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SUBJECT: UPDATE OF THE FREON 113 PUBLIC HEALTH GOAL

Under the Calderon-Sher California Safe Drinking Water Act of 1996, the Office of Environmental Health Hazard Assessment (OEHHA) develops public health goals (PHGs) for regulated chemicals in drinking water and reviews and updates the risk assessments every five years (Health and Safety Code Section 116365(e)(1)) or when possible. This memorandum represents an update of the literature review and evaluation for the existing PHG of 4 ppm for 1,1,2-trichloro-1,2,2-fluoroethane (Freon 113, CFC-113 or FC-113) (OEHHA, 1997). Our re-evaluation supports the previous PHG derivation in 1997, and no new data would justify a significant change to the document.

Summary of Review

OEHHA has reassessed the available toxicity data on Freon 113 to determine whether significant new data have become available since the current public health goal (PHG) was developed for this chemical in 1997. OEHHA also determined whether changes in

risk assessment methods since the publication of the PHG would justify a change in the health-protective value.

Freon 113 belongs to a group of chemicals called chlorofluorocarbon chemicals (CFCs) containing carbon, fluorine, and chlorine atoms. The most common commercial CFCs are marketed under the trade name Freon. CFC-113 was primarily used as a solvent, refrigerant, and aerosol propellant. The U.S. ceased production and importation of this chemical in 1996 due to its ability to cause significant stratospheric ozone depletion and contribution to global warming. Use of existing stocks was permitted.

Developing countries are still in the process of replacing CFCs with newer, chlorine-free analogues that will not affect atmospheric ozone. Because of their continued use in other countries, including Mexico, some limited exposure to banned CFCs may be on-going (U.S. EPA, 2006). The Montreal Protocol allowed continued production and importation of CFCs in developing countries until 2010. CFC-113 emissions were found in a semi-conductor and electronics industrial park in Taiwan in 2001 (Chang *et al.,* 2001) and in hospital effluents discharged into urban drainage networks in France (Boillot *et al*., 2008). However, the available measurements of ambient atmospheric concentrations of CFC-113 reveal low and declining levels, appearing to indicate that emissions have virtually ceased (Qin, 2007; Gentner *et al*., 2010; Zhang *et al*., 2010).

Freon 113 is an essential component used in some viral purification methods (Mendez *et al*., 2000) and is still used in hydrology as a transient tracer (Horneman *et al*., 2008). Occasionally, ozone-depleting Freons (generally FC-12) are smuggled into the U.S. and sold on the black market (U.S. EPA, 2010). Liquid Freon (Freons 11, 12, and 113) is used as a solvent in the clandestine manufacture of methamphetamine, so there is concern about inadvertent exposure to police officers, as well as children and the elderly who occupy dwellings where illegal drug labs have been in operation (OEHHA, 2003). Chemicals used in the manufacture of methamphetamine may be left on the premises, illegally dumped in backyards, open spaces, ditches, or municipal sewer systems. Freon 113 is very resistant to chemical and biological degradation and is likely to be a persistent contaminant if it reaches groundwater.

In 1997, OEHHA developed a Public Health Goal (PHG) of 4 mg/L (4 ppm) for CFC-113 in drinking water. The PHG is based on a 2-year chronic study in rats, and the lowest concentration tested, 15,400 mg/m^3 (2,000 ppm), was considered by the researchers to be a no observed adverse effect level (NOAEL) (Du Pont, 1985, unpublished data). OEHHA considered it to be a lowest observed effect level (LOAEL, corresponding to 1,287 mg/kg-day) because of increased liver weights in all exposure groups. Since publication of the PHG, several new case reports and epidemiological studies in the literature have reported adverse effects from exposure to Freons. Most of these studies do not entail exposure specifically to CFC-113. However, there is one study (Neghab *et al*., 1997) that does.

Neghab *et al.* (1997) examined the hepatic effects of occupational exposure to CFC-113 in a small group of steel workers in Australia who had shown some evidence of a slight increase (95-127 U/L) in the activity of serum alkaline phosphatase (ALP) (normal range 30-95 U/L). An increase in serum ALP has been considered to be a mild chronic solvent-induced liver effect (Elofsson *et al*., 1980; Lundberg *et al*., 1994; Svensson *et al*., 1992). In this study, the exposed group (*n* = 6 males) comprised individuals who had exposure to CFC-113 from use of this solvent as a degreaser during a cleaning procedure. Duration of exposure was 2.5 (± 0.6) years. A control group (*n* = 11 males) was composed of non-solvent-exposed office workers in the same company. Standard liver function tests and serum bile acids (SBA) were measured before and after exposure to CFC-113 and simultaneously in the control group by enzymatic methods and HPLC, respectively. Measurement of SBA levels is described as a sensitive indicator of liver function, although it is not a common diagnostic test (Jones *et al*., 1981; Neghab and Stacey, 1997).

Neghab *et al*. (1997) measured CFC-113 concentrations in the breathing zone using a charcoal tube personal sampler which was worn by CFC-113 exposed workers for the whole duration of exposure. The mean 8-hr time-weighted average CFC-113 exposure level was 68.2 ppm (range 45-118 ppm). A significant increase in the concentration of total SBA, some of the subgroups of SBA, and a few of the individual SBAs was reported. No other indications of adverse liver effects, as measured by conventional parameters of hepatobiliary function, were detected. Before exposure to CFC-113, subjects had SBA levels within the normal range, comparable to the control values, and elevated SBA in exposed subjects returned to normal 2 weeks after cessation of exposure. A mechanistic study in rats by the same laboratory indicated that CFC-113-induced elevation of SBA may be the result of a reversible inhibition of bile transport by the parent compound at the basolateral domain of the hepatocyte plasma membrane (Neghab *et al.,* 1996).

The lowest-observed-adverse-effect-level (LOAEL) for hepatobiliary dysfunction in the study of Neghab *et al*. (1997) would be 68 ppm (523 mg/m^3) CFC-113 in air. The dose (in mg/kg-day) can be calculated using the conversion factors of 8-hr human breathing volume = 10 m^3/day, exposure for 5 days/7 days, absorption = 0.5 (a common default for volatile solvents), body weight (BW) = 70 kg, as follows:

$$\frac{523\ \text{mg/m}^3 \times 10\ \text{m}^3\text{/day} \times 5\ \text{day} \times 0.5}{70\ \text{kg} \times 7\ \text{day}} = 26.7\ \text{mg/kg-day}$$

A public health –protective concentration for CFC-113 in drinking water (in mg/L) could be calculated using the general equation for non-carcinogenic endpoints:

$$C = \frac{\text{LOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{Leq/day}} = \text{mg/L}$$

where

LOAEL	=	lowest-observed-adverse-effect-level (in mg/kg-day);
BW	=	adult body weight (70 kg);
RSC	=	relative source contribution (generally in the range of 0.2-0.8);
UF	=	uncertainty factor (3-fold for LOAEL to NOAEL conversion, 10-fold for human variability);
Leq/day	=	equivalent volume of water consumed, considering direct water consumption plus inhalation and dermal absorption of the volatile chemical in normal household tap water uses.

For this calculation, the same body weight is used as in the original PHG calculation. The maximum RSC of 0.8 is used because background exposures are negligible, so if any drinking water exposure occurs, it is likely to be the only exposure. A factor of 3 is used for extrapolation of the "weak" LOAEL (a reversible biochemical change, without demonstration of frank toxicity) to a NOAEL, and the standard UF of 10 for human variability. The equivalent water consumption value corresponds to the mean value from the multi-route exposure calculation (McKone, 1987) rather than the upper confidence limit value of 30.2 Leq/day used in 1997. We had subsequently decided that the upper limit values were too uncertain to be justifiable, and did not use them after 1997.

The health-protective concentration would then be calculated as follows:

$$C = \frac{26.7 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.8}{30 \times 8.02 \text{ Leq/day}} = 6.2 \text{ mg/L} = 6.2 \text{ ppm}$$

This value is slightly higher than the 1997 PHG of 4 ppm, based on a different study (in humans)**,** with several different parameters. Since the development of the CFC-113 PHG in 1997, OEHHA has also adopted new drinking water consumption default values for use in OEHHA risk assessments, which are intended to provide more protection for sensitive and highly-exposed populations. However, these new values do not include consideration of exposure by the inhalation rate in normal household uses for volatile chemicals in drinking water. For this review OEHHA has chosen to use the combined route approach, with the mean value from McKone (1987).

It is of note that the U.S. EPA (1996) oral reference dose (RfD) of 30 mg/kg-day is based on a human epidemiologic study in workers exposed to CFC-113 (Imbus and Adkins, 1972). The NOAEL of 5,358 mg/m^3 in this study was converted to a daily dose of 273 mg/kg-day and divided by an uncertainty factor of 10 to derive the RfD. OEHHA (1997) used the LOAEL identified in the Du Pont (1985) animal study mentioned above

(1,287 mg/kg-day) and divided by an uncertainty factor of 300, which would yield a value of 4.3 mg/kg-day.

The health-protective dose that can be calculated from the Neghab *et al*. (1997) study is much lower (26.7 mg/kg-day / 30 = 0.9 mg/kg-day). The small study population provides only moderate confidence in the estimate. The resulting health-protective drinking water concentration (6.2 ppm) is about the same as the 1997 PHG (4 ppm). The significant increase in SBAs in the Neghab *et al.* (1997) study is an important finding since maintenance of bile acid homeostasis is essential. Most bile acids are cytotoxic; when their concentrations reach abnormally high levels, they can cause liver injury (Hofmann, 1999) (*e.g.,* cholestasis). Elevated SBAs, in concert with elevated ALP levels, which were also seen in the same workers, can be an indication of bile duct damage (*i.e.,* cholangiodestructive cholestasis) (Jaeschle, 2008). Increased bile acid levels can also trigger compensatory mechanisms, which may limit the injury potential of cholestasis (Zollner *et al.,* 2006). Susceptibility to subsequent inflammatory insults may be enhanced by repeated exposures to a potential hepatotoxin (occupational, in this case). The existing PHG of 4 ppm is protective of this effect on SBAs.

Individuals with pre-existing diseases of the central nervous or cardiovascular system may have increased susceptibility to the effects of Freons (OSHA, 1998; DuPont, 1996). Persons exposed to sympathomimetic amines, *e.g*., bronchodilators and nasal decongestants, might be at increased risk for the cardiotoxic effects of Freons (Reprotext, 2003). Exposure to CFC-113 has been linked to ventricular arrhythmias and cardiac sudden death when inhaled in excessive concentrations (Kaufman *et al*., 1994). However, because the importation/production of CFC-113 has been banned in the U.S. since 1996, and the exposure potential is very low as shown in recent monitoring data, no additional uncertainty factor to allow for sensitive subpopulations is considered necessary.

The California MCL for CFC-113 is 1.2 mg/L (ppm), so no regulatory impact would be expected from revising the PHG based on the Neghab (1997) study and incorporating a different drinking water consumption value. Accordingly, no revision of the existing PHG value is recommended at this time.

References

Boillot C, Bazin C *et al.* (2008). Daily physicochemical, microbiological and ecotoxicological fluctuations of a hospital effluent according to technical and care activities. Sci Total Environ 403(1-3):113-29.

Chang CC, Lo GG, Tsai CH, Wang JL (2001). Concentration variability of halocarbons over an electronics industrial park and its implication in compliance with the Montreal protocol. Environ Sci Tech 35(16):3273-9.

Du Pont (1985). Two year inhalation toxicity study with 1,1,2-trichloro-1,2,2-trifluoroethane in rats. Vol 1. Medical Research Project Number 3683-001; Haskell Laboratory Report Number 488-84. Unpublished report by E.I. Du Pont de Nemours and Co., issued March 5, 1985. Du Pont toxicity studies with 1,1,2-trichloro-1,2,2-trifluoroethane. Product Information Bulletin No. S-24, Wilmington, Delaware.

DuPont (1996). Material Safety Data sheet for “Freon” 113 refrigerant. Wilmington, DE.

Elofsson SA, Gamberale F *et al*. (1980). Exposure to organic solvents: a cross-sectional epidemiological investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. Scand J Work Environ Health 6:239-73.

Gentner DR, Miller AM, Goldstein AH (2010). Seasonal variability in anthropogenic halocarbon emissions. Environ Sci Technol 44(14):5377-82.

Hofmann AF (1999). The continuing importance of bile acids in liver and intestinal disease. Arch Int Med 159:2647-58.

Horneman A, Stute M, Schlosser P *et al.* (2008). Degradation rates of CFC-11, CFC-12 and CFC-113 in anoxic shallow aquifers of Araihazar, Bangladesh. J Contam Hydrol 97(1-2):27-41.

Imbus HR, Adkins C (1972). Physical examinations of workers exposed to trichlorotrifluoroethane. Arch Environ Health 24(4):257-61.

Jaeschke H (2008). *In:* Casarett and Doull’s Toxicology: The Basic Science of Poisons (7th ed.). Chapter 13, Toxic Responses of the Liver. Klaassen, CD, ed. McGraw-Hill.

Jones MB, Weinstock S, Koretz RL, Lewin KJ, Higgins J, Gitnick GL (1981). Clinical value of serum bile acid levels in chronic hepatitis. Digest Dis Sci 26(11):978-83.

Kaufman JD, Silverstein MA, Moure-Eraso R (1994). Atrial fibrillation and sudden death related to occupational solvent exposure. Am J Ind Med 25(5):731-5.

Lundberg I, Nise G *et al.* (1994). Liver function tests and urinary albumin in house painters with previous heavy exposure to organic solvents. Occup Environ Med 51:347-53.

McKone TE (1987). Human exposure to volatile organic compounds in household tap water: the indoor inhalation pathway. Environ Sci Technol 21:1194-201.

Mendez II, Hermann LL, Hazelton PR, Coombs KM (2000). A comparative analysis of Freon substitutes in the purification of reovirus and calcivirus. J Virol Methods 90(1):59-67.

Neghab M, Hamdan H, Edwards RJ *et al*. (1996). Inhibition by trichloroethylene and 1,1,2-trichloro-1,2,2,-trifluoroethane of taurocholate uptake into basolateral rat liver plasma membrane vesicles. Toxicol In Vitro 10:665-79.

Neghab M, Qu Shuxin, Bai Cheng, Caples J, Stacey N (1997). Raised concentrations of serum bile acids following occupational exposure to halogenated solvents, 1,1,2-trichloro-1,2,2-trifluoroethane and trichloroethylene. Int Arch Occup Environ Health 70:187-94.

Neghab M, Stacey NH (1997). Toluene-induced elevation of serum bile acids: relationship to bile acid transport. J Toxicol Environ Health 52(3):249-68.

OEHHA (1997). Public Health Goal for 1,1,2-trichloro-1,2,2-trifluoroethane in drinking water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

OEHHA (2003). Technical Support Document: Toxicology Clandestine Drug Labs/Methamphetamine. Vol 1, Number 11. Freon. C Salocks and K Black Kaley. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. Accessed at: www.oehha.ca.gov/public_info/pdf/TSD%20Freon%20Meth%20Labs%2010'8'03.pdf.

OSHA (1998). Sampling and analytical method for 1,1,-dichloro-1-fluoroethane (Freon 141b), 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113). U.S. Occupational Safety and Health Administration. Accessed at: http://www.osha.gov/dts/sltc/methods/organic/org113/org113.html.

Qin D (2007). Decline in the concentrations of chlorofluorocarbons (CFC-11, CFC-12 and CFC-113) in an urban area of Beijing, China. Atmos Environ 41:8424-30.

Reprotext (2003). 1,1-Dichloro-1-fluoroethane. In: Hurlburt KM (Ed.): TOMES System. Micromedex. Greenwood Village, CO.

Stopps GJ, McLaughlin M (1967). Psychophysiological testing of human subjects exposed to solvent vapors. Amer Ind Hyg Assoc J 28:43-50.

Svensson BG, Nise G, Erfurth EM *et al*. (1992). Neuroendocrine effects in printing workers exposed to toluene. Br J Ind Med 49:402-8.

U.S. EPA (1996). 1,1,2-Trichloro-1,2,2-trifluoroethane (CFC-113) (CASRN 76-13-1). Integrated Risk Information System (IRIS), U.S. Environmental Protection Agency. Accessed at: http://www.epa.gov/ncea/iris/subst/0123.htm.

U.S. EPA (2006). News Release – Office of the United States Attorney, Southern District of California, December 7, 2006. San Diego, California. Accessed at: www.epa.gov/compliance/resources/cases/criminal/highlights/2007/alghazouli-07.pdf.

U.S. EPA (2010). Texas Man Arrested for Smuggling Freon into U.S. Arrest Underscores Federal Crackdown on Black Market in Ozone-Depleting Chemicals. http://yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/364cb762268e035d8525679a0069999c?OpenDocument.

Zhang F, Zhou L, Yao B, Vollmer MK, Greally BR *et al*. (2010). Analysis of 3-year observations of CFC-11, CFC-12 and CFC-113 from a semi-rural site in China. Atmos Environ 44:4454-62.

Zollner G, Marschall H, Wagner M, Trauner M (2006). Role of nuclear receptors in the adaptive response to bile acids and cholestasis: pathogenetic and therapeutic considerations. Mol Pharm 3 (3):231-51.