ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR 1,1,2-TRICHLOROETHANE

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ADDENDUM FOR 1,1,2-TRICHLOROETHANE

Supplement to the 1989 Toxicological Profile for 1,1,2-Trichloroethane

Background Statement

This addendum for the Toxicological Profile for 1,1,2-Trichloroethane supplements the profile that was released in 1989.

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 1989. Chapter numbers in this addendum coincide with the Toxicological Profile for 1,1,2-Trichloroethane (1989). 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

Inhalation of 1, 1, 2 trichloroethane (TCA) from indoor sources, for example, paints, adhesives, and cleaning agents is the primary route of exposure for the general population. In humans, 1,1,2 TCA is well absorbed following inhalation, and insignificant amounts may be exhaled in expired air while the remaining absorbed dose is distributed throughout the body. The Fourth National Report on Human Exposure to Environmental Chemicals (NRHEEC) reported the results of a bio-monitoring survey of a sampled population from the general public. The results of that survey showed that up to 95% of the population examined had insignificant levels of 1,1,2 TCA in their blood samples at levels below the instrumentation detection limit (NRHEEC, 2009). Those blood samples were reported in ng/L (nanograms/Liter) or parts per trillion (NRHEEC, 2009).

2.2.1.8 Cancer

Dosemeci et al. (1999) investigated the risks of renal cell carcinoma (RCC) caused by occupational exposures of men and women who performed the same jobs and were exposed to solvents in general, chlorinated aliphatic hydrocarbons (CAHCs), and nine individual CAHCs. They conducted a population-based case-control study of 438 RCC cases (273 men and 165 women) and 687 controls (462 men and 225 women), using *a priori* job exposure matrices (Dosemeci et al.1994). Job exposure matrices were developed by the National Cancer Institute for nine different CAHCs (TCA, 1,1, 2 trichloroethylene (TCE), 1,2 dichloroethane, carbon tetrachloride, chloroform, methyl chloride, methyl chloroform, methylene chloride, and perchloroethylene), for all of the nine CAHCs combined, and for all organic solvents combined for use in different case-control studies (Dosemeci et al. 1999). Information gathered

by trained interviewers from questionnaires that covered demographic and ethnic variables indicated that 34% of male cases and 21% of the female cases were exposed to all organic solvents combined, whereas the estimated exposure prevalence to all of the organic solvents combined for male and female controls was 34% and 11%, respectively. The estimated exposure prevalence for the individual CAHCs ranged from 2% to 24% for the male controls and from 2% to 7% for female controls. These authors found no significant differences in RCC risk from exposure to 1,1,2 TCA, with odds ratios and 95% confidence intervals for males and females of 0.90 (0.5–1.6) and 0.95 (0.2–4.4), respectively (Dosemeci et al. 1999).

2.2.2 Oral Exposure

2.2.2.2 Systemic effects

Hepatic Effects.

Xia and Yu (1992) conducted a series of tests to examine hepatoxicity and its relationship to free radical induction from 1,1,1 TCA and 1,1,2 TCA. During a whole animal experiment, Wistar female rats were fasted for 8 hours, and their diet was restored 4 hours after drug administration. A single gavage exposure to 1,1,1 TCA or 1,1,2 TCA dissolved in arachidic oil was administered at 5 mmol/kg to different groups of rats. Control animals received only arachidic oil at the same dosage as the treated animals. Animals were sacrificed at 6, 12, 24, 36, 48, and 72 hours following treatment. Serum was analyzed for enzyme levels, and isolated perfused livers were assayed for enzyme levels and total non-specific free radical formation. The results for the treated animals revealed a statistically significant increase in enzyme levels of glutamic pyruvic transaminase (GPT), sorbital dehydrogenase (SDH), and glutamate dehydrogenase (GDH) in serum and isolated perfused livers. Furthermore, free radical formation in isolated livers was statistically significantly elevated for 1,1,2 TCA-treated rats compared to the livers of those treated with 1,1,1 TCA. These effects were observed 24 hours post-administration (Xia and Yu 1992). The concomitant increases in enzyme and free radical levels indicate that 1,1,2 TCA-

induced free radicals may play a significant part in the mechanism of action of hepatoxicity due to 1,1,2 TCA metabolism in the liver (Xia and Yu 1992).

2.3 RELEVANCE TO PUBLIC HEALTH

Hepatic Effects.

Different groups of Wistar female rats received 1,1,1 TCA or 1,1,2 TCA by gavage in arachidic oil at 5 mmol/kg; controls received only arachidic oil. Animals were sacrificed at 6, 12, 24, 36, 48, and 72 hours post-administration, and the livers were removed and assayed for enzyme levels and the formation of free radicals. The results for the treated rats revealed a statistically significant increase in enzyme activity in serum and isolated perfused livers-i.e., glutamic pyruvic transaminase (GPT), sorbital dehydrogenase (SDH), and glutamate dehydrogenase (GDH). Furthermore, in isolated livers of rats treated with 1,1,2 TCA, free radicals and serum glutamic pyruvic transaminase (SGPT), soluble glucose dehydrogenase (SGDH), and succinate semialdehyde dehydrogenase (SSDH) formation were statistically significantly elevated in comparison to the livers of rats treated with 1,1,1 TCA and those of control animals. These effects were observed 24 hours post-administration and indicated that formation of free radicals may play a significant part in the mechanism of toxicity in hepatic injury induced from exposure to 1,1,2 TCA (Xia and Yu 1992).

Genotoxic Effects. Tafazoli and Kirch-Volders (1996) exposed human lymphocytes to several concentrations of 1,1,2 TCA in micronucleus and comet assays. An approximately two-fold increase in micronuclei was observed in human lymphocytes exposed to 1,1,2 TCA in the absence, but not the presence, of exogenous metabolic activation. However, this response did not exhibit dose-dependent characteristics (Tafazoli and Kirsch-Volders 1996). In the comet assay, there was a1,1,2 TCA- induced DNA breakage in the presence and absence of exogenous metabolic activation. Statistically significant dose-related increases in micronucleated cells were observed in human lymphoblastoid and MCL-5 cell lines (approximately 3.5- and 4-fold, respectively, compared to controls). Kinetochore staining revealed dose-related increases in kinetochore-positive signals in both cell lines (Doherty et al. 1996). 1,1,2 TCA did not induce micronucleated polychromatic erythrocytes in the bone marrow of male, or female CD-1 mice administered the chemical by single intraperitoneal injection at dose levels up to and including 400 mg/kg (Crebelli et al. 1999). 1,1,2 TCA was not mutagenic in a sex-linked recessive lethal assay of drosophila (Foureman et al. 1994). A weakly positive response was elicited in a mitotic recombination (eye mosaic) assay of 1,1,2 TCA-exposed drosophila, but only at a cytotoxic concentration (Vogel and Nivard 1993). 1,1,2 TCA was not mutagenic to *Escherichia coli* PQ37 strain in the SOS-chromotest (Mersch-Sundermann et al. 1989). Similar exposure of the AHH-1 cell line failed to induce micronuclei (Doherty et al. 1996). Milman et al. (1988) indicated that 1,1,2 TCA (1) was not mutagenic to Salmonella strains TA100 and TA1535 in the presence and absence of metabolic activation; (2) induced DNA repair in hepatocytes from male Osborne Mendel rats (but not male B6C3F1 mice); and (3) induced cell transformation in BALB/c-3T3 cells without exogenous metabolic activation.

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.3 ENVIRONMENTAL FATE

5.3.2 Transformation and Degradation

Degradation products-i,e., chloroethane, 1,2,dichloroethane, and vinyl chloride-were detected in 1,1,2 TCA-amended microcosms constructed from anaerobic wetland sediments from the Aberdeen Proving Ground, Maryland, but no chlorinated daughter products were found in abiotic (killed) 1,1,2 TCA-amended microcosms (Lorah and Voytek 2004).

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to 1,1,2-Trichloroethane

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	10 ppm[b]	ACGIH 2010
	TLV-basis (critical effect)	Central nervous system impairment, liver damage	
NIOSH	REL (10-hour TWA)	10 ppm (45 mg/m^3)[c]	NIOSH 2005
	IDLH	100 ppm	
	Potential occupational carcinogen	Yes	
	Target organs	Eyes, respiratory system, central nervous system, liver, kidneys	
OSHA	PEL (8-hour TWA) for general industry	10 ppm (45 mg/m^3)[c]	OSHA 2009

Table 7-1. Regulations and Guidelines Applicable to 1,1,2-Trichloroethane

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Drinking water standards and health advisories		EPA 2009a
	1-day health advisory for a 10-kg child	0.6 mg/L	
	10-day health advisory for a 10-kg child	0.4 mg/L	
	RfD	0.004 mg/kg/day	
	DWEL	0.1 mg/L	
	Lifetime	0.003 mg/L	
	10^{-4} Cancer risk	0.06 mg/L	
	National primary drinking water standards		EPA 2009b
	MCL	0.005 mg/L	
	MCLG	0.003 mg/L	
	Potential health effects from exposure above the MCL	Liver, kidney, or immune system problems	
	Common sources of 1,1,2-trichloroethane in drinking water	Discharge from industrial chemical factories	
	Public health goal	0.003 mg/L	
c. Other			
ACGIH	Carcinogenicity classification	A3[d]	ACGIH 2010
	Biological exposure indices	No	
EPA	Carcinogenicity classification	C[e]	IRIS 2009

Table 7-1. Regulations and Guidelines Applicable to 1,1,2-Trichloroethane

Agency	Description	Information	Reference
	RfC	No	
	RfD	4.0×10^{-3} mg/kg/day	
NTP	Carcinogenicity classification	No	NTP 2005

[a]Group 3: not classifiable as to carcinogenicity to humans.
[b]Skin: 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.
[c]Skin designation
[d]A3: confirmed animal carcinogen with unknown relevance to humans.
[e]Possible human carcinogen

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; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

8. REFERENCES

ACGIH. 2010. 2010 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 58, 73–74.

Agency for Toxic Substances and Disease Registry. 1989. Toxicological Profile for 1,1,2-Trichloroethane. Atlanta: U.S. Department of Health and Human Services.

Crebelli R, et al. 1999. Evaluation of 10 aliphatic halogenated hydrocarbons in the mouse bone marrow micronucleus test. Mutagenesis 14(2):207–215. http://mutage.oxfordjournals.org/cgi/content/abstract/14/2/207.

Doherty AT, , et al. 1996. An investigation into the activation and deactivation of chlorinated hydrocarbons to genotoxins in metabolically competent human cells. Mutagenesis 11(3):247–274. http://mutage.oxfordjournals.org/cgi/content/abstract/11/3/247.

Dosemeci M., et al. 1994. Effects of three features of a job exposure matrix on risk estimates. Epidemiology 5:124–127.

Dosemeci M,et al.. 1999. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med 36(1):54–59. http://www.ncbi.nlm.nih.gov/pubmed/10361587.

EPA. 2009b. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. Office of Ground Water and Drinking Water. EPA816F09004. http://www.epa.gov/safewater/consumer/pdf/mcl.pdf. August 7, 2009.

EPA. 2009a. 2009 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. Office of Water. EPA822-R-09-011. http://www.epa.gov/waterscience/criteria/drinking/dwstandards2009.pdf. May 19, 2010.

Foureman Pet al. 1994. Chemical mutagenesis testing in Drosophila. IX. Results of 50 coded compounds tested for the National Toxicology Program. Environ Mol Mutagen 23(1):51–63. http://www.ncbi.nlm.nih.gov/pubmed/8125083.

Fourth National Report on Humans Exposure to Environmental Chemicals. Centers for Disease Control and Prevention. 2009. www.cdc.gov-exposure report-pdf-FourthReport.pdf.

IARC. 2009. Agents reviewed by the IARC Monographs. Volumes 1–100A. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/ListagentsCASnos.pdf. May 19, 2009.

IRIS. 2009. 1,1,2-Trichloroethane. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/ncea/iris/subst/0198.htm. August 5, 2009.

Lorah MM, and Voytek MA. 2004. Degradation of 1,1,2,2-tetrachloroethane and accumulation of vinyl chloride in wetland sediment microcosms and in situ porewater: Biogeochemical controls and

associations with microbial communities. J Contam Hydrol 70(1-2):117–145. http://www.ncbi.nlm.nih.gov/pubmed/15068871.

Mersch-Sundermannet al.. 1989. Examination of mutagenicity of organic microcontaminations of the environment: Communication IV. The mutagenicity of halogenated aliphatic hydrocarbons with the SOS-Chromotest. Zentralbl Hyg Umweltmed 189(3):266–271.

Milman HA, , et al. 1988. Rat liver foci and in vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Ann N Y Acad Sci 534:521–530. http://www.ncbi.nlm.nih.gov/pubmed/3389679.

Mirsalis JC, , et al. 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: Testing of 24 compounds. Environ Mol Mutagen 14(3):155–164. http://www.ncbi.nlm.nih.gov/pubmed/2792091.

NIOSH. 2005. 1,1,2-Trichloroethane. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health. Centers for Disease Control and Prevention. NIOSH Publication 2005-149. http://www.cdc.gov/niosh/npg/npgd0628.html. August 5, 2009.

NTP. 2005. Report on carcinogens, eleventh edition. Research Triangle Park, NC: U.S. Department of Health and Human Services. Public Health Service. National Toxicology Program. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. July 31, 2008.

OSHA. 2009. Table Z-1 limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000 Subpart Z. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992. May 19, 2009.

Tafazoli M, and Kirsch-Volders M. 1996. In vitro mutagenicity and genotoxicity study of 1,2-dichloroethylene, 1,1,2-trichloroethane, 1,3-dichloropropane, 1,2,3-trichloropropane and 1,1,3-trichloropropene, using the micronucleus test and the alkaline single cell gel electrophoresis technique (comet assay) in human lymphocytes. Mutat Res 371(3-4):185–202. http://www.ncbi.nlm.nih.gov/pubmed/9008720.

Vogel EW,and Nivard MJ. 1993. Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. Mutagenesis 8(1):57–81. http://www.ncbi.nlm.nih.gov/pubmed/8450769.

WHO. 2006. Annex 4—Chemical summary tables. In: Guidelines for drinking-water quality, third edition, incorporating first and second addenda. Geneva, Switzerland: World Health Organization, 488–492. http://www.who.int/water_sanitation_health/dwq/GDWAN4rev1and2.pdf. May 19, 2009.

WHO. 2000. Summary of the guidelines. WHO air quality guidelines for Europe. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/document/aiq/3summary.pdf. May 19, 2009.

Xia L, and Yu T. 1992. Study of the relationship between the hepatotoxicity and free radical induced by 1,1,2-trichloroethane and 1,1,1-trichloroethane in rat. Biomed Environ Sci 5(4):303–313. http://www.ncbi.nlm.nih.gov/pubmed/1489524.