2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

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

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

2. HEALTH EFFECTS

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

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

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

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

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

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

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

2.2.1 Inhalation Exposure

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

2.2.1.1 Death

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

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

2.2.1.2 Systemic Effects

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

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

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

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

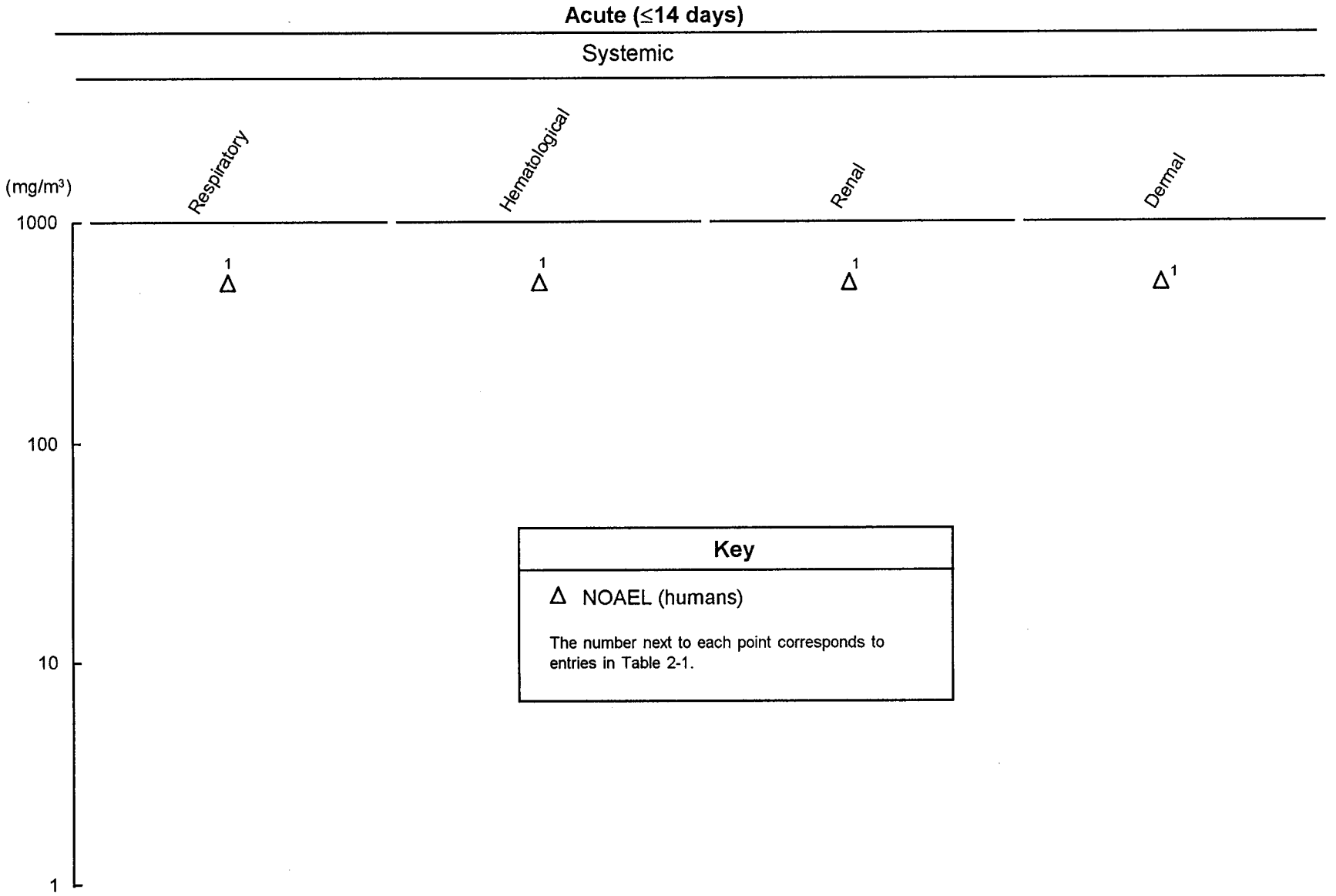
No studies were located regarding respiratory effects in animals following inhalation exposure to toxaphene

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

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

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

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



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

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

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

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

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

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

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

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

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

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

2.2.1.3 Immunological and Lymphoreticular Effects

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

2.2.1.4 Neurological Effects

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

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

2.2.1.5 Reproductive Effects

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

2.2.1.6 Developmental Effects

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

2.2.1.7 Genotoxic Effects

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

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

2.2.1.8 Cancer

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

2.2.2 Oral Exposure

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

2.2.2.1 Death

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

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

The nutritional status of an animal influences its susceptibility to the lethal effects of ingested toxaphene. Boyd and Taylor (1971) found that the oral LD_{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.

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

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

2.2.2.2 Systemic Effects

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[a]The number corresponds to entries in Figure 2-2.

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

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

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

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

Acute (≤14 days)

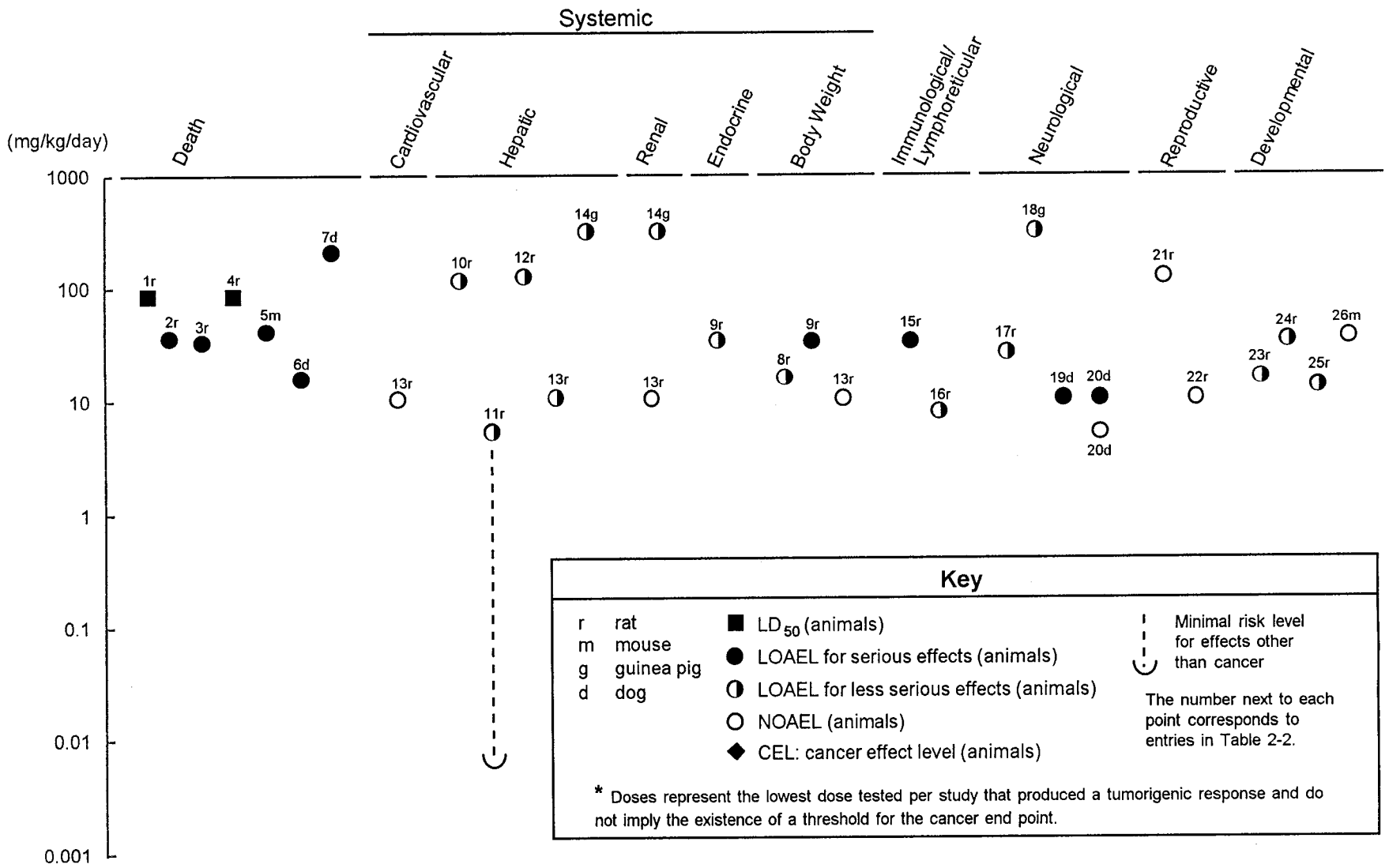


Figure 2-2. Levels of Significant Exposure to Toxaphene - Oral (cont.)

Intermediate (15-364 days)

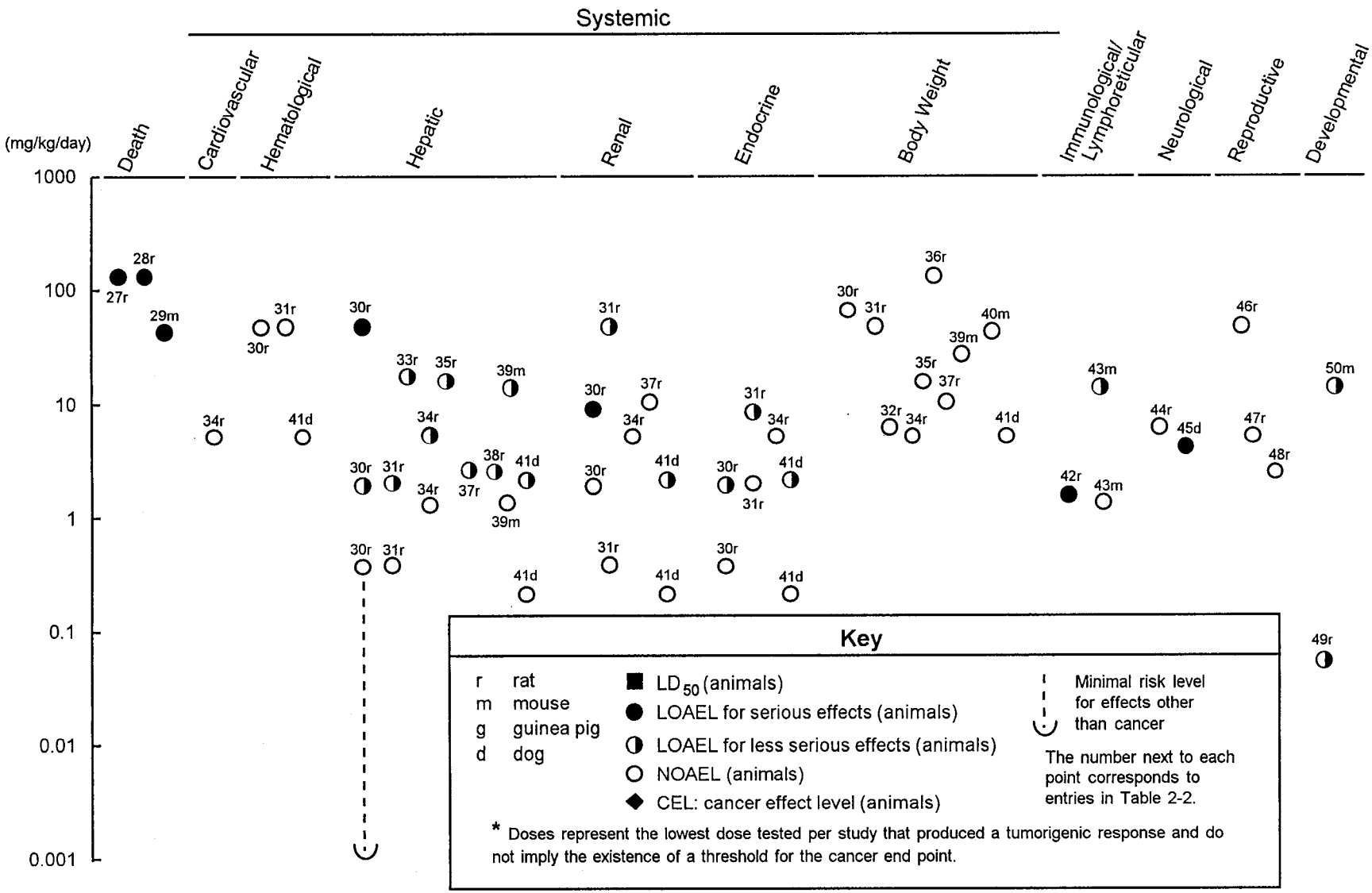
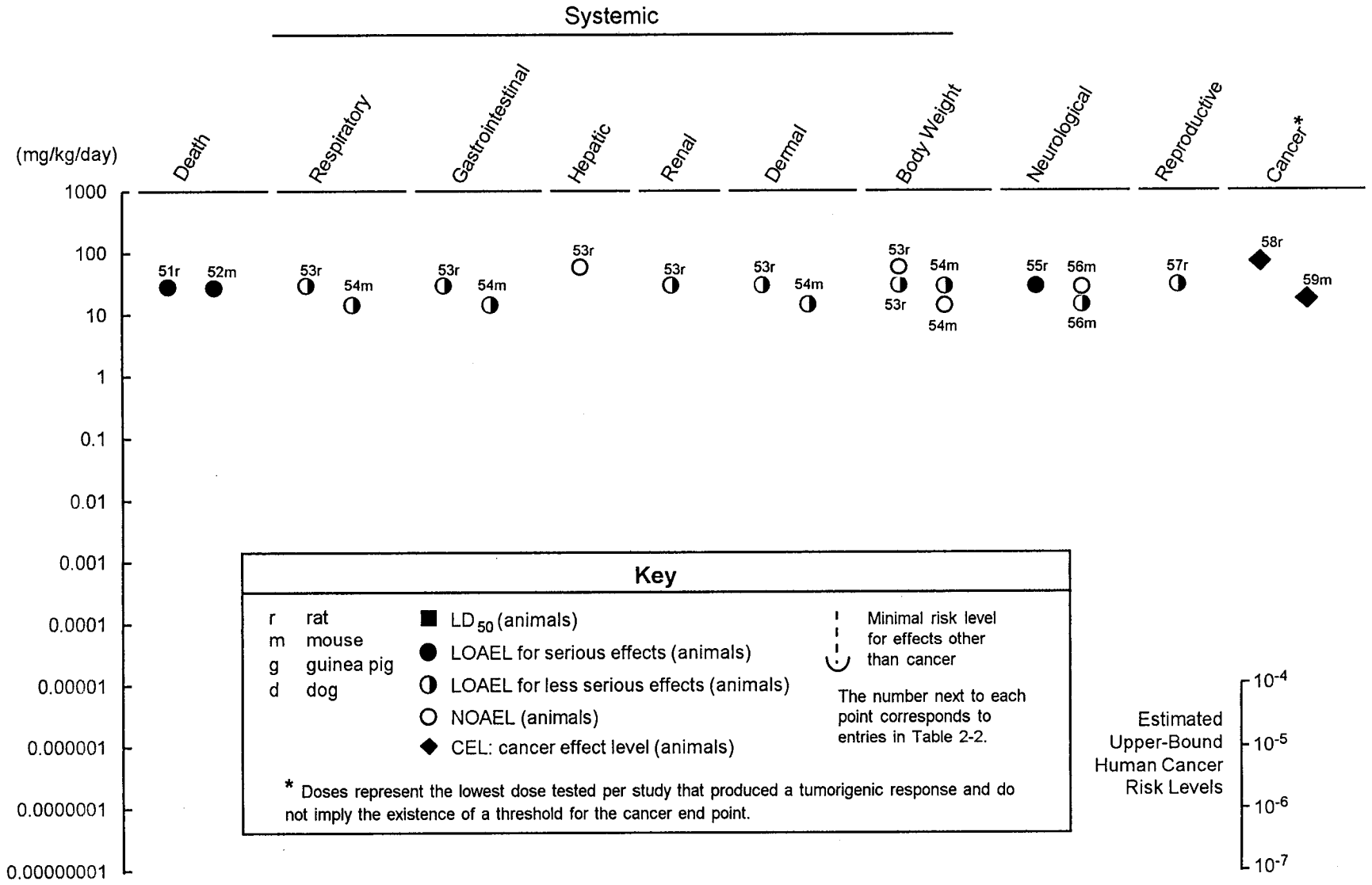


Figure 2-2. Levels of Significant Exposure to Toxaphene - Oral (cont.)

Chronic (≥365 days)



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

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

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

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

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

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

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

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

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

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

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

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

In keeping with toxaphene-induced induction of hepatic enzymes, 2.4-45 mg/kg/day toxaphene caused increased liver weight in rats (Chu et al. 1988; Koller et al. 1983; Peakall 1976) and mice (Allen et al. 1983). In rats, intermediate exposure duration NOAELs for hepatic toxicity are generally 10-20% of the corresponding LOAELs (Chu et al. 1986, 1988). An intermediate-duration exposure MRL of 0.001 mg/kg/day was derived based on the NOAEL of 0.35 mg/kg/day for hepatic toxicity in rats reported by Chu et al. (1986) and supported by Chu et al. (1988). A description of the derivation of the MRL can be found in the footnote to Table 2-2 and in Appendix A. The intermediate oral administration of 2 mg/kg/day toxaphene to dogs caused increased relative liver weight, hepatomegaly, and hepatocellular cytoplasmic vacuolation (Chu et al. 1986). This study is limited by the fact that the high-dose dogs were inadvertently fed the wrong dose for part of the study period. In rats, biochemical and histological evidence of toxaphene-induced liver toxicosis was observed in F_0 male and female rats fed 45 mg/kg/day toxaphene for at least 26 weeks (Chu et al. 1988).

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

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

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

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

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

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

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

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

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

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

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

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

2.2.2.3 Immunological and Lymphoreticular Effects

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

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

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

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

2.2.2.4 Neurological Effects

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

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

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

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

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

2.2.2.5 Reproductive Effects

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

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

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

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

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

2.2.2.6 Developmental Effects

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

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

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

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

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

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

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

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

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

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

2.2.2.7 Genotoxic Effects

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

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

2.2.2.8 Cancer

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

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

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

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

The water concentrations associated with an individual, lifetime upper-bound risk of 10^{-4} to 10^{-7} are $9.1x10^{-5}$ to $9.1x10^{-8}$ mg/kg/day, assuming that a 70-kg human ingests 2 L water per day. The 10^{-4} to 10^{-7} levels are indicated in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

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

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

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

F = female; hr = hour; LOAEL = lowest-observable-adverse-effect level; M = male; LD_{50} = lethal dose, 50% kill; M = male; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory

2.2.3.2 Systemic Effects

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

Respiratory Effects. In humans, fluoroscopic examination of the lungs following acute dermal exposure to 500 mg/m^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 (DiPietro and Haliburton 1979). Various lung lesions were observed in three affected pigs that were not treated for toxicosis by spraying with warm water. These lesions differed in the three affected pigs examined and included congested cranial lung lobes, numerous peribronchial lymphoid follicles, and moderate congestion of the lungs. Hyperemic lungs also were observed in rabbits that died following a 24-hour dermal application of 3,038 mg/kg toxaphene (Industrial Biotest 1973). It should be noted that some studies performed by Industrial Biotest have been found to be less than reliable; thus, the accuracy of the above data cannot be assured.

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

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

Hematological Effects. In humans, blood tests conducted after acute dermal exposure to 500 mg/m^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 et al. 1953). Up to 10,250 mg/kg/day technical grade toxaphene applied to intact or burned skin of rabbits for 24 hours caused enlarged gall bladders in both the intact and burned groups at doses as low as 3,038 mg/kg/day (Industrial Biotest 1973).

Renal Effects. In humans, urinalysis conducted after acute dermal exposure to 500 mg/m^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 Corp. 1973).

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

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

2.2.3.3 Immunological and Lymphoreticular Effects

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

2.2.3.4 Neurological Effects

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

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

2.2.3.5 Reproductive Effects

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

2.2.3.6 Developmental Effects

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

2.2.3.7 Genotoxic Effects

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

2.2.3.8 Cancer

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

2.3 TOXICOKINETICS

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

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

2.3.1.2 Oral Exposure

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

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

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

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

2.3.1.3 Dermal Exposure

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

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

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

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

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 Oral Exposure

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

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

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

The highest concentration of activity, except for the gastrointestinal tract, was in the brown fat following administration of 16 mg/kg ^{14}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 were observed to retain ^{36}C1 activity in fat, brain, kidney, liver, muscle, and testes. Levels were highest in fat (10.6 ppm) when tissues were analyzed 8 days after administration (Crowder and Whitson 1980).

Toxaphene and its metabolites have been detected in the liver, kidney, bone, brain, heart, lung, muscle, spleen, and testes of rats 7 days after the oral administration of 8.5 and 19 mg/kg ^{14}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 less than 10% of the dose remained in the body after one day. At 12 hours after administration, 5.3% of the dose was present in the muscle. Although this was significantly more than the amount seen in fat and other tissues, the concentration of activity in muscle is low due to the large amount of muscle in the body. Crowder and Dindal (1974) only determined the fraction of the dose based on proportions of radioactivity found in each tissue that may have been derived from a component of the original mixture or a metabolite.

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

Table 2-4. 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 6 animals.
[b]Values represent mean of 7 animals.

Source: Steele et al. 1980

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

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

Administration of ^{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 much less than 1% of the dose was transferred.

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

2.3.2.3 Dermal Exposure

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

2.3.2.4 Other Routes of Exposure

Intravenous administration of ^{14}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 the label was found in the liver. The results of the study indicate that lipid metabolism may play an important role in the tissue distribution of toxaphene and thus its toxicity.

2.3.3 Metabolism

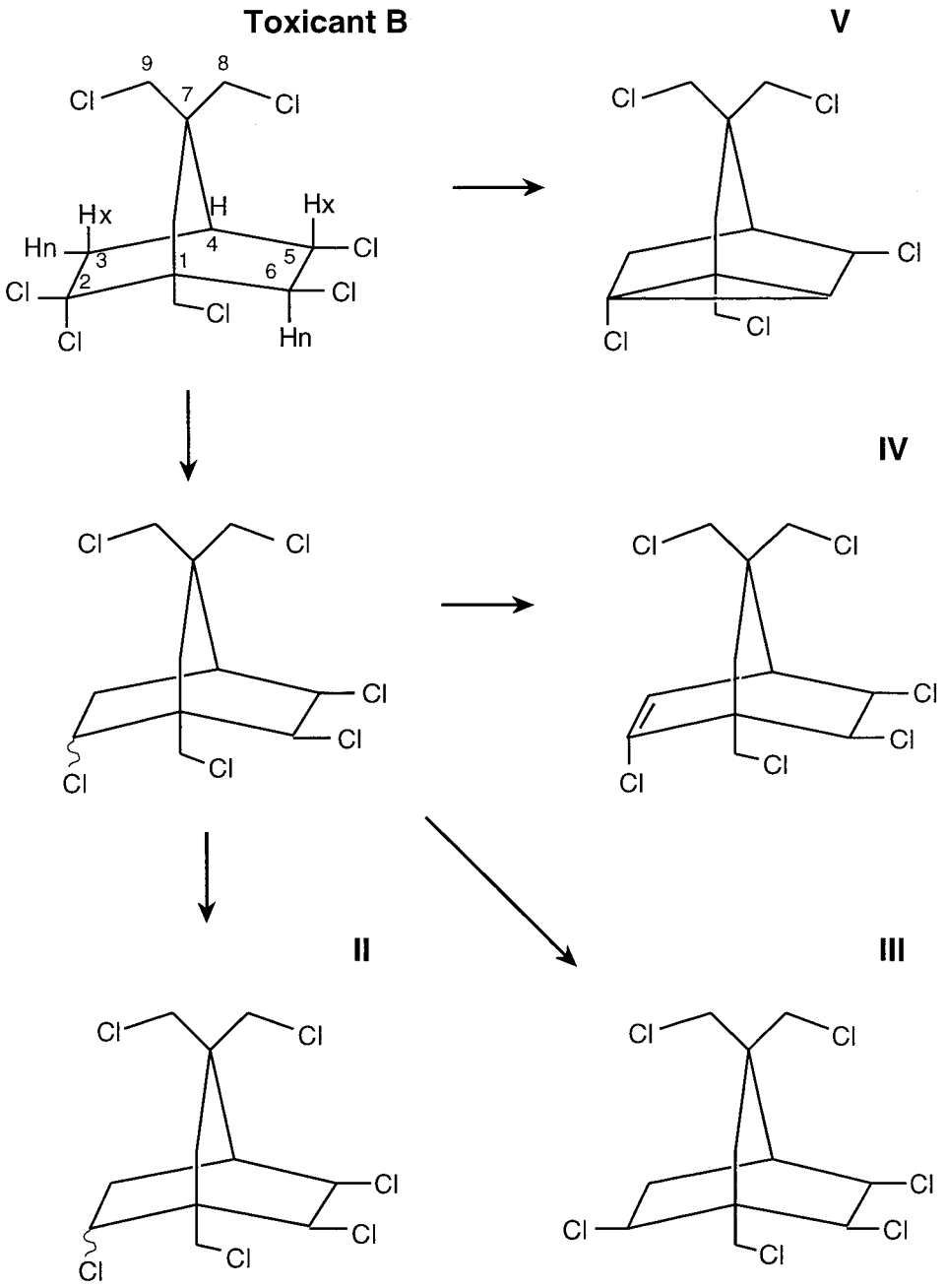
2.3.3.1 Inhalation Exposure

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

2.3.3.2 Oral Exposure

Toxaphene is rapidly and extensively degraded in mammals following oral administration (Figure 2-3). This was clearly evident after analyzing solvent extracts from urine, feces, and tissues. *In vivo* and *in vitro* studies indicated that the principal metabolic pathways involved dechlorination, dehydrodechlorination, and oxidation. Conjugation is also likely, but it is not a major route of metabolism. Administration of "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}C1- and ^{14}C-toxaphene differed. With either label, the hexane extracts of urine and feces contained some unmetabolized material. The percentage of administered activity was negligible in urine and approximately 8-12% in feces. Hence, most excreted material consisted of metabolites from toxaphene components. The combined chloroform extracts of urine and feces contained a much higher proportion of the administered ^{14}C- activity (27%) than of the ^{36}Cl-activity (11.2%). These results indicated that the chloroform fraction consisted of partially dechlorinated metabolites, and a predominance of these products were found in the urine. The aqueous fraction contained 11.4% of the ^{14}C-dose and 0.5% of the ^{36}C1 dose. The low amount of ^{36}C1 activity in the aqueous extracts indicated that this fraction contained metabolites (5-10%) that had been completely

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



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

Source: Saleh and Casida 1978

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 was metabolized mostly to partially dechlorinated products, with a small proportion being completely dechlorinated and a small proportion unmetabolized.

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

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

Pollock and Kilgore (1980b) also extracted the lipid tissue of rats treated with either ^{14}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-heptachlorobomane), a toxic component of toxaphene, yielded several fecal metabolites when administered orally to mice, rats, hamsters, guinea pigs, rabbits, monkeys, and chickens (Saleh et al. 1979). The greatest amount of fecal metabolites was seen in monkeys and rabbits (20%), with 3-9% in other species, indicating that species differ with respect to metabolic rate

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,l0-hexachlorobomane (III) (Figure 2-3). Toxicant B is also dehydrodechlorinated to 2,5-endo-6-exo-8,9,l0-hexachlorobom-2,3-ene (IV) and 2,5-endo-8,9,10-pentachlorotricyclene (V) in rats *in vivo* and in other *in vitro* systems (Saleh and Casida 1978). There is no evidence that humans either do or do not metabolize toxaphene via this pathway.

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

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

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

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 thin-layer chromatography (TLC) fractions from urine and feces revealed the presence of methylation products. This showed that fecal and urinary metabolites included acidic and other hydroxyl compounds (Chandurkhar and Matsumara 1979). Further analysis indicated that approximately 9% and 1% of the urinary and fecal metabolites, respectively, were sulfate conjugates. Glucuronide conjugates comprised 9.5% and 7.5% of the urinary and fecal metabolites, respectively. The presence of sulfate and glucuronide conjugates supported the conclusion that oxidative metabolism occurred.

2.3.3.3 Dermal Exposure

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

2.3.3.4 Other Exposure

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

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

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

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

2.3.4.2 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 16 days in the fat of animals. Metabolism studies indicated that it is rapidly and extensively biodegraded. Consequently, the rate of toxaphene elimination is very high. Table 2-5 summarizes excretion results from studies in which rats were orally administered radiolabeled toxaphene and its components.

The average percentage of an orally administered 20 mg/kg ^{36}Cl-toxaphene dose excreted over 9 days (approximate half-life of excretion) was 52.6%. Approximately 30% of this amount was excreted in the urine and 70% was excreted in the feces. Fecal excretion reached a plateau 2-3 days after administration. The cumulative urinary excretion steadily increased over the 9 days. Much of the activity in the urine and feces was attributable to ^{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 equalled the fecal elimination. Ohsawa et al. (1975) also found that ^{36}Cl-chloride ion appeared almost entirely in the urine. The half-time for the elimination of ^{36}C1 was 2-3 days, a rate equivalent to the excretion of ^{36}Cl-sodium chloride.

Rats treated orally with 8.5 mg/kg 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, more than 50% of the total activity was excreted in urine. Only 8-12% of the dose detected in the feces was suspected of being parent compound. The remainder of the activity in the urine and the feces was thought to be partially or completely dechlorinated products.

Radiolabeled toxicants A and B, obtained by chromatographic separation of ^{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.

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

Chemical	Dose (mg/kg)	Vehicle	Days after administration	% Dose		Reference
				Urine	Feces	
^{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

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 their greater persistence in fat and reduced their rate of excretion. In contrast, the nonpolar Fraction 2-derived polar metabolites were more rapidly excreted. Radioactivity measured in the urine of rats receiving Fraction 2 was significantly higher than from those administered Fraction 7 or toxaphene.

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

Excretion of radioactivity derived from ^{14}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 I st week. Decreases in milk levels after the first week were slower for animals fed toxaphene at levels greater than 20 ppm (Clabom et al. 1963) as shown in Table 2-6. Detectable amounts of toxaphene were found in the milk of cows 7-9 days after feeding of toxaphene at levels of 2.5-20 ppm commenced (Zweig et al. 1963). As with the higher feeding levels discussed above (Clabom et al. 1963), plateaus were achieved after the fourth week, except at the lowest dose of 2.5 ppm, where a maximum was achieved at 9 days. The animals were fed toxaphene for l-2.5 months. Toxaphene was no longer detected in the milk within 14 days after cessation of toxaphene administration (Zweig et al. 1963)

Table 2-6. 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 3 samples.

Source: Claborn 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 (Biesmann et al. 1983).

2.3.4.3 Dermal Exposure

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

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

2.3.4.4 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 tissues 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).

2.4 MECHANISMS OF ACTION

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

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

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

2.5 RELEVANCE TO PUBLIC HEALTH

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

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

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

Minimum Risk Levels for Toxaphene.

Inhalation MRLs.

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

Oral MRLs.

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

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

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

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

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

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

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

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

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

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

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

Systemic Effects.

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

Table 2-7. Identified Toxic Components of Toxaphene

CAS Registry No./ Molecular Formula	Chemical Abstracts Name (Ninth Collective Index)	Synonyms	Reference
51775-36-1/ $C_{10}H_{11}Cl_7$	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7,7-tris(chloromethyl)-,(5-endo,6-exo)-	2,2,5-endo,6-exo,8,9,10-hepta-chlorobornane; toxaphene toxicant B	Clark and Matsumura 1979; Saleh and Casida 1978; Saleh et al. 1979; Chandurker and Matsumura 1979
52819-39-3/ $C_{10}H_9Cl_9$	Bicyclo[2.2.1]heptane,2,3,3,5,6-pentachloro-7,7-bis(chloromethyl)-1-(dichloromethyl)-(2-endo,5-exo,6-exo)	Toxaphene toxicant C*; 2-endo,3,3,5,6-exo,8,9,10,10-nonachlorobornane	Chandurkar and Matsumura 1979
57208-55-4/ $C_{10}H_{10}Cl_8$	Bicyclo[.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl)-7-(dichloromethyl)-	Toxic fraction A: 2,2,5-endo, 6-exo,8,9,9,10-octachlorobornane	Clark and Matsumura 1979
57981-30-3/ $C_{10}H_{11}Cl_7$	Bicyclo[2.2.1]heptane,2,5,6-trichloro-3,3-bis(chloromethyl)-2-(dichloromethyl)-(exo,exo,exo)-	2,5,6-exo,8,8,9,10-heptachloro-dihydrocamphene	Swanson et al. 1978
58002-18-9/ $C_{10}H_{10}Cl_8$	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl-7-(dichloromethyl)-5-endo,6-exo,7-anti)-	2,2,5-endo,6-exo,8,8,9,10-octachlorobornane; toxaphene toxicant A-1	Pollock and Kilgore 1980b
58002-19-0/ $C_{10}H_{10}Cl_8$	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl-7-(dichloromethyl)-(5-endo,6-exo,7-syn)-	2,2,5-endo,6-exo,8,9,9,10-octachlorobornane; toxaphene toxicant A-2	Pollock and Kilgore 1980b
66860-80-8/ $C_{10}H_9Cl_9$	Bicyclo[2.2.1]heptane,2,3,5,6-tetrachloro-7-(chloromethyl)-1-7-bis(dichloromethyl)-(2-endo, 3-exo,5-endo,6-exo,7-syn)-	Toxaphene toxicant Ac	Chandurker et al. 1978
70940-13-5/ $C_{10}H_9Cl_9$	Bicyclo[2.2.1]heptane,2,3,3,5,6-pentachloro-1,7-bis(chloromethyl)-7-(dichloromethyl)-	Toxaphene toxicant C*; 2,3,3-endo,5,6-exo,8,9,10,10-nonachlorobornane	Clark and Matsumura 1979

*Prepared structures have not been confirmed.

Source: EPA 1987f

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

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

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

(1) As discussed in Section 2.2.2.2, toxaphene, like other chlorinated hydrocarbon insecticides, induces hepatic microsomal enzyme activity. This could result in hepatic cell hypertrophy and liver enlargement. When separated into polar and nonpolar fractions, no difference in the extent of enzyme induction by fraction was noted (Pollock et al. 1983). Microsomal enzyme induction has important implications with regard to altering the apparent toxicity of other xenobiotics in individuals concurrently exposed to several chemicals or drugs (see Sections 2.7 and 2.8).

(2) Kuz'minskaya and Alekhina (1976) and Gertig and Nowaczyk (1975) reported that both short- and long-term oral administration of toxaphene to rats caused disturbances in energy metabolism as evidenced by changes in hepatic lactate dehydrogenase activity. However, Peakall (1979) demonstrated that these changes are not severe enough to have definite physiological consequences (measured as serum lactate and pyruvate levels) under nonstress conditions.

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

(3) Several investigators have demonstrated both *in vivo* and in vitro that short- and long-term toxaphene exposure is associated with inhibition of various ATPases in liver (e.g., Fattah and Crowder 1980; Mourelle et al. 1985; Trottman and 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 function, which could trigger injury responses.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

+ = positive; – = negative

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

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

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

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

Toxaphene does not require metabolic activation to cause mutagenic effects in bacteria (Mortelmans et al. 1986) or to increase sister chromatid exchange in human lymphoid cell lines (Sobti et al. 1983). In fact, the addition of liver S9 fractions from Aroclor 1254-stimulated livers of rats and hamsters decreases the number of reversions in *S. typhimurium* and the incidence of sister-chromatid exchanges in the human lymphoid cell line. The findings suggest that mammalian metabolism of toxaphene may reduce the overall genotoxic effect of the mixture. The findings of Hooper et al. (1979) are of potential relevance to public health. These authors determined that certain components of the mixture of chemicals making up technical toxaphene were much less mutagenic than the mixture as a whole. Specifically, the components that Hooper et al. (1979) identified as having high insecticidal or acute mammalian toxicity activity (e.g., heptachlorobomane, gem-dichloro components, and nonpolar fractions) were less mutagenic using the Ames test with *S. typhimurium* strain TAl00 than was the complete toxaphene mixture (or the polar fraction). These findings may have relevance to public health in that the components of complex mixtures such as toxaphene may distribute unevenly in the environment (see Chapter 5). The evidence discussed above suggests that toxaphene may pose a genotoxic threat to humans although it is not known whether these effects are inheritable.

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

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

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

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

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

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

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

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

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

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Toxaphene

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

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

2.6.2 Biomarkers Used to Characterize Effects Caused by Toxaphene

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

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

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

2.7 INTERACTIONS WITH OTHER SUBSTANCES

Toxaphene is likely to interact with other chemicals, such as other pesticides, that also induce hepatic microsomal mixed-function oxidase systems. For example, Deichmann and Keplinger (1970) observed that the toxaphene 96-hour LD_{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 did significantly reduce the incidence of BP-induced lung tumors when given in combination. This reduction correlated with a toxaphene-induced reduction in BP hydroxylase activity in the lung. The results of this study suggest that toxaphene antagonizes the tumorigenic effect of BP, possibly by inhibiting the biotransformation of BP to a reactive metabolite or by promoting degradative metabolism of BP to nonactive forms in the target tissue. By this mechanism, toxaphene may have anticarcinogenic properties in mammals.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

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

Placental transfer of toxaphene has been documented in animals (Pollock and Hillstrand 1982). Toxaphene residues have also been detected in the milk of exposed cows (Clabom et al. 1963; Zweig et al. 1963). Adverse effects have been observed in the offspring of experimental animals exposed to toxaphene during gestation and nursing. Results of experimental studies indicate that maternal toxaphene exposure may induce behavioral effects in neonates and in nursing babies (Crowder et al. 1980; Olson et al. 1980).

Toxaphene exposure during gestation and nursing has been suggested to be associated with immunosuppression in offspring (Allen et al. 1983). Other effects of maternal toxaphene exposure observed in the offspring were histologic changes in fetal liver, thyroid, and kidney tissues (Chu et al. 1988). Toxaphene exposure by inhalation, ingestion, or dermal application has induced neurotoxic effects manifested in part by seizures and other functional, biochemical, and morphological alterations (Badaeva 1976; Dille and Smith 1964; DiPietro and Halibut-ton 1979; Kuz’minskaya and Ivanitskii 1979; Lawrence and Casida 1984; McGee et al. 1952; Wells and Milhom 1983). Persons with latent or clinical neurologic diseases, such as epilepsy or behavioral disorders, may be at an increased risk of adverse effects following toxaphene exposure.

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

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

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

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

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

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

2.9 METHODS FOR REDUCING TOXIC EFFECTS

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

2.9.1 Reducing Peak Absorption Following Exposure

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

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

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

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

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

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

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

2.9.2 Reducing Body Burden

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

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The most serious toxicological effects of exposure to chlorinated hydrocarbon pesticides are central nervous system excitability. Organochlorine compounds are thought to interfere with the normal flux of sodium and potassium ions across the axon membrane, disrupting central nervous system activity and resulting in generalized central nervous system excitation, which may lead to convulsions and seizures in severe cases. Toxaphene-induced central nervous system stimulation is believed to result from the noncompetitive inhibition of 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.

Toxaphene is considered to be a moderately toxic chlorinated hydrocarbon in the same toxicity category (animal LD_{50} > 50 mg/kg) as DDT, chlordane, lindane, heptachlor, kepone, and mirex. Several cases of toxaphene-induced seizures in humans have been reported (McGee et al. 1952; Wells 1983). The acute management of seizures with anticonvulsants such as diazepam (a 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. An important result of this is cardiac arrhythmias, possibly due to increased myocardial sensitivity to catecholamines (Olson 1990). The stimulatory effects on the cardiovascular system can be reduced by the administration of propranolol, a beta-adrenergic receptor blocker (Olson 1990).

2.10 ADEQUACY OF THE DATABASE

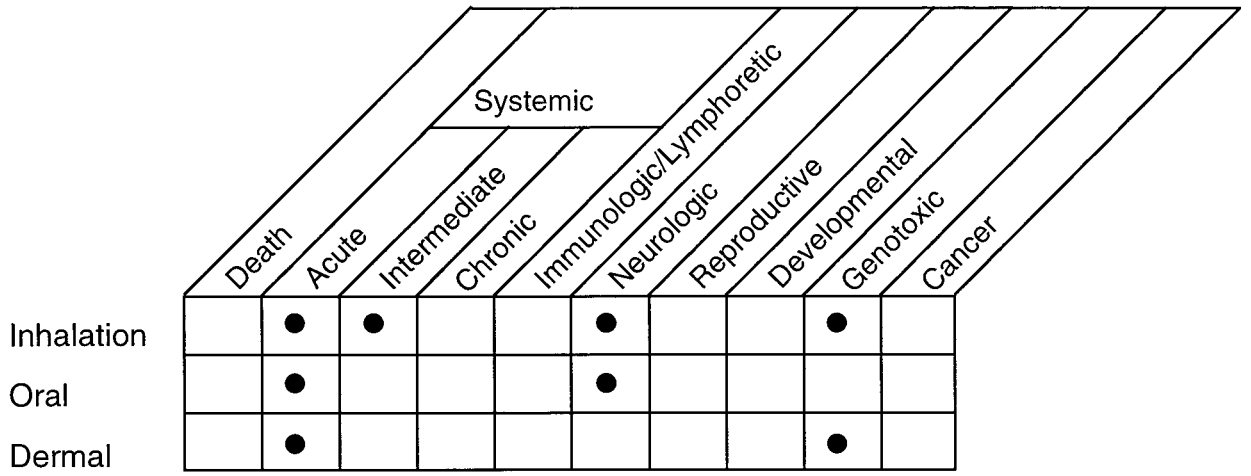
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of toxaphene is available. Where adequate information is not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

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

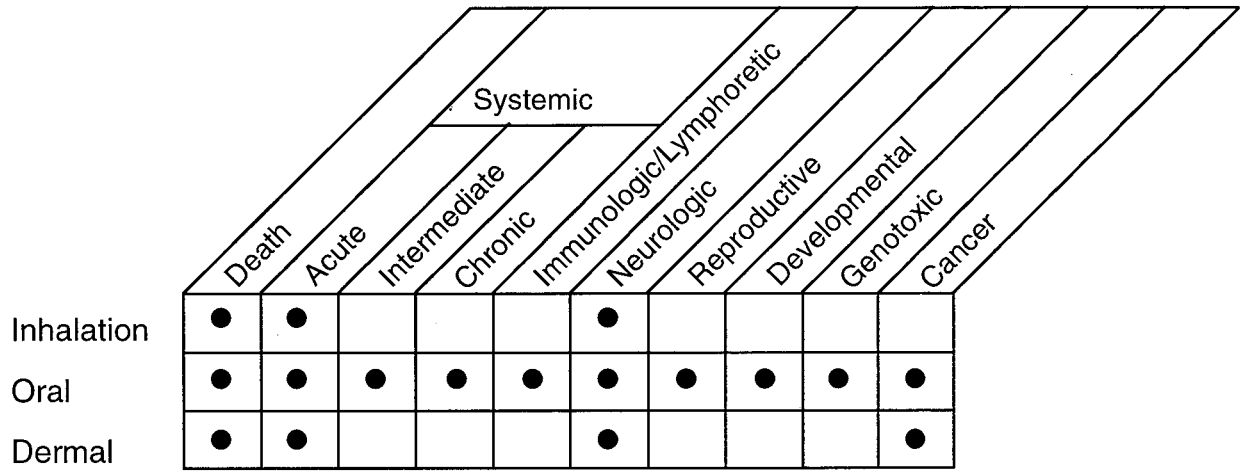
2.10.1 Existing Information on Health Effects of Toxaphene

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

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



Human



Animal

● Existing Studies

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

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

2.10.2 Identification of Data Needs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Biomarkers of Exposure and Effect.

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

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

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

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

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

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

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

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

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

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

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

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

2.10.3 Ongoing Studies

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