DRAFT

For Review Only

Public Health Goal for Toxaphene in Drinking Water

NOT A REGULATORY STANDARD

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.

9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

OEHHA specifically requests comments on the following areas:

1. Considering the mandates of the California Health and Safety Code specifically Section 116300 (a), (d), (e), and (f) and Section 116365 (c), are the methods, assumptions and results of our analyses used in developing PHGs consistent with the intent of the statute? OEHHA solicits comments on toxicity study selection, no-observed-adverse-effect-levels (NOAELs), lowest-observed-adverse-effect-levels (LOAELs), uncertainty factors, severity of effect modifications, relative source contributions, multi-route exposure assumptions for volatile chemicals and other relevant assumptions and analyses for each chemical. Are the assumptions employed sufficiently health-protective in view of the statutory definition of the PHG (above)?
2. In proposing PHGs for carcinogens, OEHHA employed new methodology proposed by U.S. EPA in their 1996 Guidelines for Carcinogen Risk Assessment. These methods were applied to low-dose extrapolation and inter-species scaling and generally resulted in approximately two-fold lower estimated carcinogen potencies or slope factors as compared to earlier methods. We invite your comments on our methodology.
3. In developing the PHGs, OEHHA considered different levels of risk. Previously, when OEHHA developed Recommended Public Health Goals (RPHGs), the recommended levels were based on a 10^{-6} level of risk , a level that has been considered negligible or de minimis. This level corresponds to a theoretical extra

lifetime cancer risk of 1 x 10^{-6}, or one fatal cancer per million exposed population over 70 years. This risk level has been identified by federal and state agencies as a level at or below which there are no public health concerns. Higher risk levels of 1 x10^{-5} and 1 x10^{-4} were also considered and are provided in the supporting documentation for the aid of risk managers. State law allows PHGs to be set at zero. U.S. EPA policy employs zero as a numerical goal (Maximum Contaminant Level goal, or MCLG) for drinking water standards for selected carcinogens. OEHHA welcomes comments on the various options that were considered in identifying the proposed PHGs presented in these technical support documents.

OEHHA expects the following process to pertain to these PHG documents:

- The Draft documents will be released for external peer review and public comment including a public workshop.
- Public comments will be received and reviewed by OEHHA and the documents revised as may be appropriate.
- In accordance with the Health and Safety Code Section 57003, the revised document drafts will be circulated for a period of 30 days following the public workshop.
- Following this 30-day comment period the documents will be finalized and the PHGs adopted by OEHHA.

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DRAFT

PUBLIC HEALTH GOAL FOR TOXAPHENE IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.00003 mg/L (0.03 ppb) is proposed for toxaphene in drinking water. Toxaphene is an organochlorine pesticide consisting of a complex mixture of chlorinated camphenes used to control a broad range of insects on diverse crops. Toxaphene has not been used world-wide for many years, but is found in the environment as residues in sediments and soil. The characteristic toxicity of toxaphene is injury to the liver, kidney and nervous system. In particular, it has been identified as an animal carcinogen based on chronic studies conducted in several species.

In 1991, OEHHA developed a Recommended Public Health Level (RPHL) for toxaphene based on our earlier evaluation of toxaphene carcinogenicity for Proposition 65 (OEHHA, 1988). The potency calculation was based on evidence for carcinogenicity in a chronic mouse study. In this study (Litton, 1978), $B6C3F_1$ mice were administered toxaphene at 0, 7, 20, or 50 ppm in the diet for 18 months. The average daily doses are calculated to be 0, 0.84, 2.4, and 6.0 mg/kg-day, respectively, based on the assumption that 1 ppm of a chemical in feed is equivalent to 0.12 mg/kg-day dose. An increase in the incidence of hepatocellular carcinoma was observed in treated male mice. The tumor incidences were 10/53, 11/54, 12/53 and 18/51 for the male control, 7, 20 and 50 ppm treatment groups, respectively. Fitting the multistage polynomial to these data resulted in a cancer potency for animals (q_{animal}) of 0.905 $(mg/kg\text{-}day)^{-1}$, and for humans (q_{human}) of 1.2 $(mg/kg\text{-}day)^{-1}$. Based on the cancer potency of 1.2 $(mg/kg\text{-}day)^{-1}$ and a one in a million cancer risk level, with the default assumption that a 70- kg adult consumes two liters of water a day, the health-protective level was set at 30 ng/L (0.03 ppb).

Since there have been no new studies which would indicate more sensitive effects from chronic exposure to toxaphene or alter the previous interpretation, the assessment of health protective level in drinking water has not been changed. The proposed PHG for toxaphene in drinking water is 0.03 ppb. The current MCL of 0.003 mg/L (3 ppb) for toxaphene in drinking water is based on the sensitivity of approved analytical methodology to monitor toxaphene in water.

INTRODUCTION

The purpose of this document is to propose a PHG for toxaphene (and its residual products) in drinking water. In the past, toxaphene was used widely in agricultural applications throughout California. Its use has been severely restricted since 1981,

and all uses were banned in 1990. However, because of its previous extensive use and its relative persistence in the environment, it may contaminate water supplies and pose a hazard in drinking water. Federal and state drinking water regulations have been developed for toxaphene. A federal Maximum Contaminant Level (MCL) of 0.003 mg/L was promulgated for toxaphene (U.S. EPA, 1991). The same value was adopted by the California Department of Health Services (DHS) as the state MCL (22 CCR 64444). This MCL value is based on analytical detection methodology for toxaphene and represents the cancer risk at the 10^{-4} level. The toxaphene health-protective level of 0.003 ppb proposed by OEHHA (1991) was based on the cancer risk level of 10^{-6}.

U.S. EPA stated that there is evidence that toxaphene has the potential to cause cancer from lifetime exposures in drinking water (U.S. EPA, 1999). There is also an evaluation of carcinogenicity in IRIS (IRIS, 1999). Under California's Proposition 65, toxaphene is considered a substance known to the State to cause cancer (22 CCR 12000).

This document focuses on evaluating the available data on the toxicity of toxaphene. To determine a public health-protective level of toxaphene in drinking water, sensitive groups were identified and considered, and relevant studies were identified, reviewed and evaluated.

CHEMICAL PROFILE

Chemical Identity

Toxaphene is a complex organochlorine pesticide consisting of chlorinated camphenes with a wide range of molecular weights. Other information related to the identity of toxaphene is provided in Table 1.

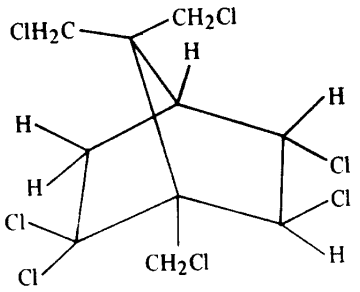
Physical and Chemical Properties

Toxaphene is a mixture of polychlorinated compounds, appearing as a waxy solid with limited solubility in water. Important physical and chemical properties of toxaphene are provided in Table 1. Representative structures of toxaphene congeners are provided in Figure 1.

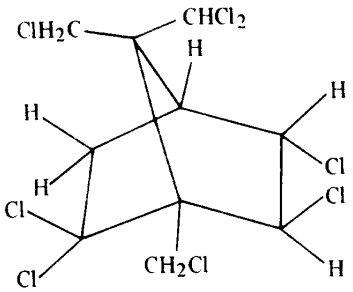
Table 1. Identity and Chemical/Physical Properties of Toxaphene (ATSDR, 1996)

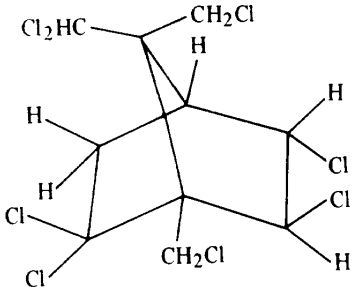
Property	Value or Information
Chemical name(s)	Toxaphene, camphechlor; chlorinated camphene
Chemical formula	$C_{10}H_{10}Cl_8$ (average; includes components with 6 to 9 chlorines)
Molecular weight	414 (average)
CAS number	8001-35-2
EPA hazardous waste code	P123
Trade names	Agricide Maggot Killer, Alltox; Camphofene Huilex, Geniphene, Hercules 3956, Hercules Toxaphene, Motto, Penphene, Phenicide, Phenatox, Strobane-T, Synthetic 3956, Toxakil
Color/Form/Odor	Yellow waxy solid with mild turpentine odor
Melting point[a]	65-90 °C
Vapor pressure[a]	0.2-0.4 or 4×10^{-6}, 5×10^{-6}, 3×10^{-7} mm Hg at 20 °C
Octanol /Water partition (K_{ow})	3.3 Log K_{ow}
Density/Specific gravity	1.65 at 25 °C
Solubility	0.0003 g/100 mL water
Odor/Taste thresholds	NA
Bioconcentration factor	NA

[a] The wide range of values may represent different toxaphene mixtures.
NA: not available



Compound 1





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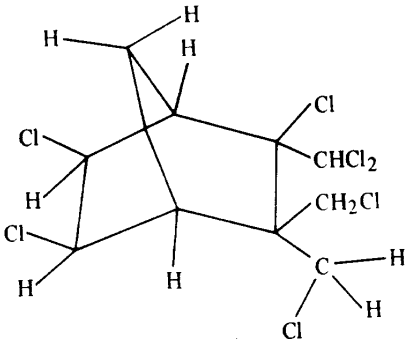

Compound 2

Figure 1. Representative Structures for Toxaphene (from Pollock and Kilgore (1978). [Note: the nomenclature used here is the authors'; for an extensive discussion regarding nomenclature for toxaphene congeners see De Geus *et al.* (1999)].

Production and Uses

Toxaphene is a mixture of at least 670 chlorinated bicyclic terpenes (ATSDR, 1996). Technical grade toxaphene is made from technical grade camphene reacted with chlorine gas using ultraviolet radiation and catalysts. Technical grade toxaphene was available in various forms: a solid, a 90 percent solution in xylene or oil, wettable powder, granules, dusts, and emulsifiable concentrates (ATSDR, 1996).

Toxaphene was produced in the early 1940s for insect control, some acaricidal properties and control of undesirable aquatic species (ATSDR, 1996). It was largely used on grain crops, particularly corn and soybeans, and on cotton. Increased use occurred in the late 1960s to early 70s when it replaced DDT in formulations combined with methyl parathion. Toxaphene was at one time the most heavily manufactured pesticide in the United States with a maximum production volume of 23,000 tons in 1973 (ATSDR, 1996). Due to its potential for environmental effects and toxicity, U.S. EPA cancelled registration for most uses in 1982 and allowed existing stocks to be depleted. In 1990, all remaining uses were cancelled and existing stocks could not be sold (ATSDR, 1996). By 1993 all tolerances and food additive regulations for toxaphene on all agricultural commodities were revoked (U.S. EPA, 1999).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

As a result of its widespread use, toxaphene has been distributed to all environmental media. In aerial and ground applications, toxaphene was released directly to the atmosphere. This release and subsequent persistence of airborne toxaphene resulted from the relatively volatile nature of the toxaphene as well as its resistance to direct photolysis. Removal of toxaphene from the atmosphere occurs principally by deposition of toxaphene bound to particles (ATSDR, 1996).

As a complex mixture of congeners, toxaphene formulations would be expected to have variable volatilities and degradation patterns complicating the monitoring of toxaphene in the environment. However, researchers have been able to identify toxaphene fractions and confirm its widespread airborne transport in remote areas of the Canadian Arctic and the South Atlantic Ocean (ATSDR, 1996).

Soil

Toxaphene strongly adsorbs to soils and particles. Once bound, toxaphene may persist in soils, especially surface soils, for over two months (Seiber *et al.*, 1979). Disappearance from surface soils appears to be primarily by volatilization, although some congeners appeared to be degraded (Seiber *et al.,* 1979). Other studies have indicated that degradation of toxaphene, primarily by dechlorination, generally occurs under anaerobic rather than aerobic conditions (ATSDR, 1996).

Water

Deposition of airborne toxaphene and/or its direct application to lakes and streams to eliminate undesirable species has resulted in the detection of significant quantities in surface waters. Toxaphene, however, has low water solubility (3 mg/L), strongly

binds to particles, and is deposited into sediments. Thus, it has been argued that significant ground water contamination should not occur. However, toxaphene has been detected in ground water as a result of normal agricultural use (ATSDR, 1996).

In water, toxaphene appears to be resistant to all forms of degradation. It is not known to undergo photolysis or photooxidation. Hydrolysis of toxaphene is insignificant; a hydrolytic half-life of 10 years was estimated for water at pH 5 to 8 (U.S. EPA, 1985). Nationwide, toxaphene has rarely been detected in public water supplies. In Flint Creek, Alabama, water supplies, toxaphene concentrations ranged from 0.05 to 0.410 ppb (ATSDR, 1996). In California, toxaphene was detected in only 2 of 5,279 public drinking water supplies sampled from 1984-1992 (Storm, 1994). In the most recent ground water survey (1996-1997) conducted by the California Department of Pesticide Regulation, toxaphene was not detected in the sampling of wells (DPR, 1998).

Food

Residues of toxaphene congeners have been detected on raw and finished agricultural commodities. At one time, primarily during the 1980s, toxaphene was one of the most commonly detected pesticides in food commodities (ATSDR, 1996). However, in the decade since its registration was suspended, detections have fallen off dramatically. In the Food and Drug Administration's Annual Food Survey of 1990 (FDA, 1991), toxaphene residues were detected in 2 percent of food tested. In the 1999 Survey, no detection of residues was reported (FDA, 2000).

Although toxaphene exposure from agriculturally derived food sources has dropped, concern over toxaphene exposure from seafood remains. It has been established through laboratory bioassay and field monitoring data that toxaphene congeners are bioconcentrated by aquatic organisms (ATSDR, 1996). However, biomagnification is limited by metabolism of higher trophic organisms. Therefore, toxaphene is not thought to be as severe a biomagnification problem as are PCBs or dioxins. Even so, ingestion of seafood remains the major food source for human toxaphene exposure.

Other Sources

Toxaphene use has been banned in the United States and Western European countries, but it is not clear whether other countries are continuing to use it, or to what extent (ATSDR, 1996). Thus toxaphene may continue to be disseminated in the global environment.

METABOLISM AND PHARMACOKINETICS

Absorption

There are a limited number of studies of toxaphene absorption from all routes of exposure. Toxaphene is likely to be taken up readily by all routes of exposure based on its physical properties (small size and lipophilicity) and the detection of toxaphene congeners and metabolites in body tissues and fluids.

Oral absorption of toxaphene appears to be enhanced when taken together with oily foods (ATSDR, 1996).

Distribution

Upon absorption, toxaphene becomes concentrated in fatty tissues. Pollock and Kilgore (1980) administered ^{14}C toxaphene at 10 mg/kg in olive oil to rats. Seven days later, 6.4 mg/kg of toxaphene and its metabolites were found in the fat, while the remaining tissues had less than 0.2 mg/kg. Administering radiolabeled toxaphene in peanut oil to rats resulted in high concentrations of toxaphene residues initially in brown fat and also in the adrenal cortex, bone marrow, liver and kidney, which peaked at three hours (Mohammed *et al.*, 1985). After 24 hours, radioactivity was found mostly in the white fat, with lesser amounts in the liver and kidney.

Metabolism

Studies indicate that toxaphene is rapidly and extensively degraded *in vivo*. Metabolism appears to occur entirely in the liver and consists of dechlorination, dehydrochlorination and oxidation. Products are eliminated primarily through the feces, although there is significant urinary excretion.

Ohsawa *et al.* (1975) noted that upon oral administration of radiolabeled (both chlorine and carbon) toxaphene to rats, about 50 percent of the label was eliminated in the urine as chloride ion along with some unmetabolized product within fourteen days. A small amount was exhaled as carbon dioxide. The rest of the urinary products were metabolites of toxaphene. Pollock and Kilgore (1980) demonstrated that all metabolic components in the urine were more polar than toxaphene.

Due to the complex nature of toxaphene, certain components would be either more or less resistant to metabolism, resulting in different metabolic fates. This complicates understanding the metabolic pathways of toxaphene. Thus the study of pathways of metabolism has been limited to the study of selected components of toxaphene.

Saleh *et al.* (1979) evaluated the metabolism of one component of toxaphene, termed ‘toxicant B,’ in several species and noted that monkey and rabbit had the most extensive metabolism of ‘toxicant B’ as compared with mice, rats, hamster, guinea

pigs and chickens. Rat liver microsomes, in the presence of NADPH under anaerobic conditions, were able to dechlorinate toxicant B. The presence of fecal metabolites and the understanding that toxicant B was metabolized to a greater extent under anaerobic conditions, suggests that metabolism of this component was occurring in the intestine (Saleh *et al.*, 1979).

Excretion

Toxaphene is rapidly eliminated from the body. Crowder and Dindal (1974) noted about 50 percent of a 20 mg dose of toxaphene given to rats was excreted in 9 days. About 70 percent of the excreted dose was found in the feces and 30 percent in the urine.

Pollock and Hillstrand (1982) evaluated the excretion of radiolabeled toxaphene in pregnant and virgin female rats. After administration of 2.6 mg/kg of toxaphene in olive oil, about 50 percent of the total activity was recovered in the urine and feces after five days. The additional fatty tissue present in pregnant rats did not appear to change the retention of toxaphene or its metabolites.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Toxaphene stimulates the central nervous system at high doses like other chlorinated hydrocarbon pesticides. The range of oral lethal values (LD_{50}s) was 80 to 295 mg/kg for rats (ATSDR, 1996). Two out of eight dogs died after receiving 15 mg/kg toxaphene in corn oil. However when the vehicle was kerosene, death did not occur until the dose reached 200 mg/kg in one of five dogs (Lackey, 1949).

Subchronic Toxicity

Toxaphene toxicity has been evaluated in a number of short-term studies. Peakall (1976) described two studies. In one, rats were given an oral dose of 120 mg toxaphene/kg and monitored for up to 15 days. Liver weight and microsomal enzyme activity increased after 5 and 15 days, respectively. Other rats were given toxaphene at 2.4 mg/kg per day for one, three, and six months. Liver and body weights increased at all time intervals compared to controls, but plasma testosterone levels were not affected.

In the NCI (1977) subchronic study, groups of five mice or rats of each sex were given toxaphene added to feed at concentrations of 150 to 2,560 ppm for rats and 40 to 1,280 ppm for mice for six weeks. A second study was performed on male and

female rats with the same parameters as the first study but at concentrations from 1,280 to 5,120 ppm, to extend the first study. Controls for both studies consisted of five animals per group administered only feed. Mean weight gains for treated animals were comparable to that of controls. In both rat studies, no deaths occurred at concentrations below 2,560 ppm. Deaths occurred in the mouse study only at 640 and 320 ppm, but not at the highest dose, thereby suggesting no dose-related lethal effects.

Adult male rats were fed toxaphene in diets at concentrations of 0, 50, 100, 150 or 200 ppm diet for 14 days (Trottman and Desaiah, 1980). No changes were observed in body weight gain, food consumption, brain, kidney, heart, or testes weights. Liver weight was increased at 200 ppm and thymus weight decreased at 150 and 200 ppm (estimated doses: 7.5 and 10 mg/kg).

In another study (Chu *et al.,* 1986), ten male and female rats were fed diets containing toxaphene at 0, 4, 20, 100 or 500 ppm (0, 0.35, 1.8, 8.6, and 45.9 mg/kg for males, and 0, 0.5, 2.6, 12.6 or 64 mg/kg for females, respectively) for thirteen weeks. No effects were noted in clinical signs or among rats dying spontaneously. The only effects noted were on the liver/body weight ratio and hepatic microsomal enzyme activities, which were increased in both sexes fed 500 ppm. Toxaphene caused kidney enlargement in male, but not female rats. Histological changes were noted in the kidney, liver and thyroid.

Chu *et al.* (1986) also evaluated the toxicity of toxaphene on dogs. Groups of six male and female dogs were administered toxaphene via gelatin capsules at doses of 0, 0.2, 2.0, or 5.0 mg/kg-day each day for 13 weeks. There was an inadvertent increase in the dose at the 2.0 mg/kg-day level. Food consumption and growth rate were not affected. Mild to moderate dose-dependent histological changes were noted in the kidney and thyroid. Large eosinophilic inclusions were found in the kidneys of high-dose males while cytoplasmic vacuolation was found in the mid- and high-dose groups. Thyroid changes included a mild increase in epithelial height and reduced colloid density. Based on these findings, the authors (Chu *et al.*, 1986) proposed a subchronic NOAEL of 0.35 mg/kg for the rat and 0.2 mg/kg for the dog.

Cardiac Toxicity

There appears to be no specific pattern of action for toxaphene on the heart. In one case, acute administration of toxaphene (up to 400 mg/kg) to rats resulted in capillary congestion and capillary hemorrhage in the hearts, but this was probably the result of an inflammatory response (Boyd and Taylor, 1971). In another instance an acute dose (>10 mg/kg) appeared to increase heart rate without other vascular effects (Lackey, 1949). For the most part, in acute, subchronic and chronic studies, toxaphene had no specific effect on the heart.

Gastrointestinal Toxicity

Chronic administration of toxaphene to rats and mice was noted to cause abdominal distension and diarrhea (NCI, 1977). This study is described in detail in the Chronic Toxicity section.

Renal Toxicity

Toxaphene has been reported to cause renal toxicity. In dogs, dosing of 5 mg/kg for 106 days resulted in degeneration of kidney tubules (Lackey, 1949). In subchronic studies conducted in rats and dogs (Chu *et al.*, 1986), toxaphene, at doses ranging from 8.6 to 12.5 mg/kg-day, caused moderate toxicity to the proximal convoluted tubules of male rats, while other effects (including increased kidney weight) occurred at doses up to 63 mg/kg-day in female rats. Dogs of both sexes receiving up to 5 mg/kg were seen to have eosinophilic inclusions occasionally accompanied by focal necrosis. In a chronic rat study (Ortega *et al.*, 1957), no adverse effects were noted on the rat kidneys. In a two year old boy poisoned by toxaphene, swelling of the kidney was noted (McGee *et al.*, 1952).

Genetic Toxicity

The many genotoxicity evaluations of toxaphene are summarized in Table 2 below. Toxaphene appears to be more genotoxic in the *in vitro* test systems than in the *in vivo* systems. In the Ames test, toxaphene has been found to be positive. Generally, rates of mutagenic activity significantly increased only with higher concentrations (500 µg/plate in Schrader *et al.*, 1998). The addition of metabolic activators generally diminished the number of revertants (Schrader *et al.*, 1998; Mortelmans *et al.*, 1976). Steinburg *et al.* (1998) noted that toxaphene was mutagenic in TA98 (only at 10,000 µg/plate) and in TA100 strains at all concentrations (lowest, 156 µg/mL) in plate systems. However, in a microsuspension/preincubation assay, toxaphene was not mutagenic to TA98, and mutagenic to strain TA100 only at concentrations of 2500, 5000, and 10000 µg/L (Steinburg *et al.*, 1998).

In mammalian systems, toxaphene has been shown to increase sister chromatid exchanges (SCEs) in two of three assays. Sobti *et al.* (1983) noted increased sister chromatid exchanges in the human lymphoid LAZ-007 cell line under both activated and non-activated conditions, with the activated cultures having fewer SCEs than the non-activated. The mammalian mutational assays have generally not been consistent indicators of toxaphene mutagenicity. Unfortunately, toxaphene has not been adequately evaluated under even a limited screening battery.

Table 2. Genotoxicity of Toxaphene (Adapted from ATSDR, 1997)

***In vitro* test systems**	**Results** (without activation / with activation)	**Reference**
E1 plasmid DNA isolated from E. coli	- / ND	Griffen *et al.*, 1978
S. typhimurium TA98	+ / ND	Hooper *et al.*, 1979
S. typhimurium TA100	- / +	Hooper *et al.*, 1979
S. typhimurium TA98	+ / (+)	Mortelmans *et al.*, 1986
S. typhimurium TA100	+ / +	Mortelmans *et al.*, 1986
S. typhimurium TA1535	- / -	Mortelmans *et al.*, 1986
S. typhimurium TA100	(+) / -	Mortelmans *et al.*, 1986
S. typhimurium TA97	+ / (+)	Schrader *et al.*, 1998
S. typhimurium TA98	+ / (+)	Schrader *et al.*, 1998
S. typhimurium TA100	+ / +	Schrader *et al.*, 1998
S. typhimurium TA102	(+) / (+)	Schrader *et al.*, 1998
S. typhimurium TA104	+ / (+)	Schrader *et al.*, 1998
S. typhimurium TA98	+ / ND	Steinburg *et al.*, 1998
S. typhimurium TA100	+ / ND	Steinburg *et al.*, 1998
HGPRT induction	- / -	Schrader *et al.*, 1998
SCE in V79	- / -	Schrader *et al.*, 1998
SCE in human lymphoid cells	+ / +	Sobti *et al.*, 1983
Neurospora crassa	+ / ND	Mortelmans *et al.*, 1986
SCE induction	+	Steinel *et al.,* 1990
***In vivo* test systems**		
Human lymphocytes	+ / ND	Samosh, 1974
Peroxisome proliferation	-	Hedli *et al.*, 1998
^{32}P-Postlabeling	-	Hedli *et al.*, 1998
Mouse dominant lethal	- / ND	Epstein *et al.,* 1972

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

The ability of toxaphene to form DNA adducts and to induce peroxisome proliferation were investigated as potential mechanisms for toxaphene induced-liver tumorigenicity. Groups of three or four male CD1 mice were treated by oral intubation with 10, 25, 50 or 100 mg/kg toxaphene in corn oil for seven consecutive

days (Hedli *et al.*, 1998). Negative control mice received corn oil alone; positive control mice were treated with 200 mg/kg clofibrate. All animals were sacrificed 24 hours after the last treatment. Livers from two animals per group were pooled and evaluated for specific isoenzyme CYP 4A1 of cytochrome P-450 with an immunodetection assay. This isoenzyme is associated with peroxisomal proliferation. No induction of this isoenzyme was noted, although total liver weight, cytochrome P-450, and cytochrome b_5 were increased over controls. Livers of the other treated animals were extracted and subjected to a ^{32}P-post labeling assay to detect DNA adduct formation. No increases in DNA adduct formation were noted.

The totality of the evidence suggests that toxaphene is genotoxic.

Developmental and Reproductive Toxicity

The reproductive effects of toxaphene were evaluated in a two-generation study (Chu *et al.*, 1988). Groups of 30 female and 15 male weanling rats were given toxaphene in their diets at 0, 4, 20, 100 or 500 ppm solubilized in corn oil. Toxaphene did not have any effects on litter size, pup weight, fertility or gestation and survival indices. Toxic effects in treated animals occurred primarily in the 500 ppm group and included depressed weight gain, elevated serum cholinesterase and increased liver and kidney weight and hepatic microsomal enzyme activities. Morphological changes were seen in the thyroid, liver and kidney. Minor effects were observed at lower doses, down to 20 ppm, but it was not clear that these minor effects were necessarily dose-related. In the thyroid, two adenomas were observed at the highest dose. In the liver, minimal to mild changes occurred in the cytoplasmic density, homogeneity, and vacuolation, with severity increasing with dose. In the kidney, dose-dependent injuries were observed in the proximal tubules of both generations of male rats, mostly at the level of cytoplasmic changes, which increased in severity with dose.

In a three-generation study (Kennedy *et al.*, 1973) male and female rats were fed diets containing 0, 3, 10, 25 or 100 ppm toxaphene for 39-42 weeks. There were no effects on litter sizes, pup survival or weanling body weights. There was a slight cytoplasmic vacuolization in the livers of parental animals at the highest concentration (corresponding to doses of about 5 mg/kg-day according to ATSDR, 1996), but no effects were seen in growth, survival, clinical parameters, or organ weights.

In another multigenerational study, mice were fed a diet of 25 ppm of toxaphene (3.25 mg/kg-day according to ATSDR, 1996) during mating, gestation and lactation, and pups received it after weaning. No effects on lactation, reproduction, average litter size, or offspring growth and viability were noted for five generations of mice (Keplinger et al, 1970). Male rats administered toxaphene at 2.4 mg/kg-day for six months had no effects on their circulating testosterone levels (Peakall, 1976).

Administration of 0, 15, 25, or 35 mg/kg-day of toxaphene to rats by gavage in oil during gestation days 7 through 16 increased fetal mortality at all doses. There was a

dose-related reduction in maternal weight gain and in the average number of sternal ossification centers in fetuses (Chernoff and Carver, 1976). No major anatomical defects were noted in this study or in several other studies in which toxaphene was administered gestationally at doses ranging from 0.05 to 75 mg/kg-day (Allen *et al.*, 1983; Chernoff and Kavlock, 1982; Crowder *et al.*, 1980; Kavlock *et al.*, 1982; Kennedy *et al.*, 1973 and Olson *et al.*, 1980).

Immunotoxicity

Toxaphene has been reported to induce specific humoral immunosuppressive effects. Male rats exposed to 1.5 mg/kg toxaphene in feed for nine weeks had impaired IgG production at some stages of the IgG response (Koller *et al.*, 1983). Similarly, female mice had impaired IgG production after being fed toxaphene for eight weeks at concentrations of 100 and 200 ppm (approximately 15 and 30 mg/kg-day) but not at 10 ppm (about 1.5 mg/kg-day) (Allen *et al.*, 1983).

Cell-mediated responses were also assessed in toxaphene-exposed animals. Weanling female mice were fed 10, 100 and 200 ppm (approximately 1.5, 15 and 20 mg/kg-day) of toxaphene in the diet (Allen *et al.*, 1983). No differences in response between treated and control animals were noted by the delayed-type hypersensitivity assay. Acute administration of 7.5 mg/kg toxaphene in the diet was reported to decrease thymus weight in rats (Trottman and Desaiah, 1980). However, the administration of 5 mg/kg-day toxaphene for 39-42 weeks to rats did not have an effect on spleen or thymus weights (Kennedy *et al.*, 1973).

Neurotoxicity

Central nervous system stimulation is an important effect of short-term exposure to toxaphene. Dogs administered 10 mg/kg of toxaphene for two days by stomach tube showed convulsions. Dogs receiving 4 mg/kg-day for 106 days by stomach tube had intermittent convulsions (Lackey, 1949). Olson *et al.* (1980) reported behavioral effects (retarded maturation based on a swimming test) in juvenile rats after prenatal treatments (to the dams) at 0.05 mg/kg-day.

The effects of toxaphene and parathion on rats exposed peri- and postnatally were examined (Crowder *et al.*, 1980). In the postnatal study with toxaphene alone, females received daily oral doses of 6 mg/kg for 21 days. In the perinatal study, females received 6 mg/kg daily from day 7 of pregnancy until parturition. No weight changes or increases in mortality were noted. Perinatal exposure did not cause significant differences in grasp-hold, startle, or initiation of the righting reflex. There were also no significant differences in maze learning and transfer of this learning (ability to learn the maze in reverse) with either post- or perinatally-exposed animals.

Endocrine Toxicity

Results from animal studies suggest that prolonged oral exposure to toxaphene may induce thyroid injury (Chu *et al.*, 1986; NCI, 1977). Specifically, increased incidences of thyroid follicular cell adenomas were noted in male rats upon chronic exposure (NCI, 1977). In another study (Waritz *et al.*, 1996), 40 male rats were given an oral dose of 100 mg/kg-day toxaphene for three days, then 75 mg/kg-day daily for an additional 25 days. After 0, 7, 14 and 28 doses, 20 test and 10 vehicle-control animals were sacrificed for gross and histopathological examination of thyroid, parathyroid and pituitary glands. There was a significant time related increase in serum TSH levels, but no increase in serum levels, T_3, T_4, rT_3, and corrected T_3. Thyroid and pituitary gland weights, and thyroid and pituitary to brain weight ratios were not significantly affected. The incidence of thyroid follicular cell hypertrophy and intrafollicular hyperplasia were increased, and thyroid colloid stores were decreased with treatment. The authors reported that the results were consistent with increased production and turnover of T_3 or T_4 resulting from induction of cytochrome P450 and UDP-glucuronyl transferases.

Chronic Toxicity/ Carcinogenicity

Chronic toxicity of toxaphene was evaluated in rats by Treon *et al.* (1950). Four groups of 20 male and female rats were fed toxaphene in the diet at 10, 100, 1000 or 1500 ppm. After 7 1/2 months to 10 months, rats in the 1500 ppm group and some in the 1000 ppm group suffered convulsions. There were no significant effects on mortality or on the hematopoietic system. Liver weight and liver to body weight ratios were increased in the 1000 and 1500 ppm groups. Upon examination, liver cells showed swelling and hypertrophy and proliferation of the smooth endoplasmic reticulum. This occurred mostly in the 1500 ppm group and only to a slight extent in the 1000 ppm group.

In a study evaluating the toxicity of four organochlorine pesticides, six male and six female Sherman rats were fed 50 and 200 ppm toxaphene (estimated to be 2.5 and 10 mg/kg by ATSDR, 1996) in the diet for up to 9 months (Ortega *et al.*, 1957). There were control groups of 25 male and 16 female rats for this study. No clinical signs of toxicity and no effects on body weight gain, food intake, or liver weights were noted. No histological changes were seen in the kidney or spleen. Three of the 12 rats in the 50 ppm group showed histological changes in the liver consisting of centrilobular cell hypertrophy, peripheral migration of cyanophilic granulation and the presence of liposphere inclusion bodies. Six out the 12 rats fed 200 ppm showed liver changes.

Groups of rats fed toxaphene in the diet at 25, 100, or 400 ppm (approximately 1, 5, 20 mg/kg, respectively for their lifetime) showed minor changes only to the liver at 100 ppm, and liver enlargement at 400 ppm levels (Fitzhugh and Nelson, 1951).

Toxaphene was administered to 9 dogs daily for 5 days a week at doses of 5, 10, or 25 mg/kg with maize oil in gelatin capsules. The dose of 25 mg/kg was fatal to all

three of the dogs treated with this dose. A dose of 10 mg/kg caused one dog to die within 33 days, while the other at this dose survived and was sacrificed after 3½ years. Four dogs survived a dose of 5 mg/kg for four years before being sacrificed (Lehman, 1952). Dogs receiving the 5 mg/kg dose were judged to be free of overt effects.

Treon *et al.* (1950) fed toxaphene six days/week for two years to three male and five female dogs, beginning when they were four months old. Toxaphene was added to the diet and in their drinking water at levels of 10 or 50 ppm. The equivalent daily dose was approximately 0.60 to 1.47 mg/kg-day or 3.12 to 6.56 mg/kg-day, respectively, based on WHO (1984) estimates. There were no reported effects on behavior, mortality, hematology, gross pathology, organ to body weight ratios and histopathology. There were increases in liver weights, liver to body weight ratios, and moderate liver degeneration at the higher dose. At the lower dose, liver changes included enlargement, slight granularity and vacuolization of the cytoplasm.

In the same study, toxaphene was given to two monkeys in their diet for 6 days per week for two years at a dose of 0.64- 0.78 mg/kg (Treon, 1950). No signs of toxicity were noted in growth rates, body weights, organ weights, organ weight ratios and histological examination of tissues.

The National Cancer Institute (NCI) commissioned a long-term toxicity study of toxaphene on rats and mice (NCI, 1977). In the rat study, 50 Osborne-Mendel male or female rats per group were treated with toxaphene at two concentrations administered in the diet for 80 weeks. The initial levels for males were 1280 ppm and 2650 ppm at the low and high levels, respectively. After observing significant toxicity, the concentrations were lowered to 640 and 1280 ppm at two weeks, and then again to 320 and 640 ppm, respectively at 53 weeks. The time-averaged concentration levels were computed to be 556 and 1112 ppm, respectively for the low and high groups. The female rats received initial concentrations of 640 and 1280 ppm, but were lowered to 320 and 640 ppm at 55 weeks. The time-averaged concentrations for females were 540 and 1080 ppm. At 80 weeks, all animals were switched to a control diet without corn oil for 20 weeks, followed by an additional 8 weeks on a diet with corn oil. The study utilized only 10 matched controls. To conduct statistical analyses, data from control groups from other NCI experiments were pooled as additional controls for this experiment.

Treatment with toxaphene resulted in decreased body weight, generalized body tremors, leg paralysis, ataxia, epistaxis, hematuria and vaginal bleeding. There was a significant increase of follicular carcinomas or adenomas of the thyroid in both male and females in the high dose group, with a dose-related trend across all doses. In males the tumor incidences were 1/7 for matched controls, 2/44 for pooled controls, 2/44 for the low level, and 7/41 for the high level. In females, the tumor incidences were 0/6 for matched controls, 1/46 for pooled controls, 1/43 for the low level and 7/42 for the high level. Two follicular–cell tumors in the high-dose males were carcinomas, the rest (in males) were adenomas. In females, the incidence of follicular-cell adenomas of the thyroid was dose-related using either the matched or pooled controls. In females, the incidences of pituitary tumors were 3/8 for matched

controls, 17/51 for pooled controls, 15/41 for the low level and 23/39 for the high level. The pituitary tumor incidences were significantly higher in high-dose females compared to the pooled control group ($p<0.05$ by Fisher's exact test). However, due to the high incidence of pituitary tumors in historical controls (sometimes as high as 60 percent), it could not be concluded that toxaphene administration was associated with this apparent increase in pituitary tumors. NCI noted that "the test results also suggest that toxaphene is carcinogenic to the thyroid of male and female Osborne-Mendel rats."

In the NCI mouse study (1977), groups of 50 $B6C3F_1$ male or female mice were administered toxaphene in the diet for 80 weeks. The initial concentrations were 160 and 320 ppm for the low and high concentration groups, respectively. These concentrations were lowered to 80 and 160 ppm, respectively, after 19 weeks. Thus, the time-averaged concentrations for the low and high dose groups were 99 and 198 ppm, respectively. Administration at this concentration continued to 80 weeks, at which time animals were switched to a control diet without corn oil for 7 weeks, then to diets with 2 percent corn oil for an additional 3-4 weeks. As with the rats, matched and pooled controls were used in statistical evaluations. Toxicity observed included abdominal distension, diarrhea, dyspnea, and rough hair coats. The incidence of hepatocellular carcinomas showed a dose-related increase. For males the incidences were 0/10 for matched controls, 4/48 for pooled controls, 34/49 for low dose, and 45/46 for high dose. For females the incidences were 0/9 for matched controls, 0/48 for pooled controls, 5/49 for the low level, and 34/49 for the high level groups. NCI concluded that "under the conditions of this bioassay, toxaphene was carcinogenic in male and female $B6C3F_1$ mice causing increased incidences of hepatocellular carcinomas."

Litton Bionetics (1978) conducted a longer-term carcinogenicity study in $B6C3F_1$ mice. Groups of 53-54 male or female mice were treated with toxaphene in corn oil at 0, 7, 20 or 50 ppm in the diet. Treatment continued for 18 months at which time mice were returned to a control diet for 6 months before termination. It should be noted that only the liver and other tissues showing gross pathology were examined histologically. Survival was 83-90 percent in male mice and 83-87 percent in female mice, and was not dose-related. Incidences of hepatocellular carcinomas at 0, 7, 20 and 50 ppm were 7/53, 11/54, 12/53 and 12/51 in male mice, and 1/53, 1/53, 3/52 and 3/52 in female mice, respectively. Incidences of hepatocellular adenomas were reported at 3/53, 0/54, 2/53 and 11/51 in male mice and 1/53, 1/53, 1/52 and 3/52 in female mice for the 0, 7, 20, and 50 ppm groups, respectively. Combining the adenomas and carcinomas, the increased tumor incidence was significant only for the high dose males and not for any other group, including females.

Triolo *et al.* (1982) conducted a study on 12 female A/J mice treated with toxaphene in corn oil in the diet at 0, 100 or 200 ppm (only 11 mice) for 12 weeks. In a 20-week study, 17 female A/J mice were fed 200 ppm toxaphene in the diet, while 17 controls received only corn oil. Histological examinations were limited to detection of only lung and forestomach tumors. In the 12-week study, at 200 ppm, one lung tumor was found among six treated mice, but no forestomach tumors. In the 20-

week study, one lung tumor was found in 15 treated mice and one in control mice and no forestomach tumors. Due to the limited nature of this study (short study period and limited examination) very little can be concluded about the carcinogenic potential of toxaphene from these results.

Toxicological Effects in Humans

Acute Toxicity

Toxaphene is acutely toxic to humans. Several fatalities have been documented by McGee *et al.* (1952). In these cases an unknown quantity of toxaphene was ingested, either intentionally, or accidentally from food contamination. Reported symptoms included convulsions without abdominal pain, vomiting and diarrhea. In one death, congestion and edema of the lungs was observed. Death was attributed to respiratory failure resulting from seizures.

Subchronic Toxicity

Keplinger (1963) exposed 25 adults (15 males and 10 females) to an aerosol containing toxaphene at a maximum concentration of 500 mg/m^3 for 39 minutes daily for 10 days. The author calculated an exposure dose to be as much as 60 mg/person/day. Three weeks after the last exposure, subjects were exposed for three more 30-minute periods. Follow-up examination of the skin, blood tests and urinalysis revealed no effects.

Genetic Toxicity

Lymphocytes cultured from eight women exposed occupationally to an unknown amount or concentration of toxaphene were examined for chromosomal breaks (Samosh, 1974). A higher incidence of chromosomal breaks was reported in exposed women (13.1 percent) compared to unexposed controls (1.6 percent).

Neurotoxicity/Behavioral

In three women who ate collard greens contaminated with toxaphene, convulsive seizures were followed by periods of memory loss (as much as a week later). The day following the convulsions, there were no reported ill effects other than weakness. The lowest estimated dose for inducing convulsions was 9.5 mg/kg (McGee *et al.*, 1952).

Chronic Toxicity/Carcinogenicity

Several epidemiological or case studies were located on the chronic effects of toxaphene exposure to humans from occupational exposure. However, these are

difficult to interpret based on the inability to estimate exposures to toxaphene or the concurrent exposure to other pesticides, which could impact the results.

Barthel (1981) reported a study of 1658 male agricultural workers and agronomists exposed to toxaphene and other pesticides between 1954 and 1972. A total of 169 malignant neoplasms was observed and a higher proportion of bronchial carcinoma was found, compared with the unexposed general population; 59 (35 percent) observed as compared to 42 (24 percent) expected, with a standard mortality ratio (SMR) of 2. The authors did not think that toxaphene among all the pesticides involved was responsible for tumor induction.

IARC (1979) reported two cases of aplastic anemia associated with dermal exposures to toxaphene and lindane mixtures. One case terminated in death due to acute myelomonocytic leukemia.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Toxaphene is known to be toxic to the lung, liver, kidney, nervous, hematopoietic system and thyroid under longer-term to lifetime exposure. Toxaphene is also associated with an increased cancer incidence and early death in experimental animals.

Several lifetime studies of toxaphene toxicity have been conducted over the years, however, none were judged to be suitable to serve as the basis for noncarcinogenic risk assessment. This assessment is based on significant study limitations, including dose adjustments, inadequate assessment of noncancer effects, and small group sizes. In the Litton (1978) study, no attempt was made to systematically evaluate all tissues, just those exhibiting "gross pathology." The NCI (1979) study conducted in rats reported an increased incidence of dyspnea, abdominal distension, diarrhea, hematuria, alopecia, and dermatitis at 27 mg/kg-day (estimated after dose-adjustment), with a trend toward increased mortality.

In studies conducted pre-1960, little information is provided to allow for reasonable dose extrapolation, single doses and small group sizes were used, and very few experimental details were provided, including those needed for accurate dose estimation. Approximated doses for which no effects are noted range from 0.5 to 5 mg/kg-day.

Most subchronic studies have similar problems regarding the estimation of doses producing minimal to no effects. However, the two subchronic studies reported by Chu *et al*. (1986, 1988) are of higher quality and are more dependable for risk assessment purposes. These studies found effects associated with toxaphene exposure at lower doses than those used in the NCI (1979) study, and provided the lowest LOAEL determinations of all the toxaphene experimental toxicity studies. The Chu *et al.* (1986, 1988) studies provide NOAELs of 0.35 mg/kg-day for slight

hepatic changes (increased liver weights) and 0.18 mg/kg-day for changes of the rat thyroid (judged to be reversible). In the study of Chu *et al.* (1986), a NOAEL of 0.2 mg/kg-day was reported for biliary and hepatocellular changes in dogs, however there is uncertainty regarding the dose level because of an inadvertent increase in the dose during part of the study period.

Carcinogenic Effects

Toxaphene (polychlorinated camphene) was listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) on January 1,1998 by the Science Advisory Panel as a chemical known to the State to cause cancer. The Reproductive and Cancer Hazard Assessment Section of OEHHA calculated a cancer potency and a no significant risk level for Proposition 65 purposes based on carcinogenic effects noted in two rodent studies (OEHHA, 1988). IARC (1979) and U.S. EPA (1999) have concluded that there is sufficient evidence to consider toxaphene an animal carcinogen, while at the same time there was insufficient evidence from human studies. As a result, toxaphene is classified in category 2B ("possibly carcinogenic to humans") by IARC (1987) and was placed in category B2 ("probable human carcinogen") by U.S. EPA (1987).

There is no new evidence since the OEHHA (1988) assessment that diminishes concern regarding the carcinogenicity of toxaphene. New evidence reported since then does not support a change to the potency estimate generated in the 1988 assessment.

CALCULATION OF THE PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, as well as for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures. In this case, certain toxaphene components may be volatile enough to consider inhalation as a possible exposure route from use of domestic water. However, the contribution to inhalation exposure from these (semi-) volatile components would be small, and difficult to estimate. Toxaphene can be dermally absorbed; however, the amount potentially absorbed from the brief-duration household water uses would be negligible when compared to the amount absorbed from inhalation or ingestion of drinking water.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for toxaphene in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL/LOAEL	=	no-observed-adverse-effect-level or lowest-observed-adverse-effect-level;
BW	=	adult body weight (a default of 70 kg);
RSC	=	relative source contribution (a default of 20 to 80 percent);
UF	=	uncertainty factors (typical defaults of 10 to account for inter-species extrapolation, 10 for uncertainty from the subchronic nature of the principal study, and 10 for human variability);
L/day	=	adult daily water consumption rate (a default of 2 L/day).

Chu *et al.* (1986) fed 10 male and female rats diets containing toxaphene at 0, 4, 20, 100 or 500 ppm for thirteen weeks. Based on the calculation made by the authors, the doses were estimated to be 0, 0.35, 1.8, 8.6 or 45.9 mg/kg-day for males and 0, 0.5, 2.6, 12.6 or 63 mg/kg-day, respectively, for females. The only effects noted were on the liver/body weight ratio and hepatic microsomal enzyme activities, which were increased in both sexes fed 500 ppm. Treatment-associated histopathology was noted at 20 ppm and above in the kidney, liver and thyroid, and was more prevalent in males. Mild changes were seen at the 4 ppm level (0.35 mg/kg-day for male rats), but was comparable to controls. Thus the NOAEL for this study would be 0.35 mg/kg-day. The health-protective concentration is therefore calculated as:

$$C = \frac{0.35\ mg/kg\text{-}day \times 70\ kg \times 0.8}{1000 \times 2\ L/day}$$

$$= 0.0098\ mg/L = 10\ \mu g/L\ (rounded) = 10\ ppb$$

The above calculation utilizes the default values for body weight and drinking water consumption, and uncertainty factors of 10 to account for inter-species extrapolation, 10 because of the subchronic nature of the principal study, and 10 for human variability. The use of an RSC of 0.8 assumes that nearly all of the toxaphene that is available for human exposure will be from the drinking water. Toxaphene and its metabolites are still being found as residues in a number of foodstuffs, particularly seafood. Although the exact contribution cannot be estimated, levels in seafood have been decreasing in frequency of occurrence and amount; thus food is no longer considered a prominent source of toxaphene. A higher RSC can therefore be used to account for toxaphene, derived predominantly from a water source.

The resultant estimated public health protective level for noncarcinogenic effects would be 10 ppb.

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C, in mg/L) for a chemical in drinking water:

$$C = \frac{BW \times R}{q_1^* \text{ or } CSF \times L/day} = mg/L$$

where,

BW	=	adult body weight (a default of 70 kg);
R	=	*de minimis* level for excess lifetime individual cancer risk (a default of 10^{-6});
q_1* or CSF	=	The q_1* is the upper 95 percent confidence limit on the cancer potency slope calculated by the LMS model, and CSF is a potency derived from the lower 95 percent confidence limit on the 10 percent (0.1) tumor dose (LED_{10}). CSF = 0.1/ LED_{10}; both potency estimates are converted to human equivalent dose [in $(mg/kg\text{-}day)^{-1}$] using $BW^{2/3}$ scaling;
L/day	=	daily volume of water consumed by an adult (a default of two L/day or other volume in Leq/day to account for additional inhalation and dermal exposures from household use of drinking water as explained above).

Pursuant to the listing of toxaphene as a chemical known to cause cancer under Proposition 65, the Reproductive and Cancer Hazard Assessment Section of OEHHA in 1988 calculated a cancer potency (OEHHA, 1988). OEHHA proposed a health-protective level in 1991 based upon the Proposition 65 evaluation of the carcinogenic potency of toxaphene (OEHHA, 1991). No additional information on cancer associated with toxaphene exposure has become available to warrant revision of the 1988 OEHHA potency estimation.

The following narrative from the OEHHA (1988) document summarizes the derivation of the cancer potency estimate:

> "The Litton (1978) study on $B6C3F_1$ mice consisted of a concurrent control group of 53 animals and three dose groups at 7, 20, or 50 ppm in the diet for 18 months. The average daily doses are calculated to be 0.84, 2.4, and 6.0 mg/kg-day based on the assumption that 1 ppm of a chemical in feed is equivalent to 0.12 mg/kg-day, respectively. An increase of hepatocellular carcinoma incidences was observed in treated male mice but not in female mice. The tumor incidences were 10/53, 11/54. 12/53 and 18/51 for the male control, 7 ppm, 20 ppm and 50 ppm treatment groups, respectively. Fitting the multistage polynomial to this bioassay data results in a cancer potency for

> animals (q_{animal}) of 0.905 $(mg/kg\text{-}day)^{-1}$, and for humans (q_{human}) of 1.2 $(mg/kg\text{-}day)^{-1}$."

Using the NCI mouse and rat study, OEHHA also calculated potencies for thyroid and follicular cell carcinomas or adenomas for male rats, resulting in cancer potencies (q_{animal}) of 5.0×10^{-2} and 5.6×10^{-2} $(mg/kg\text{-}day)^{-1}$ for matched controls and pooled controls, respectively. OEHHA determined that the NCI (1979) study was less reliable for potency estimation than the Litton (1978) study. The Litton (1978) study was conducted with groups fed much lower concentrations of toxaphene than those used in the NCI study. The NCI (1979) study also had doses adjusted lower during the course of the study, resulting in greater uncertainty over the dose-response. Furthermore, there were fewer concurrent controls in the NCI (1979) than in the Litton (1978) study. Therefore OEHHA concluded that the Litton (1978) study was better for risk extrapolation. U.S. EPA (1987) also based its dose estimates on the Litton (1978) study.

The current evaluation uses the same rationale for estimating a human health protective level as used earlier (OEHHA, 1991), which was described as follows:

> "DHS has evaluated two major bioassays for toxaphene (Litton, 1978; NCI, 1979) and concluded that the Litton (1978) study is more reliable for potency determination, because toxaphene was tested at a lower dose and in more dose groups…. The cancer potency ($q1^*_{human}$) estimated from the incidences of hepatocellular carcinomas is 1.2 $(mg/kg\text{-}day)^{-1}$. The DHS and EPA potencies are very similar. Based on the cancer potency of 1.2 $(mg/kg\text{-}day)^{-1}$, using the default assumption that a 70-kg adult consumes 2 L of water a day, the RPHL is 30 ng/L (30 ppt)."

Thus,

$$C = \frac{70\ kg \times 10^{-6}}{1.2\ (mg/kg\text{-}day)^{-1} \times 2\ L/day} = 2.9 \times 10^{-5}\ mg/L = 0.03\ \mu g/L\ (ppb)$$

Because the human health protective level calculated based upon carcinogenic endpoints (30 ppt, 0.03 ppb) is considerably lower than that calculated from noncarcinogenic endpoints (10 ppb), the cancer risk value is considered to be a more appropriate basis for the PHG. Therefore, OEHHA proposes that the PHG for toxaphene in drinking water be set at 0.03 ppb.

RISK CHARACTERIZATION

It is OEHHA's policy that when no additional information is available to characterize the human risk of a chemical, the results of previous assessments should be used. Such is the case for toxaphene. There is no substantive new information

that would warrant revision of the cancer potency estimates of the 1988 Proposition 65 risk assessment.

The primary sources of uncertainty lie in the strength of the underlying data and the nature of risk extrapolation. With toxaphene there is substantial evidence from animal experimental studies to indicate that toxaphene is carcinogenic. This evidence consists of three chronic studies, some of which are of less than adequate quality based on current standards for chronic FIFRA studies. There is no conclusive evidence for carcinogenicity of toxaphene in limited human studies. Mutagenicity and genetic toxicity testing indicates toxaphene is probably mutagenic. Toxaphene is considered a probable human carcinogen by the U.S.EPA (1985, 1998) and as a possible human carcinogen by IARC (1987), and is classified as a substance known to the state to cause cancer under Proposition 65 (OEHHA, 1988).

To derive the potency values, OEHHA used the 95 percent upper confidence limit estimate of the linearized multistage model. This is still the most common extrapolation method currently used, but it is also recognized that it probably overestimates the risk.

The risk computation for drinking water from OEHHA (1991) was very similar to that calculated by U.S. EPA, as the following narrative from OEHHA (1991) explains:

> "EPA proposed a MCLG of zero and a MCL of 3×10^{-2} mg/L or 30 ng/L (30 ppt). The cancer potency ($q1^*_{human}$) reported in IRIS is 1.1 $(mg/kg\text{-}day)^{-1}$, which was derived from the combined tumor incidences of hepatocellular carcinomas and neoplastic nodules in the Litton (1978) mouse study. The concentration of toxaphene in drinking water that poses a lifetime cancer risk of 10^{-6}, as calculated based on this cancer potency using the default assumption that a 70-kg adult consumes 2 L of water a day, is 32 ng/L, which was rounded off to 30 ng/L (30 ppt)."

The slight difference (before rounding) between these two estimates (U.S. EPA and OEHHA) is because U.S. EPA assumed that one ppm of toxaphene in the diet is equivalent to 0.13 mg/kg-day and OEHHA assumed that it was 0.12 mg/kg-day (OEHHA, 1988). However, the final U.S. EPA MCL for toxaphene is based on analytical considerations as explained in the next section.

Recently Goodman *et al.* (2000) estimated another toxaphene cancer potency. The authors selected the female liver tumor data set rather than the male liver tumor data set used by U.S. EPA and OEHHA in their toxaphene cancer potency assessments. The authors had an expert pathology working group reevaluate the NCI (1979) liver tumors on the basis of more current diagnostic criteria. The group determined that some tumors could be reclassified. The Litton (1978) tumor data could not be evaluated, as the slides/tissues were not available. The authors felt justified to combine the liver tumor data sets from the Litton and NCI studies (with reevaluated NCI data) based on their view that neither study alone was adequate for potency determination. The authors presented an argument that toxaphene was not a genotoxic carcinogen, but ultimately estimated a cancer potency by linear

extrapolation from the ED_{10} to the origin. The resulting cancer potency was 0.1 $(mg/kg\text{-}day)^{-1}$, which is 10-fold lower than the U.S. EPA and OEHHA potency estimates.

Estimating potencies using the reevaluated data sets from the NCI studies in the multistage model (not combined with the Litton data) supports the earlier OEHHA and U.S. EPA finding that male mice are considerably more sensitive than female mice to the carcinogenic effects of toxaphene. Goodman *et al.* (2000) argued that the background rate of the liver tumors in the control male mice was higher and more erratic compared with females, thus justifying the selection of female mice as the basis for the potency selection. The Goodman *et al.* (2000) approach combines two data sets based on different evaluation guidelines, which the authors acknowledge as being incongruous, but justify their use on the reasoning that the tumor incidences are similar in both data sets. However, OEHHA does not concur with this approach, and does not feel that there is sufficient evidence to consider toxaphene as a nongenotoxic carcinogen. Therefore, the use of the linearized multistage model is retained for this evaluation, which is consistent with the assumption that toxaphene is genotoxic and is appropriate for cancer potency estimation using the multistage model. OEHHA believes that the proposed PHG is appropriate to protect potentially sensitive subpopulations, including infants and children, women, and the elderly from adverse effects of toxaphene.

The proposed PHG level of 0.03 ppb is based on lifetime exposure, and a *de minimis* risk of 10^{-6} (one in a million). Drinking water levels associated with a 10^{-4} or 10^{-5} risk level would be 3 ppb or 0.3 ppb, respectively.

OTHER GUIDANCE VALUES AND REGULATORY STANDARDS

Federal and state drinking water regulations for toxaphene in drinking water have been based on the potential carcinogenic hazards of toxaphene. The federal Maximum Contaminant Level Goal (MCLG) for toxaphene is zero, and the MCL is 0.003 mg/L for drinking water (U.S. EPA, 1991; 1999). This MCL is based on the Practical Quantitation Limit (PQL) derived by the U.S. EPA (1991) and reflects the risk of toxaphene ingestion at the 10^{-4} level risk level, applying the same human potency factor as mentioned before.

A Maximum Contaminant Level (MCL) of 0.003 mg/L was established by the California Department of Health Services (DHS) (22 CCR 64444). This value is identical to the U.S. EPA's MCL for toxaphene, and is based on the same considerations. The Agency for Toxic Substances Disease Registry (ATSDR, 1996) developed a long term Minimum Risk Level (MRL) of 0.001 mg/kg-day based on the subchronic study conducted by Chu *et al.* (1986). It declined to derive a chronic duration MRL, stating there was insufficient information to do so.

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