M E M O R A N D U M

TO: Val F. Siebal
Chief Deputy Director

VIA: George V. Alexeeff, Ph.D.
Deputy Director for Scientific Affairs

VIA: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

VIA: Robert A. Howd, Ph.D., Chief
Water Toxicology Unit
Pesticide and Environmental Toxicology Section

FROM: Lubow Jowa, Ph.D.
Staff Toxicologist
Pesticide and Environmental Toxicology Section

DATE: Sept 16, 2005

SUBJECT: Update of the Public Health Goal for 1,2 Dichloroethane

---

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). This memorandum represents an update of the literature review and reevaluation of the existing PHG for 1,2-dichloroethane, also known as ethylene dichloride (OEHHA, 1999). Our re-evaluation supports the previous PHG derivation in 1999. We conclude that the PHG for 1,2-dichloroethane should remain at 0.4 ppb.

Summary of Review

We have surveyed the scientific literature for recently published research studies to determine if there are new toxicity studies on 1,2-dichloroethane that would warrant revising the PHG of 0.4 ppb or making substantive changes to the PHG support document. We also searched for new risk assessments of 1,2-dichloroethane since the publication of the PHG document in 1999, including U.S. EPA reviews, and new risk assessment methods that might be applied to evaluation of 1,2-dichloroethane.

No new studies were found that affect the choice of the critical study used as the basis for the existing PHG value. Risk assessment methods for consideration of the effect of early-life exposures on carcinogenic potency are under consideration, but OEHHA guidelines have not yet been developed. New data were found that can provide some further insight on the toxic effects of 1,2-dichloroethane, but nothing was found that sheds any further degree of certainty upon the carcinogenicity status of 1,2-dichloroethane. Although there is no basis for proposing a change to the PHG, a few recent studies that provide additional information on the toxicity of 1,2-dichloroethane are described here.

Literature Review

General toxicity

In two related studies, Cottalasso *et al.* (2000, 2002) assess the acute response of rat liver to 1, 2-dichloroethane from the perspective of production of dolichol, one of the lipoglycoproteins necessary for hepatic cell membrane integrity. Dolichol content in rat hepatocytes was significantly ($p < 0.1$) depleted in rats treated with 628 mg/kg of 1,2-dichloroethane. Pretreatment with vitamin E prevented this depletion (Cottalasso *et al.*, 2002). Furthermore, pretreatment with ethanol resulted in enhanced depletion of dolicol upon treatment with 1,2-dichloroethane when compared with 1,2-dichloroethane treatment alone.

Effects of orally administered 1,2-dichloroethane on rat lung were studied with biochemical and histological evaluations. Eighty rats were given a single gavage dose of 136 mg/kg in oleum solution and bronchioalveolar lavage fluid and lung homogenates were examined on posttreatment days 1, 5, 15 and 30. The most significant effects were seen on day one, with transitory elevations of lactate dehydrogenase, alkaline phosphatase, catalase, superoxide dismutase and glutathione peroxidase. Histologically, the lungs showed signs of congestion, edema, and interstitial inflammatory changes. The authors concluded that a single large dose of 1,2-dichloroethane might elicit mild to moderate, albeit transitory changes in the lungs of exposed animals.

Mutagenicity studies

1,2-Dichloroethane was used to demonstrate a new assay to detect mutants of the gene for haloalkane dehalogenase found in *Xanthobacter autotrophicus* GJ10 (Chang *et al.*, 1999). Also, among ten other aliphatic halogenated hydrocarbons, 1,2-dichloroethane was evaluated in the mouse bone marrow micronucleus test for its potential genotoxicity *in vivo* (Crebelli *et al.*, 1999); all these results were negative.

Human population studies

In Taiwan, investigators (Cheng *et al.*, 1999, 2000) monitored a group of workers involved in vinyl chloride manufacture for health effects due to exposure to 1,2-dichloroethane and vinyl chloride at occupational exposure limits. In the first study, Cheng *et al.* (1999) evaluated the liver function of workers exposed to both vinyl chloride and its 1,2-dichloroethane precursor. A total of 251 subjects were evaluated and classified as low, moderate and high exposure groups based on a fraction of the PEL (Permissible Exposure Levels as defined by U.S. Occupational Safety and Health Administration). No control group was identified. The investigators reported that a dose-response relationship was observed with increasing levels of enzymatic indicators of liver damage in subjects identified as exposed to higher levels of both compounds. However, the dose-response was apparent only for serum alanine aminotransferase, and not clearly with aspartate amino transferase or γ-glutamyl transferase. In the second study (Chang *et al.*, 2000), 51 workers exposed to vinyl chloride and/or 1,2-dichloroethane were monitored for sister chromatid exchange frequency, compared with 21 non-exposed workers. Exposure to 1,2-dichloroethane at estimated levels of 1 ppm was associated with elevation of sister chromatid exchange frequency compared to the workers with no known exposure or with vinyl chloride-only exposed workers.

Two studies were found that evaluated workers exposed to 1,2-dichloroethane during cleanup of production facilities utilizing this compound. In one study, summarized by abstract, Ruffalo *et al.* (2000) reported that a small number of workers (17) were exposed to chronic, sublethal levels (not specified) of 1,2-dichloroethane. Four from this population were identified as more heavily exposed than the others. The overall population was tested for sensory and perceptual skills, intellectual functioning and memory capability. In this intragroup comparison, no differences were found in sensory and perceptual skills; however, the more heavily exposed group was more impaired than the regular group in intellectual and memory functioning.

In the other study, Bowler *et al.* (2003) studied about 221 workers exposed to 1,2-dichloroethane from a population of hazardous waste cleanup workers assigned to clean up 1,2-dichloroethane spills. They reported that these workers showed impairment when tested for neuropsychological functioning in areas of processing speed, attention, cognitive flexibility, motor coordination and speed, verbal memory, verbal fluency, and visuo-spatial abilities when compared against averages for their ethnic populations. Workers also exhibited disturbed mood and impaired vision. It appears that the Ruffalo *et al.* (2000) study is related to Bowler *et al.* (2003) in that they both encompass the same overall population of affected workers: part of the group was assigned to be evaluated by Ruffalo *et al.* (2000), and the rest to Bowler *et al.* (2003). In either case, it is difficult to determine the extent to which these workers were exposed to 1,2-dichloroethane, both in duration and dose, or if they had exposures to other compounds as well. It is clear that this was a self-selected group of workers who had hired these neuropsychologists for litigation against their former employers.

Overall, the human exposure studies suggest that harmful effects may be attributable to 1,2-dichloroethane exposure; however, they do not provide information that can be used for quantitative risk assessment.

Review of the Existing PHG Value

As stated in the 1999 support document for the 1,2-dichloroethane PHG, the critical concern is carcinogenicity, and the most important issue for the risk assessment is deriving the carcinogenic potency factor. At this time, no studies exist which would either change the carcinogenic determination or provide a basis for a better potency factor. The basis of the current federal MCL of 5 ppb (U.S. EPA, 2004) is an increased incidence of male mouse hepatocellular carcinomas from the NCI rat and mouse studies (1978). The basis of the OEHHA PHG was the same NCI (1978) studies, but we selected the cancer potency from the male rat hemangiosarcoma data for deriving the PHG, because this appeared to be a more sensitive indicator of tumorigenicity. Our present review confirms this choice.

After finalization of the new U.S. EPA cancer guidelines (U.S. EPA, 2005a) and the supplemental guidance for early-life exposures (U.S. EPA, 2005b), OEHHA is currently reviewing its procedures for assessing cancer potency, especially to ensure adequate protection of sensitive subpopulations. The U.S. EPA has proposed increasing cancer potency values that are based on animal studies which did not incorporate early-life exposures by specific amounts to allow for infant and child exposures to the chemicals (U.S. EPA, 2005b). This requires some judgment concerning how to apply the principles to specific types of chemicals in drinking water. Discussion of these factors is presently underway at OEHHA. In the meantime, in the absence of updated procedures, OEHHA concludes that the PHG of 0.4 ppb is adequate to protect sensitive subpopulations, including pregnant women and their fetuses, infants, and the elderly.

From the perspective of noncancer risk determinations, no new studies exist which would be more appropriate to replace the one selected for the noncancer assessment in the existing PHG.

Other Positions on 1,2-Dichloroethane:

The current U.S. EPA MCL of 5 ppb is based on potential carcinogenicity (U.S. EPA, 2004a,b). U.S. EPA has also stated that it is continuing to review the risk assessment for 1,2-dichloroethane for the National Primary Drinking Water Regulations (U.S. EPA, 2003). U.S. EPA has not yet completed any risk assessments for drinking water contaminants which

incorporate the recommendations in its new supplemental guidance for early-life exposures (U.S. EPA, 2005).

The California Department of Health Services (DHS) MCL for 1,2-dichloroethane is 0.5 ppb. DHS reported five exceedances of the MCL for 1,2-dichloroethane in municipal water sources in 2001 and 2002, and two exceedances of the MCL in 2003 (DHS, 2004). Since the MCL value for 1,2-dichloroethane and the PHG are rather close, DHS has concluded that no further review of the MCL is needed (DHS, 2005).

References

Bowler RM, Gysens S, Hartley C (2003). Neuropsychological effects of ethylene dichloride exposure. Neurotoxicology 24:553-562.

Cottalasso D, Bellocchio A, Norese R, Domenicotti C, Pronzato MA, Fontana L, Nanni G (2000). Effects of vitamin E on dolicol content of rats acutely treated with 1,2-dichloroethane. Toxicology 143:283-292.

Cottalasso D, Domenicotti C, Traverso N, Pronzato M, Nanni G (2002). Influence of chronic ethanol consumption on toxic effects of 1,2-dichloroethane: glycolipoprotein retention and impairment of dolichol concentration in rat liver microsomes and Golgi apparatus. Toxicology 178(3):229-240.

Chang CH, Schindler JF, Unkefer CJ, Vanderberg LA, Rainard JR, Terwelliger TC (1999). *In vivo* screening of haloalkane dehalogenase mutants. Biorg Med Chem 7:2175-2181.

Cheng TJ, Huang ML, You NC, Du CL, Chau TT (1999). Abnormal liver function in workers exposed to low levels of ethylene dichloride and vinyl chloride monomer. J Occup Environ Med 41(12):1128-33.

Cheng TJ, Chou PY, Huang ML, Du CL, Wong RH, Chen PC (2000). Increased lymphocyte sister chromatid exchange frequency in workers with exposure to low level of ethylene dichloride. Mutat Res 470(2):109-14.

Crebelli R, Carere A, Leopardi P, Conti L, Fassio F, Raiteri F, Barone D, Ciliutti P, Cinelli S, Vericat JA (1999). Evaluation of 10 aliphatic halogenated hydrocarbons in the mouse bone marrow micronucleus test. Mutagenesis 14(2):207-15.

DHS (2004). Drinking Water: Overview of Monitoring Results 1994-2003, and an Indication of Dominant Contaminants. Accessed at:
http://www.dhs.ca.gov/ps/ddwem/chemicals/monitoring/results94-03.htm

DHS (2005). Status of MCL reviews in response to PHGs. March 2005 update. California Department of Health Services, Sacramento, CA. Revised March 22, 2004. Accessed at:
http://www.dhs.ca.gov/ps/ddwem/chemicals/PHGs/reviewstatus.htm.

OEHHA (1999). Public Health Goal for 1,2-dichloroethane. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. February 1999.

Morel G, Ban M, Hettich D, Huguet N (1999). Role of SAM-dependent thiol methylation in the renal toxicity of several solvents in mice. J Appl Toxicol 19(1):47-54.

NCI (1978). Bioassay of 1,2-dichloroethane for possible carcinogenicity. Technical Report Series No.55. U.S. Department of Health, Education and Welfare, National Cancer Institute, Bethesda, MD.

Ruffalo CA, Gouvier WE, Pickston JB, Tucker KA, Hartman DE, Dahlgren JG, Parker FM (2002). Ethylene dichloride: Neuropsychological effects of chronic exposure. Arch Clin Neuropsychol 15:726-7. Abstract.

Salovsky P, Shopova V, Dancheva V, Yordanov Y, Marinov E (2002). Early pneumotoxic effects after oral administration of 1,2-dichloroethane. J Occup Environ Med 44(5):475-80.

U.S. EPA (2003). Fact Sheet: Announcement of completion of EPA's review of existing drinking water standards. U.S. Environmental Protection Agency, Washington, DC. Accessed at: http://www.epa.gov/OGWDW/standard/review/pdfs/fact_sixyearjuly03.pdf

U.S. EPA (2004a). 1,2-Dichloroethyene. Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC. Accessed at: http://www.epa.gov/iris/subst/index.html.

U.S. EPA (2004b). List of drinking water contaminants and MCLs. Office of Water, U.S. Environmental Protection Agency, Washington, DC. Accessed at: http://www.epa.gov/safewater/mcl.html#mcls.

U.S. EPA (2005a). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. EPA/630/P-03/001B. Accessed at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

U.S. EPA (2005b). Supplemental Guidance for Assessing Susceptibility from Early-life Exposure to Carcinogens. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. EPA/630/R-03/003F. Accessed at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.