September 1995

TOXAPHENE

Drinking Water Health Advisory
Office of Water
U. S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State, and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10 percent of an individual's lifetime), and lifetime exposures based on data describing noncarcinogenic endpoints of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifelong exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linearized multistage model with 95 percent upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 8001-35-2

Structural Formula

- Since the technical grade product is produced by free radical reactions initiated by chlorine and ultraviolet light, toxaphene is a complex mixture of polychlorinated camphenes and bornanes with an average empirical formula of $C_{10}H_{10}CL_8$ and an average molecular weight of 414. In fact, more than 177 incompletely characterized components have been separated (Holmstead et al., 1974).

Synonyms

- Agricide Maggot Killer (F); Alltex; Camphechlor; Chlorinated Camphene; Crestoxo; Estonox; Geniphene; Hercules 3956; Milipax; Motox; Octachlorocamphene; PCC; Penphene; Phenacide; Phenatox; Polychlorocamphene; Polychlorocamthene; Strobane-T; Toxakil; Vertac 90% (Budavari et al., 1989; Montgomery and Welkom, 1990; Sine et al., 1989).

Uses

- In the U.S., prior to being banned, toxaphene was used primarily as an insecticide to combat cotton insects (such as the cotton boll weevils; it was also used to control some ectoparasites on livestock, poultry, as well as a few other field crop insects (U.S. DHHS, 1994).

Properties (Budavari et al., 1989; Howard et al., 1991; Montgomery and Welkom, 1990; U.S. DHHS, 1995; U.S. EPA, 1987; Verschueren, 1983)

Chemical Formula	$C_{10}H_{10}Cl_8$ (average)
Molecular Weight	414 (average)
Physical State (25°C)	Amber, waxy solid
Boiling Point	NA (begins to dehydrochlorinate at 120 to 155°C)
Melting Point	65 to 90°C
Density (25°C)	1.65 g/cm^3
Vapor Pressure (25°C)	0.2 to 0.4 mm Hg or 0.69 x 10^{-6} mm Hg (calculated)
Specific Gravity (25°C)	1.519 to 1.567
Water Solubility (25°C)	0.5, 0.74, 1.75, or ~3 mg/L
Log Octanol/Water Partition Coefficient	3.23, 3.30, 4.82 (calculated) or 5.50
Taste Threshold (Water)	--
Odor Threshold (Water)	0.14 mg/kg
Conversion Factor (ppm air to mg/m^3)	--

Occurrence

- The registrations for most uses of toxaphene were canceled and the rest were restricted in 1982 by the EPA, then all registered uses were banned in 1990 (U.S. DHHS, 1995, 1994). Reported usage in the United States prior to the 1982 restrictions has been estimated at >3 x 10^5 tons (Swackhamer et al., 1993).

- There are very few reports of detectable levels of toxaphene in drinking water supplies. Faust and Suffet (1966) reported that between 1959 and 1963, treated water in Flint Creek, Alabama contained toxaphene concentrations ranging from 5 to 410 ppt (Howard et al., 1991; U.S. DHHS, 1995). In a study by Maddy et al. (1982), toxaphene was detected but not quantified in one or more California drinking water wells (Howard et al., 1991).

- Reports by Faust and Aly (1964), Gilliom et al. (1985), Granstrom et al. (1984), Lichtenberg et al. (1970), Mattraw, Jr. (1975) and Schulze et al. (1973) suggest that toxaphene was only rarely found in surface waters of most of the United States from 1950 to approximately 1980 (Howard et al., 1991). STORET data reported by Staples et al. (1985) for 1980 to 1982 detected toxaphene in 32 percent of ambient water samples tested, at a median concentration of 0.05 ppb (Howard et al., 1991). In two Mississippi watershed areas, one studied during 1977 to 1979 and the other during 1982 to 1985, toxaphene levels in surface waters ranged from <0.01 µg/L (0.01 µg/L - detection limit) to 0.40 or 1.07 µg/L (Cooper, 1991; Cooper et al., 1987). Levels generally exceeded the detection limit only after major run-off events.

- In addition to the Maddy et al. study (1982) indicating the presence to toxaphene in one or more California drinking water wells, Cohen (1986) reported its presence in 5 out of 2,963 California groundwater samples (Howard et al., 1991). The groundwater associated with 479 waste disposal sites located throughout the United States was examined for the presence of toxaphene and a variety of chemicals and other pesticides (Plumb, Jr., 1991). Pesticides were analyzed for an average of 4,100 times (range of 1,600 to 9,000), and toxaphene was detected 32 times at 13 sites in 3 different U.S. EPA Regions.

- Anonymous data for the United States during 1963 to 1969 [illegible]icated that 0 to 3.6% of sampled food composites tested positive [illegible] toxaphene, with daily intakes ranging from 0 to 4.0 µg (H[illegible]d et al., 1991). Duggan et al. (1983) reported that between 19[illegible] and 1976, positive food composites and daily intakes ranged fr[illegible]ot detected to 0.8% and from not detected to 0.5 µg, respecti[illegible] (Howard et al., 1991). Johnson et al. (1984) reported that [illegible]om August, 1976 to September, 1977, 3.3% of food composites w[illegible] positive with toxaphene levels of 0.026 to 0.597 ppm; and [illegible]ebarac (1984) reported numbers of 1.7% and 0.173 to 0.469 ppm for [illegible]e period from October 1977 to September 1978 (Howard et al., 1991). Gartrell

et al. (1986) calculated an adult daily dietary average intake of 1.59 μg for 1980 to 1982, and Hundley et al. (1988) reported toxaphene being found in 5 of 6,391 domestic agricultural commodity samples at 0.1 to >2.0 ppm (Howard et al., 1991). More recently, of thousands of food samples analyzed in 10 state laboratories, 0.143% and 0.168% tested positive for toxaphene in 1988 and 1989, respectively (Minyard, Jr. and Roberts, 1991). Of 6,970 produce samples taken during 1989 to 1991, only 1 cucumber sample had a toxaphene level above the detection limit of 2.000 ppm (Schattenberg and Hsu, 1992). Geometric mean residue concentrations of toxaphene in fish at 112 stations throughout the United States declined from 0.34 mg/kg in 1976 to 77 to 0.14 mg/kg in 1984, with the percentage of stations having any detections falling from 88% in 1980 to 1981 to 69% in 1984 (Schmitt et al., 1990).

- Toxaphene has in the past (1967 to 1981) been detected in ambient air in the United States at concentrations ranging from <0.02 to 8,700 $\mu g/m^3$ (Howard et al., 1991; U.S. DHHS, 1995). More current data were not located.

Environmental Fate

- Toxaphene is apparently resistant to physical-chemical and biological transformation in water. Early EPA studies (1979, 1976) concluded that it was not likely to undergo direct photolysis or photo-oxidation, and that its estimated hydrolytic half-life at pH 5 to 8 (25°C) was >10 years (U.S. DHHS, 1995).

- Analysis of toxaphene's aquatic fate and transport is complicated by evolving analytical methodologies that render comparing earlier with later monitoring data difficult, and by the potential production of toxaphene-like materials by the paper and pulp industry (U.S. DHHS, 1995).

- While a wide range of vapor pressure values has been reported (see Properties, above), at least the higher estimates suggest significant volatility and ready partitioning from water to the atmosphere. The various field dissipation, atmospheric monitoring and model ecosystem studies reported by Seiber et al. (1979), Willis et al. (1983, 1980), Nash et al. (1977) and Glotfelty et al. (1989) confirm this to be the case (U.S DHHS, 1995)

- Toxaphene's high soil organic carbon partition coefficient and field studies such as those of Seiber et al. (1979), Swoboda et al. (1971) and McDowell et al. (1981) indicate that it strongly sorbs to soils and sediments, with only minimal leaching to groundwater (U.S. DHHS, 1995). This finding is reinforced by later studies of different Mississippi watershed areas (Cooper et al., 1987; Cooper, 1991).

- A variety of studies have demonstrated that toxaphene is bioconcentrated in the tissues of aquatic organisms (reviewed in U.S. DHHS, 1995). In one of several studies describing the biomagnification of toxaphene, its concentration increased by an average factor of 4.7 from plankton to fish, through several trophic levels (Evans et al., 1991).

- Enhanced microbial degradation of toxaphene by natural microorganisms was reported to occur in organically amended soils and sediments under anaerobic (flooded) laboratory and field conditions (Mirsatari et al., 1987). At 10 ppm of technical toxaphene, dissipation half-life in the laboratory was approximately 3 weeks; the rate was slower at 500 ppm. In the field, toxaphene residues were reduced from 63 to 23 ppm in 120 days. More than half of a toxaphene concentration was degraded in 28 days by the combined action of 254 nm UV light and a UV-resistant strain of white rot fungus under laboratory conditions (Katayama and Matsumura, 1991).

III. PHARMACOKINETICS

Absorption

- No information was found in the available literature that provided direct data on gastrointestinal (GI) tract, respiratory system or dermal absorption of toxaphene. However, the excretion studies referred to below suggest that at least 45 to 65% of an oral dose is absorbed (Chandurkar and Matsumura, 1979; Crowder and Dindal, 1974; Crowder and Whitson, 1980; Pollock and Kilgore, 1980).

Distribution

- Groups of three 30-day-old albino rats were deprived of food for 24 hr prior to being dosed with ^{36}Cl-toxaphene (20 mg/kg) in a peanut oil-gum acacia solution via a stomach tube (Crowder and Dindal, 1974). Radioactivity was measured in various tissues after 3, 6, and 12 hr, and after 1, 2, 3, 5, 7, 9 and 20 days. Maximum and minimum tissue radioactivity (expressed as a percentage of administered dose) and the associated sampling times were reported as follows: kidney, 0.43 (12 hr) and 0 (7 and 20 days); muscle, 5.3 (12 hr) and 0 (2 days); fat, 3.65 (9 days) and 0.02 (7 days); testes, 0.28 (12 hr) and 0 (20 days); brain, 0.23 (12 hr) and 0 (3, 5, 7 and 20 days); blood cells 3.1 (3 hr) and 0 (6 and 12 hr, 5 and 7 days); blood supernatant, 2.35 (12 hr) and 0 (5 days); liver, 2.33 (12 hr) and 0 (3, 7 and 20 days); small intestine (first 2 cm), 0.34 (6 and 12 hr) and 0 (3, 5 and 7 days); small intestine (last 2 cm), 0.34 (6 hr) and 0 (5, 7, 9 and 20 days); large intestine, 1.20 (12 hr) and 0 (9 and 20 days); esophagus, 0.04 (3 and 12 hr) and 0 (6 hr, 7 and 20 days); spleen, 0.24 (7 days) and 0 (20 days); and stomach, 77.2 (12 hr) and 0 (20 days). Thus, with the exception of fat, blood cells and the spleen, peak radioactivity was observed about 12 hr after dosing. Disregarding the stomach, radioactivity was highest in muscle, blood

components, liver and the large intestine during the first 12 hr after exposure, but was highest in fat after 9 days and blood cells after 20 days. Substantial metabolism of toxaphene occurred, and much of the excreted radioactivity was water-soluble and ionic in form.

- In female Sprague-Dawley rats dosed with 10 mg/kg of ^{14}C-toxaphene in olive oil by gastric intubation, residual levels of toxaphene after 7 days were less than 0.2 ppm (0.2 mg/kg) in brain, heart, lung, liver, kidney and spleen tissue (Pollock and Kilgore, 1980). However, levels in abdominal and subcutaneous fat were similar and averaged 6.4 ppm (6.4 mg/kg).

- Groups of four adult female Sprague-Dawley rats were injected ip with 90 μCi/0.0130 mmol/kg (90 μCi/5.382 mg/kg) ^{14}C-toxaphene, and blood was drawn from two rats either 10 min or 2 hr later (Mohammed et al., 1990a). Of the radioactivity that was distributed to plasma, approximately 41% and 36% were found after 10 min in the albumin-rich bottom (BF) and cholesterol-rich high density lipoprotein (HLD_2) fractions, respectively. After 2 hr, total plasma radioactivity dropped by 69%, with the principal fractions again being BF (52%) and HLD_2 (30%). Percent radioactivity in other plasma fractions ranged from about 4 to 9%.

- Male Swiss mice were dosed with 25 mg/kg ^{36}Cl-toxaphene in corn oil by gastric intubation (Crowder and Whitson, 1980). Retention of radioactive chlorine (ppm, presumably expressed as ppm of toxaphene) after 8 days in the tissues of a single mouse was reported to be: lipid (10.6), muscle (1.2), testes (0.8), kidney (0.7), liver (0.5) and brain (0.2).

- Normolipidemic, female NMRI mice (3/group) were injected iv with ^{14}C-toxaphene in solutions of low density lipoprotein (LDL), high density lipoprotein (HDL) or DMSO (Mohammed et al., 1990b). After 20 min, relative radioactivity (dpm/g or ml tissue per dpm dose/g body weight) was found to approximately range from 0.05 to 0.4 under all conditions for the heart, spleen, muscle and plasma. Abdominal fat was reported to be 0.2 to 0.3 (LDL, HDL) or about 1.1 (DMSO); kidneys about 1.0 (LDL, DMSO) or 0.4 (HDL); adrenals about 2.6 (LDL), 1.4 (HDL), or 4.3 (DMSO); and liver 3.2 to 3.3 (LDL, DMSO) or about 2.2 (HDL). The principal changes after 4 hr were 2- to 4-fold reductions in liver and adrenal levels, and an approximate 3- to 10-fold increase in abdominal fat levels. In mice made hypolipidemic by pretreatment with 4-aminopyrazolo-(3,4-d)-pyrimidine, relatively lower levels accumulated initially in the liver and adrenals, while more was seen in the kidneys and heart.

- Mixed-breed heifer calves (6 to 7/group) were dosed with 50, 100 or 150 mg/kg of toxaphene in water via gastric intubation (Steele et al., 1980). After 7 days, mean concentrations (ppm) found in the liver, kidney and brain were 2.88, 3.45 and 2.67 (50 mg/kg dose); 7.66, 2.75 and 4.02 (100 mg/kg dose); and 22.26, 5.50 and 3.88 (150

mg/kg dose). Liver residues were geometrically (logarithmically) related to dose. Results from five field animals suspected of dying as a result of being dipped in 0.5% toxaphene solution were qualitatively similar, with liver concentrations being two- to five-fold higher than those measured in kidney and brain.

Metabolism

- Groups of three 30-day-old albino rats were deprived of food for 24 hr prior to being dosed with ^{36}Cl-toxaphene (20 mg/kg) in a peanut oil-gum acacia solution via a stomach tube (Crowder and Dindal, 1974). Extensive metabolism, including dechlorination, was suggested by the partitioning patterns of excreted ^{36}Cl radioactivity into hexane, aqueous-nonionic and aqueous-ionic fractions: 10.5, 21.3 and 68.2% in feces, and 0.2, 23.3 and 76.2% in urine, respectively.

- Groups of four male Sprague-Dawley rats were given a single dose of ^{14}C-toxaphene (15 mg/kg) in corn oil via gastric intubation (Chandurkar and Matsumura, 1979). Thin-layer chromatography of collected feces and urine indicated that most of the toxaphene was metabolized, largely to polar with some hexane-insoluble and inextractable metabolites. Methylated, acidic and other hydroxylated compounds were revealed, as were the presence of sulfate conjugates (about 8.9 and 0.7% of total metabolites in the urine and feces, respectively) and other acid-hydrolyzable metabolites (about 9.5 and 7.5% of total metabolites in urine and feces, respectively). These results and those of associated in vitro experiments indicate a prominent role for hepatic NADPH-dependent mixed-function oxidases and GSH S-transferases in the metabolism of toxaphene.

- Female Sprague-Dawley rats were dosed with 10 mg/kg of ^{14}C-toxaphene in olive oil by gastric intubation (Pollock and Kilgore, 1980). Analysis of urine and fat residues of toxaphene, as well as of polar and nonpolar fractions of toxaphene that were similarly administered, indicated metabolism of a large percentage of the materials (>99% for toxaphene as measured in the urine). Residues of toxaphene and the nonpolar fraction were more polar than the parent compounds, while those identified from the polar fraction were somewhat less polar in nature.

- Metabolism of toxaphene (13 mg/kg) and one of its major components (heptachlorobornane I, 3 mg/kg) was examined in a comparative study using male rabbits, male Swiss-Webster mice, male Sprague-Dawley rats, male Hartley guinea pigs, male hamsters, male long-tailed monkeys and female white leghorn chickens (Saleh et al., 1979). The chemicals were administered in soybean oil to mice, rats, monkeys and chickens via gastric intubation; for the other species, treatment solutions were applied to lettuce that was quickly consumed. After 72 hr, the percentages of administered heptachlorobornane I excreted in the feces were 17.7 (chicken), 2.8 (mouse), 2.5 (rabbit), 2.3 (guinea pig), 0.6 (hamster), 0.2 (rat) and 0.0 (monkey). Percentages

of two dechlorinated and one dehydrochlorinated metabolites that were monitored ranged from 0.2 to 10.7% in the various species. Total levels were highest in rabbits and monkeys, and lowest in mice and hamsters. Seventy-two hours after toxaphene administration, the chromatographic patterns of extracted fat samples from all tested species were reported to be very similar to toxaphene. The patterns of extracted liver and fecal samples, however, were species-specific and contained significant differences from that of toxaphene.

Excretion

- Groups of three 30-day-old albino rats were deprived of food for 24 hr prior to being dosed with ^{36}Cl-toxaphene (20 mg/kg) in a peanut oil-gum acacia solution via a stomach tube (Crowder and Dindal, 1974). Within 9 days, 52.6% of the administered radioactivity was excreted, 37.3% in the feces and 15.3% in the urine. Upon extraction, most of the radioactivity was found in the water fractions as ionic chloride.

- Groups of four male Sprague-Dawley rats were given a single dose of ^{14}C-toxaphene (15 mg/kg) in corn oil via gastric intubation (Chandurkar and Matsumura, 1979). After 5 days, approximately 56.5% and 9% of the administered dose was excreted in the feces and urine, respectively.

- Female Sprague-Dawley rats were dosed with 10 mg/kg of ^{14}C-toxaphene in olive oil by gastric intubation (Pollock and Kilgore, 1980). After 7 days, fecal, urinary and total excretion were 35.7, 22.5 and 58.2% of the administered dose. Retention of toxaphene was less than 0.2 ppm in brain, heart, lung, liver, kidney, and spleen, but averaged 6.4 ppm in abdominal and subcutaneous fat.

- Male Swiss mice were dosed with 25 mg/kg ^{36}Cl-toxaphene in corn oil by gastric intubation (Crowder and Whitson, 1980). After 8 days, fecal, urinary and total excretion of radioactivity were 42.5, 18.2 and 60.7% of the administered dose. Retention of ^{36}Cl (ppm) in various tissues was 10.6 (lipid), 1.2 (muscle), 0.8 (testes), 0.7 (kidney), 0.5 (liver) and 0.2 (brain).

- When dairy cows were sprayed with a 0.5% solution of toxaphene, the insecticide was detected in the cows milk for at least 21 days (Claborn et al., 1963). Detected levels (ppm) were 0.60 (1 day), 0.61 (2 days), 0.44 (3 days), 0.23 (5 days), 0.16 (7 days), 0.06 (14 days) and 0.08 (21 days). Similarly, toxaphene was detected in the milk of cows fed 20, 60, 100 and 140 ppm of toxaphene in the diet for 8 wk. Using the conversion factor of 0.015 mg/kg/day per ppm in food for maintenance feeding of cattle (Lehman, 1959), these doses would correspond to 0.3, 0.9, 1.5 and 2.1 mg/kg/day. Average toxaphene concentrations (ppm) in milk were fairly constant during the 8 wk of exposure: 0.20 to 0.37 (20 ppm dose), 0.48 to 0.75 (60 ppm dose), 0.86 to 1.15 (100 ppm dose) and 1.44 to 1.82 (140 ppm dose). Milk

levels declined during the 3 wk following termination of exposure, with average levels (ppm) after 3 wk measured at nondetectable, 0.07, 0.12 and 0.20 for the 20, 60, 100 and 140 ppm doses, respectively.

- Toxaphene was excreted in the milk of cows fed 0 to 20 ppm (equivalent to 0 to 0.3 mg/kg/day using the 1959 Lehman conversion described above) toxaphene in the diet for 77 days. Toxaphene levels in milk ranged from 0.043 to 0.179 mg/L and were dependent on the administered concentration (Zweig et al., 1963). Following cessation of exposure, residues in milk decreased to undetectable levels after 2 wk in cows given levels lower than 10 ppm (0.15 mg/kg/day). At the 20 ppm (0.3 mg/kg/day) level, residues were still detected 30 days after administration of the test diet was terminated.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Toxaphene poisoning in humans is characterized by diffuse stimulation of the central nervous system (CNS) resulting in salivation, restlessness, hyperexcitability, muscle tremors or spasms, generalized convulsions and sometimes loss of consciousness. Nausea and vomiting may follow ingestion. Clonic convulsions also may occur and can be prevented by barbiturates (McGee et al., 1952).

- The IUPAC (1979) has estimated an acute oral LD_{50} of 60 mg/kg for toxaphene.

- At least thirteen deaths from toxaphene poisoning have been recorded (Hayes, 1975). Most of the fatal cases involved ingestion of toxaphene by small children.

- A toxaphene aerosol (5%) at a maximum concentration of 500 mg/m^3 was inhaled by 25 humans for 30 min/day over a period of 10 days (Keplinger, 1963). Calculation by the author equates this exposure to a maximum of 60 mg/person/day (or about 0.86 mg/kg/day for a 70 kg adult). After an interval of 3 wk, the subjects received three more of these daily doses. No adverse effects were reported by the subjects or noted by an examining dermatologist or internist.

- Two men involved for approximately 2 months in spraying a toxaphene solution (60 % toxaphene, 35% kerosine, 3% xylol and 2% emulsifier) suffered from acute pulmonary insufficiency and were diagnosed as having extensive bilateral allergic bronchopneumonia (Warraki, 1963). One or both men exhibited extensive miliary shadows and marked bilateral hilar lymphadenopathy on their x-rays, as well as increased sedimentation rates, blood eosinophilia and high serum globulin.

Long-term Exposure

- Studies of human exposure to toxaphene in the workplace are confounded because exposure to many chemicals occurred in all of the reported studies. Two cases of acute aplastic anemia after dermal exposure to a toxaphene/lindane mixture have been reported (IARC, 1979).

Mutagenicity

- Eight women occupationally exposed to toxaphene were reported to have elevated levels of chromosomal aberrations (13.1% compared with 1.6 % in controls) in cultures of peripheral lymphocytes from blood taken 8 days after exposure (Samosh, 1974). The women had prematurely entered a field that had been sprayed with 2 kg/ha of toxaphene. Unspecified mild-to-moderate symptoms were reported to have occurred in the women beginning about 4 to 5 hr after starting their field work.

Carcinogenicity

- In a case-control study involving 622 white men from Iowa and Minnesota with newly diagnosed non-Hodgkin's lymphoma (NHL) and 1,245 population based controls, an elevated risk for developing NHL (odds ratio = 1.5, 95% confidence interval = 0.6 to 3.5) was found for farmers who had ever handled toxaphene (Cantor et al., 1992). The elevated risk was even more notable for those who had handled toxaphene prior to 1965 (OR = 2.4, CI = 0.7 to 8.2). However, because of the small numbers of farmers who had handled toxaphene (10 ever, 6 before 1965), these elevated risks were considered nonsignificant.

Animals

Short-term Exposure

- Toxaphene is a CNS stimulant in mammals. Effects of toxic exposures in humans (hypersensitivity, tremors and convulsions) are similar to those observed in both rats and dogs (Lehman, 1951).

- Male rats were given orally (via capsule) a single, one-half LD_{50}, 120 mg/kg dose of toxaphene and were sacrificed after 1, 5, or 15 days (Peakall, 1979). Despite the presence of toxaphene in liver and brain tissue, no alterations in blood plasma levels of pyruvic or lactic acids were observed. The NOAEL for this effect after a single exposure was thus 120 mg/kg. When exposures in a second experiment were extended to 6 months at a dose of 2.4 mg/kg/day, no alterations after 1,3 or 6 months in these parameters were again observed. A NOAEL for this effect after exposures of 1,3, and 6 months is therefore 2.4 mg/kg/day.

- Groups of 10 male guinea pigs received either a single oral LD_{50} dose of 300 mg/kg of toxaphene (99% pure) in groundnut oil, or daily oral doses of 2 or 5 mg/kg/day for a period of 60 days (Chandra and Durairaj, 1993, 1992). Within 72 hr of the acute dose, toxaphene was observed to affect body weight and the weights of brain (absolute), liver (absolute and relative) and kidney (absolute and relative). No appreciable changes in the ultrastructures of these tissues were observed. The treatment significantly reduced sodium potassium ATPase activity in the liver and kidney, magnesium ATPase and total ATPase activities in the brain, liver and kidney, and the specific activity of acetyl cholinesterase in all three tissues. Furthermore, the backbone's collagen content was lowered, while its calcium content was elevated. After 60 days in the subacute experiment, both 2 and 5 mg/kg/day doses caused significant body weight loss, as well as increased absolute and relative liver weight. Neuronal disorganization and enlargement observed in the brain was attributed to hypoxia and/or anoxia. Cerebral oligodendrial cells suffered depletion of cytoplasmic organelles, and fluid accumulation in myelinated axons resulted in abnormal myelin appearance. Chronic venous congestion was observed in the liver, as was mononuclear infiltration, hepatocytic hyperplasia, fatty changes and proliferation of the endoplasmic reticulum. In the kidney, both doses caused cellular vacuolation, degeneration and mitochondrial proliferation. Both doses reduced acetyl cholinesterase and total ATPase activities in the brain, liver and kidney, and elevated both cytochrome P_{450} content and aniline hydroxylase activity in the liver and kidney. K_m values for the latter enzyme were lowered in a dose dependent fashion. Finally, collagen reduction and calcium elevation in the backbone was observed at both doses. This study thus reflects frank toxic effects at 2 mg/kg/day and above for a variety of adverse effects in the brain, liver and kidney.

- Mixed-breed heifer calves (6 to 7/group) were dosed once with 50, 100 or 150 mg/kg of toxaphene in water via gastric intubation (Steele et al., 1980). Within the first 7 days, treatment was lethal to 2/6, 6/7 and 5/6 animals at the 50, 100 and 150 mg/kg doses. Clinical signs included apprehension, hyperexcitability, muscle fasiculations and generalized twitching, clonic-tonic convulsions, excessive salivation, licking and chewing movements, nystagmus, abnormal posturing, belligerence and frenzied movements. Death occurred between 4 5 hr and 5 days after treatment.

- Groups of 6 male Sprague-Dawley rats were dosed by oral intubation with 0, 25, 50 and 100 mg/kg/day of toxaphene in corn oil for 3 days (Moorthy et al., 1987; Rao et al., 1986). In these experiments, rats demonstrated dose-dependent nervousness and mild tremors prior to sacrifice at 24 hr. In brain tissue preparations, nuclear and P_2 fraction (synaptosomal) calmodulin levels were significantly reduced at all doses, as were P_2 fraction Ca^{2+}-ATPase activity, $^{45}Ca^{2+}$ uptake and calmodulin levels. The LOAEL for these effects following a 3 day exposure is 25 mg/kg/day. A NOAEL could not be established.

- Groups of 40 to 50 male ICR mice were dosed via oral intubation with 0, 50, 100 or 200 mg/kg/day of toxaphene in corn oil for up to 14 days prior to sacrifice or an additional 7 days of observation (Kuntz et al., 1990). Dose-dependent decreases in body-weight gain were observed at all three treatment levels, while increases were found for relative liver weight and serum glutamic pyruvic transaminase activity. Serum cholinesterase (ChE) activity was first depressed, then elevated by all treatment levels, although no significant effects on brain ChE activity were observed. Toxaphene produced 60% (50 mg/kg/day dose) and 80% (100 mg/kg/day dose) decreases in pentobarbital-induced sleep time, while 50 mg/kg/day (the only dose examined) significantly lowered pentobarbital concentrations in serum, brain, liver and kidneys. No structural changes were detected by light microscopy in the brain or liver after 50 mg/kg/day (the only dose examined), but electron microscopy revealed dilatation of the endoplasmic reticulum in both tissues, and hydropic changes in the liver. Based on a variety of observed effects, the LOAEL for this study is 50 mg/kg/day.

- Rats fed a protein-deficient diet were more susceptible to toxaphene poisoning than were rats fed regular laboratory chow, with LD_{50} values of 80 and 220 mg/kg bw, respectively (Boyd and Taylor, 1971). Clinical signs of depression and stimulation of the CNS were the same in both groups; however, signs appeared earlier and at lower toxaphene concentrations in protein-deficient rats. This suggests that humans who ingest a protein-deficient diet may represent a sensitive subpopulation.

- Allen et al. (1983) reported that humoral antibody responses (IgG antibody titers to bovine serum albumin) were depressed significantly in young adult female Swiss-Webster mice (10 animals/group) administered toxaphene for 8 wk at dietary concentrations of 100 ppm and 200 ppm, but not at 10 ppm (approximately 15, 30 and 1.5 mg/kg/day, respectively, based on the dietary assumptions of Lehman (1959)). Liver weights were increased in a dose-dependent manner at the 100 and 200 ppm doses (23-26 animals/group), as was abnormal variation in hepatocyte size. Cell-mediated, delayed hypersensitivity responses were not significantly affected at any dose. Based on these immunologic and hepatic effects, the study established a NOAEL and LOAEL of 10 and 100 ppm (1.5 and 15 mg/kg/day), respectively, in young adult female mice.

- In a study by Lackey (1949), fasted dogs (breed not indicated, 3 to 8 per dosage group) were administered single doses toxaphene in corn oil by gavage at 5, 10, 15, 20, 25, 30, 40 or 50 mg/kg. Deaths occurred in all dosage groups except the two lowest (5 and 10 mg/kg/day), and were attributed to respiratory failure. No convulsions were induced after a single dose of 5 mg/kg, but were observed in 4/5 animals receiving the 10 mg/kg dose. Therefore, 5 mg/kg and 10 mg/kg were the NOAEL and LOAEL, respectively, for convulsions in fasted dogs after a single gavage exposure to

toxaphene in corn oil. The author also reported that at daily exposure of 5 mg/kg, convulsions were observed after a few days (number not stated).

Dermal-Ocular Effects

- No information was found in the available literature regarding the dermal-ocular effects of toxaphene.

Long-term Exposure

- In a second part of the Lackey (1949) study discussed above, dogs were administered toxaphene by oral gavage at large cumulative doses (176 to 424 mg/kg), at 4 mg/kg/day for 44 to 106 days. At that level there was widespread degeneration of the renal tubular epithelium, occasionally accompanied by pyelitis (inflammation of the renal pelvis). Therefore, 4 mg/kg/day is identified as the LOAEL for renal effects in this study.

- Weanling Sprague-Dawley rats (10/sex/group) were fed diets containing 0, 4, 20, 100 or 500 ppm toxaphene solubilized in corn oil for 13 wk (Chu et al. 1986). Based on measured food consumption, the authors converted these intakes to dosages of 0, 0.35, 1.8, 8.6 and 45.9 mg/kg/day for males, and 0, 0.50, 2.6, 12.6 and 63 mg/kg/day for females. No significant dose-related clinical signs, gross pathology findings or weight gain and food consumption effects were observed. Increased liver weight, relative kidney weight (males) and hepatic aniline hydroxylase and aminopyrine demethylase activities occurred at the 500 ppm dose. Mild to moderate histological effects in the liver, kidneys and thyroid were described by the authors to be significant at doses of 20 ppm or more. These included mild focal necrosis and increased anisokaryosis of the liver, mild to severe renal tubular injury and focal necrosis (males), and mild to moderate follicular abnormalities, papillary proliferation, cytoplasmic vacuolation and reduced colloid density in the thyroid. This study appears to define a NOAEL of 4 ppm (0.35 mg/kg/day for males, 0.50 mg/kg/day for females) and a LOAEL of 20 ppm (1.8 mg/kg/day for males, 2.6 mg/kg/day for females) based on the described histological effects.

- Groups of 7 to 8 month-old beagle dogs (6/sex/group) were ılly dosed via gel capsule with 0, 0.2, 2.0 or 5 to 10 mg/kg/d. f toxaphene for 13 wk (Chu et al., 1986). Brief convulsions, salivation and vomiting were noted in several high-dose anir ı before the dose was lowered from 10 to 5 mg/kg/day. Signif: t increases in relative liver weight were reported at the mid males) and high doses, and in alkaline phosphatase activity at the h ;h dose. Mild histopathological effects noted to be significar n one or both sexes at the mid and/or high doses included increase relative liver weight, hepatocyte vacuolation and increased cytoplasmic density, and follicle abnormalities, interstitial-cell

hyperplasia and reduced colloid density in the thyroid. Based on these histopathological effects in the liver and thyroid, the NOAEL and LOAEL were established at 0.2 and 2.0 mg/kg/day, respectively.

- Male and female dogs of mixed breed were fed toxaphene at levels of 0, 10 or 50 ppm for 2 years (Treon et al., 1952). Using the equivalency factors of Lehman (1959), these doses were approximately 0, 0.25 and 1.25 mg/kg/day. At 50 ppm (1.25 mg/kg/day), a slight degeneration of the liver was observed that was characterized by granularity and nonsudanophilic vacuolation of hepatocyte cytoplasm. No pathological changes in other viscera were reported. Based on slight hepatic degeneration, the NOAEL and LOAEL for this study are 0.25 and 1.25 mg/kg/day.

- In a lifetime feeding study, Fitzhugh and Nelson (1951) observed increased liver weights with minimal liver cell enlargement in rats fed a diet containing toxaphene at 25 ppm (approximately 1.25 mg/kg/day based on the dietary assumptions of Lehman (1959)). In a lifetime study in rats by Lehman (1952), this level resulted in no effects, whereas 100 ppm (approximately 5 mg/kg/day based on Lehman (1959)) resulted in fatty degeneration of the liver. Boots Hercules Agrochemicals, Inc. (not dated) reported liver necrosis in rats fed toxaphene at 200 ppm (author's conversion: approximately 5 mg/kg/day) for 3.7 years. Clapp et al. (1971), however, observed no adverse effects on liver histology even at doses up to 189 ppm (approximately 9.45 mg/kg/day, based on Lehman (1959)). Based on these combined observations, the LOAEL for liver effects is determined to be 1.25 mg/kg/day, as reported in the Fitzhugh and Nelson (1951) study.

Reproductive Effects

- Groups of weanling Sprague-Dawley rats (15 males, 30 females) were fed diets containing 0, 4, 20, 100 or 500 ppm toxaphene (Chu et al., 1988). Corn oil was used as a solubilizing agent (4% w/w of the diet, including controls). Based on measured food consumption, the authors calculated corresponding dose levels of 0, 0.36, 1.8, 9.2 and 45 mg/kg/day for males, and 0, 0.36, 1.9, 8.5 and 46 mg/kg/day for females. The duration of parental exposure was 26 wk, with matings at 14 and 21 wk. With respect to systemic effects, higher level exposures were reported to depress weight gain, elevate serum cholesterol and hepatic aminopyrine demethylase activity, and increase liver and kidney weights. More subtle indications of toxicity in the form of various histological changes in the liver, kidney and thyroid were significant at exposures as low as 20 ppm (1.8 to 1.9 mg/kg/day). These effects included increased weight and cytoplasmic density in the livers of females, mild renal tubular injury in the kidneys of females, and increased anisokaryosis in the livers and kidneys of males. A NOAEL of 4 ppm, or 0.36 mg/kg/day, can be identified for these parental systemic effects. The corresponding LOAEL for this study is 20 ppm, or 1.8 mg/kg/day for

males and 1.9 mg/kg/day for females. Toxaphene had no significant, treatment-related effects at any dose on mating behavior, or on fertility, gestation and survival indices. Calculated dose levels were similar for the F_{1a} and F_{1b} generations, which were fed toxaphene diets upon weaning. Treatment had no significant effect on litter size, pup weight, or pup survival index, and no other development-specific effects were noted. Therefore, based on the examined parameters, this study established NOAELs of 500 ppm, or approximately 45 mg/kg/day, for both reproductive and developmental effects.

Developmental Effects

- Pregnant CD rats received 0, 15, 25 or 35 mg/kg/day of toxaphene in corn oil during the period of organogenesis, i.e., gestation days 7 to 16 (Chernoff and Carver, 1976). The numbers of dams in the respective groups were 33, 39, 39 and 16. There were dose-related decreases in number of maternal animals reaching term, maternal mortality (0, 5, 8 and 31%, respectively) and average maternal weight gain. Average fetal weight was lower in toxaphene-treated fetuses, and dose-related reductions in sternal and caudal ossification centers were noted. No dose-related changes in fetal mortality or other anomalies were observed. Based on a reduction in average number of sternal ossification centers, the developmental LOAEL for this study is 15 mg/kg/day.

- Approximately 25 pregnant Sprague-Dawley rats were dosed by oral gavage with 32 mg/kg/day of toxaphene in corn oil from gestation days 6 to 15 (Chernoff et al., 1990). This dose depressed maternal weight gain, altered maternal thymus, spleen and adrenal weights, and was lethal to half the treated dams. While mean fetus weight was reduced, the only statistically significant developmental effect noted was an increase in supernumerary ribs. Concomitant results with other chemicals tested suggests that the fetal effects were not simply a result of maternal toxicity. The study's LOAEL was the only dose tested, 32 mg/kg/day.

- Groups of five pregnant CR rats were dosed orally (details not provided) with 0, 12.5 or 25 mg/kg/day of toxaphene during days 7 through 16 of gestation (Kavlock et al., 1982). No external malformations were identified and fetal weight was not reduced. As measured by various biochemical parameters, brain, lung and liver development was normal, whereas kidney development was abnormal in terms of total protein (both doses) and alkaline phosphatase activity (high dose). Based on a composite kidney index, toxaphene in this study exerted a weak developmental effect at a LOAEL of 12.5 mg/kg/day, the lowest dose tested.

- Behavioral effects were studied in albino rats exposed prenatally (from gestation day 5 on, 3 dams/group) and postnatally (4 male and 4 female pups/group) through days 70 to 90, to either 0 or

0.05 mg/kg/day of toxaphene in the diet (Olson et al., 1980). Although this study is deficient with respect to standard protocols in terms of the number of animals treated, statistically significant deficits in righting ability and retarded development of swimming ability were noted in treated offspring. Similar deficits at 0.002 mg/kg/day were observed for two toxic fractions of toxaphene (toxicants "A" and "B"). The LOAEL for the behavioral developmental endpoints examined in this study is the only dose tested, 0.05 mg/kg/day. However, because of statistical limitations arising from the use of small numbers of animals in this study, the significance of these data is uncertain.

- Groups of pregnant CD-1 albino mice (26 to 90/group) were administered 0, 15, 25 or 35 mg/kg/day of toxaphene in corn oil via gastric intubation from gestation days 7 through 16 (Chernoff and Carver, 1976). At the highest dose, maternal mortality was 8%, and there were dose-related reductions in maternal weight gains and increases in maternal relative liver weights. There were no significant dose-related responses in fetal mortality or weight, number of caudal or sternal ossification centers, or incidence of supernumerary ribs. At the high dose, however, five litters had one or more pups displaying encephaloceles (none were observed at lower doses or in the controls). Based on this effect, the study's NOAEL and LOAEL for developmental effects are 25 and 35 mg/kg/day, respectively.

- In a study separate from the one discussed under Short-term Exposure, Allen et al. (1983) exposed adult female Swiss-Webster mice (36 total, 3/cage, apparently 9/dose level) to 0, 10, 100 or 200 ppm toxaphene in the diet (0, 1.5, 15 or 30 mg/kg/day using the 1959 Lehman conversion), from 3 wk prior to mating through gestation and lactation. Offspring (11 to 40/dose/endpoint) were weaned at 3 wk, put on toxaphene-free control diet and tested 5 weeks later (at 8 wk) for cell-mediated, delayed-type hypersensitivity response, humoral immune response (antibody titers to bovine serum albumin), and macrophage phagocytic activity. Effects on cell-mediated immune response and antibody formation were noted at the mid and/or high doses, while a dose-dependent decrease in macrophage phagocytic ability was observed even at the 1.5 mg/kg/day dose ($p<0.05$). Based on this decreased phagocytosis, the study's LOAEL is 10 ppm (1.5 mg/kg/day) for developmental immunotoxic effects.

Mutagenicity

- Toxaphene has been reported to be mutagenic in tester strains TA98 and TA100 of the *Salmonella typhimurium* reverse mutation assay, both with and without activation by exogenous rat liver microsomal preparations (Hill, 1977, summarizing assays performed by Litton Bionetics, Inc., 1978; Hooper et al., 1979; Mortelmans et al., 1986; NTP, 1983).

- Sobti et al. (1983) reported that toxaphene induced sister chromatid exchanges (SCEs) in the cultured human lymphoid cell line of B cell origin, LAZ-007. Positive responses were obtained at molar concentrations of 10^{-4} and 10^{-5}, but not at 10^{-6} (41.4, 4.14 and 0.414 mg/L, respectively). The response was slightly less in the presence of rat liver microsomal preparations used to simulate in vivo liver metabolism.

- Epstein et al. (1972) used a modified dominant lethal assay in ICR/Ha Swiss mice to examine toxaphene's in vivo potential to induce major genotoxicity in mammalian germ cells. The assay is most sensitive to structural and chromosomal anomalies. Male mice either were injected ip once with 36 or 180 mg/kg of toxaphene, or received 40 or 80 mg/kg/day of the insecticide by gavage for 5 consecutive days. They were then continually mated with untreated females for 8 consecutive weeks. Lethality ratios (number of deaths/number of treated males) were 0/7, 2/9, 2/12 and 9/12, respectively. Results were negative, as the numbers of early fetal deaths and preimplantation losses were within control limits for all toxaphene treatments.

Carcinogenicity

- The most definitive study of toxaphene carcinogenicity was conducted by the Tracor Jitco Co. under contract to the National Cancer Institute (NCI, 1979), despite the fact that the study was not conducted in strict accordance with NCI guidelines (control groups contained only 10 animals each and paired-feeding was not done). Osborne-Mendel rats and $B6C3F_1$ mice (50/sex/treatment group; 10/sex/control group) were used. Diets fed to male rats initially contained toxaphene at 2,560 and 1,280 ppm, and the females received 1,280 and 640 ppm. For mice of both sexes, the doses were 320 and 160 ppm. Because of overt toxicity, these concentrations were lowered later. For male rats, the high dose was lowered to 1,280 ppm at 2 wk, and to 640 ppm at 53 wk after initiation of the study for an average dose of 1,112 ppm. The low dose was similarly lowered to 640 ppm after 2 wk and 320 ppm 53 wk after feeding had begun for an average does of 556 ppm. For female rats, both dose levels were halved after 55 wk, and average doses were calculated to be 540 and 1,080 ppm. For both sexes, toxaphene treatment was discontinued after 80 wk, and the animals were fed control diets without corn oil for 20 wk and then with corn oil for an additional 8 wk. In male and female mice, both doses were halved 19 wk after treatment was initiated and average doses were 99 and 198 ppm. Toxaphene treatment was discontinued after 80 wk, and animals were fed control diets without corn oil for 7 wk then diets with corn oil for an additional 3 to 4 wk.

  Although none of the tumors observed in the animals was uncommon for the animal strain used, certain tumors and hyperplastic lesions were present with higher incidence in the treated animals. In rats these

included thyroid follicular cell adenomas and carcinomas 7/41 (17%) at the low dose; 9/35 (26%) at the high dose; and 1/7 (14%) in control males). Taking thyroid follicular cell adenomas and carcinomas together, a statistically significant increase was found for the high-dose group compared with the matched controls for both male and female rats. Increased incidence of these lesions was also significant in comparison with historical controls from the same laboratory. In the female rats, there was also an elevated cumulative incidence of tumors of the pituitary (chromophobe adenomas, chromophobe carcinomas) in the high dose group, when compared with the control group.

In the mice, toxaphene was reported to be more toxic. Hepatocellular carcinomas were observed with incidences of 69% and 98% in males at the low and high doses, respectively, and at 10% and 69% in females at the low and high doses, respectively. These neoplasms were observed in 20% of matched-control males, but not in females. On the basis of these findings, toxaphene was carcinogenic in $B6C3F_1$ mice and caused an increased incidence of thyroid tumors in Osborne-Mendel rats.

- Litton Bionetics (1978) reported a long-term carcinogenicity bioassay in which groups of B6C3F1 mice (54/sex/group) were administered 0, 7, 20 or 50 ppm of toxaphene in the diet for 18 mon (U.S. EPA, 1995). Using the conversion factor of 1 ppm in the diet per 0.15 mg/kg/day (Lehman, 1959), these doses were equivalent to approximately 0, 1.05, 3 or 7.5 mg/kg/day. Animals were observed for up to 6 mon after treatment was stopped. The incidence of hepatocellular carcinomas and neoplastic nodules (adenomas) was increased in both sexes, and was statistically significant in males at the high dose.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (____ \text{ L/day})} = ____ \text{ mg/L (rounded to } ____ \ \mu g/L)$$

where

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or National Academy of Sciences/Office of Water (NAS/OW) guidelines.

____ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for determining the One-day HA for toxaphene. The Ten-day HA of 4 µg/L, calculated below, is recommended for use as a conservative estimate for a 1-day exposure.

Ten-day Health Advisory

Several studies were considered for deriving the Ten-day HA. The study by Lackey (1949) provides evidence of well-documented effects potentially occurring at the lowest reported dose for this exposure duration. The study reports that dogs orally exposed to 4 mg/kg/day of toxaphene for 44 to 106 days suffered from degeneration of the renal tubular epithelium and inflammation of the renal pelvis (pyelitis), as well as from occasional convulsions. Because it may be that dogs are somewhat more sensitive than rodents to the short-term effects of toxaphene, and because the dog study is unclear as to whether any or all of the reported effects occurred during the first 10 to 30 days of exposure (although it appears likely that at least sporadic convulsions did), 4 mg/kg/day has been taken as the LOAEL for these effects after subacute exposure to toxaphene.

Groups of weanling Sprague-Dawley rats (15 males, 30 females) were fed diets containing 0, 4, 20, 100 or 500 ppm toxaphene (Chu et al., 1988). Corn oil was used as a solubilizing agent (4% w/w of the diet, including controls). Based on measured food consumption, the authors calculated corresponding dose levels of 0, 0.36, 1.8, 9.2 and 45 mg/kg/day for males, and 0, 0.36, 1.9, 8.5 and 46 mg/kg/day for females. The duration of parental exposure was 26 wk, with matings at 14 and 21 wk. With respect to systemic effects, higher level exposures were reported to depress weight gain, elevate serum cholesterol and hepatic aminopyrine demethylase activity, and increase liver and kidney weights. More subtle indications of toxicity in the form of various histological changes in the liver, kidney and thyroid were significant at exposures as low as 20 ppm (1.8 to 1.9 mg/kg/day). These effects included increased weight and cytoplasmic density in the livers of females, mild renal tubular injury in the kidneys of females, and increased anisokaryosis in the livers and kidneys of males. A NOAEL of 4 ppm, or 0.36 mg/kg/day, can be identified for these parental systemic effects, and was selected for use the calculation below to derive the Ten-day HA.

It should be noted that while a Ten-day HA based on this NOAEL is likely to be protective against the commonly studied adverse fetal effects of death, retarded growth and malformations, there is suggestive, but unconfirmed preliminary evidence that toxaphene could cause immunocompetence (Allen et

al., 1983) and functional developmental deficits in behavior (Olson et al., 1980) at low levels of exposure (at least as low as 1.5 and 0.05 mg/kg/day, respectively).

The Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.36\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (10)\ (1\ \text{L/day})} = 0.0036\ \text{mg/L (rounded to 4 } \mu\text{g/L)}$$

where:

0.36 mg/kg/day = NOAEL for maternal kidney, liver and thyroid effects in the rat.

10 kg = assumed weight of child.

100 = uncertainty factor; this uncertainty factor was chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from an animal study is employed.

10 = modifying factor; this modifying factor was chosen to account for data gaps relevant to potential developmental behavioral and immunological effects.

1 L/day = assumed water consumption by a 10-kg child.

Longer-term Health Advisory

The subchronic rat study by Chu et al. (1986) has been selected to serve as the basis for the Longer-term HA because it provides both a NOAEL and a LOAEL for relatively mild effects in three of the principal target organs of toxaphene--the liver, kidney and thyroid. Rats were exposed for 13 wk to 0, 4, 20, 100 or 500 ppm of toxaphene in the diet (equivalent to 0, 0.35 or 0.50, 1.8 or 2.6, 8.6 or 12.6, or 45.9 or 63 mg/kg/day for males and females, respectively). Based on mild to moderate histological effects (focal necrosis, anisokaryosis, cytoplasmic vacuolation, etc.) in the liver, kidney and thyroid, the study defined a NOAEL of 4 ppm (0.35 mg/kg/day for males) and a LOAEL of 20 ppm (1.8 mg/kg/day for males). These results are supported by findings in a subchronic dog described in the same publication (Chu et al., 1986), and in a rat reproduction study using the same doses (Chu et al. 1988).

The subchronic dog study (Chu et al., 1986), which supported a slightly lower NOAEL of 0.2 mg/kg/day, was not selected as the principal basis for the Longer-term HA primarily because the gel capsule dosing methodology was considered less relevant to likely human exposure conditions than the more continuous feeding exposure of the rat study. Furthermore, there may be some degree of uncertainty as to whether these studies firmly establish a NOAEL or LOAEL for the described critical effects, which were often reported in such a way (e.g., as being minimal to mild, moderate to severe, etc.) as to make difficult the precise determination of the relationship between severity of effect and dose.

As noted above for the Ten-day HA, although a Longer-term HA based on this NOAEL is likely to be protective against the commonly studied adverse fetal effects of death, retarded growth and malformations, there is suggestive, but unconfirmed preliminary evidence that toxaphene could cause immunocompetence (Allen et al., 1983) and functional developmental deficits in behavior (Olson et al., 1980) at low levels of exposure (at least as low as 1.5 and 0.05 mg/kg/day, respectively).

The Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.35\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (10)\ (1\ \text{L/day})} = 0.0035\ \text{mg/L (rounded to 4 } \mu\text{g/L)}$$

where:

0.35 mg/kg/day = NOAEL, based on histological effects in the liver, kidney and thyroid of the rat exposed to toxaphene via the diet for 13 wk.

10 kg = assumed weight of child.

100 = uncertainty factor; this uncertainty factor was chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from an animal study is employed.

10 = modifying factor; this modifying factor was chosen to account for data gaps relevant to potential developmental behavioral and immunological effects.

1 L/day = assumed water consumption by a 10-kg child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.35\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (10)\ (2\ \text{L/day})} = 0.01225\ \text{mg/L (rounded to 10 } \mu\text{g/L)}$$

where:

0.35 mg/kg/day = NOAEL, based on histological effects in the liver, kidney and thyroid of the rat exposed to toxaphene via the diet for 13 wk.

70 kg = assumed weight of adult.

100 = uncertainty factor; this uncertainty factor was chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from an animal study is employed.

10 - modifying factor; this modifying factor was chosen to account for data gaps relevant to potential developmental behavioral and immunological effects.

2 L/day - assumed water consumption by a 70-kg adult.

Lifetime Health Advisory and DWEL

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data is not available, a value of 20% is assumed.

If the contaminant is classified as a known, probable or possible carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. For human (A) or probable human (B) carcinogens, a Lifetime HA is not recommended. For possible human carcinogens (C), an additional 10-fold safety factor is used to calculate the Lifetime HA. The risk manager must balance this assessment of carcinogenic potential and the quality of the data against the likelihood of occurrence and significance of health effects related to noncarcinogenic end points of toxicity. To assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of 1 in 10,000 to 1 in 1,000,000 for the 70-kg adult drinking 2 L of water/day are provided in the Evaluation of Carcinogenic Potential section.

The reproduction study by Chu et al. (1988), described above for the derivation of the Longer-term HA, has been selected to serve as the basis for the RfD. The results of this study are supported by the 13-week subchronic studies in both the rat and the dog (Chu et al., 1986).

In a two-year feeding study in dogs (Treon et al., 1952), toxaphene was fed at levels of 0, 10 or 50 ppm (0, 0.25 or 1.25 mg/kg/day, using the Lehman (1959) conversion factor). At 50 ppm (1.25 mg/kg/day), a slight degeneration of the liver was observed that was characterized by granularity and

nonsudanophilic vacuolation of hepatocyte cytoplasm. No pathological changes in other viscera were reported. Based on slight hepatic degeneration, the NOAEL and LOAEL for this study are 0.25 and 1.25 mg/kg/day, respectively. While such values are supported by comparable values in the Chu et al. (1988) reproduction study, the 2-year dog study by Treon et al. (1952) could not serve as the basis of the RfD calculation because only summary documentation of the study is available, apparently only a limited number of animals were exposed per dose level and the strain of dogs was undetermined. As a result of these deficiencies, Treon et al. (1952) was considered inadequate for use as the critical study for the calculation of the RfD.

Collectively, these chronic and subchronic studies identify certain relatively subtle histopathological effects in the liver, kidney and thyroid of two species as being critical indicators of toxicity resulting from longer-term oral exposure to toxaphene. Although they agree remarkably well in defining NOAEL and LOAEL levels, two concerns remain regarding their use in establishing the chronic oral RfD. Firstly, there may be some degree of uncertainty as to whether these studies firmly established a NOAEL or LOAEL for the reported critical effects, largely due to imprecise toxicity grading levels as discussed previously in the Longer-term HA section. Secondly, there is some preliminary evidence that suggests certain neurological, developmental behavioral and/or immunological effects may turn out to be more sensitive indicators of toxaphene toxicity. These concerns have been accounted for in the derivation of the chronic oral RfD by including a 10-fold modifying factor to account for the data deficiencies.

Therefore, the RfD for toxaphene is based on the reproduction study by Chu et al. (1988). It should be noted that the 2-year dog study (Treon et al., 1952) does in fact provide support for the NOAEL/LOAEL values determined from the more rigorously performed rat studies (Chu et al., 1988, 1986), which were selected as the basis for derivation of the chronic oral RfD..

Step 1: Determination of Reference Dose (RfD)

Based upon the study cited above (Chu et al., 1988), the RfD may be calculated as shown below:

$$RfD = \frac{(0.36\ mg/kg/day)}{(100)\ (10)} = 0.00036\ mg/kg/day\ (\text{rounded to } 0.0004\ mg/kg/day)$$

where:

0.36 mg/kg/day = NOAEL, based on absence of liver, kidney and thyroid effects in the rat exposed to toxaphene via the oral route for 26 weeks.

100 = uncertainty factor; this uncertainty factor was chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from an animal reproduction study is employed, and which is supported by a 2-year dog study.

10 = modifying factor; this modifying factor was chosen to account for data gaps relevant to potential developmental, behavioral and immunological effects.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0004\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.014\ mg/L\ (rounded\ to\ 10\ \mu g/L)$$

where:

0.0004 mg/kg/day = RfD

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by 70-kg adult.

Step 3: Determination of the Lifetime HA

Toxaphene has been classified in Group B: Probable human carcinogen, thus a Lifetime HA is not recommended. The estimated excess cancer risk associated with lifetime exposure to drinking water containing toxaphene at 0.003 mg/L is 1×10^{-4}. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized multistage model. The actual risk is unlikely to exceed this value.

Evaluation of Carcinogenic Potential

- The results of two bioassays (NCI, 1979; Litton Bionetics, Inc., 1978) were positive for cancer induction, thus estimated risk levels for toxaphene in drinking water can be calculated using the linearized multistage model as discussed in the appendices to the Federal Register notice regarding the availability of Water Quality Criteria Documents (U.S. EPA, 1980a). Data from human studies are inadequate to determine toxaphene carcinogenicity.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), toxaphene may be classified Group B2: Probable Human Carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- Additionally, the International Agency for Research on Cancer (IARC, 1979) has placed toxaphene in Category 2B, meaning that toxaphene is probably carcinogenic in humans.

- Drinking water concentrations estimated to result in lifetime excess cancer risks of 10^{-4}, 10^{-5} and 10^{-6} for a 70 kg adult drinking 2 liters of water per day over a 70 year lifespan are 3 μg/L, 0.3 μg/L and 0.03 μg/L, respectively (upper 95% confidence limit).

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- A Time Weighted Average (TWA) of 500 $\mu g/m^3$ and a short-term exposure limit of 1.0 mg/m^3 have been set for toxaphene by ACGIH (1986).

- The National Interim Primary Drinking Water Standard of 5 $\mu g/L$ (U.S. EPA, 1980b) is superseded by the 1991 MCL of 3 ug/L.

- The NAS (1977) estimated the ADI of toxaphene for humans at 1.25 $\mu g/kg$.

- A Permissible Exposure Limit (PEL) (TWA) of 0.5 mg/m^3 has been set by Occupational Safety and Health Administration (OSHA) for occupationally exposed workers over an 8-hour workday (OSHA 1989).

VII. ANALYTICAL METHODS

Toxaphene can be analyzed by EPA Methods 505, 508 and 525.2.

- Determination of toxaphene using EPA Method 505 -- sample is extracted with hexane, and an aliquot of the extract is injected into a gas chromatograph equipped with an electron capture detector for separation and analysis (U.S. EPA, 1991).

- Determination of toxaphene using EPA Method 508 -- sample is extracted with methylene chloride. The methylene chloride extract is then dried and concentrated during a solvent exchange to methyl tert-butyl ether. An aliquot of the extract is injected into a gas chromatograph equipped with a nitrogen-phosphorous detector for separation and analysis. Confirmation of the compound's identity may be obtained using a dissimilar column or by the use of GC-MS (U.S. EPA, 1991).

- Determination of toxaphene using EPA Method 525.2 -- sample is passed through a cartridge or disk containing a solid matrix with a chemically bonded C_{18} organic phase (liquid-solid extraction, LSE). The organic compounds are eluted from the LSE cartridge or disk with ethyl acetate followed by methylene chloride and the extract is concentrated. An aliquot of the concentrated extract is injected into a high-resolution fused-silica capillary column of a gas chromatography/mass spectrometry system for separation and identification (U.S. EPA, 1994).

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies with limited data for removal of toxaphene from drinking water are adsorption by granular activated carbon (GAC) and powdered activated carbon (PAC), air stripping and coagulation/filtration. Other technologies adaptable to drinking water systems might be able to remove toxaphene; however, such data are not readily available.

- GAC columns mounted in a mobile unit have been used for the treatment of hazardous waste spills. This unit proved to be 97% effective in removing toxaphene from pond water in Virginia from an initial concentration of 36 µg/L. The GAC columns, with a contact time of 26 minutes, treated the water at a rate of 70,000 gallons per day.

- Another study examined the effectiveness of PAC for the removal of several fish poisons, including toxaphene. PAC was added to water containing 0.3 mg/L of toxaphene. Toxaphene removals of 95% were achieved at a carbon dosage of 9 mg/L. The results of this experiment indicate that PAC is effective for toxaphene removal (U.S. EPA, 1985).

- A theoretical model of an air stripping column was developed and applied to the removal of some synthetic organic chemicals (SOC) including toxaphene. The mass transfer coefficients for each SOC were developed according to Perry and Chilton (1973). The results show that toxaphene was 99% theoretically removed at an air-to-water ratio of 30. Actual air stripping performance data for removal of toxaphene are not readily available.

- Air stripping is a simple and relatively inexpensive process for removing organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure, and various hazards associated with the chemical.

- A conventional water treatment plant consisting of coagulation, sedimentation and filtration reportedly had little effect on reducing toxaphene from water. The influent toxaphene concentrations did not exceed 0.41 µg/L (U.S. EPA, 1985).

- Treatment technologies for the removal of toxaphene from drinking water have not been extensively evaluated except on an experimental level. Individual or combinations of technologies selected for toxaphene reduction must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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