ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR TOXAPHENE

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ADDENDUM FOR TOXAPHENE

Supplement to the 1996 Toxicological Profile for Toxaphene

Background Statement

This addendum for the Toxicological Profile for Toxaphene supplements the profile that was released in 1996.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and other federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1996.

Chapter numbers in this addendum coincide with the Toxicological Profile for Toxaphene (1996). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.8 Cancer

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

2.2.2 Oral Exposure

2.2.2.2 Systemic Effects

Hepatic Effects. In a study described in the Toxicological Profile for Toxaphene (1996),guinea pigs administered a single oral dose of 300mg/kg toxaphene experienced increased liver weight (Chandra and Durairaj 1992). In a subsequent study, the same exposure scenario also resulted in a significant decrease

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

Male CD1 mice (four per group; three at high dose) were administered toxaphene by daily gavage for 7 days at doses of 0, 10, 25, 50, or 100 mg/kg/day (Hedli et al. 1998). The 50- and 100-mg/kg/day groups exhibited significantly increased absolute (43 and 71%, respectively) and relative (48 and 78%, respectively) liver weights compared to controls; liver weights in mice receiving 10 or 25 mg/kg/day were not significantly different from controls. The study authors noted that toxaphene-treated mice exhibited increased levels of total hepatic CYP and cytochrome b_5, although statistical analysis of these levels was not included in the study report.

Increased hepatic microsomal activity (aminopyrene, ethoxyresorufin, and methoxyresorufin) was noted in male and female cynomolgus monkeys (two per sex) administered toxaphene in glycerol/corn oil via gelatin capsule at 1 mg/kg/day for 52 weeks compared to vehicle controls (Bryce et al. 2001). However, there were no histopathological signs of treatment-related effects.

2.2.2.3 Immunological and Lymphoreticular Effects

Bryce and coworkers (Bryce et al. 2001; Tryphonas et al. 2000, 2001) studied the effects of toxaphene on the immune system of cynomolgus monkeys. In a pilot study (Bryce et al. 2001; Tryphonas et al. 2000), groups of four monkeys (two males, two females) were administered toxaphene in glycerol/corn oil via gelatin capsule at 0 or 1 mg/kg/day for 52 weeks. Testing for immune effects began at week 24. Results included reduced anti-sheep red blood cell (SRBC) titres for immunoglobulins (Ig) M and G; increased IgG titres to pneumococcal antigens (but not to the tetanus toxoid antigen); reduced T-helper/inducer,

mean lymphocyte numbers, and mean T-helper/inducer,T-suppressor/cytotoxic cell ratio; and reduced respiratory burst activity in peripheral blood monocytes and granulocytes. None of these responses were statistically significantly different from those of controls; however, the study authors indicated that the responses provide suggestive evidence of an immunosuppressive response. Necropsy revealed increased absolute and relative spleen and thymus weights compared to those of controls; however, statistical analysis was not performed due to the small number of animals per group (Bryce et al. 2001). Histopathological examinations of spleen and thymus revealed no remarkable treatment-related effects.

A second study was performed with larger numbers of cynomolgus monkeys to more rigorously assess the effects of toxaphene on their immune system (Tryphonas et al. 2001). Groups of female cynomolgus monkeys (10 per group) were administered toxaphene in glycerol/corn oil via gelatin capsule at 0, 0.1, 0.4, or 0.8 mg/kg/day for 74 weeks. Groups of male cynomolgus monkeys (five per group) were treated similarly to 0 or 0.8 mg/kg/day of toxaphene. Testing for immune effects was initiated at 33 weeks, at which time toxaphene levels in blood and fat had reached a steady state. Immunization with SRBC was performed at week 44 (primary; males and females) and week 50 (secondary; females only). The female monkeys exposed to 0.8 mg/kg/day exhibited significantly reduced mean primary and secondary anti-SRBC IgM responses (33–48% lower than controls), reduced mean primary (but not secondary) anti-SRBC IgG responses (43–51% lower than controls), and reduced mean CD20+ B-lymphocyte counts (37% lower than controls). Females of the 0.4 mg/kg/day dose level exhibited significantly reduced mean primary and secondary anti-SRBC IgM responses (18–35% lower than controls). Toxaphene-treated males (0.8 mg/kg/day) exhibited significantly reduced mean primary anti-SRBC IgM responses (28–36% lower than controls). There were no other significant treatment-related effects on the immune system of male or female monkeys, including natural killer cell activity, delayed-type hypersensitivity response, lymphoproliferative response of peripheral blood leukocytes to the concanavalin A and pokeweed mitogens, and serum cortisol levels. The study identified a NOAEL of 0.1 mg/kg/day and a LOAEL of 0.4 mg/kg/day for effects on humoral immunity.

2.2.2.4 Neurological Effects

In a study described in the Toxicological Profile for Toxaphene (1996),guinea pigs administered a single oral dose of 300mg/kg toxaphene experienced increased liver weight (Chandra and Durairaj 1992). In a subsequent study, the same exposure scenario also resulted in a significant decrease of brain phospholipid content and a significant increase in brain neutral lipid and cholesterol content (Chandra and Durairaj 1995). Similar effects were observed in other guinea pigs receiving toxaphene by gavage at 5 mg/kg/day for 60 days (Chandra and Durairaj 1995).

2.3 TOXICOKINETICS

2.3.2 Distribution

2.3.2.2 Oral Exposure

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

2.3.3 Metabolism

2.3.3.2 Oral Exposure

Drenth et al. (2000b) noted that toxaphene induced hepatic CYP450 activity in the rat at a single oral dose level of 40 mg/kg, but not at lower dose levels.

Toxaphene has been shown to induce selected CYP450 isozymes both *in vitro* and *in vivo*. Hedli et al. (1998) reported dose-related increased levels of total CYP450 and cytochrome b_5 in hepatic microsomal fractions from male CD1 mice administered toxaphene by daily gavage for 7 days at doses of 10, 25, 50, or 100 mg/kg/day. Toxaphene induced significant increases in immunodetectable levels of CYP2B, but not CYP4A1, as compared to controls.

2.3.3.4 Other exposure

Dehn et al. (2005) observed significantly increased CYP1A and CYP2B activities in human HepC2 cells exposed to toxaphene for 24 hours at high concentrations (1, 5, or 10 mM) or for 48 hours at lower concentrations (0.01–1 mM). The increases in CYP2B were of greater magnitude than those of CYP1A. Dehn et al. (2005) noted that glutathione levels declined when CYP2B activity was significantly elevated, and they significantly increased in the absence of significant CYP450 activation, suggesting that activities of glutathione and CYP450 isozymes may influence one another.

2.3.4 Excretion

In a national survey of human exposure to various substances in southern Canada versus northern Canada, toxaphene was detected at a mean concentration of 67.7 ng/g fat in human milk samples collected between July 1996 and April 1997 from 12 residents of Kewatin, an arctic region of northern Canada (Newsome and Ryan 1999). Mean toxaphene concentrations ranging from 6.03 to 12.1 ng/g fat were detected in human milk samples that had been collected from other regions of Canada at earlier times (Newsome and Ryan 1999).

Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PB) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points. PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile

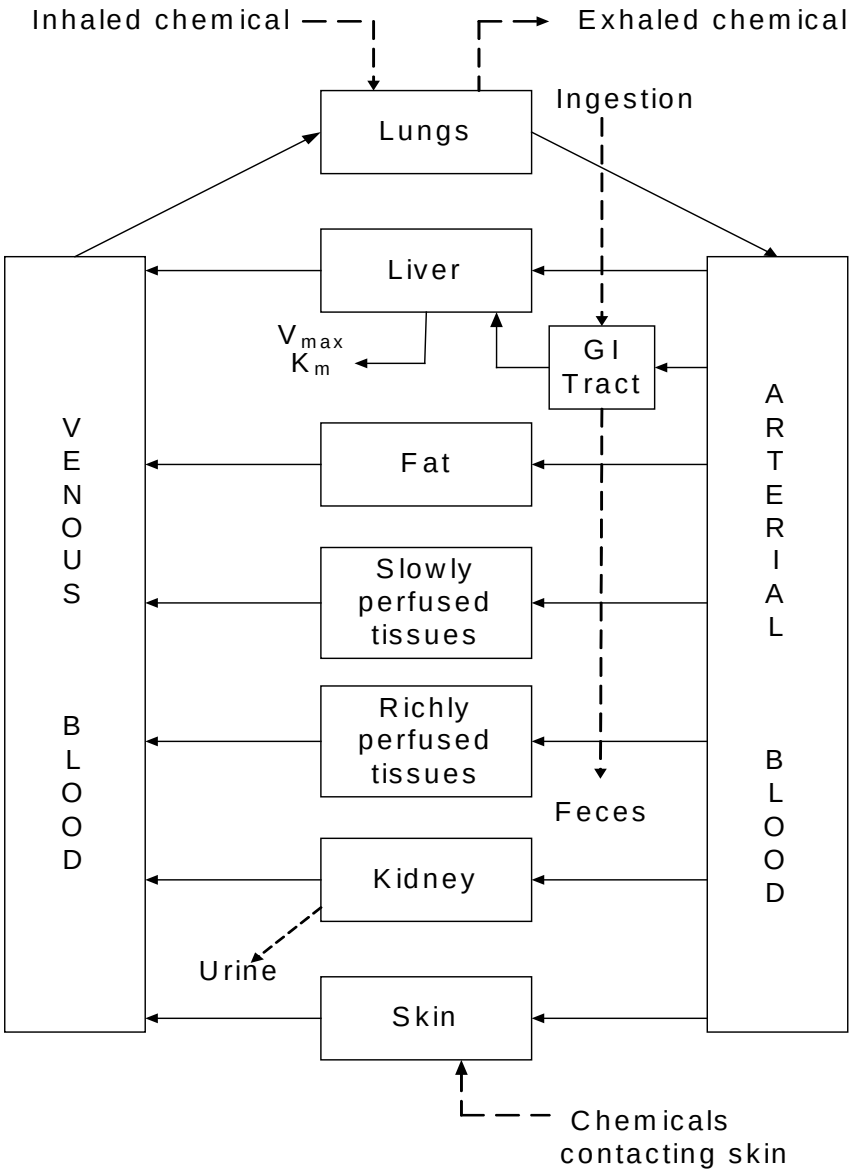
(Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substancespecific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

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

Figure 2-1 shows a conceptualized representation of a PBPK model.

Figure 2-1. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

Source: Adapted from Krishnan and Andersen 1994

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

2.4 MECHANISMS OF ACTION

Hedli et al. (1998) designed a study to test whether toxaphene-induced carcinogenicity might include peroxisomal proliferation or DNA binding. Male CD1 mice were administered toxaphene by gavage for 7 days at doses of 0, 10, 25, 50, or 100 mg/kg/day. The animals were sacrificed 24 hours after the last dose and livers from two mice per group were pooled, and microsomal fractions were prepared. Immunodetectable levels of microsomal protein reacting with specific isozymes of CYP450 were evaluated by Western blot analysis. Hepatic microsomal proteins probed with anti-CYP2B revealed a toxaphene dose-dependent increase in immunodetectable protein levels, suggesting that toxaphene induces CYP2B. Similar analysis probed with anti-CYP4A1 revealed no qualitative effect, suggesting that toxaphene does not induce CYP4A1. The study authors noted that the apparent lack of induction of

CYP4A1, a CYP isozyme that is specifically induced by peroxisomal proliferators, suggests that peroxisomal proliferation may not play a significant role in toxaphene carcinogenicity. Analysis of DNA adducts was performed by use of frozen liver tissue and a modification of DNA ^{32}P-post-labeling, a highly sensitive method of adduct detection. No evidence of DNA-adduct formation was seen in either control or toxaphene-treated mice. The authors suggested that adducts were either not formed under the conditions of this study, were formed but rapidly repaired, or were formed below the limits of detection. The authors further suggested that the hepatocarcinogenicity of toxaphene might involve a nongenotoxic or promotional mechanism.

Toxaphene caused dose-dependent inhibition of gap junctional intercellular communication in normal human breast epithelial cells (Kang et al. 1996). The study authors indicated that this result suggests a possible tumor-promoting potential for toxaphene. Besselink et al. (2000) reported toxaphene-induced dose-dependent inhibition of gap junctional intercellular communication in hepatoma (hepa 1c1c7) cells.

Rought et al. (1999) reported that toxaphene at 10–50 μM reduced retinoblastoma tumor suppressor gene levels in human lymphocytes in a concentration-dependent manner. The study authors suggested that subversion of tumor suppressor genes may compromise controls on cell proliferation and represent a key event in tumorigenic processes.

2.5 RELEVANCE TO PUBLIC HEALTH

In vitro Studies

Endocrine Effects. Results of available assays indicate that toxaphene may be weakly estrogenic. Toxaphene was reported to induce weak estrogenic effects in most assays of human breast estrogen-sensitive MCF7 cells (Bonefeld et al. 1997; Soto et al. 1994, 1995; Stelzer and Chan 1999) and in one

assay of rat uterine leiomyoma-derived cells (Hodges et al. 2000). The results of Graham et al. (2003) indicated that toxaphene may exhibit estrogen-like activity by modulating prolactin mRNA levels in GH_3 pituitary-derived cells. Toxaphene did not induce an estrogenic response in other assays using mouse uterus cells and MCF7 cells (Arcaro et al. 2000; Ramamoorthy et al. 1997) or yeast-based estrogen reporter genes (Ramamoorthy et al. 1997; Rehmann et al. 1999).

Drenth et al. (2000a) reported that technical toxaphene exerted an antiestrogenic effect in stably transfected human T47D.luc breast cancer cells, as noted by inhibition of luciferase activity induced by 17b-estradiol; a maximum inhibition of 45% and an EC_{50} of 0.58 mM were calculated.

Genotoxic Effects. Toxaphene induced the SOS repair system in *Escherichia coli* PQ37, but not in the *umu*C test system of *Salmonella typhimurium* strain TA1535/pSK1002 (Bartoš et al. 2005). Toxaphene was mutagenic to *S. typhimurium* strains TA 97, TA98, TA100, TA102, and TA104 in the presence and absence of S9 metabolic activation; negative results were obtained in a Chinese hamster V79/HGPRT mutagenesis assay (Schrader et al. 1998).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

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

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Burniston et al. (2005) reported toxaphene concentrations ranging from 0.25 to 1.5 ng/L in precipitation samples collected at a location on Lake Ontario from November 1994 through December 1998. The highest concentrations were measured during the spring months.

Bidleman and Leone (2004) investigated volatilization of toxaphene from soil at selected farms in the southern United States by measuring toxaphene concentrations in soil and in air 40 cm above the soil during June 1999 and June 2000. The concentration of total toxaphene ranged over several orders of magnitude, from <3 to 6,500 ng/g dry weight in soil and from <3 to 42 ng/m^3 in air. A log-log plot of total toxaphene concentrations in soil and overlying air showed a significant ($p<0.001$) positive relationship.

Jantunen and Bidleman (2003) measured toxaphene concentrations in parallel air and water samples collected in Lake Superior during August 1996 and May 1997. The reported average toxaphene concentration in the water samples was 918 pg/L; levels were constant across the lake and did not vary between seasons. Atmospheric levels averaged 13 pg/m^3 in May and 28 pg/m^3 in August. Water-air fugacity ratios varied from 1.4 to 2.6 in August and from 1.3 to 4.7 in May, implying volatilization from the lake during all months.

Stapleton et al. (2001) reported an approximate five-fold trophic biomagnification of toxaphene from plankton to fish in assessments of various food web members collected from Grand Traverse Bay in Lake Michigan between April 1997 and September 1998.

5.3.2 Transformation and Degradation

5.3.2.3 Sediment and Soil

Lacayo-Romero et al. (2005) identified a toxaphene-degrading anaerobic bacterium related to *Enterobacter cloacae* strain D1 isolated from aged contaminated soil in Nicaragua.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

James and Hites (2002) reported median air concentrations of 11, 25, 160, and 950 pg toxaphene/m^3 near Sleeping Bear Dunes, Michigan; Bloomington, Indiana; Lubbock, Texas; and Rohwer, Arkansas, respectively, in samples taken between March 2000 and June 2001. Similar analyses between February 2002 and September 2003 found median toxaphene air concentrations of 12, 44, 1,100, and 45 pg/m^3 near Sleeping Bear Dunes, Michigan; Bloomington, Indiana; Rohwer, Arkansas; and Cocodrie, Louisianna, respectively. Toxaphene (chlorobornanes) concentrations between 39 and 483 pg/m^3 were measured in ambient air of Columbia, SC between August 1994 and January 1995 (Bidleman et al. 1998).

5.4.2 Water

Raff and Hites (2004) measured toxaphene levels in suspended sediment at approximately 30 sampling sites along the Mississippi River and six of its major tributaries. Toxaphene levels ranged from 0.4 to 39 ng/g suspended sediment. On the basis of water discharge volumes and suspended sediment concentrations at the sampling sites, the study authors estimated that between 200 and 1,000 kg of toxaphene were released into the Gulf of Mexico from the Mississippi River in 2002.

5.4.3 Sediment and Soil

Toxaphene concentrations up to 2,500 ng/g dry weight were measured in soil samples taken from 32 cotton fields in Georgia and South Carolina in 1999 (Kannan et al. 2003).

5.4.4 Other Environmental Media

Mean toxaphene levels in largemouth bass collected from 5 different areas of the Mobile River basin, Alabama in October 2004 ranged from 13 to 104 ng/g (Hinck et al. 2009).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Toxaphene congeners Parlar 26 and Parlar 50 were detected at median concentrations of 1.97 and 2.36 ng/g fat in adipose tissues of children in Stralsund, Germany (Witt and Niessen 2000). Toxaphene was also detected at levels ranging from 6.03 to 67.7 ng/g fat in human milk samples collected from various regions of Canada (Newsome and Ryan 1999).

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No[b]	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	0.5 mg/m^3 [c]	ACGIH 2010
	STEL	1 mg/m^3 [c]	
	TLV-basis (critical effect)	Central nervous system convulsions; liver damage	
NIOSH	REL (10-hour TWA)	No[d]	NIOSH 2005
	IDLH	200 mg/m^3	
	Potential occupational carcinogen	Yes	
	Target organs	Central nervous	

Table 7-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference
		system, skin	
OSHA	PEL (8-hour TWA) for general industry	100 ppm[d]	OSHA 2009
b. Water			
EPA	Drinking water standards and health advisories		EPA 2006
	1-Day health advisory for a 10-kg child	0.004 mg/L	
	10-Day health advisory for a 10-kg child	0.004 mg/L	
	DWEL	0.01 mg/L	
	Lifetime	No	
	10^{-4} Cancer risk	0.003 mg/L	
	National primary drinking water standards		EPA 2010
	MCL	0.005 mg/L	
	MCLG	0 mg/L	
	Potential health effects from exposure above the MCL	Liver problems; increased risk of cancer	
	Common sources of Tetrachloroethylene in drinking water	Discharge from factories and dry cleaners	

Table 7-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference
	Public health goal	zero	
NATIONAL *(cont.)*			
c. Other			
ACGIH	Carcinogenicity classification	A3[e]	ACGIH 2010
	Biological exposure indices	No	
EPA	Carcinogenicity classification	B2[f]	IRIS 2009
	Oral slope factor	1.1 $(mg/kg\text{-}day)^{-1}$	
	Drinking water unit risk	3.2×10^{-5} $(\mu g/L)^{-1}$	
	Inhalation unit risk	3.2×10^{-4} $(\mu g/m^3)^{-1}$	
	RfC	No	
	RfD	No	
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen[g]	NTP 2005

[a]Group 2A: possibly carcinogenic to humans.

[b]Excluded from guideline value derivation because of determination that toxaphene is unlikely to occur in drinking water.

[c]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids.

[d]Skin designation: indicates the potential for dermal absorption.

[e]A3: confirmed animal carcinogen with unknown relevance to humans.

[f]B2: probable human carcinogen; based on increased incidence of hepatocellular tumors in mice and thyroid tumors in rats and is supported by mutagenicity in Salmonella.

Table 7-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	Information	Reference

[g]Based on sufficient evidence of carcinogenicity in experimental animals.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short term exposure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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