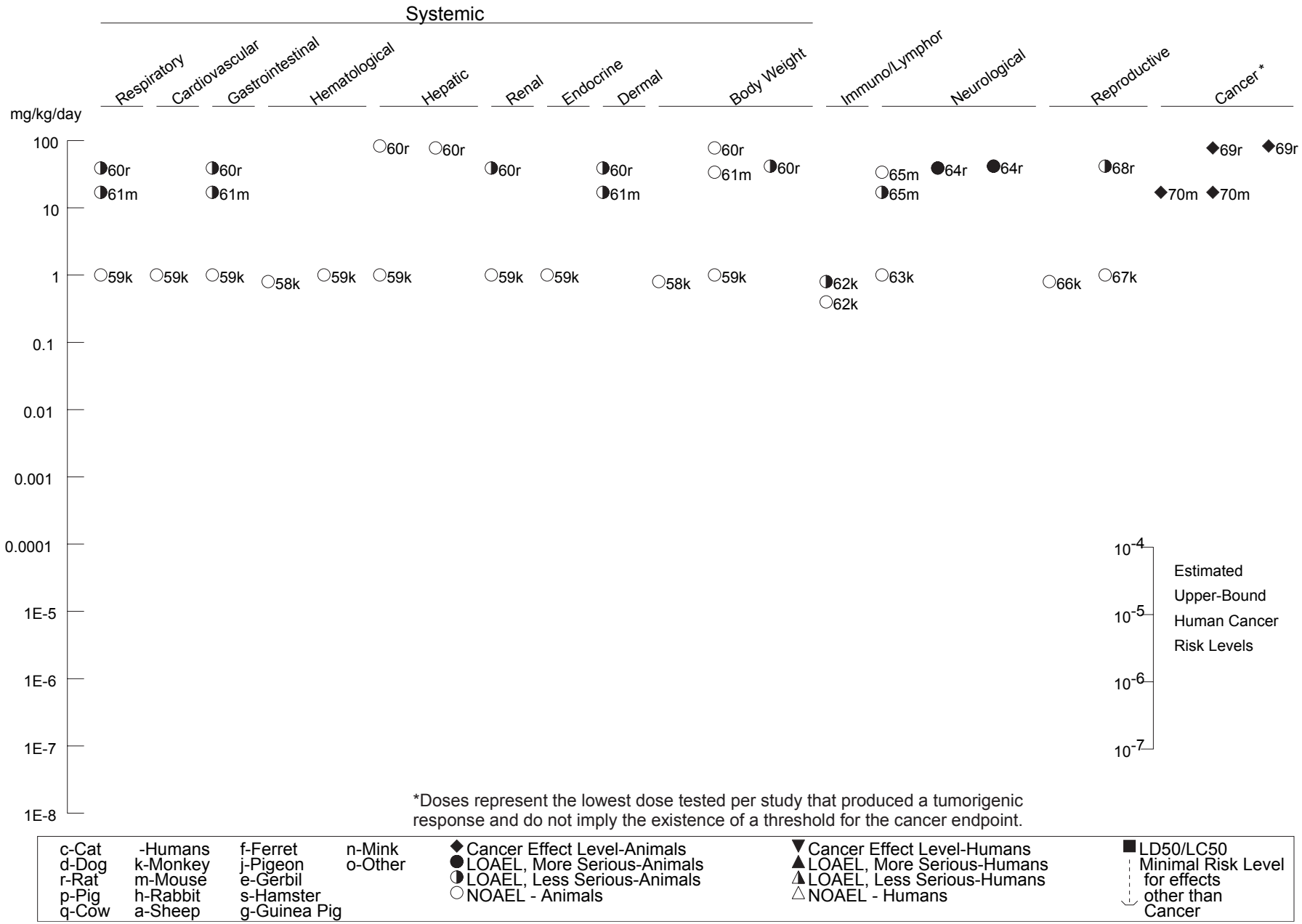
Figure 3-2 Levels of Significant Exposure to Toxaphene - Oral *(Continued)*

Chronic (≥365 days)



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 1979). Bryce et al. (2001) noted no remarkable histopathology following examination of tissues (including lung tissue) from cynomolgus monkeys administered toxaphene by oral capsule at 1 mg/kg/day for 52 weeks.

Cardiovascular Effects. Available information regarding cardiovascular effects in humans following oral exposure to toxaphene is limited to a report of dilatation of the heart at autopsy of a 2-year-old boy who ingested an unspecified but lethal amount of toxaphene (McGee et al. 1952).

Available information in animals is limited. Congestion and hemorrhage of cardiac capillaries were observed in rats that died following single gavage administration of an unspecified dose of toxaphene (Boyd and Taylor 1971). These effects are indicative of a generalized inflammatory response. Increased heart rate, in the absence of apparent effects on the vascular system, was noted in dogs following administration of a 10 mg/kg dose of toxaphene (Lackey 1949). Progressive neural degeneration was noted in the hearts of pregnant rats following daily gavage administration of toxaphene at 12 mg/kg/day 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.

No treatment-related effects on heart weight were observed in rats fed toxaphene in the diet for 14 days at 10 mg/kg/day (Trottman and Desaiah 1980) or up to 42 days at 8.6 mg/kg/day (males) or 9.8 mg/kg/day (females) (Kennedy et al. 1973). Bryce et al. (2001) noted no remarkable histopathology following examination of tissues (including heart tissue) from cynomolgus monkeys administered toxaphene by oral capsule at 1 mg/kg/day for 52 weeks.

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 normal protein content, in keeping with the apparent “diet-dependency” of toxaphene toxicity. Abdominal distension and diarrhea were observed in rats and mice receiving toxaphene from the

diet during 80 weeks at doses ≥39 mg/kg/day (rats) or ≥17 mg/kg/day (mice) (NCI 1979). These effects were most prominent in the high-dose (78 mg/kg/day) male rats. Bryce et al. (2001) noted no remarkable histopathology following examination of tissues (including esophagus, stomach, and small and large intestine) from cynomolgus monkeys administered toxaphene by oral capsule at 1 mg/kg/day for 52 weeks.

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 106 days (Lackey 1949); male and female rats receiving toxaphene from the diet for 13 weeks at estimated doses of 45.9 or 63 mg/kg/day, respectively (Chu et al. 1986); or male rats receiving 45 mg/kg/day from the diet for 26 weeks (Chu et al. 1988). There was no evidence of treatment-related hematological effects in cynomolgus monkeys administered toxaphene in oral capsules at 1 mg/kg/day for 52 weeks (Bryce et al. 2001) or 0.1–0.8 mg/kg/day for up to 75 weeks (Arnold et al. 2001). 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; the study authors attributed this to a generalized stress reaction (Boyd and Taylor 1971).

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 Milhorn 1983).

Oral administration of toxaphene has been shown to result in increased liver weight in some studies of rats and mice (Allen et al. 1983; Chernoff and Carver 1976; Chu et al. 1986, 1988; Hedli et al. 1998; Koller et al. 1983; Peakall 1976).

Chandra and Durairaj (1992) reported 13% increased absolute (but not relative) liver weight in guinea pigs administered a single gavage dose of toxaphene at 300 mg/kg (in groundnut oil) in the absence of indications of treatment-related histopathologic liver lesions. In a subsequent study by the same investigators (Chandra and Durairaj 1995), a similar exposure scenario resulted in significantly decreased

hepatic phospholipid content and significantly increased hepatic neutral lipid content. Similar effects were noted in other guinea pigs receiving toxaphene by gavage at 5 mg/kg/day for 60 days (Chandra and Durairaj 1995).

Inhibition of hepatobiliary function was reported in perfused livers from male rats exposed to 5 mg/kg/day toxaphene in feed for 8 days (Mehendale 1978). Induction of hepatic microsomal enzymes and increased liver weights were noted in male rats given 120 mg/kg/day by capsule or 10 mg/kg/day in feed for 14 days (Peakall 1976; Trottman and Desaiah 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). Increased hepatic microsomal activity (aminopyrene, ethoxyresorufin, and methoxyresorufin) was noted in male and female cynomolgus monkeys (two per sex) administered toxaphene in glycerol/corn oil via gelatin capsule at 1 mg/kg/day for 52 weeks compared to vehicle controls (Bryce et al. 2001). 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 is not generally considered adverse, but enzyme induction may precede the onset of more serious hepatic effects.

Morphological and degenerative changes were 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 was also observed in rats following intermediate exposure to toxaphene at 2.4 mg/kg/day (Peakall 1976) or 16.5 mg/kg/day (Garcia and Mourelle 1984). The study of Peakall (1976) did not include a concurrent control group. Toxaphene may also induce hypoxia and alter hepatic energy metabolism because it has been shown to decrease lactate dehydrogenase activity (Gertig and Nowaczyk 1975; Kuz'minskaya and Alekhina 1976). The intermediate-duration oral administration of 2 mg/kg/day toxaphene to dogs caused increased relative liver weight, hepatomegaly, and hepato-cellular 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_0 male and female rats fed toxaphene at 45 mg/kg/day for at least 26 weeks (Chu et al. 1988).

Liver necrosis was observed in dogs chronically administered 5 mg/kg/day toxaphene in the feed (EPA 1985c; summary of an unpublished report for Boots Hercules Agrochemicals). The unpublished report was not available to ATSDR. Histopathologic examinations of livers from male and female rats and mice receiving toxaphene from the diet for up to 80 weeks at estimated time-weighted average (TWA) doses as high as 78–83 mg/kg/day (rats) and 34 mg/kg/day (mice) revealed no evidence of treatment-related nonneoplastic lesions (NCI 1979). See Section 3.2.2.7 for discussion of cancer results from the NCI (1979) study. Bryce et al. (2001) noted no remarkable histopathology following examination of tissues (including liver) from cynomolgus monkeys administered 1 mg/kg/day of toxaphene by oral capsule for 52 weeks.

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 Milhorn 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. 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 Desaiah 1980). Renal injury has also been reported to occur following intermediate exposure to toxaphene. Guinea pigs given toxaphene orally at 2 or 5 mg/kg/day for 60 days exhibited histopathologic lesions that included intense vacuolation in the kidney's collection cells and glomerulus, cortical tubule cellular degeneration, and tubular epithelial cell vacuolation (Chandra and Durairaj 1992). Ultrastructural evaluation revealed an increase in the number of mitochondria in the tubular epithelial cells. However, NOAEL and LOAEL values for this study were not established because the study report did not include incidence data for the kidney lesions. Dose-dependent injuries of the proximal convoluted tubules that were focally severe were observed in rats fed 8.6 (males) and 12.6 (females) mg/kg/day toxaphene for 13 weeks (Chu et al. 1986). Chu et al. (1988) reported 18% increased kidney weight and renal tubular injury in male rats receiving toxaphene from the diet for 26 weeks at 45 mg/kg/day and renal tubular injury in similarly-treated female rats. However, Ortega et al. (1957) reported that a dose level of 10 mg/kg/day of toxaphene was not nephrotoxic to rats. 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).

Hematuria was reported in rats receiving toxaphene from the diet for up to 80 weeks at doses in the range of 39–83 mg/kg/day (NCI 1979). Bryce et al. (2001) noted no remarkable histopathology following examination of tissues (including kidney and urinary bladder) from cynomolgus monkeys administered toxaphene by oral capsule at 1 mg/kg/day for 52 weeks.

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

Histopathological evidence of toxaphene-related effects on the thyroid gland (angular collapse of follicles, increased epithelial height with multifocal papillary proliferation, and reduced colloid density) of male rats was observed following intermediate-duration oral administration at 1.8 mg/kg/day (Chu et al. 1986). The morphological changes were dose-dependent, considered mild to moderate in severity, and adaptive in nature. The LOAEL for histopathologic thyroid lesions in female rats was 63 mg/kg/day; NOAELs were 0.35 mg/kg/day for males and 12.6 mg/kg/day for females. A similarly-designed study by Chu et al. (1988) found no evidence of treatment-related histopathological thyroid lesions at 1.8 mg/kg/day (male rats) and 1.9 mg/kg/day (female rats).

In a 28-day gavage study designed to assess thyroid function in toxaphene-treated male rats, Waritz et al. (1996) reported significant ($p<0.05$) time-related increases in serum TSH and histopathological evidence of treatment-related effects that included increased incidences of thyroid follicular cell hypertrophy, diffuse intrafollicular hyperplasia, and decreased follicular size (indicative of depletion of colloid stores). This study employed a single dose level of 75 mg toxaphene/kg (100 mg/kg/day for the first 3 treatment days); the thyroid effects were considered to be associated with increased excretion of T_3 and/or T_4 resulting from the induction of hepatic CYPs.

In a study of male rats receiving toxaphene from the diet for 14 days, respective mean relative thymus weights at estimated doses of 13.5 and 18 mg/kg/day were 36 and 27% lower than that of controls; these effects were not seen at doses of 4.5 or 9 mg/kg/day (Trottman and Desaiah 1980). In another rat study, dietary exposure at estimated doses up to and including 8.6 mg/kg/day (males) and 9.8 mg/kg/day (females) for 39–42 weeks did not affect spleen or thymus weights (Kennedy et al. 1973).

Bryce et al. (2001) noted no remarkable histopathology following examination of tissues (including thyroid, pituitary, and adrenal glands) from cynomolgus monkeys administered toxaphene by oral capsule at 1 mg/kg/day for 52 weeks.

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

Alopecia and rough hair coats were reported in rats and mice receiving toxaphene from the diet for up to 80 weeks at estimated TWA doses ≥39 and ≥17 mg/kg/day, respectively (NCI 1979).

Ocular Effects. No information was located regarding ocular effects in humans following oral exposure to toxaphene.

Available information in animals is limited to a report of inflammation and/or enlargement of tarsal glands of the eye in three of four cynomolgus monkeys and impacted diverticulae of the eyelid of all four monkeys during oral administration of toxaphene at 1 mg/kg/day for 52 weeks (Bryce et al. 2001).

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

The influence of oral toxaphene on body weight has been widely studied in laboratory animals. Some rat studies employed relatively low single- or multiple-dose levels (<20 mg/kg/day) and found no evidence of toxaphene-induced body weight effects following acute- or intermediate-duration oral exposure (Crowder et al. 1980; Kennedy et al. 1973; Ortega et al. 1957; Trottman and Desaiah 1980). There was no evidence of toxaphene-related body weight effects in intermediate-duration multiple-dose studies of rats or mice where the highest toxaphene doses ranged from 26 to 39 mg/kg/day (Allen et al. 1983; Chu et al. 1986, 1988; Koller et al. 1983).

NCI (1979) found no evidence of a treatment-related effect on body weight in a range-finding study of male and female rats and mice administered toxaphene in the diet for 6 weeks at doses as high as 242 mg/kg/day (rats) and 250 mg/kg/day (mice). However, in the subsequent chronic study that included 80 weeks of dietary exposure to toxaphene, groups of male rats receiving toxaphene from the diet at 131 and 270 mg/kg/day for the first 2 treatment weeks exhibited approximately 14 and 26% lower mean body weights, respectively, than their matched controls (NCI 1979). Throughout the remaining 78 weeks

of treatment, which included two 50% reductions in toxaphene concentrations (after treatment weeks 2 and 53 due to clinical signs of neurotoxicity), body weights of the toxaphene-treated male rats appeared similar to those of matched controls. Estimated TWA doses of approximately 42 and 83 mg/kg/day to the low- and high-dose female rats resulted in lower mean body weights throughout most of the study, as much as 10 and 16% lower than those of matched controls (NCI 1979). In the mouse portion of the study (estimated toxaphene doses of 17 and 34 mg/kg/day for the low- and high-dose groups, respectively), mean body weights of the high-dose males were slightly lower than those of matched controls; there appeared to be no treatment-related effects on body weight in low-dose males or low- or high-dose females.

Lackey (1949) reported weight loss during the initial portion of a study in which four dogs were administered toxaphene by oral capsule at 4 mg/kg/day for 44 or 106 days; convulsions were seen on occasion. Another dog study found no indication of treatment-related effects on body weight during oral dosing of toxaphene at 0.2–5 mg/kg/day for 13 weeks (Chu et al. 1986). There were no signs of treatment-related effects on body weight in cynomolgus monkeys administered toxaphene by oral capsule for 52–75 weeks, but doses were ≤1 mg/kg/day (Arnold et al. 2001; Bryce et al. 2001).

Available animal data indicate that pregnant rats may be particularly sensitive to toxaphene-induced effects on body weight. Rat dams administered toxaphene by gavage at 32 mg/kg/day (the only dose level tested) gained only 50% of the weight gained by control rats (Chernoff et al. 1990). In another developmental toxicity study, rat dams administered toxaphene by gavage at 15 mg/kg/day (the lowest dose tested) on gestation days 7–16 exhibited 22% decreased body weight gain relative to controls (Chernoff and Carver 1976). Crowder et al. (1980) found no evidence of treatment-related effects on body weight in pregnant rats administered toxaphene at 6 mg/kg/day (the only dose tested) from gestation day 7 to parturition.

3.2.2.3 Immunological and Lymphoreticular Effects

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

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 receiving toxaphene from the diet for 9 weeks at an estimated dose of 2.6 mg/kg/day (Koller

et al. 1983). Similar results were obtained in female mice receiving toxaphene from the diet for 8 weeks at an estimated dose of 19.5 mg/kg/day, but not at 2 mg/kg/day (Allen et al. 1983). The study of Allen et al. (1983) found no evidence of a delayed hypersensitivity response.

Immunological end points have also been assessed in cynomolgus monkeys administered toxaphene by oral capsule for periods up to 75 weeks (Tryphonas et al. 2001). Groups of 10 female cynomolgus monkeys were administered toxaphene in capsules at doses of 0 (vehicle controls), 0.1, 0.4, or 0.8 mg/kg/day for 75 weeks. Groups of male cynomolgus monkeys (5/group) were dosed at 0 (vehicle controls) or 0.8 mg/kg/day. Flow cytometry, lymphocyte transformation, natural killer cell activity, and serum cortisol levels were evaluated during treatment weeks 33–46. Immunization with SRBC was performed on treatment week 44 for a primary response and week 48 for a secondary response (observations made through treatment week 52). Immunizations with tetanus toxoid (TT) and pneumococcus antigens were performed on treatment week 53 (observations made through treatment week 63). Delayed type hypersensitivity testing was initiated on treatment week 66 and completed on treatment week 70. No treatment-related effects were observed in the 0.1 mg/kg/day group of treated female monkeys. Treatment with toxaphene at 0.4 mg/kg/day resulted in significant ($p<0.05$) reductions in mean primary anti-SRBC IgM responses (indicative of depressed humoral immunity) at post-immunization weeks 1 and 4 (27 and 35% lower than that of controls) and secondary anti-SRBC IgM responses at post-immunization week 5 (10% lower than that of controls). The dose level of 0.8 mg/kg/day resulted in significantly reduced mean primary anti-SRBC IgM responses at post-immunization weeks 1–4, significantly reduced mean secondary anti SRBC IgM response at post-immunization weeks 5 and 8, and significantly reduced primary anti-SRBC IgG responses at post-immunization weeks 2 and 3 (51 and 43% lower than that of controls). In males, 0.8 mg/kg/day toxaphene induced a significant reduction in mean primary anti-SRBC IgM response at post-immunization weeks 1–3. The mean anti-TT titers were significantly reduced in 0.8 mg/kg/day females at post-immunization weeks 2–4. Flow cytometry tests showed that the only effect on leukocyte and lymphocyte subsets was a reduction in absolute B lymphocytes (CD20) in 0.8 mg/kg/day females (62% lower than controls). There were no detectable treatment-related effects on natural killer cell activity, delayed type hypersensitivity, lymphoproliferative response to mitogens, or serum cortisol levels. The toxaphene-induced reduction in mean primary anti-SRBC IgM response served as the critical effect for deriving an intermediate-duration oral MRL for toxaphene.

All reliable LOAEL values for immunological and lymphoreticular effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 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 Milhorn 1983). The dose necessary to induce nonfatal convulsions in humans has been estimated to be approximately 10 mg/kg (CDC 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).

Convulsions and other clinical signs of toxaphene-induced neurotoxicity have been observed in laboratory animals. Chandra and Durairaj (1995) reported clinical signs that included convulsions and sedation in guinea pigs receiving a single oral dose of toxaphene at 300 mg/kg. Lackey (1949) administered single gavage doses of toxaphene to dogs at doses ranging from 5 to 50 mg/kg and noted convulsions at dose levels ≥10 mg/kg. In the same study report, occasional convulsions were noted in dogs dosed at 4 mg/kg/day during 44- and 106-day treatment periods. Single oral administration of toxaphene to heifer calves at 50–150 mg/kg elicited numerous clinical signs that included hyperexcitability, nystagmus, convulsions, and seizures (Steele et al. 1980). In a 13-week oral toxicity dog study, clinical signs of neurotoxicity (convulsions, salivation, and vomiting) were elicited during the first 2 days of oral dosing at 10 mg/kg; these clinical signs were no longer elicited after the dose was reduced to 5 mg/kg/day on treatment day 3 (Chu et al. 1986). Tremors and nervousness were reported in rats administered toxaphene by gavage for 3 days at doses ≥25 mg/kg/day; a NOAEL was not identified (Rao et al. 1986). Hyperreflexia was observed in rats at an unspecified dose (Boyd and Taylor 1971).

In a chronic toxicity and carcinogenicity study of male and female rats and mice (NCI 1979), hyper-excitability was reported in high-dose male rats during the first 2 weeks of exposure to toxaphene in the diet when the initial concentration (2,560 ppm) delivered an estimated dose of 270 mg/kg/day; this effect was not observed in male rats receiving 130 mg/kg/day or in groups of similarly-treated females receiving toxaphene at 70 or 147 mg/kg/day during the same 2-week period. Based on the hyperexcitability in the high-dose male rats, dietary concentrations were reduced by 50% at treatment week 3 and another 50% at treatment week 55 when generalized body tremors were noted in most high-dose male and female rats. The study authors reported clinical signs that included tremors, leg paralysis, and ataxia from treatment

weeks 52 through 80, predominantly in toxaphene-treated rats. In the mouse study, hyperexcitability was reported during treatment weeks 60–76 in the low-dose male mice (estimated dose of 17 mg/kg/day), but not in the high-dose males (34 mg/kg/day); there were no signs of hyperexcitability in either dose group (17 and 34 mg/kg/day) of female mice.

There were no clinical signs or histopathological evidence of toxaphene-induced neurological effects in male or female cynomolgus monkeys administered toxaphene in a daily capsule for 52 weeks at 1 mg/kg/day (Bryce et al. 2001).

The electroencephalographic (EEG) pattern of squirrel monkeys was altered by exposure to 1 mg/kg toxaphene (Santolucito 1975). In addition to affecting behavior, an oral dose of 120 mg/kg toxaphene was reported to alter brain catecholamine metabolism in rats (Kuz'minskaya and Ivanitskiĭ 1979). Badaeva (1976) reported brain cell death in pregnant rats gavaged with toxaphene at 12 mg/kg/day during gestation. However, the methods used to identify the lesions are not well described in this study and the effects were not quantitatively evaluated.

Dietary administration of toxaphene to rats for 14 days at estimated doses as high as 18 mg/kg/day did not affect whole brain weight in rats (Trottman and Desaiah 1980), but this is a gross measure and effects on specific neuronal populations would not be detected by this measure. Toxaphene-related decreases in brain weight were reported in guinea pigs following a single oral dose of 300 mg/kg toxaphene (Chandra and Durairaj 1992). The same exposure scenario resulted in a significant decrease of brain phospholipid content and a significant increase in brain neutral lipid and cholesterol content (Chandra and Durairaj 1995). Similar effects were observed in other guinea pigs receiving toxaphene by gavage at 5 mg/kg/day for 60 days (Chandra and Durairaj 1995). However, the toxicological significance of these finding is uncertain.

The highest NOAEL values and all reliable LOAEL values for neurological effects for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

Oral toxicity animal studies that assessed neurodevelopmental end points are summarized in Section 3.2.6 (Developmental Effects).

3.2.2.5 Reproductive Effects

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

Testicular weight was not affected in rats receiving toxaphene from the diet for 14 days at estimated doses as high as 18 mg/kg/day (Trottman and Desaiah 1980). Vaginal bleeding was reported in rats receiving toxaphene from the diet for 80 weeks at estimated TWA doses of 41.6 and 83.3 mg/kg/day; incidence data were not provided in the study report (NCI 1979). There were no effects on litter sizes, pup survival, or weanling body weights and no evidence of treatment-related teratogenic effects in a three-generation study of male and female rats that received toxaphene from the diet for up to 42 weeks at estimated doses as high as 8.6 and 9.8 mg/kg/day, respectively (Kennedy et al. 1973). In another reproductive toxicity study (Chu et al. 1988), fertility and offspring growth and viability were not affected by dietary exposure of male and female rats to toxaphene at estimated doses as high as 45–46 mg/kg/day; the treatment period included 13 weeks prior to mating and continued through the production of F_{1a} and F_{1b} litters. Plasma testosterone levels were not affected in male rats administered a single gavage dose of 120 mg toxaphene/kg/day or in other rats dosed at 2.6 mg/kg/day for up to 6 months (Peakall 1976).

Keplinger et al. (1970) performed a multi-generation reproductive toxicity study in which male and female Swiss mice received toxaphene from the diet at estimated dose of 4.5 and 4.9 mg/kg/day, respectively, through the production of five generations of offspring. There were no indications of toxaphene-related adverse effects on lactation, reproduction, average litter size, or offspring growth or on viability through five generations.

Bryce et al. (2001) noted no remarkable histopathology following examination of tissues (including reproductive tissues) from cynomolgus monkeys administered toxaphene by oral capsule at 1 mg/kg/day for 52 weeks. Arnold et al. (2001) found no evidence of toxaphene-related effects on menstrual cycle in cynomolgus monkeys administered the chemical in capsules at daily doses ranging from 0.1 to 0.8 mg/kg/day for up to 75 weeks.

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

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

Available developmental toxicity studies in animals indicate that toxaphene is not teratogenic. No major anatomical defects were seen in rat or mouse fetuses following gestational oral exposure of pregnant dams at doses in the range 0.05 to 75 mg/kg/day (Allen et al. 1983; Chernoff and Carver 1976; Chernoff and Kavlock 1982; Chernoff et al. 1990; Crowder et al. 1980; Kavlock et al. 1982; Kennedy et al. 1973; Olson et al. 1980).

Toxaphene (15, 25, or 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 (Chernoff and Carver 1976). Keplinger et al. (1970) found no evidence of treatment-related effects on litter size or offspring growth and viability in mice receiving toxaphene from the diet at approximate doses of 4.5–5 mg/kg/day throughout the production of five generations of offspring.

Some of the available developmental toxicity animal studies reported treatment-related effects on development. Chernoff and Kavlock (1982) noted transient decreases in offspring body weight on postnatal day 1 following gavage administration of toxaphene to rat dams at 75 mg/kg/day on gestation days 8–12; however, the dose was maternal toxic, as evidenced by 2/25 maternal deaths and >45% depressed maternal weight gain. Chernoff et al. (1990) reported significantly increased incidences of supernumerary ribs in fetuses from rat dams gavaged at 32 mg/kg/day during gestation days 6–15; however, 50% of the treated dams died. Chernoff and Carver (1976) reported significantly decreased numbers of sternal ossification centers in 21-day-old fetuses from rat dams administered toxaphene by gavage at 15 or 25 mg/kg/day during gestation days 7–16, but not at a dose level of 35 mg/kg/day.

Kavlock et al. (1982) reported significantly decreased renal protein in the kidneys of 21-day-old rat fetuses whose mothers had been administered toxaphene by gavage at 12.5 or 25 mg/kg/day during gestation days 7–16 and significantly decreased alkaline phosphatase activity in fetal kidneys of the 25 mg/kg/day dose group.

Allen et al. (1983) assessed immunological end points in 8-week-old offspring of mouse dams that had received toxaphene from the diet at estimated doses of 2, 19.5, or 39 mg/kg/day for 3 weeks premating and throughout mating, gestation, and lactation. Assessment included a delayed-type hypersensitivity assay for cell-mediated immune response, an enzyme-linked immunosorbent assay for humoral immune response, and a phagocytosis assay to assess the ability of peritoneal macrophages to engulf SRBCs.

Toxaphene treatment resulted in significant suppression of macrophage phagocytic function in the offspring at all dose levels (32, 79, and 63% suppression in the 2, 19.5, and 39 mg/kg/day dose groups, respectively) compared to controls. The humoral antibody response was significantly suppressed at 19.5 mg/kg/day, but was significantly enhanced at 39 mg/kg/day. The cell-mediated immune response was suppressed at 19.5 mg/kg/day, but was not significantly different from controls at the low- and high-dose levels. These results indicate that the perinatal immunological system may be at risk for toxaphene toxicity.

Crowder et al. (1980) assessed the effects of toxaphene on results of selected behavioral tests (grasp-hold, righting, startle, and placing reflexes; open field and maze performance) in pups from rat dams administered toxaphene by gavage at 6 mg/kg/day during mating and throughout gestation (Crowder et al. 1980). Reflex testing, initiated at 7 days postpartum, revealed no significant treatment-related effects on performance; however, the study authors stated that 3 more days were required for 90% of the pups from the toxaphene-treated group to correctly respond in the righting reflex test compared to control pups ($p \leq 0.05$). There were no significant differences between toxaphene-treated groups and control in maze performance assessed beginning at 55 days postpartum.

Olson et al. (1980) examined the effects of toxaphene on selected behavioral parameters in pups of rat dams ingesting the chemical at 0.05 mg/kg/day from gestation day 5 until postpartum day 30. Tests of swimming ability and righting reflex were performed daily on postpartum days 7–16. Significantly retarded swimming ability was noted on postpartum days 10 ($p<0.001$), 11 ($p<0.0001$), and 12 ($p<0.05$); however, the effect was transient and pups exhibited normal swimming ability at testing on postpartum day 16. The study authors stated that pups of the toxaphene treatment group also exhibited significantly retarded overall righting reflex ($p<0.005$), but quantitative data were not provided in the study report. Maze testing, initiated on postpartum day 70, revealed no apparent treatment-related effect.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

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

NCI (1979) assessed the toxicity and carcinogenicity of toxaphene in groups of male and female Osborne-Mendel rats and male and female B6C3F1 mice exposed to the chemical for 80 weeks via the diet followed by 28–30 weeks of recovery prior to terminal sacrifice. Among the mice, respective incidences of neoplastic liver nodules or hepatic carcinomas (combined) in concurrent controls, pooled controls, and low- and high-dose animals were 2/10, 7/48, 40/49, and 45/46 for males and 0/9, 0/48, 18/49, and 40/49 for females. Incidences at the low- and high-dose levels (estimated TWA doses of 77.9 and 83.3 mg/kg/day, respectively) were significantly higher than those of respective concurrent controls. Among the rats, incidences of thyroid follicular cell adenomas or carcinomas (combined) in concurrent controls, pooled controls, and low- and high-dose animals were 1/7, 2/44, 7/41, and 9/35 for males and 0/6, 1/46, 1/43, and 7/42 for females. Incidences in high-dose male and female rats (estimated TWA doses of 77.9 and 83.3 mg/kg/day, respectively) were significantly higher than those of respective controls. Significantly increased incidences of hepatocellular carcinomas were observed in low- and high-dose (17 and 34 mg/kg/day, respectively) male mice and high-dose (34 mg/kg/day) female mice. In light of more contemporary diagnostic criteria for classification of histopathological liver tumors, an expert pathology working group (PWG) was convened to review the original liver slides from the male and female mice. A primary report of the PWG findings was not available to ATSDR. However, Goodman et al. (2000) provided a summary of the results which indicates that, although many of the tumors originally classified as carcinomas were reclassified as adenomas, the incidences of reclassified combined adenomas or carcinomas were similar to the incidences of combined neoplastic nodules or carcinomas presented in the original study report.

Litton Bionetics, Inc. produced an unpublished report of a cancer bioassay in mice administered toxaphene in the diet. The study results were summarized by EPA in an Ambient Water Quality Criteria document (EPA 1980a). EPA's Integrated Risk Information System includes a summary for toxaphene in which the results of the unpublished study were used by EPA to derive an oral slope factor (IRIS 2010). The following summary of the unpublished study was extracted from EPA (1980a) because the study was not available to ATSDR: Groups of male and female B6C3F1 mice (54/sex/group) were administered toxaphene in the diet at 0, 7, 20, or 50 ppm for 18 months followed by a 6-month observation period. Based on EPA (1988d) chronic reference values for body weight and food consumption in male and female B6C3F1 mice, respective estimated doses were 0, 1.2, 3.4, and 8.6 mg/kg/day for the males and 0, 1.2, 3.5, and 8.6 mg/kg/day for the females. At unscheduled or terminal sacrifice, histopathological evaluation of major organs was initiated. A statistically significant (p=0.048) excess of hepatocellular tumors (adenomas plus carcinomas) was noted in the high-dose male mice (18/51 versus 10/53 in controls). The Cochran Armitage trend test was significant (p=0.020) for dose-related increased

incidence of hepatocellular tumors in the male mice. There were no significant treatment-related effects on the incidence of hepatocellular tumors in any group of treated female mice.

In a study designed to assess the effect of insecticides (including toxaphene) on the induction of lung tumors by benzo[a]pyrene, toxaphene was given to female A/J mice (11–12/group) for 12 weeks at 0, 100, or 200 ppm (Triolo et al. 1982). The study assessed a limited number of end points and found no evidence for toxaphene-related lung or stomach tumors.

The oral doses associated with individual, lifetime upper-bound cancer risk of 10^{-4}–10^{-7} are $9x10^{-5}$–$9x10^{-8}$ mg/kg/day, assuming that a 70-kg human ingests 2 L water/day. The 10^{-4}–10^{-7} risk levels are indicated in Figure 3-2.

3.2.3 Dermal Exposure

3.2.3.1 Death

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

Acute dermal LD_{50} values obtained in laboratory animals range from 780 to 4,556 mg/kg (Gaines 1969; Industrial Biotest 1973; Johnston and Eden 1953; Jones et al. 1968). All of these studies except Gaines (1969) reported LD_{50} values of 1,075 and 780 mg/kg/day for male and female Sherman rats, respectively; these values are plotted in Table 3-3. The other studies are limited in design and/or reporting which preclude their inclusion in Table 3-3.

3.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, musculoskeletal, endocrine, or body weight effects in humans or 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 3-3.

Respiratory Effects. In humans, fluoroscopic examination of the lungs following acute dermal exposure to 500 mg/m^3 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

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Death									
Rat (Sherman)	once					1075 M mg/kg	(LD50)	Gaines 1969	
						780 F mg/kg	(LD50)		
Systemic									
Rabbit (New Zealand)	4 hr	Dermal		130 B mg/kg	(erythema and edema)			International Research and Development Corporation 1973	
Pig (NS)	once	Resp		13500 mg/kg	(lung congestion and presence of peribronchia lymphoid follicles)			Dipietro and Haliburton 1979	
		Renal		13500 mg/kg	(cystic kidney cortex)				
Neurological									
Pig (NS)	once					13500 mg/kg	(convulsions)	Dipietro and Haliburton 1979	

B = both; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory

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(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 and Eden 1953).

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

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

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 wettable powder of toxaphene for 2 minutes had pale and mottled livers (Johnston and Eden 1953). 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 ≥3,038 mg/kg (Industrial Biotest 1973).

Renal Effects. In humans, urinalysis conducted after acute dermal exposure to 500 mg/m^3 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^3 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 Corporation 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 eyes were not affected, and the lids cleared completely in 10 days (EPA 1985c; summary of an unpublished report for Boots Hercules Agrochemicals). The unpublished report was not available to ATSDR.

3.2.3.3 Immunological and Lymphoreticular Effects

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

3.2.3.4 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). Inhalation and/or oral exposure may have also occurred. Clinical signs included head-pressing, 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 was reported in rabbits exposed by 24-hour dermal application of a 90% w/v solution of toxaphene in xylene at doses

≥6,834 mg/kg, but not at doses ≤4,556 mg/kg (Industrial Biotest 1973); however, this study was limited in that the solvent, xylene, was not tested alone. Similar dermal application to burned skin resulted in muscular weakness at doses ≥3,038 mg/kg; there was no indication of muscular weakness at a dose of 2,025 mg/kg.

No studies were located regarding the following effects in humans or animals following dermal exposure to toxaphene:

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

Table 3-4 summarizes available *in vivo* genotoxicity information for toxaphene.

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. The women were likely to have been exposed by both inhalation and dermal routes.

In a dominant lethality test, toxaphene did not cause increased fetal death or decreased numbers of implants in mouse dams mated to males that had been administered toxaphene orally at doses of 40 or 80 mg/kg/day for 5 days or by single intraperitoneal injection at 36 or 180 mg/kg (Epstein et al. 1972). Mortality was noted in 9/12 and 2/9 of the high-dose orally- and intraperitoneally-exposed males, respectively, indicating that sufficiently high doses were tested.

Toxaphene did not cause liver deoxyribonucleic acid (DNA) damage in 90-day-old female Sprague-Dawley rats administered the chemical twice (21 and 4 hours prior to sacrifice) by gavage at up to 36 mg/kg/dose (Kitchin and Brown 1994). Hedli et al. (1998) found no evidence of DNA adduct formation in livers of male CD-1 mice administered toxaphene by gavage for 7 days at doses up to and including 100 mg/kg/day.

Table 3-4. 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
Mouse liver cells	DNA adducts	–	Hedli et al. 1998

– = negative

Table 3-5 summarizes available *in vitro* genotoxicity information for toxaphene.

Toxaphene was mutagenic in reverse mutation assays using *Salmonella typhimurium* strains TA98 and TA100 (containing the pKm101 plasmid) in the absence of metabolic activation systems (Hooper et al. 1979; Mortelmans et al. 1986; Schrader et al. 1998; Steinberg et al. 1998). However, mutagenic responses were diminished or abolished with the addition of metabolic activation systems (Hooper et al. 1979; Schrader et al. 1998). Negative or only weakly positive results were obtained in reverse mutation assays using *S. typhimurium* strains TA 1535 and TA1537 (non-plasmid containing strains). Young et al. (2009) reported weakly mutagenic responses in *S. typhimurium* strain TA100 in the presence and absence of exogenous metabolic activation.

Hooper et al. (1979) 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 were considered to possess the highest insecticidal or acute mammalian toxicity activity (e.g., heptachlorobornane, *gem*-dichloro components, and nonpolar fractions) were less mutagenic to *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 6).

Mortelmans et al. (1986) reported positive results for gene mutation in *N. crassa* in the absence of metabolic activation. Positive results were obtained in an assay for the induction of λ prophage in *Escherichia coli* (Houk and DeMartini 1987). Significantly increased frequency of sister chromatid exchanges in the presence and absence of metabolic activation (S9) were reported in a cultured cell line derived from human lymphoid cells; however, the increases were <2-fold greater than solvent controls (Sobti et al. 1983). Significantly increased frequency of sister chromatid exchanges were observed in toxaphene-treated Chinese hamster lung cells; the increase was slightly <2-fold higher than that of controls (Steinel et al. 1990). Toxaphene did not significantly increase the frequency of sister chromatid exchanges in Chinese hamster V79 cells with or without metabolic activation and did not significantly alter the frequency of HGPRT mutations at concentrations up to and including those resulting in cytotoxicity (Schrader et al. 1998). Bartoš et al. (2005) reported positive results for toxaphene-induced DNA damage in an SOS Chromotest using *E. coli* PQ37 in the absence of metabolic activation, but reported negative results in a *umu*C test for DNA damage in *S. typhimurium* strain TA1535/pSK1002 in the absence of metabolic activation. Both assays test induction of the SOS repair system. Toxaphene did

Table 3-5. Genotoxicity of Toxaphene *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms				
Salmonella typhimurium strain TA100	Gene mutation	–	+	Hooper et al. 1979
S. typhimurium strain TA98	Gene mutation	ND	+	Hooper et al. 1979
S. typhimurium strain TA98	Gene mutation	–	+	Mortelmans et al. 1986
S. typhimurium strain TA100	Gene mutation	+	+	Mortelmans et al. 1986
S. typhimurium strain TA1535	Gene mutation	–	–	Mortelmans et al. 1986
S. typhimurium strain TA1537	Gene mutation	–	(+)	Mortelmans et al. 1986
S. typhimurium strain TA98	Gene mutation	ND	+	Steinberg et al. 1998
S. typhimurium strain TA100	Gene mutation	ND	+	Steinberg et al. 1998
S. typhimurium strain TA100	Gene mutation	+	+	Young et al. 2009
S. typhimurium strain TA97	Gene mutation	(+)	+	Schrader et al. 1998
S. typhimurium strain TA98	Gene mutation	(+)	+	Schrader et al. 1998
S. typhimurium strain TA100	Gene mutation	+	+	Schrader et al. 1998
S. typhimurium strain TA102	Gene mutation	–	–	Schrader et al. 1998
S. typhimurium strain TA104	Gene mutation	(+)	(+)	Schrader et al. 1998
S. typhimurium strain TA1535	DNA damage (*umu*C test)	NT	–	Bartoš et al. 2005
Escherichia coli K-12	Λ prophage induction	+	+	Houk and DeMarini 1987
E. coli PQ37	DNA damage (SOS chromotest)	NT	+	Bartoš et al. 2005
Plasmid DNA isolated from *E. coli*	DNA damage	ND	–	Griffin and Hill 1978
Fungi and plant systems	Gene mutation			
Neurospora crassa	Gene mutation	ND	+	Mortelmans et al. 1986
Mammalian cells				
Human lymphoid cells LAZ-007	Sister chromatid exchange	–	–	Sobti et al. 1983
Chinese hamster V79 fibroblasts	Gene mutation	–	–	Schrader et al. 1998
Chinese hamster V79 fibroblasts	Sister chromatid exchange	–	NT	Schrader et al. 1998
Chinese hamster lung (Don) cells	Sister chromatid exchange	NT	±	Steinel et al. 1990

ND = no data; NT = not tested; – = negative; + = positive; (+) = weakly positive; (±) = equivocal

not induce DNA damage in plasmid DNA isolated from *E. coli* in the absence of metabolic activation (Griffin and Hill 1978).

In summary, the weight of evidence from available *in vitro* assays indicates that toxaphene is genotoxic. Only limited information was located regarding the potential genotoxicity of toxaphene *in vivo*.

3.4 TOXICOKINETICS

Studies in laboratory animals indicate that toxaphene is well absorbed by the intestinal tract and probably well absorbed by the lungs. Dermal absorption has also been demonstrated. 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 indicate that the principal metabolic pathways involve 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.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Limited human data indicate that inhaled toxaphene is absorbed (Keplinger 1963; Warraki 1963); however, no quantitative data are available. Limited unpublished animal data also indicate that inhaled toxaphene is absorbed; hepatic effects were reported in rats that survived inhalation exposure to toxaphene dust (4 or 12 mg/m^3) for 3 months (cited in EPA 1985c as an unpublished report for Hercules Incorporated; the primary report was not available to ATSDR).

3.4.1.2 Oral Exposure

No data were located regarding the extent of oral absorption of toxaphene in humans. However, accounts of death and systemic effects from accidental ingestion of toxaphene-contaminated food provide evidence that gastrointestinal absorption occurs (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 demonstrates that ingested toxaphene is absorbed. The identification of toxaphene in the milk of cows following ingestion is also evidence of its absorption (Claborn 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 (Chadurkar and Matsumura 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.

3.4.1.3 Dermal Exposure

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

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 is absorbed following dermal exposure (Keating 1979). Toxaphene toxicosis was reported in swine 36 hours after the dermal application of toxaphene in a 61% 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).

3.4.2 Distribution

3.4.2.1 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.

3.4.2.2 Oral Exposure

Limited information is available regarding distribution in humans following oral exposure to toxaphene. Toxaphene residues have been detected in samples of adipose tissue taken from children (Witt and Niessen 2000) and in maternal and cord blood (Butler Walker et al. 2003). Ingestion of contaminated food, particularly fish and marine mammals, was the assumed exposure route.

Results of tissue analysis following the oral administration of radiolabeled toxaphene to rats indicate 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}C-toxaphene in olive oil to rats at a dose of 10 mg/kg resulted in toxaphene residue levels of 6.4 mg/kg in fat 7 days following administration. Residue levels in all other tissues were <0.2 mg/kg (Pollock and Kilgore 1980b). The oral administration of ^{14}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, in fat 7 days after administration. Residue levels in all other tissues were <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 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.

The highest level of activity, except for the gastrointestinal tract, was in the brown fat following administration of 16 mg/kg ^{14}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}Cl-toxaphene in corn oil retained ^{36}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 were 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}C-toxaphene (Ohsawa et al. 1975). After the oral administration of a single dose of 20 mg/kg ^{36}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 <10% of the dose remained in the body after 1 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.

Cynomolgus monkeys were administered toxaphene in glycerol/corn oil via gelatin capsule at 1 mg/kg/day for 1 year (Andrews et al. 1996). At 10 weeks, the blood levels appeared to peak out at approximately 40 ppb; levels in adipose tissue leveled out at 4,000 ppb between weeks 15 and 20.

Heifer calves receiving toxaphene at oral bolus doses of 50, 100, or 150 mg/kg ^{14}C-toxaphene had 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 3-6.

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

Table 3-6. Mean Toxaphene Residues in Cows Following Oral Exposure to Toxaphene

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

[a]Values represent mean of six animals.
[b]Values represent mean of seven animals.

Source: Steele et al. 1980

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. Oral administration of 16 mg/kg ^{14}C-toxaphene to rats resulted in distribution of radioactivity to the adrenal cortex, 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 ^{14}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 <1% of the dose was transferred.

All studies reviewed consistently demonstrate that toxaphene is distributed throughout the body and preferentially stored in fat. Although toxaphene was identified in the fat up to 30 days after administration, the overall tissue activity level was very low. Apparently, toxaphene is rapidly metabolized, and its metabolites and components are 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. Toxaphene has been shown to cross the placenta and become 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.

3.4.2.3 Dermal Exposure

No human or animal data were located regarding distribution of toxaphene following dermal exposure.

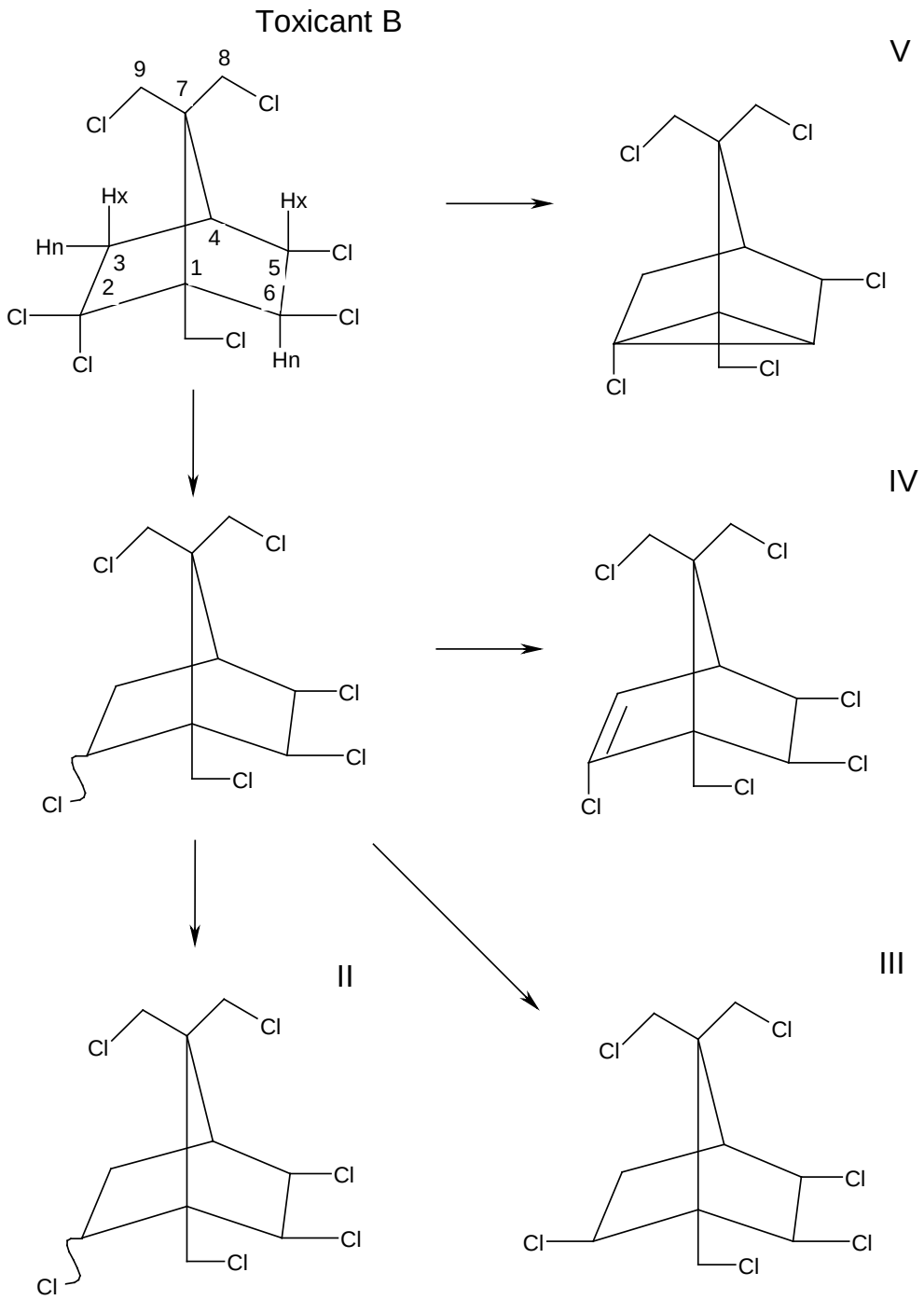
3.4.2.4 Other Routes of Exposure

Intravenous administration of ^{14}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}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 the transplacental transfer of toxaphene after intravenous administration is relatively low. The tissue accumulation of intravenously administered ^{14}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 of 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.

3.4.3 Metabolism

Toxaphene is rapidly and extensively degraded in mammals following oral administration (Figure 3-3). *In vivo* and *in vitro* studies indicate that the principal metabolic pathways involve dechlorination, dehydrodechlorination, and oxidation. Conjugation is also likely, but it is not a major route of metabolism. Administration of ^{36}Cl-toxaphene to rats at a dose of 13 mg/kg resulted in the excretion of ^{36}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}Cl- and ^{14}C-toxaphene differed. With either label, the hexane extracts of urine and feces contained some

Figure 3-3. 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-heptachlorogornene
Metabolite V = 2,5-endo-8,9,10-pentachlorotricyclene

Source: Saleh and Casida 1978

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}C-activity (27%) than of the ^{36}Cl-activity (11.2%). These results indicate that the chloroform fraction consists of partially dechlorinated metabolites, and a predominance of these products were found in the urine. The aqueous fraction contained 11.4% of the ^{14}C-dose and 0.5% of the ^{36}Cl dose. The low amount of ^{36}Cl activity in the aqueous extracts indicated that this fraction contained metabolites (5–10%) that had been completely dechlorinated (Ohsawa et al. 1975). About 2% of the ^{14}C-activity appeared as expired products, probably ^{14}C-carbon dioxide. Thus, these results indicate that toxaphene is 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}C-toxaphene was extractable from urine into hexane. Thin-layer chromatography (TLC) of the urine extract indicated that the components in the urine were more polar than toxaphene. No parent compound was found in the urine. These results provide additional evidence that most of the toxaphene absorbed is metabolized.

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}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}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-heptachlorobornane), 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 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-hexachlorobornane (III) (Figure 3-3). Toxicant B is also dehydrodechlorinated to 2,5-endo-6-exo-8,9,10-hexachloroborn-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 hexachlorobornane 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 (Chadurkar and Matsumura 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 (Chadurkar and Matsumura 1979; Saleh and Casida 1978).

Acetonitrile extracts of feces and urine from rats receiving a single oral dose of ^{14}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 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 (Chadurkar and Matsumura 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.

Drenth et al. (1998) noted that toxaphene induced hepatic CYP450 activity in the rat at a single oral dose level of 40 mg/kg, but not at lower dose levels.

Toxaphene has been shown to induce selected CYP450 isozymes both *in vitro* and *in vivo*. Hedli et al. (1998) reported dose-related increased levels of total CYP450 and cytochrome b_5 in hepatic microsomal fractions from male CD-1 mice administered toxaphene by daily gavage for 7 days at doses of 0, 10, 25, 50, or 100 mg/kg/day. Significant, toxaphene-induced increases in immunodetectable levels of CYP2B, but not CYP4A1, were detected. Dehn et al. (2005) observed significantly increased CYP1A and CYP2B activities in human HepG2 cells exposed to toxaphene for 24 hours at high concentrations (1, 5, or 10 mM) or 48 hours at lower concentrations (0.01–1 mM). The increases in CYP2B were of greater magnitude than those of CYP1A. Dehn et al. (2005) noted that glutathione levels declined when CYP2B activity was significantly elevated, but increased significantly in the absence of significant CYP450 activation, suggesting that activities of glutathione and CYP450 isozymes may influence one another.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No human or animal data were located regarding excretion following known inhalation exposure to toxaphene.

3.4.4.2 Oral Exposure

It is evident from distribution studies that toxaphene and its metabolites are not persistent in tissues; ^{36}Cl-labeled metabolites remained for 9 days and ^{14}C-labeled metabolites remained for 16 days in the fat of animals. Metabolism studies indicate that toxaphene is rapidly and extensively biodegraded. Consequently, the rate of toxaphene elimination is very high. Table 3-7 summarizes excretion results from studies in which rats were orally administered radiolabeled toxaphene and its components.

An average of 52.6% of an orally administered 20 mg/kg ^{36}Cl-toxaphene dose was excreted over 9 days (approximate half-life of excretion). 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 the ^{36}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 ^{36}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 equaled the fecal elimination. Ohsawa et al. (1975) also found that the ^{36}Cl-chloride ion appeared almost entirely in the urine. The half-time for the elimination of ^{36}Cl was 2–3 days, a rate equivalent to the excretion of ^{36}Cl-sodium chloride.

Rats treated orally with 8.5 and 19 mg/kg of ^{14}C-toxaphene showed no dose-related differences with respect to the excretion of radioactivity (Ohsawa et al. 1975). After 14 days, >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.

Table 3-7. 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	Percent dose		Reference
				Urine	Feces	
^{36}Cl-Toxaphene	20	Peanut oil/gum acacia	1	1.5	23.4	Crowder and Dindal 1974
^{36}Cl-Toxaphene	20	Peanut oil/gum acacia	9	15.3	37.3	Crowder and Dindal 1974
^{36}Cl-Toxaphene	14	Corn oil	14	49.1	26.9	Ohsawa et al. 1975
^{14}C-Toxaphene	8.5	Corn oil	14	21.3	34.7	Ohsawa et al. 1975
^{14}C-Toxaphene	19	Corn oil	14	31.8	27.8	Ohsawa et al. 1975
^{14}C-Toxaphene	2.6	Olive oil	5	22.0	28.3	Pollock and Hillstrand 1982
^{14}C-Toxaphene	10	Olive oil	7	22.5	35.7	Pollock and Kilgore 1980b
^{14}C-Fraction 2	1	Olive oil	7	30.8	38.6	Pollock and Kilgore 1980b
^{14}C-Fraction 7	0.6	Olive oil	7	23.5	32.6	Pollock and Kilgore 1980b
^{14}C-Toxicant A	0.84	Corn oil	14	28.3	38.4	Oshawa et al. 1975
^{14}C-Toxicant B	2.6	Corn oil	9	26.7	47.8	Ohsawa et al. 1975

Radiolabeled toxicants A and B, obtained by chromatographic separation of ^{14}C-toxaphene, were orally administered to rats at doses of 0.84 and 2.6 mg/kg, respectively. Radioactivity from the ^{14}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. Rats orally administered 10 mg/kg ^{14}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}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 greater persistence in fat and a reduced 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}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}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 >20 ppm (Claborn et al. 1963), as shown in Table 3-8. Detectable amounts of toxaphene were found in the milk of cows 7–9 days after feeding of

Table 3-8. Toxaphene Levels in Milk from Cows Fed Toxaphene in Their Diet

Diet concentration (ppm)	Concentration of milk (ppm)[a]				
	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

[a]Values represent means of three samples.

Source: Claborn et al. 1963

toxaphene at levels of 2.5–20 ppm commenced (Zweig et al. 1963). As with the higher feeding levels discussed above (Claborn 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).

The high concentration of radioactivity in the gall bladder from ^{14}C-toxaphene orally administered to quail confirmed the likelihood that the biliary pathway plays an important role in toxaphene excretion (Biessmann et al. 1983).

The detection of toxaphene residue in human breast milk samples is testament to its pharmacokinetics in humans. Ingestion of contaminated food and/or water is the most likely primary source of exposure. Toxaphene residues were detected at a mean concentration of 67.7 ng/g fat in human milk samples collected between July 1996 and April 1997 from 12 residents of Kewatin, an arctic region of northern Canada (Newsome and Ryan 1999). Mean toxaphene residue concentrations ranging from 6.03 to 12.1 ng/g fat were determined from human milk samples that had been collected from other regions of Canada at earlier times (Newsome and Ryan 1999). Toxaphene residues detected in breast milk samples from women living in different parts of Finland were estimated to be 10 ng/g fat (Mussalo-Rauhamaa et al. 1988). Toxaphene-like chlorinated bornanes have been measured in breast milk samples from women in areas of Russia (Polder et al. 1998, 2003), Germany (Skopp et al. 2002b), and Hong Kong and south China (Hedley et al. 2010).

3.4.4.3 Dermal Exposure

No human data were located regarding excretion following dermal exposure to toxaphene.

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.

3.4.4.4 Other Routes of Exposure

Mohammed et al. (1983) reported that ^{14}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}C-toxaphene and its metabolites. Sixteen days after administration, the tissue showing the highest concentration of ^{14}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).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from

route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

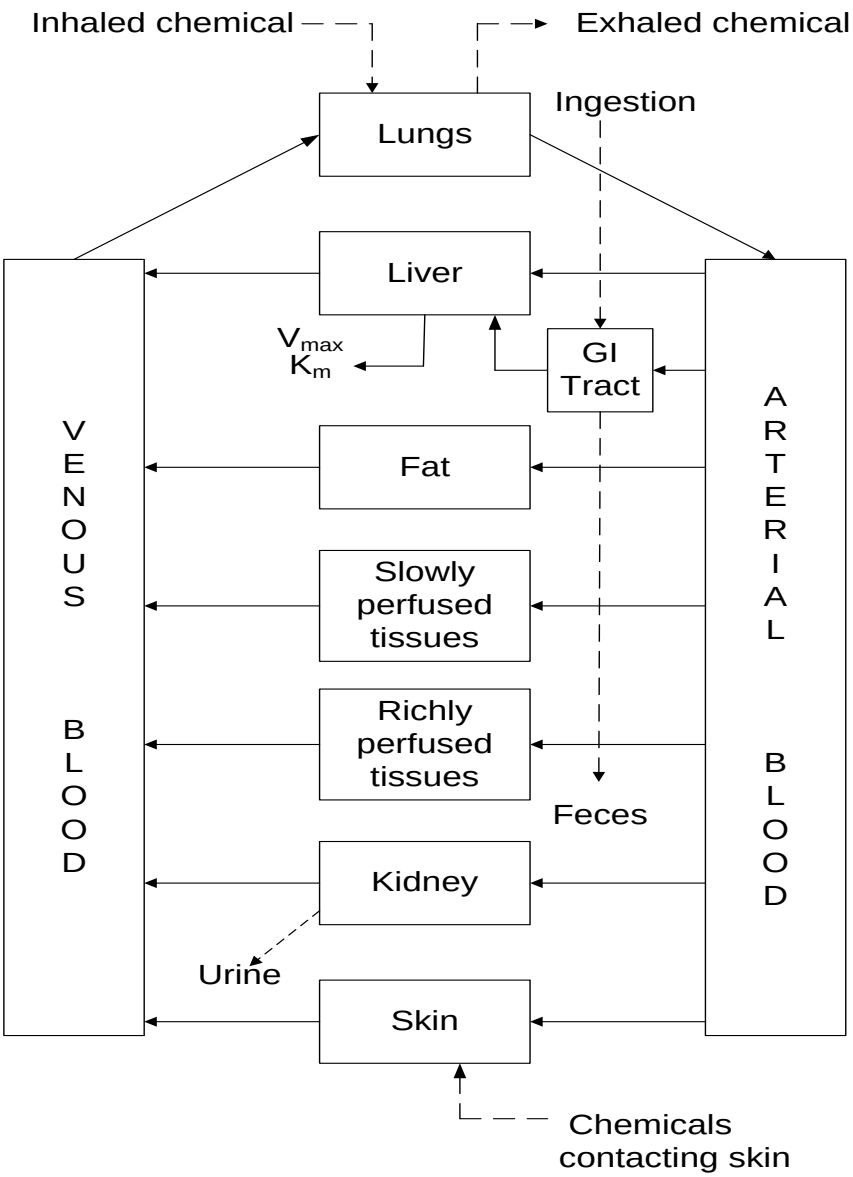
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

If PBPK models for toxaphene exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

Wen and Chan (2000) developed a two-compartment pharmacokinetic model to predict absorption, elimination, and tissue burden of toxaphene in rats; it does not incorporate data regarding biotransformation or clearance of toxaphene metabolites. The model includes six tissue compartments (blood, brain, liver, muscle, fat, and carcass) and incorporates dose-dependent flux rates and first-order absorption and elimination kinetics. Time-course tissue distribution data from male albino rats administered ^{36}Cl-toxaphene served as basis for model development. The model was partially validated using time-course tissue distribution and depuration data from pregnant Sprague-Dawley rats administered ^{14}C-toxaphene orally. Pharmacokinetically based dosimetry indicated that absorption of toxaphene was fast in fat, whole body, carcass, and blood; relatively slow in liver and muscle; and slow in brain. Elimination was rapid in whole body, muscle, and blood; moderate in carcass and brain; and slow in liver and fat. Tissue burden was highest in fat, whole body, and blood; intermediate in liver; and lowest in brain. In male rats, fecal and urinary excretion represented the major and minor elimination routes, respectively. Fecal and urinary excretion were of approximately equal magnitude in pregnant female rats.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Pharmacokinetic mechanisms of action for toxaphene have not been well studied. Toxaphene is rapidly absorbed by the gastrointestinal tract and lungs. Absorption through the skin can also occur, but appears to be less efficient because 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.

3.5.2 Mechanisms of Toxicity

Toxaphene-induced neurological effects 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; Trottman and Desaiah 1979; Trottman et al. 1985). Results of *in*

vitro assays performed by Morrow et al. (1986) indicated that polar toxaphene fractions were more potent inhibitors of rat brain ATPase than other nonpolar or intermediate polar fractions or even toxaphene itself. Pollock and Kilgore (1980a) reported that nonpolar fractions of toxaphene were more toxic to houseflies and mice (*in vivo*) than polar fractions. 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 preparation of cell membranes in the *in vitro* assays could cause disruption within the hydrophobic environment and result in the exposure of polar groups. In any event, diminished ATPase activity in nervous tissue could have a profound effect on neural transmission because of the tissue's high metabolic rate.

Several investigators have demonstrated that toxaphene inhibits ATPases in the liver and kidney as well (e.g., Fattah and Crowder 1980; Mourelle et al. 1985; Trottman and Desaiah 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 and renal function, which could trigger injury responses.

Toxaphene has the potential to alter central nervous system neurotransmitter activity. Toxaphene acted as a noncompetitive γ-aminobutyric acid (GABA-A) antagonist at the chloride channel (also known as the picrotoxin binding site) in brain synaptosomes (Lawrence and Casida 1984; Matsumura and Tanaka 1984). GABA is an inhibitory neurotransmitter; 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 Ivanitskiĭ 1979).

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, results of Peakall (1979) indicated that these changes are not severe enough to have definite physiological consequences (measured as serum lactate and pyruvate levels) under nonstress conditions. The results of Kuz'minskaya and Alekhina (1976) and Gertig and Nowaczyk (1975) suggest that toxaphene exposure, coupled with stress, could result in detrimental effects on hepatic energy utilization and, ultimately, in hepatic injury.

Mechanisms responsible for toxaphene-induced immunosuppressive effects in laboratory animals are not presently known. Gauthier and coworkers demonstrated that toxaphene induces phagocytosis, production

of reactive oxygen species (ROS), and apoptosis in human neutrophils *in vitro* (Gauthier et al. 2001), and that caspases and ROS are likely involved in the degradation of cytoskeletal proteins (Lavastre et al. 2002).

Possible modes of action for toxaphene carcinogenicity have been assessed to some extent; available information is summarized in reports of de Geus et al. (1999), Goodman et al. (2000), and Lamb et al. (2008). Results of available *in vivo* genotoxicity assays have not demonstrated a genotoxic response. Although toxaphene was mutagenic in bacterial systems in the absence of metabolic activation, the mutagenic effect was reduced or abolished in the presence of metabolic activation; this finding suggests that toxaphene may be inactivated *in vivo*. There was no evidence of toxaphene-induced DNA adduct formation or peroxisomal proliferation in hepatic DNA or microsomes from mice administered toxaphene at oral doses as high as 100 mg/kg; however, these mice exhibited significant increases in immunodetectable levels of hepatic CYP 2B (Hedli et al. 1998). Toxaphene-induced increases in hepatic CYP 2B levels and liver enlargement are consistent with the action of phenobarbital, a nongenotoxic rodent liver tumor promoter. Toxaphene and phenobarbital have each been shown to inhibit intercellular communication, a possible mode of nongenotoxic carcinogenicity. The weight of evidence presently suggests a nongenotoxic mode of action for toxaphene tumorigenicity.

3.5.3 Animal-to-Human Extrapolations

Due to a lack of information regarding potential interspecies differences in the toxicokinetics of toxaphene, it is assumed that humans and animals share similar metabolic pathways. Comparative information regarding the toxic effects of toxaphene is limited to findings of similar neurological effects in humans and laboratory animals following exposure to high levels of toxaphene. In the absence of information regarding other systemic effects of toxaphene toxicity in humans, it is assumed that the systemic effects observed in laboratory animals are of human relevance as well.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a

naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Results of some assays suggest that toxaphene may be weakly estrogenic. Toxaphene was reported to induce weak estrogenic effects in most assays of human breast estrogen-sensitive MCF7 cells (Jørgensen et al. 1997; Soto et al. 1994, 1995; Stelzer and Chan 1999) and one assay of rat uterine leiomyoma-derived cells (Hodges et al. 2000). In an assay that employed human hepatoma cells transfected with estrogen receptor and luciferase reporter gene, Kim et al (2004) reported that toxaphene exerted an agonistic effect on estrogen receptor α and an antagonistic effect on estrogen receptor β. Results of Graham et al. (2003) indicate that toxaphene may exhibit estrogen-like activity by modulating prolactin mRNA levels in GH_3 pituitary-derived cells. Toxaphene did not induce an estrogenic response in other assays using mouse uterus cells and MCF7 cells (Arcaro et al. 2000; Ramamoorthy et al. 1997) or yeast-based estrogen reporter genes (Ramamoorthy et al. 1997; Rehmann et al. 1999). Yang and Chen (1999) reported that toxaphene acted as an antagonist of estrogen-related receptor α-1. Drenth et al. (2000) reported that technical toxaphene exerted an antiestrogenic effect in stably transfected human T47D.Luc breast cancer cells.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion,

particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

It is not known whether children are more susceptible than adults to toxaphene toxicity. No human data are available regarding age-related susceptibility to toxaphene. Results of one animal study (Olsen et al. 1980) indicate that critical stages of neurological development may be periods of increased vulnerability. Olson et al. (1980) reported significantly retarded swimming ability and righting reflex in 10–12-day-old pups of rat dams that ingested toxaphene throughout gestation and lactation; however, the effect was transient and pups exhibited normal swimming ability at testing on postpartum day 16. Immunosuppression has been demonstrated in some animals exposed to toxaphene (Allen et al. 1983; Koller et al. 1983; Tryphonas et al. 2001). Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10–12 years of age (Calabrese 1978).

3.8 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).

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 (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, 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 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 3.8.1.

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 3.8.2.

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 3.10, Populations That Are Unusually Susceptible.

3.8.1 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). Toxaphene and/or toxaphene residues have been detected in breast milk, urine, stomach washings, umbilical cord blood, and adipose tissue samples from children (Munn et al. 1985; Tewari and Sharma 1977; Vaz and Blomkvist 1985; Butler Walker et al. 2003; Witt and Niessen 2000). 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 Center 1966). Levels detected in tissues generally reflect only very recent exposures (<1 week) because toxaphene is rapidly 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.

3.8.2 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, and immune suppression. However, none of these effects is specific to toxaphene exposure.

For more information on biomarkers for renal and hepatic effects of chemicals see Agency for Toxic Substances and Disease Registry/CDC (1990) and for information on biomarkers for neurological effects, see OTA (1990).

3.9 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_{50} 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 parathion, diazinon, or trithion yielded LD_{50} 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 significantly reduced 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.

3.10 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 may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of toxaphene, or compromised function of organs affected by toxaphene. Populations who are at greater risk due to their unusually high exposure to toxaphene are discussed in Section 6.7, Populations with Potentially High Exposures.

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, 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 (Claborn 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 at doses that typically elicited maternal toxicity. 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 Haliburton 1979; Kuz'minskaya and Ivanitskiĭ 1979; Lawrence and Casida 1984; McGee et al. 1952; Wells and Milhorn 1983). Persons with latent or clinical neurologic diseases may be at an increased risk of adverse effects following toxaphene exposure.

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 (Allen et al. 1983; Boyd and Taylor 1971; Chandra and Durairaj 1992, 1995; Chu et al. 1986, 1988; Garcia and Mourelle 1984; Gertig and Nowaczyk 1975; Hedli et al. 1998; Kennedy et al. 1973; Koller et al. 1983; Kuz'minskaya and Alekhina 1976; Lackey 1949; Mehendale 1978; Peakall 1976; Trottman and Desaiah 1980).

Persons with diseases that affect 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 (Warraki 1963). The kidney (Boyd and Taylor 1971; Chu et al. 1986; Fattah and Crowder 1980; Trottman and Desaiah 1979; Trottman et al. 1985) and adrenal gland (Kuz'minskaya and Ivanitskiĭ 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 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; Tryphonas et al. 2001).

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 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.

3.11 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. The following texts provide specific information about treatment following exposures to toxaphene:

Dart RC, ed. 2004. Pesticides. In: Medical toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1489-1496.

Holland MG. 2002. Insecticides: Organochlorines, pyrethrins, and DEET. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. Goldfrank’s toxicologic emergencies. 7th ed. New York, NY: Mc-Graw-Hill Medical Publishing Division, 1366-1378.

Leikin JB, Paloucek FP, eds. 2002. Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 1199.

Rhee JW, Aks SE. 2007. Organochlorine insecticides. In: Shannon MW, Borron SW, Burns MJ, eds. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders Elsevier, 1231-1236.

3.11.1 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 nonvolatile, absorption following inhalation exposure to dusts and sprays probably occurs through mucociliary trapping and transport followed by gastrointestinal absorption. Toxaphene caused toxicosis following dermal application of the pesticide to farm animals; therefore, absorption across the skin is a health concern as well.

For oral exposure, do not induce emesis. Gastric lavage may be considered if the patient presents in a timely manner. Precaution should be taken to avoid aspiration, however. Activated charcoal may be administered to potentially decrease absorption following ingestion, although the efficacy of this treatment is uncertain.

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. Provide emergency airway support and 100% humidified supplemental oxygen with assisted ventilation if needed.

Decontamination is the first step in reducing absorption following dermal exposure. Contaminated clothing should be removed. Skin should be washed with soap and water. Decontamination includes irrigation of the eyes with copious amounts of water or saline (if available).

3.11.2 Reducing Body Burden

Once absorbed, toxaphene bioaccumulates in adipose tissue and is metabolized and excreted over several days to a few weeks following exposure. For organochlorines that undergo enterohepatic and enteroenteric recirculation, cholestyramine has been administered to potentially increase fecal elimination, although the efficacy of this treatment for toxaphene poisoning is uncertain. 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.

3.11.3 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 γ-aminobutyric acid-dependent chloride ion channels that are found on the neuron. The putative role of γ-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.

Although mechanisms of neurotoxicity vary among individual chlorinated hydrocarbon pesticides, toxaphene, DDT, chlordane, lindane, heptachlor, kepone, and mirex are each considered moderately toxic following acute oral administration (animal LD_{50} >50 mg/kg). Several cases of toxaphene-induced seizures in humans have been reported (McGee et al. 1952; Wells and Milhorn 1983). The acute management of seizures with anticonvulsants such as diazepam (a γ-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. Seizure control can be achieved by administration of GABA agonists such as benzodiazepines; phenobarbital or propofol may be considered if benzodiazepines are ineffective.

3.12 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.

3.12.1 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 3-5. 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 Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 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 3-5, 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.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Limited human and animal data are available regarding effects of acute-duration inhalation exposure to toxaphene. One controlled human study reported a NOAEL of 500 mg/m^3 for repeated 30-minute exposures to toxaphene aerosols (Keplinger 1963). Animal data are

Figure 3-5. Existing Information on Health Effects of Toxaphene

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

Human

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

Animal

● Existing Studies

restricted to secondary source accounts of death and hepatocellular necrosis in laboratory animals exposed to toxaphene by inhalation; the primary sources for this information were unpublished reports that were not available to ATSDR. Data on the acute effects of inhaled toxaphene do not appear necessary because all uses for toxaphene have been banned in the United States and its territories (EPA 1990b).

No adequate human data are available regarding the effects of acute-duration oral exposure to toxaphene. Available animal data include acute lethality studies in multiple laboratory species (Boyd and Taylor 1971; Chandra and Durairaj 1995; Chernoff and Carver 1976; Chernoff et al. 1990; Epstein et al. 1972; Gaines 1969; Jones et al. 1968; Lackey 1949). Acute-duration oral exposure to toxaphene has resulted in adverse effects on the nervous system, immunological system, body weight, and liver (Chandra and Durairaj 1995; Chernoff and Carver 1976; Chernoff et al. 1990; Chu et al. 1986; Hedli et al. 1998; Lackey 1949; Rao et al. 1986; Steele et al. 1980; Trottman and Desaiah 1980; Waritz et al. 1996). The study of Chu et al. (1986) identified the highest NOAEL (5 mg/kg/day) associated with the lowest LOAEL (10 mg/kg/day for clinical signs of neurotoxicity in dogs) and serves as the point of departure for deriving an acute-duration oral MRL for toxaphene. Additional animal studies of acute-duration oral exposure to toxaphene are not necessary.

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). Additional acute-duration dermal studies do not appear necessary because all uses for toxaphene have been banned in the United States and its territories (EPA 1990b).

Intermediate-Duration Exposure. Available information regarding intermediate-duration exposure to toxaphene is limited to animal studies that employed the oral exposure route and identified neurological, hepatic, renal, developmental, and immunological end points (Allen et al. 1983; Chu et al. 1986, 1988; Kennedy et al. 1973; Koller et al. 1983; Lackey 1949; NCI 1979; Olsen et al. 1980; Tryphonas et al. 2001; Waritz et al. 1996). The study of Tryphonas et al. (2001) identified the highest NOAEL (0.1 mg/kg/day) associated with the lowest reliable LOAEL (0.4 mg/kg/day for depressed humoral immunity in cynomolgus monkeys) and served as the basis for deriving the MRL. Additional animal studies do not appear necessary. All uses for toxaphene have been banned in the United States and its territories (EPA 1990b). Monitoring of workers at waste sites where toxaphene is found and people living in close proximity to such sites might provide useful information. Additional information

regarding the potential for health effects in human populations consuming food sources such as fish with documented levels of toxaphene residues would be useful.

Chronic-Duration Exposure and Cancer. Available information regarding noncancer and cancer effects is limited to chronic-duration oral studies in animals. Neurological, immunological, and body weight effects were reported in rats and mice (NCI 1979) and cynomolgus monkeys (Arnold et al. 2001; Bryce et al. 2001; Tryphonas et al. 2001) administered toxaphene orally for chronic durations. A chronic-duration oral MRL was not derived for toxaphene because the study that identified the highest NOAEL (0.4 mg/kg/day) associated with the lowest LOAEL (0.8 mg/kg/day for significantly depressed humoral immune response) after 52 weeks of toxaphene treatment identified a LOAEL of 0.4 mg/kg/day for another measure of humoral immune response after <52 weeks of toxaphene treatment (Tryphonas et al. 2001). Therefore, the intermediate-duration oral MRL should be protective of immunological effects following chronic-duration oral exposure to toxaphene. Lifetime oral studies found increased incidences of thyroid tumors in rats and hepatic tumors in mice exposed to high oral doses of toxaphene (NCI 1979). Additional chronic-duration toxicity and carcinogenicity studies in animals do not appear necessary. All uses for toxaphene have been banned in the United States and its territories (EPA 1990b). Monitoring of workers at waste sites where toxaphene is found and people living in close proximity to such sites might provide useful information. Additional information regarding potential for health effects in human populations consuming food sources such as fish with documented levels of toxaphene residues would be useful.

Genotoxicity. Limited information is available regarding the genotoxicity of toxaphene in humans. A higher incidence of chromosomal aberrations was observed in cultured lymphocytes taken from the blood of eight women exposed to toxaphene compared to lymphocytes taken from unexposed women (Samosh 1974). Additional assessment of the genotoxic potential of toxaphene would be helpful in the unlikely event that populations with significant exposure to toxaphene can be identified.

Available *in vivo* genotoxicity data from animals are limited to a dominant lethality test in which toxaphene did not cause increased fetal death or decreased numbers of implants in mouse dams mated to males that had been administered toxaphene orally (Epstein et al. 1972); a study that reported the lack of DNA damage in rats administered toxaphene once by gavage at up to 36 mg/kg/day (Kitchin and Brown 1994); and a study that found no evidence of DNA adduct formation in livers of mice administered toxaphene by gavage for 7 days at doses up to and including 100 mg/kg/day (Hedli et al. 1998).

Available *in vitro* assays provide positive and negative results. Bacterial reverse mutation assays provide evidence of a mutagenic effect in the absence of metabolic activation systems (Hooper et al. 1979; Mortelmans et al. 1986; Schrader et al. 1998; Steinberg et al. 1998) and diminished or abolished mutagenic responses with the addition of metabolic activation systems (Hooper et al. 1979; Schrader et al. 1998). Other *in vitro* genotoxicity assays provide equivocal results (Bartoš et al. 2005; Griffin and Hill 1978; Houk and DeMartini 1987; Mortelmans et al. 1986; Schrader et al. 1998; Sobti et al. 1983; Steinel et al. 1990). Additional *in vivo* data would be useful to more rigorously assess the potential genotoxicity of toxaphene.

Reproductive Toxicity. No information was located regarding toxaphene-induced reproductive effects in humans. 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). Additional studies do not appear necessary.

Developmental Toxicity. No information was located regarding toxaphene-induced developmental effects in humans. Toxaphene was reported to cause inferior swimming and righting ability in young mouse pups (9–12 days postpartum, but not at 16 days postpartum) of dams administered toxaphene by gavage at 0.05 mg/kg/day (the only dose tested) throughout gestation and lactation (Olson et al. 1980). Allen et al. (1983) reported suppression of phagocytic function in peritoneal macrophages from offspring of rat dams receiving toxaphene in the diet at 19.5 mg/kg/day prior to mating and during gestation and lactation; however, phagocytic function was enhanced at a higher dose level (39 mg/kg/day). Crowder et al. (1980) found no evidence of developmental toxicity following oral exposure of rat dams to toxaphene at 6 mg/kg/day (the only dose tested) during gestation. A comprehensive developmental toxicity study could be designed to provide supporting or refuting evidence to the findings of Olson et al. (1980).

Immunotoxicity. No information was located regarding immunologic effects of toxaphene in humans. Toxaphene-related depressed IgG production was reported in adult rats (Koller et al. 1983). Depressed humoral responses were noted in rat neonates exposed via their mothers (Allen et al. 1983) and in cynomolgus monkeys administered toxaphene orally for up to 75 weeks (Tryphonas et al. 2001). Additional studies of toxaphene-induced immunotoxicity in laboratory animals do not appear necessary at this time.

Neurotoxicity. Neurological effects have been reported in several cases of inadvertent or intentional ingestion of unknown “large amounts” of toxaphene (McGee et al. 1952; Wells and Milhorn 1983).

Convulsions were induced in dogs (Chu et al. 1986; Lackey 1949) and heifers (Steele et al. 1980) following acute oral exposure to toxaphene. NCI (1979) reported clinical signs of neurotoxicity in rats and mice administered toxaphene orally for chronic durations. The animal data indicate that dogs are particularly sensitive to toxaphene neurotoxicity. Additional studies of the neurological effects in toxaphene-exposed animals do not appear necessary. All uses for toxaphene have been banned in the United States and its territories (EPA 1990b). Monitoring of workers at waste sites where toxaphene is found and people living in close proximity to such sites might provide useful information. Additional information regarding the potential for health effects in human populations consuming food sources such as fish with documented levels of toxaphene residues would be useful.

Epidemiological and Human Dosimetry Studies. Most of the available information on the effects of toxaphene in humans comes from cases of acute poisoning following 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; Wells and Milhorn 1983). All uses for toxaphene have been banned in the United States and its territories (EPA 1990b). Monitoring of workers at waste sites where toxaphene is found and people living in close proximity to such sites might provide useful information. Additional information regarding the potential for health effects in human populations consuming food sources such as fish with documented levels of toxaphene residues would be useful.

Biomarkers of Exposure and Effect.

Exposure. Toxaphene levels have been measured in blood, fat, urine, and feces (Ohsawa et al. 1975; Pollock and Kilgore 1980b). No studies demonstrate a reliable correlation between blood levels and levels of exposure. Fat samples contain toxaphene levels proportional to treatment levels (Pollock 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 useful measure only shortly following exposure to toxaphene. Persistent toxaphene congeners in fat might serve as useful biomarkers of exposure and would be most likely associated with exposure to weathered toxaphene.

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. These effects are not specific for toxaphene and no studies exist that 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 that 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.

Absorption, Distribution, Metabolism, and Excretion. Quantitative evidence on the absorption of toxaphene in humans and animals following all routes of exposure is very limited. Female animals dipped in toxaphene excrete the substance in 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 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. Excretion data from animal studies are available for oral and dermal exposure routes. 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 be beneficial to conduct studies that would establish elimination rates for each toxaphene metabolite or for similar metabolic products. 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- or chronic-duration 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- or chronic-duration exposure would be useful.

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 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.

Methods for Reducing Toxic Effects. The medical procedures used to reduce the toxic effects of toxaphene are well established and are 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 γ-aminobutyric acid-dependent chloride ion channels would be useful.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No human data are available regarding age-related susceptibility to toxaphene. Results of one animal study (Olsen et al. 1980) indicate that critical stages of neurological development may be periods of increased vulnerability. Immunosuppression has been demonstrated in some animals exposed to toxaphene (Allen et al. 1983; Koller et al. 1983; Tryphonas et al. 2001), and it is known that infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10–12 years of age (Calabrese 1978). As identified in the Developmental Toxicity subsection, a well-designed, developmental toxicity animal study could provide additional insight into age-related susceptibility to toxaphene.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Search of the Federal Research in Progress database (FEDRIP 2010) revealed no ongoing studies of toxaphene-related health effects.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

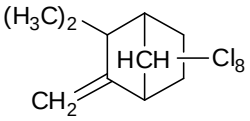
Information regarding the chemical identity of toxaphene is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of toxaphene is located in Table 4-2. Toxaphene is not a single molecular substance; rather, it is a complex mixture of congeners including chlorinated bornanes, bornenes, bornadienes, camphenes, and dihydrocamphenes (de Geus et al. 1999). The congeners typically contain 6–10 chlorine atoms each (de Geus et al. 1999; Lau et al. 1996). Representative structures for the different types of toxaphene congeners are shown in Figure 4-1. Although thousands of toxaphene congeners are theoretically possible based on these structures, only a few hundred are expected to be present at significant concentrations in technical toxaphene (de Geus et al. 1999; Lamb et al. 2008; Simon and Manning 2006).

The chemical structure of specific toxaphene congeners has been described using a variety of nomenclature systems, some of which are summarized in de Geus et al. (1999). This Toxicological Profile for Toxaphene employs the nomenclature system developed by Dr. Harun Parlar to refer to specific congeners (Coelhan and Parlar 1996).

Table 4-1. Chemical Identity of Toxaphene

Characteristic	Information	Reference
Chemical name	Toxaphene	ChemIDplus Advanced 2010
Synonym(s)	Campheclor; chlorinated camphene; polychlorocamphene; chlorocamphene; octachlorocamphene; technical toxaphene	ChemIDplus Advanced 2010
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	$C_{10}H_{10}Cl_8$ (approximately)	O'Neil et al. 2006
Chemical structure[a]		Paris and Lewis 1973
Identification numbers:		
CAS Registry	8001-35-2	ChemIDplus Advanced 2010; NIOSH 2005
NIOSH RTECS	XW5250000	
EPA Hazardous Waste	P123	HSDB 2010
DOT/UN/NA/IMCO	NA 2761/toxaphene	NIOSH 2005
HSDB	1616	HSDB 2010

[a]Structure representative of the predominant chlorinated camphene compounds present in technical toxaphene.

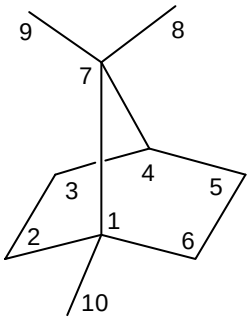
CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Toxaphene[a]

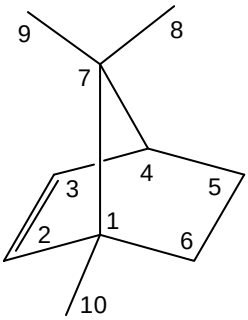
Property	Information	Reference
Molecular weight	431.8 (approximately)	BCPC 2003
Color/form	Yellow, waxy, amber	NIOSH 2005; O'Neil et al. 2006
Physical state	Solid	O'Neil et al. 2006
Melting point	65–90 °C	O'Neil et al. 2006
Boiling point	Not applicable (dechlorinates at 155 °C)	O'Neil et al. 2006
Density at 25 °C	1.65 g/cm^3	BCPC 2003
Odor	Mild, piney, chlorine- and camphor-like odor	NIOSH 2005
Odor threshold:		
Air	0.14 ppm (detection)	Sigworth 1965; Ruth 1986
Water	2.4 mg/m^3 0.14 ppm (detection)	HSDB 2010
Solubility:		Murphy et al. 1987
Water	0.55 mg/L	
Organic solvent(s)	Freely soluble in aromatic hydrocarbons Readily soluble in organic solvents, including petroleum oils	BCPC 2003; O'Neil et al. 2006
Partition coefficients:		
Log K_{ow}	3.3–6.64	EPA 1981a; Fisk et al. 1999
Log K_{oc}	3–5	EPA 1981a; Soubaneh et al. 2008; Wauchope et al. 1992
Vapor pressure	6.69x10^{-6} mm Hg at 20 °C	Murphy et al. 1987
Henry's law constant	6x10^{-6} atm-m^3/mol at 20 °C	Murphy et al. 1987
Autoignition temperature	No data	
Flashpoint	135 °C (closed cup, 60% solution) 115 °C (tag closed cup, 90% solution)	HSDB 2010
Flammability limits in air	Solid is not flammable, but is usually dissolved in combustible liquid	HSDB 2010
Conversion factors (25 °C)	1 ppm x 17.95(average)=1 mg/m^3; 1 mg/m^3 x 0.056 (average)=1 ppm	Calculated
Explosive limits	No data	

[a]Technical toxaphene is a complex mixture of hundreds of polychlorinated bicyclic terpenes consisting predominantly of chlorinated camphenes (Jansson and Wideqvist 1983; Paris and Lewis 1973). Toxaphene contains 67–69% chlorine by weight (de Geus et al. 1983).

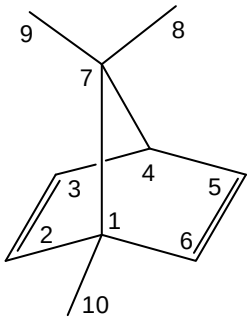
Figure 4-1. Representative Carbon Skeleton Structures of the Toxaphene Congeners with Numbered Carbon Atoms[a]



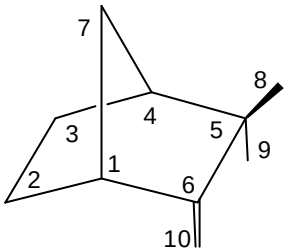
Bornane



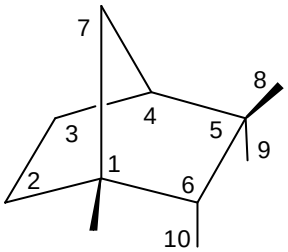
Bornene



Bornadiene



Camphene



Dihydrocamphene

[a]Congeners typically contain 6–10 chlorine atoms.

Source: de Geus et al. 1999

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 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; Vetter and Scherer 1998). 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; Penumarthy 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 of the pesticide 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 (Penumarthy 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). 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 2010). In 1982, it was estimated that 3.7 million pounds (<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). The Toxics Release Inventory (TRI) lists one facility in Idaho and one facility in Texas that were involved in toxaphene production during 2008 (TRI08 2010). No other information regarding recent production of toxaphene in the United States was found.

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." Hercules Incorporated has essentially let the name of toxaphene lapse into the public

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).

Since the early 2000s, efforts have been underway to eliminate the production and use of toxaphene worldwide. The Stockholm Convention, an international treaty designed to restrict the production and use of various chemical substances among its member nations, includes toxaphene on a list of persistent organic pollutants or POPs (Stockholm Convention 2008). Under the rules of the convention, production or use of toxaphene is completely banned and exemptions are not available. The convention, which initially went into effect in 2005, listed over 150 participating nations as of June, 2010.

While most attention has been focused on the intentional production of polychlorinated camphenes (PCCs) as pesticide agents, there is 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).

Because toxaphene is a Priority Pollutant under the Clean Water Act, it is required to be included in the TRI (EPA 2005). All registered uses of toxaphene on food commodities were canceled by 1990 (EPA 1982a, 1990b), and the sale and use of existing stocks of the pesticide in the United States were prohibited after March 1, 1990 (USDA 1995). Therefore, current information included in the TRI regarding the processing or use of toxaphene at industrial facilities is expected to be related to the storage and disposal of toxaphene supplies or the use of this substance in onsite processing and as a manufacturing aid. These facilities are not expected to be involved in production or import of toxaphene for pesticidal use in the United States. Table 5-1 summarizes the number of facilities in each state that processed or used toxaphene in 2008, the ranges of maximum amounts on site, if reported, and the activities and uses as reported in the TRI (TRI08 2010). The data listed in this table should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Toxaphene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	0	99	12
AR	5	0	99,999	2, 5, 7, 9, 12
CA	3	0	9,999	12
ID	1	0	99	1, 3, 12
IL	2	0	999	12
IN	3	0	9,999	2, 3, 12, 13, 14
KY	1	1,000	9,999	12
LA	3	0	9,999	12
MI	3	0	999	12, 14
MS	1	1,000	9,999	2, 3, 8
NE	3	100	999,999	12
NJ	1	100	999	12
NV	2	1,000	99,999	2, 3, 12
OH	4	0	99,999	12
OK	2	0	99,999	12
OR	2	100	9,999	12
PA	1	0	99	12
SC	1	10,000	99,999	12
TX	6	0	9,999,999	1[d], 3, 12
UT	2	0	9,999	12
WI	1	0	99	8

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

[d]Production is reported for only one facility in Texas.

Source: TRI08 2010 (Data are from 2008)

5.2 IMPORT/EXPORT

In 1972, a total of 8,000 metric tons (7.25 million kg) of toxaphene, or 35% of the annual production, was exported (EPA 1974b; SRI 1993; USITC 1991). The TRI lists four states containing facilities that were involved with the import of toxaphene into the United States during 2008 (TRI08 2010). No other information was found regarding the import of toxaphene into or the export of toxaphene from the United States.

5.3 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 Cassia obtusifola 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). Toxaphene's 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 <1% on sorghum (IARC 1979). Based on estimates of EPA (1974b) 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 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; grasshopper and army worm infestations on cotton, corn, and small grains; and 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).

5.4 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 1989a). 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 1989a). Landfill has also been identified as a recommendable method of disposal of toxaphene (IRPTC 1985). Thermal desorption is reported to be 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 8.

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

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6. POTENTIAL FOR HUMAN EXPOSURE

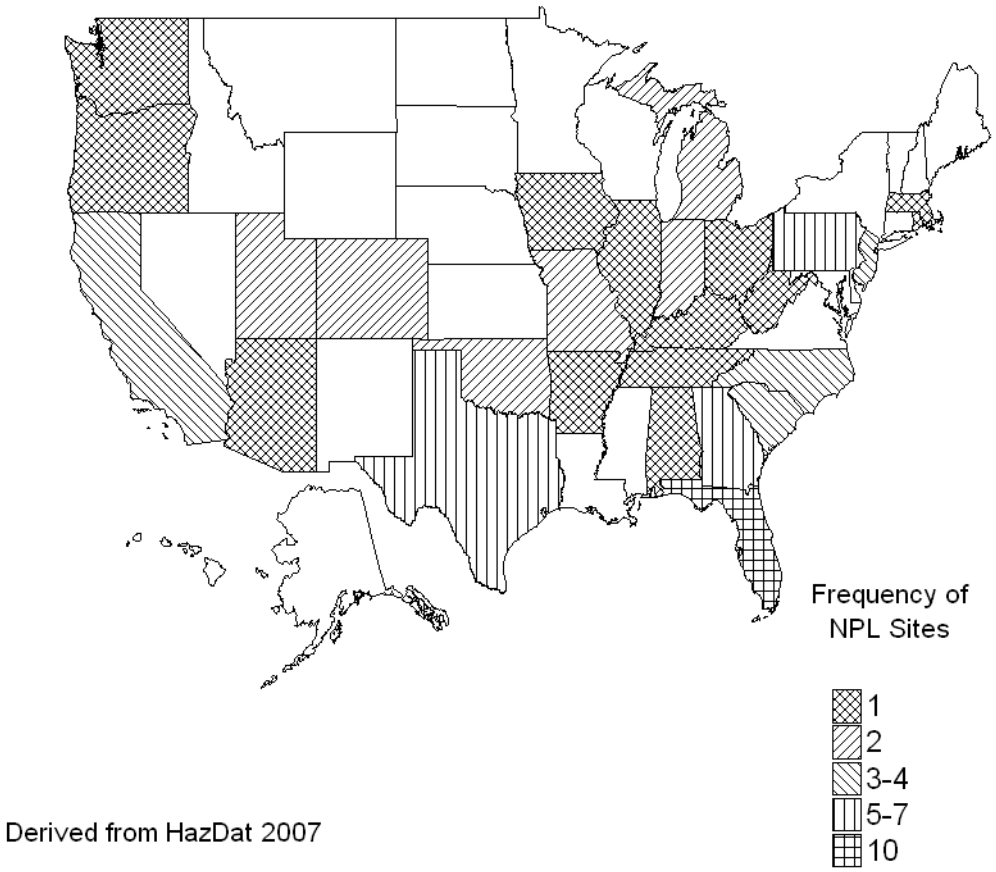
6.1 OVERVIEW

Toxaphene has been identified in at least 68 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for toxaphene is not known. The frequency of these sites can be seen in Figure 6-1.

Toxaphene is a complex mixture of several hundred polychlorinated bicyclic terpene congeners (de Geus et al. 1999; Jansson and Wideqvist 1983; Lamb et al. 2008; Lau et al. 1996; Paris and Lewis 1973; Simon and Manning 2006). 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.

Toxaphene has been widely dispersed 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 environmental persistence, toxaphene continues to be transported over long distances in the atmosphere (Andersson et al. 1988; Bidleman and Olney 1975; MacLeod et al. 2002; Paasivirta et al. 2009; Swackhamer and Hites 1988; Zell and Ballschmiter 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 for vapor-phase components of toxaphene (Howard 1991; Kelly et al. 1994); however, many congeners exist predominantly in the particulate phase and subsequently have longer atmospheric residence times and greater potential for long-range transport. Toxaphene strongly adsorbs to particles and is relatively immobile in soils (EPA 1981a; Soubaneh et al. 2008; 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 4,200–60,000 (Sanborn et al. 1976; Schimmel et al. 1977). 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; de Geus et al. 1999; Nash and Woolson 1967; Parr and Smith 1976; Smith and Willis 1978).

Figure 6-1. Frequency of NPL Sites with Toxaphene Contamination



Recently, efforts have been made to differentiate between the form of toxaphene as it was formerly used as a pesticide, known as technical toxaphene, and the "weathered" form of this substance after years of environmental transport and degradation processes have had their effect (EPA 2010e). Weathered toxaphene is considered to be the most relevant form when assessing the current potential for human exposure to toxaphene. In order to achieve the best understanding of what individuals may be exposed to in the environment, recent studies have measured the levels of individual toxaphene congeners present in environmental samples. Congeners p-26, p-50, and p-62 are reported to be persistent in fish, marine mammals, human serum, and breast milk (Simon and Manning 2006). The toxicological implications of environmentally-persistent congeners of weathered toxaphene have not been adequately assessed.

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), recreational or subsistence hunters in the southern United States that consume significant amounts of game animals (especially species like raccoons) (Ford and Hill 1990), and people who consume certain types of sportfish caught in the Great Lakes (ATSDR 2009).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report releases into the environment (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and

if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

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 past use as an agricultural insecticide (EPA 1979f). Toxaphene-like mixtures of PCC congeners may also be released to the environment as unintentional byproducts from manufacturing processes involving chlorination, such as those used for paper and pulp (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 TRI (EPA 2005). 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, most releases of toxaphene reported to TRI for 2008 were disposals to landfills (TRI08 2010).

Current sources of toxaphene in the environment that may result in exposure for the U.S. population is long-range atmospheric transport 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.

6.2.1 Air

Estimated releases of 64 pounds (0.029 metric tons) of toxaphene to the atmosphere from 14 domestic manufacturing and processing facilities in 2008, accounted for <0.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI08 2010). These releases are summarized in Table 6-1.

As a result of its past use as an insecticide on crops in the southern United States, toxaphene was dispersed 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.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Toxaphene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	2	10	0	0	0	833	10	833	843
IL	1	0	0	0	0	1	0	1	1
LA	1	3	0	0	9	0	12	0	12
NV	1	0	0	0	28	0	28	0	28
OH	3	0	0	0	79	75	0	154	155
OK	1	40	0	0	415,473	0	415,513	0	415,513
OR	1	1	0	0	1,961	0	1,962	0	1,962
TX	2	6	0	0	0	0	6	0	6
UT	1	3	0	0	0	0	3	0	3
WI	1	0	0	0	0	0	0	0	0
Total	14	64	0	0	417,550	908	417,535	988	418,523

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI08 2010 (Data are from 2008)

(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.

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. 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 m. 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 has been identified in air samples collected at 3 of the 68 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.2.2 Water

No releases of toxaphene to surface water from domestic manufacturing and processing facilities required to report to the TRI were reported for 2008 (TRI08 2010). Estimated releases of 988 million pounds (0.448 metric tons) of toxaphene off-site, which include transfers to publicly owned treatment works (POTWs), accounted for 0.23% of the estimated total environmental releases from facilities required to report to the TRI. The 2008 TRI release information is summarized in Table 6-1.

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). NOAA (1974) reported that toxaphene 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, which increased the mobility of toxaphene in soils. 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 been identified in surface water and groundwater samples collected at 14 and 27 of the 68 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2007). 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.

6.2.3 Soil

Estimated releases of 0.418 million pounds (189 metric tons) of toxaphene to soils from 17 domestic manufacturing and processing facilities in 2008, accounted for about 99.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI08 2010). No underground injection releases were reported (TRI08 2010). The TRI release data are summarized in Table 6-1.

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 Superfund 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 Superfund sites in Litchfield, Arizona; Albany, Georgia; Marrianna, Florida; and Malone, Florida; concentrations in these soils ranged from 18 to

1,505 mg/kg (ppm) (Troxler et al. 1993). Toxaphene has been identified in soil and sediment samples collected at 40 and 22 of the 68 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2007).

6.3 ENVIRONMENTAL FATE

6.3.1 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 showed 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 (Hoh and Hites 2004; James and Hites 2002; MacLeod et al. 2002; Voldner and Schroeder 1989, 1990).

A 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 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, 1995; 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.

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, 1995). Comparisons of levels in environmental media during the 1990s with baseline concentrations in the 1970s and early 1980s did 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 were still a matter of concern nearly a decade after the United States began phasing out the use of toxaphene as a pesticide agent.

Toxaphene is a mixture of many congeners, each of which has its own unique Henry's law constant. A Henry's law constant of $6x10^{-6}$ atm-m^3/mol at 20 °C was measured for the mixture, which suggests that

many components of toxaphene will volatilize to the atmosphere from water and soil surfaces. A half-life (first-order kinetics) of 6 hours to 12 days has been estimated for the volatilization of toxaphene from a model river, one meter deep, with a flow rate of 1 m/second and a wind velocity of 3 m/second (Howard 1991). The results of 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 6.2.1 (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 originated from the aerial transport and deposition of the mixture from application sites in the southern United States (EPA 1984b; Hoh and Hites 2004; James and Hites 2002; Ma et al. 2005a, 2005b; MacLeod et al. 2002). 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). The presence of toxaphene in biota of the Barents Sea in Northern Europe has been attributed to transport via air currents from areas of historical use in southeastern Europe and around the rivers that flow into the Aral Sea (Paasivirta et al. 2009). 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. 1990); fish from pristine areas in the North Atlantic Ocean, North Pacific Ocean, and Antarctic Ocean (Zell and Ballschmiter 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 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. Burniston et al. (2005) measured toxaphene concentrations in precipitation into Lake Ontario from 1994 to 1998. These authors reported that estimates of wet deposition flux were 50% of the estimated gas deposition flux based on loadings of toxaphene for Lake Ontario via precipitation during 1998.

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}=3–5) (EPA 1981a; Soubaneh et al. 2008; 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) to 14 years (Nash and Woolson 1967) have been reported for toxaphene in soils. In surface soils, where volatilization will be a significant transport process, half-lives of 2 and 4 months have

been reported for samples taken at the top 2.5 and 7.5 cm, respectively (Seiber 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 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). Raff and Hites (2004) measured toxaphene levels in suspended sediment samples along the Mississippi River. Based on these data and water discharge rates, the authors estimated a release of 200–1,000 kg of toxaphene into the Gulf of Mexico from the main stem of the river during 2002. The source of toxaphene was attributed to nonpoint source runoff from agricultural lands.

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 and erosion 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 voltatilization 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 post-application. Leaf residues declined from 661 ppm on the day of application to 135 ppm on day 50 post-application, 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 (0.55 mg/L) (Murphy et al. 1987). 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 that are consumed by other organisms and, consequently, would be expected to bioaccumulate up the food chain.

Uptake factors (mg toxaphene sorbed per microorganism/concentration of toxaphene in the medium) ranged from 3.4×10^3 to 1.7×10^4 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_7–Cl_9 camphenes (i.e., hepta-, octa-, and nonachlorobornenes) (Bruns and Birkholz 1993).

Experimentally determined bioconcentration factors (BCFs) for several aquatic organisms have been found to range from 4,200 to 60,000. 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 (Sanborn et al. 1976).

Toxaphene has also been detected in the tissues of aquatic organisms in numerous field studies (see Section 6.4.4). 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 (*Catastomus 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, octachlorobornane T2 and nonachlorobornane 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 PCBs or other chlorinated insecticides, such as DDT. Stapleton et al. (2001) found that PCB burdens were greater than toxaphene burdens for each Great Lakes fish species collected during 1997–1998 with the exception of deepwater sculpin. 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. Whittle et al (2000) measured food web toxaphene concentrations in four of the Great Lakes (Table 6-2). Based on these data, toxaphene biomagnification factors were determined to be 32.03 in

Table 6-2. Food Web Total Toxaphene Concentrations (μg/g Wet Weight) Measured in Lake Superior, Lake Huron, Lake Erie, and Lake Ontario

Species	Lake Superior	Lake Huron	Lake Erie	Lake Ontario
Lake trout	1.926	0.365	0.081	0.639
Herring	1.024	–[a]	–	–
Sculpin	0.546	0.312	–	0.245
Smelt	0.291	0.119	0.016	0.066
Alewife	–	0.139	–	0.049
Diporeia	0.197	0.131	0.029	0.090
Mysis	0.091	0.020	–	0.034
Plankton	0.062	0.015	<0.015	0.021

[a]Not analyzed.

Source: Whittle et al. 2000

Lake Superior, 24.33 in Lake Huron, 10.08 in Lake Erie, and 30.43 in Lake Ontario. 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 (Niethammer 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 received heavy pesticide applications. Biomagnification was also reported in a study that included analyses of tissue residue levels in eight 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). 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 nonachlorobornane, 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 (*Globicephala melaena*) 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.

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/beluga (0.4–1.1); *Eurythenes gyrillus*/arctic cod and char (9.1–11.1); *E. gyrillus*/narwhal (2.8–3.2); *E. gyrillus*/beluga (4.6–4.8); *E. gyrillus*/ringed seal (55.3–65.3); *E. gyrillus*/eelpout (4.4–19.2); and eelpout/small lysianassid amphipods (0.2–2.7).

6.3.2 Transformation and Degradation

Toxaphene is not a single molecular substance, but rather a mixture of hundreds of congeners including chlorinated bornanes, bornenes, bornadienes, camphenes, and dihydrocamphenes (see Section 4.2). The form of toxaphene as it was originally applied in the past as a pesticide is referred to as technical toxaphene. The composition of technical toxaphene released to the environment changes over time as the congeners degrade at different rates. Degradation proceeds mainly through dechlorination and dehydrochlorination, resulting in a shift in composition toward lower chlorinated homologs (Buser et al. 2000; Lamb et al. 2008). The changed form of toxaphene is commonly referred to as weathered toxaphene (Lamb et al. 2008; Simon and Manning 2006). In order to achieve the best understanding of what individuals may be exposed to in the environment, recent studies have measured the levels of individual toxaphene congeners present in environmental samples. Some of the toxaphene congeners that have been reported in the literature are listed in Table 6-3. Congeners p-26, p-50, and p-62 are reported to be persistent in fish, marine mammals, human serum, and breast milk (Simon and Manning 2006). The

Table 6-3. Names and Parlar Identification Numbers of Some Toxaphene Congeners Reported in the Literature

Name	CAS number	Parlar number
2,2,3-exo,8,9,10(E)-Hexachlorocamphene	–	p-11
2-exo,3-endo,8,8,9,10(E)-Hexachlorocamphene	–	p-12
2,2,5,5,9,10,10-Heptachlorobornane	–	p-21
2-endo,3-exo,5-endo,6-exo,8,8,10,10-Octachlorobornane	142534-71-2	p-26
2,2,5-endo,6-exo,8,9,10-Heptachlorobornane (Toxicant B)	–	p-32
2,2,5,5,9,9,10,10-Octachlorobornane	–	p-38
2,2,3-exo,5-endo,6-exo,8,9,10-Octachlorobornane	–	p-39
2-endo,3-exo,5-endo,6-exo,8,9,10,10-Octachlorobornane	166021-27-8	p-40
2-exo,3-endo,5-exo,8,9,9,10,10-Octachlorobornane	165820-16-6	p-41
2,2,5-endo,6-exo,8,8,9,10-Octachlorobornane (Toxicant A1)	–	p-42a
2,2,5-endo,6-exo,8,9,9,10-Octachlorobornane (Toxicant A2)	–	p-42b
2-exo,5,5,8,9,9,10,10-Octachlorobornane	165820-17-7	p-44
2-endo,3-exo,5-endo,6-exo,8,8,9,10,10-Nonachlorobornane	6680-80-8	p-50
2,2,5,5,8,9,10,10-Octachlorobornane	–	p-51
2,2,5-endo,6-exo,8,8,9,10,10-Nonachlorohornane	–	p-56
2,2,5-endo,6-exo,8,9,9,10,10-Nonachlorobornane	–	p-59
2,2,5,5,8,9,9,10,10-Nonachlorobornane	154159-06-5	p-62
2-exo,3-endo,5-exo,6-exo,8,8,9,10,10-Nonachlorobornane	–	p-63
2,2,5,5,6-exo,8,9,9,10,10-Decachlorobornane	–	p-69
2-exo,3-endo,6-exo,8,9,10-Hexachlorobornane (Hx-Sed)	–	–
2-endo,3-exo,5-endo,6-exo,8,9,10-Heptachlorobornane (Hp-Sed)	–	–
2-exo,3-endo,5-exo,8,9,10,10-Heptachlorobornane (TMX-1)	–	–
2-exo,3-endo,-5-exo,9,9,10,10-Octachlorobornane (B7-1453)	–	–
2-endo,3-exo,5-endo,6-exo,8,8,9,10-Octachlorobornane (B8-1412)	–	–

Sources: de Geus et al. 1999; EPA 2010e; Gooch and Matsumura 1985; Lau et al. 1996; Vetter et al. 2001; Xia et al. 2009

congeners Hx-Sed and Hp-Sed are known degradation products of toxaphene (Buser et al. 2000; EPA 2010e).

6.3.2.1 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). The higher chlorinated congeners have longer half-lives since they tend to exist in the particulate phase rather than the vapor phase. 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.

6.3.2.2 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 (de Geus et al. 1999). 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 >10 years for pH 5–8 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 (EPA 1977).

Buser et al. (2000) measured half-lives ranging from <1 day to several days for technical toxaphene congeners in anaerobic sewage sludge from a municipal waste water treatment plant. The non-gem-chloro-substituted congeners P26 and P50 degraded less rapidly than the gem-chloro-substituted congeners, which is consistent with the relatively high percentage of the P26 and P50 congeners detected in environmental samples (Buser et al. 2000; Lamb et al. 2008). Degradation was said to proceed through reductive dechlorination resulting formation of Hp-Sed and Hx-Sed and other metabolites. Lacayo et al. (2004) studied the degradation of toxaphene in water in aerobic and anaerobic bioreactors operating in sequence using a mixed culture inoculum. Reported degradation was 87% after 6 weeks and 98% after

39 weeks, with the majority of the degradation occurring under anaerobic conditions. Levels of toxaphene congeners with greater chlorine substitution decreased more rapidly than those with lesser chlorine substitution.

6.3.2.3 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 (congener p-32), 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 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.

Lacayo-Romero et al. (2006) studied the degradation of toxaphene congeners in contaminated soils using anaerobic bioreactors. These authors reported that the congeners p-11 and p-12 were degraded while the concentration of p-15 increased, suggesting that the less chlorine substituent toxaphene congeners are formed during the degradation of the greater chlorine substituted congeners. Ruppe et al. (2004) identified 20 metabolites resulting from anerobic bacterial transformation of technical toxaphene in sediments and soils. The most recalcitrant of the toxaphene metabolites were 2-exo,3-endo, 6-exo,8,9,10-hexachlorobornane (B6-923) and 2-endo,3-exo,5-endo,6-exo,8,9,10-heptachlorobornane (B7-1001).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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. Concentrations of toxaphene in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on toxaphene levels monitored or estimated 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. The analytical methods available for monitoring toxaphene in a variety of environmental media are detailed in Chapter 7.

As a result of its 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 GC 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 or NCBP) started in the 1970s; however, due to problems in quantification with the older analytical technologies, results of these programs cannot be compared with toxaphene sampling results obtained since 1990 (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 of the PCC congeners are the result of hemispheric or global atmospheric transport pathways, but in some cases, PCC from paper and pulp wastes may help explain localized hotspots (Jarnuzi et al. 1992a, 1992b; Paasivirta and Rantio 1991; Rantio et al. 1993). Shanks et al. (1999) concluded that pulp and paper mills were not sources of toxaphene to Lake Superior or northern Lake Michigan at the time of the study based on similar concentrations measured in samples upstream from the mills compared with those measured in downstream samples.

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. Also, analytical

methods used in the past have been based on analysis of technical toxaphene and may not have detected some congeners that are expected to be present in the weathered form of toxaphene (EPA 2010e).

6.4.1 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 <0.04–1.6 ng/m^3 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^3 (±0.45 ng/m^3 standard deviation [SD]) and 0.72 ng/m^3 (±0.09 ng/m^3 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^3 (detected in 11 of 90 samples), 2,520 ng/m^3 (9 of 99 samples), and 1,340 ng/m^3 (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 1970–1972, toxaphene was detected in 3.5% of the 2,479 samples collected at mean and maximum concentrations of 17 and 8,700 ng/m^3, respectively; the mean of the positive samples was 1,890 ng/m^3 (Kutz et al. 1976). In 1981, toxaphene was detected at maximum concentrations of 9.05, 1.73, 0.44, and 0.14 ng/m^3 in Greenville, Mississippi; Saint Louis, Missouri; Bridgeman, Michigan; and Beaver Island, Michigan, respectively (EPA 1984b; Rice et al. 1986).

Concentrations of chlorobornanes measured in air samples from Columbia, South Caroline during 1994–1995 ranged from 39 to 183 pg/m^3 (Bidleman et al. 1998). Air samples collected at a height of 40 cm above the soil at farms in Alabama, Louisiana, and Texas during June 1999 and June 2000 contained total toxaphene at concentrations ranging from 0.47 to 42.1 ng/m^3 (Bidleman and Leone 2004).

The average gas-phase concentrations of toxaphene were 1,600, 280, 34, and 10 pg/m^3 in air samples collected during 2000–2001 in Rohwer, Arkansas; Lubbock, Texas; Bloomington, Indiana; and Sleeping Bear Dunes, Michigan (Lake Michigan), respectively (James and Hites 2002). The average gas-phase concentrations of toxaphene were 61, 1,400, 60, and 23 pg/m^3 in air samples collected during 2002–2003 in Cocodrie, Louisiana; Rohwer, Arkansas; Bloomington, Indiana; and Sleeping Bear Dunes, Michigan (Lake Michigan), respectively (Hoh and Hites 2004). Based on these concentrations and analysis of air trajectories, the authors of these studies concluded that toxaphene detected in air from Indiana and the Great Lakes region originates in the southern United States (Hoh and Hites 2004; James and Hites 2002). Mean concentrations of total toxaphene and the congeners p-26 and p-50 measured in the air at locations over Lake Superior, Lake Huron, and Lake Erie were 28, 2.2, and 1.9 pg/L, respectively, in August 1996 and 12, 0.32, and 0.26 pg/L, respectively, in May 1997 (Jantunen and Bidleman 2003).

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^3. Average monthly levels were 258, 82, and 160 ng/m^3 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^3 in February to 110 pg/m^3 in July; the overall maximum and mean concentrations (n=114) were 580 and 26 pg/m^3, respectively. Shoeib et al. (1999) measured total toxaphene concentrations ranging from 0.9 to 10.1 pg/m^3 in the air at Point Petre, Ontario sampled during 1992 and from 1995 to 1997. The summer-to-winter concentration ratio was reported to be about 6. Glassmeyer et al. (1998) reported vapor-phase toxaphene concentrations ranging from 1.0 to 42 pg/m^3 measured in the air at Eagle Harbor, Michigan (Lake Superior) during 1996 and 1997.

Toxaphene has been identified in air samples collected at 3 of the 68 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.4.2 Water

Toxaphene has been detected very rarely in drinking water supplies. Toxaphene concentrations ranged from 5 to 410 ppt (0.005–0.410 ppb) in drinking water samples collected in Flint Creek, Alabama, between 1959 and 1963 (Faust and Suffet 1966). 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 to 1992, at mean and maximum concentrations of 0.30 and 0.50 ppb, respectively (Storm 1994). Concentrations did not exceed the Maximum Contaminant Level (MCL) of 5.0 ppb.

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 <0.2 ppb.

In a study of toxaphene concentrations in surface water and runoff from the Bear Creek, Mississippi, watershed conducted in 1976–1979, 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) 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 Kow used in these calculations was an average for the toxaphene mixture and that, because Kow 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). 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.

Swackhamer et al. (1999) reported mean dissolved toxaphene concentrations of 1.12 ng/m^3 in Lake Superior surface water collected in 1996 and 0.38 ng/m^3 in Lake Michigan surface water collected in 1994–1995. Surface water concentrations were estimated to be <0.5 ng/m^3 in Lakes Huron, Erie, and Ontario. The higher levels in Lake Superior were attributed to colder temperatures (lower volatilization rate) and lower sedimentation rates (James et al. 2001; Swackhamer et al. 1999). The mean concentration of total toxaphene and the congeners p-26 and p-50 measured in surface water collected at locations across Lake Superior in 1996 and 1997 were 918, 3.5, and 13 pg/L, respectively (Jantunen and Bidleman 2003).

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 two of nine disposal ponds at a Superfund site (EPA 1986a). In a study of the chemical composition of leachates 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 ≤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. Toxaphene has been identified in surface water and groundwater samples collected at 14 and 27 of the 68 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2007).

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). Burniston et al. (2005) reported annual average toxaphene concentrations of 0.68–0.85 ng/L (38–47 ppt) measured in Lake Ontario precipitation samples collected continuously from November 1994 through December 1998.

No additional information was found in the literature for concentrations of toxaphene in rainwater samples collected in the United States.

6.4.3 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 three of eight 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 0.6 ppm. Carey et al. (1979a) monitored soils in five 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). Toxaphene was found in 73 of 1,729 soil samples collected in 43 states during 1969 with a mean concentration of 0.07 ppm and a range of 0.10–11.72 ppm (Wiersma et al. 1972b). Toxaphene was found in 76 of 1,483 soil samples collected in 37 states during 1972 with a mean concentration of 0.24 ppm and a range of 0.22–46.58 ppm (Carey et al. 1979b).

Toxaphene was detected in 38 of 39 agricultural soil samples collected at locations across the state of Alabama (Harner et al. 1999). The geometric mean concentration of toxaphene in these samples was 84 ng/g dry weight and the maximum concentration was 2,423 ng/g dry weight. The concentrations of toxaphene measured in soil samples collected from 32 cotton fields in southern South Carolina and eastern Georgia ranged from 3.3 to 2,500 ng/g dry weight (Kannan et al. 2003). The median of the reported concentrations was 85.3 ng/g dry weight for the South Carolina soils and 67.25 for the Georgia soils. Soil samples collected at farms in Alabama, Louisiana, and Texas during June 1999 and June 2000 contained total toxaphene at concentrations ranging from 3.2 to 6,520 ng/g dry weight (Bidleman and Leone 2004).

Toxaphene levels were measured in soil samples collected during 2000–2001 from three schools and one field ballpark in Brunswick, Georgia (Agency for Toxic Substances and Disease Registry 2005). These sites are all located within 0.5 miles of the Hercules, Incorporated industrial facility, which manufactured

toxaphene from the mid 1940s until 1982. Maximum toxaphene levels measured in the soil from the sampling locations were <0.010, 0.180, 0.030, and 0.380 ppm, respectively.

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 <1 ppb (detection limit) to 30 ppb. 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 nine confined disposal facilities in the Great Lakes region (Beyer and Stafford 1993).

Toxaphene has also been detected in sediment samples throughout the 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 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 (Mattraw 1975). Toxaphene was not detected in 27 sediment samples collected in Delaware and in the Raritan Canal, New Jersey, from 1979 to 1980 (Granstrom 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).

During an 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 and 25.4–30.48 cm) along eight different drainages (Ford and Hill 1991). The geometric mean and maximum wet weight toxaphene concentrations were 0.12 and 2.80 ppm for the shallow samples, and 0.07 and 4.60 ppm for the deeper samples, respectively. There was no significant difference in toxaphene concentrations between corresponding shallow and deep samples. Raff and Hites (2004) measured toxaphene levels ranging from 0.4 to 39 ng/g in suspended sediment samples collected from 32 locations along the Mississippi River during 2002–2003. The concentrations of toxaphene in the sediments were found to increase rapidly as the river passes through the cotton-growing regions of the southern United States. Studies in agricultural areas of the Mississippi Delta have provided 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.

Shanks et al. (1999) reported toxaphene concentrations of 1.4–9.0 ng/g dry weight measured in sediment from rivers near pulp and paper mills near Lakes Michigan and Superior. These authors also measured toxaphene concentrations of 6.0–43 ng/g dry weight in sediments from rivers near sites where this pesticide was previously used. Maximum toxaphene concentrations measured in sediment cores collected from Lake Michigan, Lake Superior, and Lake Ontario during the early 1990s were 48, 42, and 29 ng/g, respectively (Pearson et al. 1997). Surficial accumulation rates of 0.097–1.01 ng/cm^2-year were determined (Pearson et al. 1997). Analysis of sediment cores showed that in most cases, toxaphene accumulations peaked in the early 1970s to early 1980s and then declined in following years (Pearson et al. 1997; Schneider et al. 2001). Howdeshell and Hites (1996) observed similar trends in eight Lake Ontario sediment cores collected in 1993 and cited contaminated flow from the Niagara River in addition to atmospheric deposition as sources of toxaphene in the lake. Analysis of sediment cores from two lakes in Canada that were treated with toxaphene during 1961–1962 revealed maximum toxaphene concentrations of 500 and 1,602 ng/g dry weight at depths corresponding to the time of treatment (Miskimmin et al. 1995). Surface concentrations in these lakes were 53 and 112 ng/g dry weight. Toxaphene was not detected in untreated lake sediments. Toxaphene sediment concentrations from five Canadian lakes previously treated with this pesticide ranged from 2.6 to 110 µg/kg dry weight (Donald et al. 1998). Toxaphene was also detected at 0.2 µg/kg dry weight in an oligotrophic glacial fed lake that had no record of treatment.

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 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 two of nine 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; Marrianna, Florida; and Malone, Florida (Troxler et al. 1993). More recently, toxaphene has been identified in soil and sediment samples collected at 40 and 22 of the 68 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2007).

6.4.4 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 (Agency for Toxic Substances and Disease Registry 2009; Ford and Hill 1990; Xia et al. 2009), 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 Food and Drug Administration's (FDA) Total Diet Studies. In a 1980–1982 survey of pesticides, toxaphene was detected in samples of food groups that comprised typical infant and toddler diets. Concentrations of 0.1–0.2 ppm (number positive samples, 3) and 0.7–0.12 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 summary of data from 1985 to 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, 1994c, 1995). Concentrations were not reported; however, <1% of the surveillance samples 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 to 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, 1994c, 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 μg/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 μg/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 μg/g (ppm) (strawberries) to 0.12 μg/g (ppm) (dry-roasted peanuts). During the period 1989–1991, estimated toxaphene intakes were <0.01 μg/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 6.5 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 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 fourteen fish consumption advisories in effect for this compound (see Section 6.7) (EPA 2010d).

Toxaphene is of particular concern as a major contaminant of Great Lakes fish. Xia et al. (2009) detected the toxaphene congeners, p-26, TMX-1, p-38, p-40, p-41, p-44, p-50, and p-62, in fish composites from Lake Michigan, Lake Superior, Lake Huron, Lake Ontario, and Lake Erie collected during 2004. Reported total toxaphene concentrations were 39 ng/g wet weight in Lake Erie walleye, 155 ng/g wet weight in Lake Huron lake trout, 243 ng/g wet weight in Lake Michigan lake trout, 113 ng/g wet weight in Lake Ontario lake trout, 398 ng/g in Lake Superior lake trout, and 846 ng/g wet weight in a Lake Superior lake trout Standard Reference Material labeled SRM 1946. Congeners p-26, p-50, and p-62 were reported to be the dominant peaks, together accounting for 2–44% of the amount of total toxaphene in the fish samples.

Swackhamer et al. (1998) measured toxaphene in plankton from Lake Michigan and fish from Lake Superior. Reported mean toxaphene concentrations were 51.3 ng/g dry weight in phytoplankton, 243 ng/g dry weight in zooplankton, 92.4 ng/g dry weight in mysis, 162 ng/g dry weight in bythotrephes, 411 ng/g dry weight in diporeia, 225 ng/g dry weight in sculpin, and 2,373 ng/g dry weight in lake trout. Mean total toxaphene concentrations of 92 and 198 ng/g wet weight were measured in bloater chub and alewife samples, respectively, collected from Grand Traverse Bay, Lake Michigan during 1997 and 1998 (Stapleton et al. 2002). Kucklick and Baker (1998) reported toxaphene concentrations of 99–210 ng/g wet weight in smelt, 560–720 ng/g wet weight in herring, 840–1,360 ng/g wet weight in bloater, 260–460 ng/g wet weight in sculpins, 21–40 ng/g in mysis, 110–180 ng/g wet weight in limnocatanus, 100 ng/g wet weight in amphipod, and 250–540 ng/g wet weight in lake trout collected from Lake Superior during the summer of 1994.

Whittle et al. (2000) reported toxaphene concentrations of 0.081–1.926 μg/g wet weight in lake trout, 1.024 μg/g wet weight in herring, 0.245–0.546 μg/g wet weight in sculpin, 0.016–0.291 μg/g wet weight in smelt, 0.049–0.139 μg/g wet weight in alewife, 0.029–0.197 μg/g wet weight in diporeia, 0.020–0.091 μg/g wet weight in mysis, and <0.015–0.062 μg/g wet weight in plankton collected from Lake Superior, Lake Huron, Lake Erie, and Lake Ontario. Results of this study are summarized in Table 6-2. Levels in Lake Superior samples were consistently higher than levels in samples from the other lakes. Henry et al. (1998) measured toxaphene in smallmouth bass collected from Fumee Lake in the Upper Peninsula of Michigan. Mean toxaphene concentrations were 137 ng/g wet weight in 0–20 cm length fish, 255 ng/g wet weight in 20–30 cm length fish, and 312 ng/g wet weight in >30 cm length fish.

Glassmeyer et al. (1997) measured toxaphene in lake trout, walleye, and smelt archival samples collected in 1982 and 1992/1994 from the Great Lakes. Reported 1982 toxaphene levels were 4.5–5.2 μg/g wet

weight in lake trout, 0.25 μg/g wet weight in walleye, and 0.16–0.83 μg/g wet weight in smelt. Reported 1992/1994 levels were 0.54–6.7 μg/g wet weight in lake trout, 0.13 μg/g wet weight in walleye, and 0.059–0.16 μg/g wet weight in smelt. While concentrations in the Lake Superior samples were not significantly different between the 2 years, the results showed a decline in toxaphene concentrations in the fish from the other Great Lakes from 1982 to 1992.

Residues of toxaphene and other pesticides in fish were examined as part of the 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 percentages of stations where detectable residues were present were 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 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 five 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 (p-42a and p-42b) and B (p-32) 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 4.70.5 ppm), and in 9 of 10 samples of lake trout collected in Lake Superior (mean concentration 1.6±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±0.2 ppm), and in 4 of 8 samples of chinook salmon collected in Lake Michigan in 1983 (mean concentration 1.0±0.0 ppm). 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 skin-on fillets. Zabik et al. (1995a, 1995b) 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).

The mean concentrations of toxaphene measured in largemouth bass at five different locations in the Mobile River basin in Alabama ranged from 13 to 104 ng/g in 2004 (Hinck et al. 2009). Maruya and Lee (1998) reported toxaphene concentrations of 0.5–1 μg/g lipid in fish collected from the Turtle/Brunswick River Estuary near Brunswick, Georgia. 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 to 1972, a period when toxaphene was heavily used (Butler 1973). Toxaphene was detected at concentrations <0.10 ppm wet weight in eggs, ovary, liver, and muscle tissue

of three pallid sturgeon (*Scaphirnyncus albus*) samples from the Missouri River in North Dakota and Nebraska (Ruelle and Keenlyne 1993).

The concentrations of total toxaphene measured in 19 fish samples collected from different locations in the Yukon, Canada ranged from 42 to 242 ng/g with a mean of 107 ng/g (Chan and Yeboah 2000). The sum of the concentrations of the three congeners, p-26, p-50, and p-62, ranged from 10 to 55 ng/g. Donald et al. (1998) reported higher chlorobornane concentrations in fish (75.7–303 μg/kg wet weight) from untreated oligotrophic lakes at higher elevations than in fish (3.3–82 μg/kg wet weight) from treated trophic lakes at lower elevations in western Canada. 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.

Tuerk et al. (2005) reported total toxaphene concentrations of 13.0–10.7 μg/g wet mass measured in the blubber of Atlantic white-sided dolphins and 1.49–3.33 μg/g wet mass measured in the blubber of rough-toothed dolphins. The relative proportions of the toxaphene congeners, p-50, p-26, and p-62, in the blubber samples were approximately 50, 35, and 15%, respectively. Mean concentrations of total toxaphene were 11.7 and 1.03 μg/g lipid in the blubber of bottlenose dolphins from the Turtle/Brunswick River Estuary and the Savannah Area Estuary, respectively, along the coast of Georgia (Pulster et al. 2009). Fourteen toxaphene congeners were identified in the blubber samples. Congener p-42a, which is one of the most abundant congeners in technical toxaphene, was present in the highest concentrations (maximum of 3,950 μg/g lipid). Toxaphene congeners, p-25, p-40, p-50, Hx-Sed, and Hp-Sed, were frequently detected at concentrations ranging from 100 to 1,000 ng/g lipid.

Gouteux et al. (2003) measured toxaphene congeners in blubber samples of 26 male and 26 female beluga whales from the St. Lawrence Estuary. The mean concentrations of the toxaphene congeners p-26 and p-50 were 710 and 1,510 ng/g wet weight, respectively, in the males and 280 and 520 ng/g wet weight, respectively, in the females. Maximum concentrations of these congeners were 1,240 and 3,060 ng wet weight, respectively, in the males and 1,110 and 1,690 ng/g wet weight, respectively, in the females. The authors stated that on average, toxaphene concentrations decreased by a factor of two between 1988 and 1999. Gouteux et al. (2005) measured chlorobornanes in blubber samples from six seal species in the St. Lawrence marine ecosystem. Toxaphene congeners, p-26, p-40/41, p-44, p-50, and p-62, were all detected, with p-26 and p-50 comprising 50–80% of the total chlorobornanes in each sample. The mean concentrations of total chlorobornanes were 49 ng/g lipid weight in gray seals, 80 ng/g lipid weight in

harbor seals, 18 ng/g lipid weight in ringed seals, 370 ng/g lipid weight in harp seals, and 680 ng/g lipid weight in hooded seals.

Vetter et al. (2001) detected eight toxaphene congeners in the blubber of seals from the Baltic Sea, the North Sea, and the Antarctic. Congeners p-26, p-50, B8-1412, p-44, and p-62 were detected in the greatest concentrations, followed by B7-1453, p-40, and p-41. Total toxaphene concentrations ranged from 5 μg/kg wet weight in an Antarctic elephant seal to 1,457 μg/kg wet weight in a harp seal from the North Sea. Concentrations in three Weddell seals in Antarctica ranged from 161 to 489 μg/kg wet weight. Total toxaphene concentrations were 68–303 μg/kg in cod liver samples, 1,194 μg/kg in cod liver oil, and 4–98 μg/g in two penguins.

Alder et al. (1997) measured the levels of the three toxaphene congeners, p-26, p-50, and p-62, in >100 samples of fish species that are consumed in Germany. Reported mean concentrations for the sum of these congeners were 12.1 μg/kg wet weight in herring, 0.2 μg/kg wet weight in Alaska Pollock, 0.8 μg/kg wet weight in saithe, 15.1 μg/kg wet weight in redfish, 0.1 μg/kg wet weight in hake, 7.9 μg/kg wet weight in mackerel, 1.1 μg/kg wet weight in cod, 2.2 μg/kg wet weight in sardine, and 36.7 μg/kg wet weight in halibut. Mean concentrations of congeners p-26, p-50, and p-62 were 5.87, 8.70, and 1.59 μg/kg fresh weight, respectively, in salmon collected along the Swedish east coast of the Baltic Sea (Atuma et al. 2000).

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 subsistence-level 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 1963–1972. Toxaphene was detected in about 4% of the samples at maximum concentrations exceeding 100 ppm. Toxaphene was also detected in six brands of cigar tobacco sampled in 1972 at an average concentration of 0.92 ppm; four of the six samples had toxaphene concentrations of <0.5 ppm. McDonald and Hites (2003) measured the concentrations of toxaphene in 46 tree bark samples collected in the United States and Canada. Higher concentrations (>20 ng/g bark) were found in samples collected from the South and Southeastern United States, between 40 and 32 degrees latitude, where toxaphene was used heavily in the past. Two samples had toxaphene concentrations as high as 250 and 300 ng/g bark. Toxaphene concentrations generally ranged from 1 to 11 ng/g bark in samples collected at locations further north or south.

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.

6.5 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 μg/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. Toxaphene intakes, in μg/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 μg/kg body weight/day, by eight age/sex groups was 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; and 60–65-year-old males, 0.0077 (FDA 1993; Gunderson 1995). 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).

Toxaphene has been detected at a concentration of 0.1 mg/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 mg/kg lipid weight in human breast milk samples from Nicaragua, where toxaphene is still being produced and used (de Boer and Wester 1993). Mean concentrations of total toxaphene and the toxaphene congeners p-26 and p-50 were 0.8, 0.4, and 0.6 ng/g fat, respectively, in 10 pools of human milk collected during 2002–2003 from 238 primiparous women living in Hong Kong and south China (Hedley et al. 2010). The toxaphene congener p-62 was not detected in any of the samples. Newsome and Ryan (1999) measured toxaphene levels in human milk samples collected from women living in northern and southern Canada. These authors found that toxaphene concentrations in the northern samples were approximately 10-fold higher than those measured in the southern samples and stated that this disparity may be due to differences in types of food consumed. Mean concentrations of total toxaphene, congener 26, and congener 50 were 6.03, 1.32, and 2.35 ng/g lipid, respectively, in samples collected across southern Canada in 1992 (n=58); 7.28, 1.32, and 1.15 ng/g lipid, respectively, in samples collected in the Great Lakes basin in 1992 (n=24); 12.1, 2.83, and 4.37 ng/g lipid, respectively, in samples collected across southern Canada in 1986 (n=30); and 67.7, 24.9, and 33.1 ng/g lipid, respectively, in samples collected in Keewatin, Northwest Territories in 1997 (n=12). Toxaphene was measured in pooled human milk samples collected from individuals living in sub-arctic and arctic locations in northwestern Russia (Polder et al. 2003). Concentrations of the toxaphene congeners p-26, p-50, and

p-62 measured in these samples were 2.34–4.33, 3.70–5.75, and 1.32–1.67 μg/kg milk fat, respectively. Polder et al. (2008) reported a mean concentration of 11 ng/g lipid weight measured in 10 human milk samples collected during 2000–2001 from primipara mothers living in the town of Tromso in northern Norway. Skopp et al. (2002b) found the sum of congeners p-26, p-41, p-44, and p-50 to range from 7 to 24 μg/kg milk fat in breast milk samples from women in an area of northern Germany. Levels of toxaphene in human milk from U.S. populations are not available.

Barr et al. (2004) measured the levels of two toxaphene congeners, p-26 and p-50, in old serum pools originally collected in Atlanta, Georgia in 1987, Chicago, Illinois in 1992, and Cincinnati, Ohio in 1994. Reported concentrations in these samples were 14.3, 3.5, and 28.9 pg/mL, respectively, for p-26 and 10.5, 10.0, and 25.2 pg/mL, respectively, for p-50. Patel et al. (2004) measured toxaphene levels in pools of 108 serum samples collected from pregnant women in Barrow and Bethel, Alaska. p-26 and p-50 were detected in >50% of the samples with geometric mean concentrations of 1.10 and 1.61 ng/g lipid-weight, respectively.

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 μg/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.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths,

sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children may be exposed to toxaphene by breathing contaminated air, drinking contaminated water, eating contaminated soil, or eating contaminated fish or animals. Children living near areas where toxaphene was used heavily or near hazardous waste sites contaminated with toxaphene may have higher exposure to this substance. Based on the maximum concentration (0.380 ppm) of toxaphene measured in soil from school grounds and a park located near a former production facility in Brunswick, Georgia, an exposure dose of 0.000015 mg/kg/day was estimated for a child if exposure through pica is excluded (Agency for Toxic Substances and Disease Registry 2005). The estimated exposure dose for a child rose to 0.0006 mg/kg/day if exposure through pica was included. Both of these values were below the intermediate-duration oral MRL of 0.002 mg/kg/day derived for toxaphene.

Witt and Niessen (2000) measured levels of toxaphenes in the adipose tissue of 48 children living in Germany, Russia, and Kazakhstan. Median and maximum concentrations at the different sampling locations were 0.37–1.97 and 0.69–6.02 μg/kg, respectively, for congener p-26 and 0.65–2.36 and 1.22–6.12 μg/kg, respectively, for congener p-50. Levels of toxaphene measured in neonatal blood, cord blood, meconium fluid, or the blood or urine of children were not located.

Nursing infants may 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. There are several documented cases of toxaphene congeners in fats from human breast milk (Hedley et al. 2010; Mussalo-Rauhamaa et al. 1988; Newsome and Ryan 1999; Polder et al. 1998, 2003, 2008; Skopp et al. 2002b; Vaz and Blomkvist 1985). Toxaphene congeners were also found in the fats in human breast milk in Nicaragua, while toxaphene was still being produced and used (de Boer 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.

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 Ballschmiter 1991).

Oetjen and Karl (1998) measured levels of three toxaphene indicator congeners in fish oils from Europe ranging from 13 µg/kg fat in sand eel oil to 206 µg/kg fat in cod oil. 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).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Members of the general population currently having potentially higher intakes of toxaphene include residents living near 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.

In September 2010, toxaphene was cited as the causative pollutant in three fish consumption advisories in Arizona (Gila River, Hassayampa River, and Salt River), two in Delaware (Army Creek and Army Pond), five in Georgia (Back River, Back River from Causeway to St. Simons Sound, Coastal Georgia, Middle and South Georgia, Terry And Dupree Creeks), one in Louisiana (Tensas River), two in Mississippi (Delta Region and Roebuck Lake), and one in Oklahoma (Bitter Creek) (EPA 2010d).

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 2010d).

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 NCBP 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 (Schmitt et al. 1990). There may still be the potential for localized contamination of fish in the vicinity of hazardous waste sites and in the Great Lakes.

As noted in Section 6.4.4, there could also be risks of high exposures for three 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 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). The third includes individuals who regularly consume sport fish caught from the Great Lakes (ATSDR 2009).

6.8 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 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.

6.8.1 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; Budavari et al. 1989; EPA 1981a; NIOSH/OSHA 1978; Worthing 1979). 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.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2008, became available in February of 2010. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Recent U.S. production data for toxaphene are not available; however, it is assumed that this substance is no longer being produced for use as a pesticide in the United State since all registered uses were canceled in 1990 (EPA 1990b; USDA 1995). 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). The TRI lists one facility in Idaho and one facility in Texas that were involved in toxaphene production during 2008 (TRI08 2010). No other information regarding recent production of toxaphene in the United States was found.

In other parts of the world, toxaphene use continues at very high levels (Bidleman et al. 1989; Stern 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; Stern 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) (Rantio et al. 1993; Swackhamer et al. 1993) would also be useful in developing estimates of global production and emissions for toxaphene.

The TRI lists four states containing facilities that were involved with the import of toxaphene into the United States during 2008 (TRI08 2010). Export of toxaphene to foreign nations for use as a pesticide is not expected since nations around the globe have adopted similar bans under the Stockholm Convention. No other information was found regarding the import of toxaphene into or the export of toxaphene from the United States.

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 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 1989a). 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.

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; EPA 2010e; Lamb et al. 2008; 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. Toxaphene metabolites

such as Hp-Sed and Hx-Sed have been identified (Buser et al. 2000; EPA 2010e). Further information regarding the identity, toxicity, and environmental fate of the major toxaphene transformation products will be useful in making a more critical assessment of potential human exposure.

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. 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; Whittle et al. 2000). 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; Niethammer et al. 1984; Stapleton et al. 2001). While several studies show that 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. Reliable monitoring data for the levels of toxaphene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of toxaphene in the environment can be used in combination with the known body burden of toxaphene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Although a large amount of monitoring data is available for toxaphene, most of the data were collected 20–30 years ago when the mixture was widely used as a pesticide (Cole et al. 1984; Cooper et al. 1987; EPA 1984b; Faust and Suffet 1966; Kutz et al. 1976; Plumb 1987; Stanley et al. 1971; Staples et al. 1985). Some recent monitoring data are available for air (Bidleman and Leone 2004; Hoh and Hites 2004; James and Hites 2002; Jantunen and Bidleman 2003), surface water (Jantunen and Bidleman 2003), soil (Agency for Toxic Substances and Disease Registry 2005; Bidleman and Leone 2004; Harner et al. 1999; Kannan et al. 2003), and sediment (Raff and Hites 2004; Schneider et al. 2001). 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 place (EPA 2010d), 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 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 expected to be 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; Hedley et al. 2010; Mussalo-Rauhamaa et al. 1988; Newsome and Ryan 1999; Polder et al. 2008; Vaz and Blomkvist 1985). Levels of toxaphene have been measured in serum (Barr et al. 2004; Patel et al. 2004). 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.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Limited data are available regarding the exposures of children to toxaphene. Agency for Toxic Substances and Disease Registry (2005) assessed the potential for toxaphene exposure of children attending school near a former production facility. The estimated exposure dose for these children was calculated as 0.000015–0.0006 mg/kg/day. A few foreign studies are available that report toxaphene levels measured in human milk and adipose tissue of children (Hedley et al. 2010; Mussalo-Rauhamaa et al. 1988; Newsome and Ryan 1999; Polder et al. 2003, 2008; Vaz and Blomkvist 1985; Witt and Niessen 2000). Levels of toxaphene in human milk, amniotic fluid, meconium, umbilical cord blood, neonatal blood, childhood serum, or childhood adipose tissue of individuals living in the United States were not located.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for toxaphene were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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.

6.8.2 Ongoing Studies

No ongoing studies were located regarding the potential for human exposure to toxaphene.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, 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.

7.1 BIOLOGICAL MATERIALS

Table 7-1 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 PCBs, 1,1-dichloro-2-2-bis (chlorphenyl)-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 (de Geus et al. 1999; Gooch and Matsumura 1985; Matsumura et al. 1975; Nelson and Matsumura 1975).

Table 7-1. 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_2SO_4 and acetone; filtration of solution and addition of water and saturated Na_2SO_4 solution to extract; extraction with chloroform; addition of 5% KOH to chloroform extract; extraction with water; water removal (Na_2SO_4); 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; cleanup 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_2SO_4; cleanup 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_2SO_4; 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_2SO_4 and extraction with hexane; filtration of extract through anhydrous Na_2SO_4 and evaporation to dryness; dissolution of residue in acetone	TLC	1 μg/sample	94	Tewari and Sharma 1977
Human blood	Addition of 60% H_2SO_4 to blood sample; extraction with hexane:acetone (9:1); centrifugation and evaporation to dryness; dissolution of residue in hexane	GC/ECDGC/MC	No data 10–40 ppb	100 100	Griffith and Blanke 1974

Table 7-1. Analytical Methods for Determining Toxaphene in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Addition of sample to a solution of dilute H_2SO_4 and 10% sodium tungstate; filtration of solution and wash of residue with water; water removal with (Na_2SO_4) and extraction with hexane; filtration of extract through anhydrous Na_2SO_4 and evaporation to dryness; dissolution of residue in acetone	TLC	1 μg/sample	94	Tewari and Sharma 1977

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

Cautions regarding potential transformations of toxaphene components during sample clean-up operations are described below in Section 7.2. 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 (GC/MC), 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/NCIMS because it has shown the greatest sensitivity to these types of chlorinated compounds (Lau et al. 1996; Xia et al. 2009). Vaz and Blomkvist (1985) developed a GC/NCIMS method to quantitatively and selectively detect components of toxaphene at ppb (ng/g) levels in human breast milk. These authors demonstrated that several mass (M) fragments containing mainly (M-35)-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. One disadvantage of GC/NCIMS is the potential for obtaining false negative results for certain congeners (Lau et al. 1996; Santos et al. 1997; Xia et al. 2009).

An alternative method is gas chromatography/electron impact/mass spectrometry (GC/EI/MS) (Lau et al. 1996). This method is less sensitive than GC/NCIMS; however, it is better at overcoming interferences (Lau et al. 1996; Xia et al. 2009). In efforts to improve sensitivity, methods using high resolution GC/EI coupled with tandem MS/MS have been developed (Chan et al. 1998; Gouteux et al. 2002; Skopp et al. 2002a; Xia et al. 2009).

GC/ECD has also been widely used as a low-cost and sensitive method for toxaphene analysis. Griffith and Blanke (1974) and Head and Burse (1987) employed GC/ECD for analysis of toxaphene in human blood and breast fat, respectively. MS detection techniques have been favored over ECD since ECD has lower selectivity and higher risk for the coelution of congeners (Bordajandi et al. 2006; de Geus et al. 1999; Fowler 2000; Lau et al. 1996). A number of studies have explored multidimensional gas chromatography (MDGC) or similar techniques coupled with ECD as a way to increase selectivity (Bordajandi et al. 2006; De Boer et al. 1997; Korytar et al. 2003; Shoeib et al. 2000). Enantiomeric determination of chiral toxaphene congeners has been achieved using MDGC/ECD (Bordajandi et al. 2006).

Detection of the individual toxaphene congener enantiomers, referred to as enantioselective determination, has been demonstrated using both GC/NCIMS and MDGC/ECD (Bordajandi et al. 2006; de Geus et al. 1999; Vetter and Luckas 1995, 2000). Enantiomers tend to show differences in biological behavior due to chiral-specific interactions despite their identical physical properties (Vetter and Luckas 2000). The enantiomers of a single congener may be biodegraded or metabolized at different rates and they may show differences in toxicity. Therefore, analysis of the enantiomeric ratios of the congeners found in biological and environmental samples may provide further insight into the environmental fate and toxicity of toxaphene.

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 and more specific, and a lower temperature is generally required to vaporize the compound in the GC column.

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 35S tertiary butylbicyclo-phosphorothioate 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 $1x10^{-6}$ 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 is, however, laborious and time consuming.

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 (Lamb et al. 2008).

7.2 ENVIRONMENTAL SAMPLES

Table 7-2 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 (Foreid et al. 2000; Gill et al. 1996; Muir and de Boer 1993; Vetter et al. 2000). 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). Most recently, the focus of analytical toxaphene research has been to develop methods capable of sensitive, selective, and accurate determination of the many different individual toxaphene congeners present in samples (Bordajandi et al. 2006; EPA 2010e; Gill et al. 1996; MacEachen and Cocks 2002; Vander Pol et al. 2010; Vetter et al. 2005; Xia et al. 2009).

Since the formerly used commercial form of toxaphene, called technical toxaphene, undergoes "weathering" through environmental transformation and degradation processes, methods that are strictly based on technical toxaphene analysis may not give the most accurate picture regarding the form that humans may be exposed to in the environment. Therefore, recent efforts have also been made to differentiate between the congener profiles for technical toxaphene and weathered toxaphene (EPA 2010e).

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

Table 7-2. 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^3	100	Thomas and Nishioka 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^3	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^3 (10,000 m^3 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; cleanup using alumina column chromatography and concentration using K-D (EPA Method TO4)	GC/ECD (EPA Method 608)	Generally >1 ng/m^3	No data	EPA 1984a
Drinking water	Extraction of sample with 15% dichloromethane in hexane; water removal using anhydrous Na_2SO_4; 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

Table 7-2. Analytical Methods for Determining Toxaphene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water, groundwater, soil, sludges, wastes	Extraction of sample with organic solvent and cleanup 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_{18} 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
Waste water	Extraction with dichloromethane	Tandem MS	5 μg/sample		Hunt et al. 1985
Waste water	Extraction with dichloromethane, solvent exchange to hexane; Florisil cleanup	GC/ECD (packed column)	0.24 μg/L	96	EPA 1984c
Waste water	Extraction with 15% dichloro-methane in hexane followed by water removal with sodium sulfate and concentration with K-D; additional cleanup, 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 1998a
Municipal and industrial discharges	Extraction with dichloromethane (no pH adjustment) and solvent exchange to hexane during concentration; magnesia-silica gel cleanup and concentration	GC/ECD	0.24 μg/L	80	APHA 1998b

Table 7-2. Analytical Methods for Determining Toxaphene in Environmental Samples

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 accept-able	EPA 1992d
Primary sludge	Extraction of sample with hexane: dichloromethane: acetone (83:15:2); extract concentration and cleanup 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 cleanup	GC/ECD or GC/ELCD (EPA Method 8081B)	No data	No data	EPA 2007a
Soil, water	Extraction of sample with organic solvent or mixture of organic solvents, depending on the sample matrix, followed by open-column, chromato-graphic cleanup	GC/NIMS (EPA Method 8276)	No data	No data	EPA 2010e
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 cleanup	GC/MS and HPLC	0.05 μg/g	76–91	Crist et al. 1980

Table 7-2. Analytical Methods for Determining Toxaphene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Soxhlet extraction using methylene chloride or sonication with methylene chloride:acetone (1:1, v/v); GPC or SPE cleanup	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 cleanup	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% >0.25–5.0 μg/g	EPA 1996
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
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 $\mu g/cm^2$	No data	Bigley et al. 1981

Table 7-2. Analytical Methods for Determining Toxaphene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Non-fatty foods	Extraction of homogenized sample with solvent (acetone, acetonitrile, or acetonitrile/ water, depending on moisture and sugan content) followed by water removal and Florisil cleanup	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
Cucumber	Blending of sample with acetone folloed by extraction with petroleum ether and dichloromethane (1:1); water removal (Na_2SO_4) and concentration followed by Florisil column cleanup	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	Spectro-photometer (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

Table 7-2. Analytical Methods for Determining Toxaphene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Meat	Blending with ethyl acetate followed by drying (Na_2SO_4) and filtration; treatment of extract with KOH and heat; extraction with hexane; Florisil column cleanup	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
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_2SO_4; 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 Spurgeon 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 cleanup using Florisil	GC/ECD	No data	78–88	Boshoff and Pretorius 1979

Table 7-2. Analytical Methods for Determining Toxaphene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
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_2SO_4; cleanup 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_2SO_4; extraction in a column with hexane: acetone (1:1), followed by methanol	GC/NCIMS	75 pg/sample	98	Swack-hamer et al. 1987
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_2SO_4 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_2SO_4 and cleanup 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 (^{13}C-PCBs), and cleanup using GPC and Florisil	GC/HRMS (SIM)	10 ppb (wet weight)	No data	Andrews et al. 1993

Table 7-2. Analytical Methods for Determining Toxaphene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish tissue	Pulverization of tissue with anhydrous sodium sulfate and extraction with acetone; solvent exchange to hexane and volume reduction; cleanup 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; PCBs = polychlorinated biphenyls; PUF = polyurethane foam; SIM = selected ion monitoring; RSD = relative standard deviation; SIM = selected ion monitoring; SPE = solid phase extraction; TLC = thin-layer chromatography; v/v = volume/volume; wt/wt = weight/weight

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.

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, 2007a; 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 8081B) for determining toxaphene in water and soil samples (EPA 2007a). 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 2007b). More recently, EPA Method 8276 has been developed to detect congeners typically found in weathered toxaphene such as p-26, p-40, p-41, p-44, p-50, p-62, Hx-Sed, and Hp-Sed (EPA 2010e). This method uses fused-silica, open tubular capillary columns with negative ion mass spectrometry (NIMS) and is considered an appropriate alternative to EPA Method 8081.

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 of 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 <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 quadruple 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 <30 minutes. A disadvantage is that tandem MS is somewhat less specific than GC/MS in the identification of some isomeric compounds.

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 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 preseparation 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 <1 ppm of toxaphene was reported (Graupner and Dunn 1960).

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 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.

7.3 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 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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. 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 following an efficient sample preparation and rigorous clean-up procedures. TLC has been used for analysis of toxaphene metabolites (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.

Effect. 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 (2007a) to determine toxaphene in soil and water samples at ppb levels. A newer EPA method (8276) has been developed as an alternative to method 8081, which uses GC/NIMS (EPA 2010e). 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 0.002 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 70 ppb (70 μg/L or 70 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; Jarnuzi and Wakimoto 1991; Swackhamer et al. 1987). Limits of detection in 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.

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.

7.3.2 Ongoing Studies

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

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An MRL of 0.05 mg/kg/day has been derived for acute-duration oral exposure (≤14 days) to toxaphene. The MRL is based on a NOAEL of 5 mg/kg/day and a serious LOAEL of 10 mg/kg/day for neurological effects (convulsions, salivation, and vomiting) in male and female beagle dogs (Chu et al. 1986). The NOAEL of 5 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

An MRL of 0.002 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to toxaphene based on decreased anti-SRBC (IgM) titers as an indicator of depressed humoral immunity in monkeys. Benchmark dose (BMD) modeling was conducted using mean anti-SRBC (IgM) titre data collected from female cynomolgus monkeys that received toxaphene from the diet for 44 weeks prior to primary immunization with SRBC (Tryphonas et al. 2001). The resulting $BMDL_{1SD}$ of 0.22 mg/kg/day was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive individuals).

EPA (IRIS 2010) has not established an oral reference dose (RfD) or inhalation reference concentration (RfC) for toxaphene.

The International Agency for Research on Cancer (IARC) has classified toxaphene as a Group 2B carcinogen (possibly carcinogenic to humans) (IARC 2009). The National Toxicology Program (NTP) has determined that toxaphene is reasonably anticipated to be a human carcinogen (NTP 2005), and EPA has classified toxaphene as a B2 carcinogen (probable human carcinogen) (IRIS 2010). The American Conference of Governmental Industrial Hygienists (ACGIH) has classified toxaphene as an A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans) (ACGIH 2009).

OSHA has required employers of workers who are occupationally exposed to toxaphene to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2009). The employer must use engineering and work practice controls to reduce toxaphene exposures to or below 0.5 mg/m^3 at any time (ceiling) (OSHA 2009).

EPA has designated toxaphene as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) (EPA 2006b). Toxaphene is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 1 pound (EPA 2009e). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

The international and national regulations, advisories, and guidelines regarding toxaphene in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No[b]	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	0.5 mg/m^3 [c]	ACGIH 2009
	STEL (15-minute TWA)	1 mg/m^3 [c]	
	TLV-basis (critical effect)	Central nervous system convulsions; liver damage	
AIHA	ERPG values	No	AIHA 2010
DOE	TEELs		DOE 2010
	TEEL-0[d]	0.5 mg/m^3	
	PAC-1[e]	1 mg/m^3	
	PAC-2[f]	20 mg/m^3	
	PAC-3[g]	200 mg/m^3	
EPA	AEGL values	No	EPA 2010b
	Hazardous air pollutant	Yes	EPA 2006b 42 USC 7412
	Regulated toxic substances and threshold quantities for accidental release prevention	No	EPA 2009h 40 CFR 68.130
	Second AEGL Chemical Priority List	Yes[h]	EPA 2008
NIOSH	REL (10-hour TWA)	No[i]	NIOSH 2005
	IDLH	200 mg/m^3	
	Potential Occupational Carcinogen	Yes	
	Target organs	Central nervous system, skin	
	Category of Pesticide	Group I[j]	NIOSH 1992
OSHA	PEL (8-hour TWA) for general industry	0.5 mg/m^3 [i]	OSHA 2009 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2009b 40 CFR 116.4

Table 8-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference
NATIONAL (*cont.*)			
EPA	Drinking water standards and health advisories		EPA 2009c
	1-Day health advisory for a 10-kg child	0.004 mg/L	
	10-Day health advisory for a 10-kg child	0.004 mg/L	
	DWEL	0.01 mg/L	
	Lifetime	No	
	10^{-4} Cancer risk	0.003 mg/L	
	Drinking water contaminants list	Yes	EPA 2010c
	National primary drinking water regulations		EPA 2009d
	MCL	0.003 mg/L	
	Potential health effects from exposure above the MCL	Kidney, liver, or thyroid problems; increased risk of cancer	
	Common sources of toxaphene in drinking water	Runoff/leaching from insecticide used on cotton and cattle	
	Public health goal	Zero	
	National recommended water quality criteria	Yes	EPA 2006a
	Freshwater		
	CMC (acute)	0.73 μg/L	
	CCC (chronic)	0.0002 μg/L[k]	
	Saltwater		
	CMC (acute)	0.21 μg/L	
	CCC (chronic)	0.0002 μg/L[k]	
	Human health for the consumption of:		
	Water + organism	0.00028 μg/L[l,m]	
	Organism only	0.00028 μg/L[l,m]	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	1 pound	EPA 2009i 40 CFR 117.3
	Groundwater Monitoring List	Yes	EPA 2009a 40 CFR 264, Appendix IX
c. Food			
FDA	Bottled drinking water	0.003 mg/L	FDA 2010a 21 CFR 165.110

Table 8-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference
NATIONAL (*cont.*)			
FDA	EAFUS[n]	No	FDA 2010b
d. Other			
ACGIH	Carcinogenicity classification	A3[o]	ACGIH 2009
	Biological exposure indices (end of shift at end of workweek)	No	
EPA	Carcinogenicity classification	B2[p]	IRIS 2010
	Oral slope factor	1.1 $(mg/kg\text{-}day)^{-1}$	
	Drinking water unit risk	$3.2x10^{-5}$ $(\mu g/L)^{-1}$	
	Inhalation unit risk	$3.2x10^{-4}$ $(\mu g/m^3)^{-1}$	
	RfC	No	
	RfD	No	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes[q]	EPA 2009a 40 CFR 302.4
	Reportable quantity	1 pound	
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2009g 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity	No	EPA 2009f 40 CFR 355, Appendix A
	Toxic pollutants designated pursuant to Section 307(a)(1) of the Clean Water Act	Yes	EPA 2009j 40 CFR 401.15
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen[r]	NTP 2005

Table 8-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference

[a]Group 2B: possibly carcinogenic to humans.
[b]Chemical is excluded from guideline value derivation because of determination that toxaphene is unlikely to occur in drinking water.
[c]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, and by contact with vapors, liquids, and solids.
[d]TEEL-0 is the threshold concentration below which most people will experience no adverse health effects.
[e]PAC-1 is the airborne concentration (expressed as or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience discomfort, irritation, or certain asymptomatic, nonsensory effects. However, these effects are not disabling and are transient and reversible upon cessation of exposure.
[f]PAC-2 is the airborne concentration (expressed as mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape.
[g]PAC-3 is the airborne concentration (expressed as mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.
[h]Campheclor is included on the list of 371 priority chemicals that are acutely toxic and represent the selection of chemicals for AEGL development by the NAC/AEGL committee during the next several years.
[i]Skin designation: indicates the potential for dermal absorption.
[j]Group I pesticides pose a significant risk of adverse acute health effects at low concentrations, or carcinogenic, teratogenic, neurotoxic, or reproductive effects.
[k]This criterion is based on a 304(a) aquatic life criterion issued in 1980 or 1986, and was issued in toxaphene (EPA 440/5-86-006). This CCC is currently based on the FRV procedure. Since the publication of the Great Lakes Aquatic Life Criteria Guidelines in 1995 (60 FR 15393-15399, March 23, 1995), the Agency no longer uses the Final Residue Value procedure for deriving CCCs for new or revised 304(a) aquatic life criteria. Therefore, the Agency anticipates that future revisions of this CCC will not be based on the FRV procedure (EPA 2006b).
[l]This criterion has been revised to reflect The EPA's q1* or RfD, as contained in IRIS as of May 17, 2002. The fish tissue bioconcentration factor from the 1980 Ambient Water Quality Criteria document was retained in each case (EPA 2006b).
[m]This criterion is based on carcinogenicity of 10^{-6} risk.
[n]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[o]A3: confirmed animal carcinogen with unknown relevance to humans.
[p]B2: probable human carcinogen; based on increased incidence of hepatocellular tumors in mice and thyroid tumors in rats and supported by mutagenicity in Salmonella.
[q]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act, section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA.
[r]Based on sufficient evidence of carcinogenicity in experimental animals.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CCC = criterion continuous concentration; CMC = criterion maximum concentration; DOE = U.S. Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = U.S. Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FRV = final residue value; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MTL = Master Testing List; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term expsoure limit; TEEL = temporary emergency exposure limit; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

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

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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 (Kd)—The amount of a chemical adsorbed by 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.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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.

Biomarkers—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.

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.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

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.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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.

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

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

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

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

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—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$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—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 exposure level 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.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Maximum Contaminant Level (MCL) —The highest level of a contaminant that is allowed in drinking water.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a 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_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Parlar—A system (after Dr. H. Parlar, a pioneer in toxaphene analytical chemistry) for naming toxaphene congeners, numbered in the order in which the chemical is detected by laboratory equipment (elution order).

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* 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^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) 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 Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

Toxic Dose$_{(50)}$ (TD$_{50}$)—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.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) 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 lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

10. GLOSSARY

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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. 99–499], 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 100-fold 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 and Environmental Medicine, expert panel peer reviews, and agency-wide 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 and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toxaphene
CAS Numbers: 8001-35-2
Date: September 2010
Profile Status: Final Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 26
Species: Dog

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: Chu I, Villeneuve DC, Sun CW, 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): Groups of male and female beagle dogs (6/sex/group) were given gelatin capsules containing toxaphene at 0, 0.2, 2.0, or 5.0 mg/kg daily for 13 weeks. During the first 2 treatment days, the high-dose group received toxaphene at 10 mg/kg/day. This dose was reduced to 5 mg/kg/day on treatment day 3 because the 10 mg/kg/day dose level elicited convulsions, salivation, and vomiting in 1/6 males and 2/6 females. These clinical signs were not observed in any of the toxaphene-treated dogs throughout the remainder of the scheduled 13-week treatment period.

Effect noted in study and corresponding doses: Serious neurological effects (convulsions, salivation, and vomiting in 1/6 males and 2/6 females) were elicited during the first 2 days of oral treatment at 10 mg/kg/day. These effects were not elicited after the highest dose was reduced to 5 mg/kg/day on treatment day 3 and maintained at that level throughout the remainder of the scheduled 13-week treatment period.

Dose and end point used for MRL derivation: NOAEL of 5 mg/kg/day for neurological effects; the LOAEL was 10 mg/kg/day for clinical signs (convulsions, salivation, and vomiting in 1/6 males and 2/6 females).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Lackey (1949) reported convulsions in 4/5 fasted dogs administered toxaphene (in corn oil) once by capsule at 10 mg/kg. Higher single dose levels (15–50 mg/kg) resulted in convulsions and mortalities; there were no signs of

convulsions in three dogs dosed at 5 mg/kg. Seriously depressed maternal weight gain in pregnant rats and mice have been observed at toxaphene doses in the range of 15–32 mg/kg/day (Chernoff and Carver 1976; Chernoff et al. 1990). The dose necessary to induce nonfatal convulsions in humans has been estimated to be approximately 10 mg/kg (CDC 1963).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toxaphene
CAS Numbers: 8001-35-2
Date: September 2010
Profile Status: Final Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 47
Species: Monkey

Minimal Risk Level: 0.002 [X] mg/kg/day [ ] ppm

Reference: Tryphonas H, Arnold DL, Bryce F, et al. 2001. Effects of toxaphene on the immune system of cynomolgus (*Macaca fascicularis*) monkeys. Food Chem Toxicol 39:947-958.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 10 female cynomolgus monkeys/dose group were administered toxaphene by oral capsules at 0, 0.1, 0.4, or 0.8 mg/kg/day for up to 75 weeks. Groups of five males were similarly dosed at 0 or 0.8 mg/kg/day. Testing for immune effects was initiated on week 33 and included flow cytometry, lymphocyte transformation, natural killer cell activity, and determination of serum cortisol during weeks 33–46 and immunizations with SRBC at treatment week 44 a primary response and week 48 for a secondary response (observations made through treatment week 52).

Effect noted in study and corresponding doses: Treatment with toxaphene at 0.4 mg/kg/day resulted in significant ($p<0.05$) reductions in mean primary anti-SRBC IgM responses at weeks 1 and 4 following primary immunization (27 and 35% lower than that of controls) and secondary anti-SRBC IgM responses at week 1 following secondary immunization (10% lower than that of controls). The dose level of 0.8 mg/kg/day resulted in significantly reduced mean primary anti-SRBC IgM responses at weeks 1–4 following primary immunization, significantly reduced mean secondary anti SRBC IgM response at weeks 1 and 4 following secondary immunization, and significantly reduced primary anti-SRBC IgG responses at weeks 2 and 3 following primary immunization (51 and 43% lower than that of controls). In males, 0.8 mg/kg/day toxaphene induced a significant reduction in mean primary anti-SRBC IgM response at weeks 1–3 following primary immunization. Flow cytometry tests showed that the only effect on leukocyte and lymphocyte subsets was a reduction in absolute B lymphocytes (CD20) in 0.8 mg/kg/day females (62% lower than controls). There were no detectable treatment-related effects on natural killer cell activity, lymphoproliferative response to mitogens, or serum cortisol levels. Table A-1 shows the results of primary anti-SRBC IgM responses.

Table A-1. Mean Anti-SRBC (IgM) Titres at 1–4 Weeks Post-Immunization in Female Cynomolgus Monkeys Administered Toxaphene in Gelatin Capsule Daily for 75 Weeks Including 44 Weeks Prior to Immunization

Toxaphene dose (mg/kg/day)	Weeks post-immunization (mean $\log_2$ titres ± standard error)[a]			
	1	2	3	4
0	7.10±0.35	6.40±0.31	5.30±0.34	4.90±0.41
0.1	6.40±0.54	5.20±0.73	4.50±0.64	4.00±0.61
0.4	5.20±0.79[b]	4.60±0.78	3.80±0.85	3.20±0.63[b]
0.8	3.70±0.83[b]	3.00±0.88[b]	3.00±0.75[b]	2.80±0.61[b]

[a]Mean values calculated from 10 animals per treatment group.
[b]$p<0.05$.

Source: Tryphonas et al. 2001

All continuous variable models in the EPA Benchmark Dose Software (Version 2.1.1) were fit to the mean anti-SRBC (IgM) titre data at week 1 post-immunization; standard error values were converted to standard deviation values prior to running the models. A default benchmark response (BMR) of 1 standard deviation (1 SD) from the control mean was selected in the absence of a toxicological rationale for selecting an alternative BMR. Model results for the mean anti-SRBC (IgM) titre data are shown in Table A-2. The linear model was initially fit to the data using constant variance, but failed to meet conventional goodness-of-fit criteria for modeled variance (p=0.04395). Adequate fit for modeled variance was obtained, however, when fit to the data using non-constant variance. Therefore, non-constant variance was selected to fit the remaining continuous variable models to the data. The Hill model failed the test for mean fit (degrees of freedom <0) and was not considered further. Using non-homogeneous variance, the polynomial (2- and 3-degree), and power models converged on the linear model and provided identical predictions of the BMD_{1SD} (0.34 mg/kg/day) and the 95% lower confidence limit on the BMD_{1SD} ($BMDL_{1SD}$; 0.22 mg/kg/day). The fit of the linear model to the malformation data is presented in Figure A-1. This figure is identical to those generated from the polynomial (2- and 3-degree), and power models.

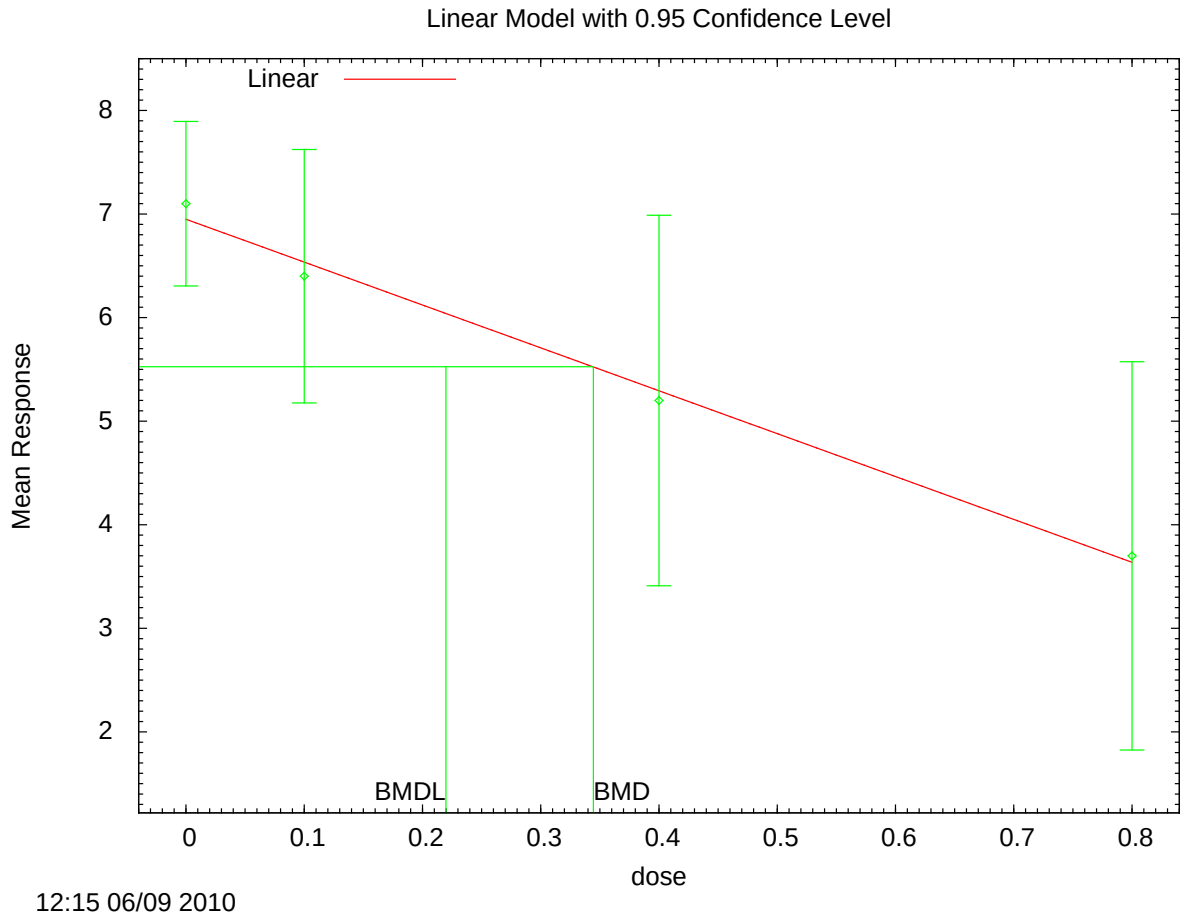
Table A-2. Model Predictions for Mean Anti-SRBC (IgM) Titre Data at Week 1 Post-Immunization from Female Cynomolgus Monkeys Administered Toxaphene in Gelatin Capsule Daily for 75 Weeks Including 44 Weeks Prior to Immunization

Model	Variance *p*-value[a]	Means *p*-value[a]	Scaled residual of interest[b]	AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
		Constant variance				
Linear[c]	0.04395	0.9335	-0.15	100.43	–	–
		Nonconstant variance				
Linear[c]	0.48	0.41	-0.16	97.45	0.34	0.22
Polynomial (2-degree)[c]	0.48	0.41	-0.16	97.45	0.34	0.22
Polynomial (3-degree)[c]	0.48	0.41	-0.16	97.45	0.34	0.22
Power[d]	0.48	0.41	-0.16	97.45	0.34	0.22
Hill[c]	0.48	NA[e]	0.26	99.68	0.14	0.04

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residual at measured response closest to the benchmark response.
[c]Coefficients restricted to be negative.
[d]Power restricted to ≥1.
[e]Degrees of freedom for test of mean fit are less than or equal to 0; the χ^2 test for fit is not valid.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; SD = standard deviation

Figure A-1. Predicted and Observed Mean Anti-SRBC (IgM) Titres from Female Cynomolgus Monkeys Administered Toxaphene in Gelatin Capsule Daily for 75 Weeks Including 44 Weeks Prior to Immunization*



*BMD and BMDL associated with a 10% extra risk increase over control are shown; doses given in units of mg/kg/day.

Dose and end point used for MRL derivation: A $BMDL_{1SD}$ of 0.22 mg/kg/day for decreased anti-SRBC (IgM) titers as an indicator of decreased humoral immunity.

[ ] NOAEL [ ] LOAEL [X] BMD

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: In an enzyme-linked immunosorbent assay (ELISA) performed on female mice that received toxaphene from the diet at doses ≥19 mg/kg/day for up to 8 weeks, Allen et al. (1983) reported suppressed antibody production, indicating depressed humoral immunity; the study identified a NOAEL of 2 mg/kg/day for the effect. Koller et al. (1983) reported a 46% decrease in the IgG primary antibody response in male rats receiving toxaphene from the diet at 2.6 mg/kg/day for up to 9 weeks and challenged twice (after 8 and 15 days on test) with keyhole limpet hemocyanin (KLH).

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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

Relevance to Public Health

This chapter 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 end points 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 chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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 chapter.

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 end points (if derived) and the end points 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 Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

MRLs 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, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point 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 end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, MRLs to humans for noncancer end points, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) 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 two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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 regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 end point 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 9 of the profile.

(11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate 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^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL 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

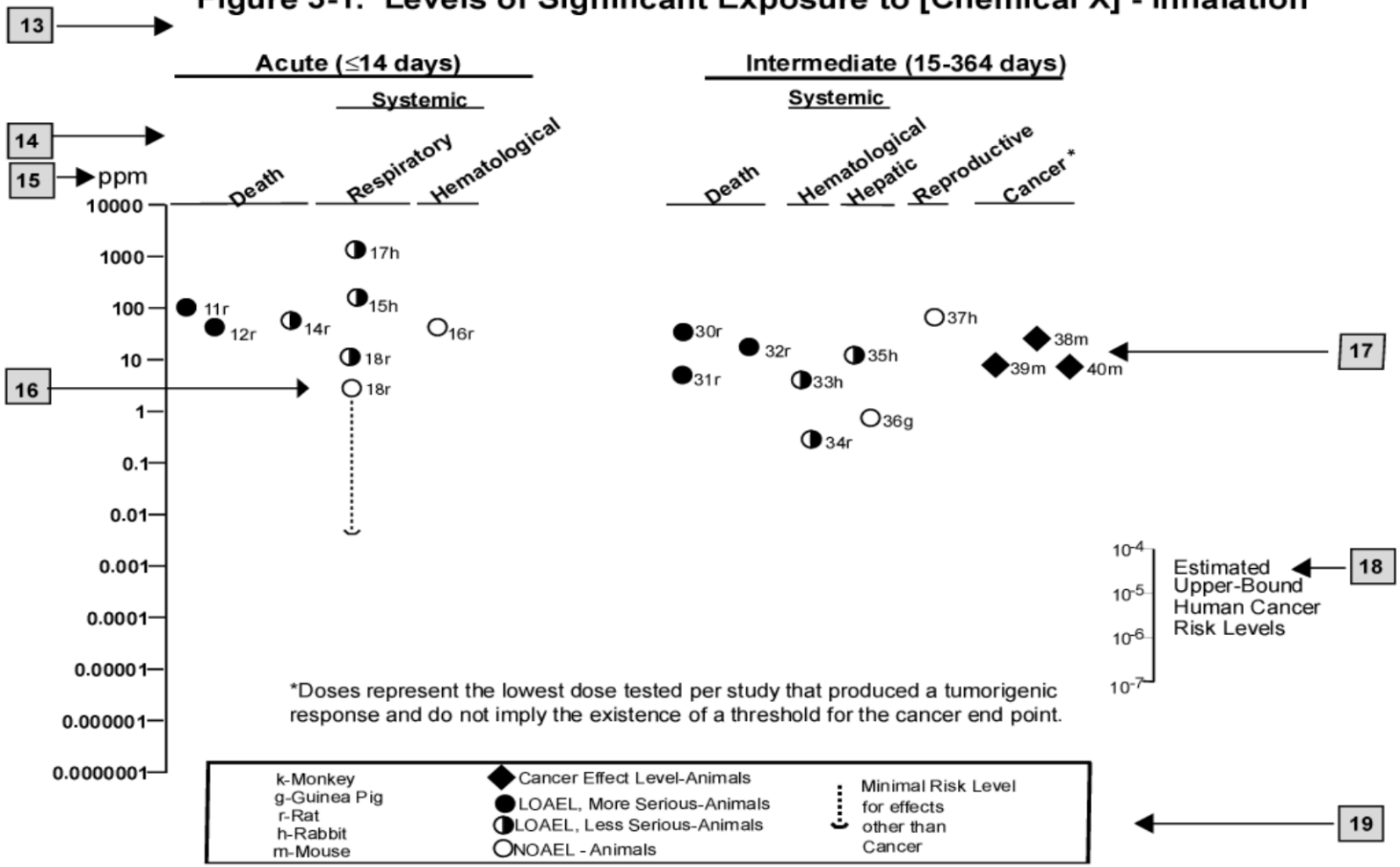
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer						11	
							↓	
	38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMF	biomagnification factor
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CCC	criterion continuous concentration
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CMC	criterion maximum concentration
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid

DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/NA/IMDG	Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter

MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio

OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCBs	polychlorinated biphenyls
PCCs	polychlorinated camphenes
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

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