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SUBJECT: UPDATE OF PHG – 1,2-DICHLOROBENZENE

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 evaluation of the existing PHG for 1,2-dichlorobenzene (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 developed the PHG of 0.6 mg/L (0.6 ppm) for 1,2-dichlorobenzene (also known as *ortho*-dichlorobenzene) and published it in December 1997. 1,2-Dichlorobenzene is used as a solvent in the manufacture of toluene diisocyanate, waxes, rubbers, oils, asphalts, and dyes; as a

degreaser for metals, leather, and wood; as a deodorizing agent for garbage and sewage treatment (OEHHA, 1997); and in the production of chemicals and herbicides (NTP, 1985).

No adequate cancer or genotoxicity studies were identified in the scientific literature. Accordingly, the International Agency for Research on Cancer (IARC) (1982) and U.S. Environmental Protection Agency (U.S. EPA) (1992) defined 1,2-dichlorobenzene as not classifiable as to human carcinogenicity. The 1997 PHG was based on a no-observed-adverse-effect level (NOAEL) of 125 mg/kg-day (the critical effect being hepatotoxicity in rats) estimated in a 13-week subchronic experiment carried out as part of the dose-range finding for the chronic study (NTP, 1985). The PHG is the same as the U.S. EPA's Maximum Contaminant Level Goal (MCLG) and the California and federal Maximum Contaminant Level (MCL) of 0.6 mg/L (U.S. EPA, 1995).

In the most recent toxicity review for 1,2-dichlorobenzene, the Agency for Toxic Substances and Disease Registry (ATSDR) (2006) calculated an oral chronic minimal risk level (MRL) of 0.3 mg/kg-day using the results of the chronic component of the National Toxicology Program (NTP) (1985) study and the benchmark approach. In this NTP study there was a significant increase in renal tubular regeneration in male $B6C3F_1$ mice only at the highest dose (controls, 8/48; 60 mg/kg-day, 12/50; 120 mg/kg-day, 17/49). ATSDR estimated the benchmark dose associated with 10 percent extra risk ($BMDL_{10}$) at 30.74 mg/kg-day based on the kidney lesions after exposure for 103 weeks (ATSDR, 2006). This is a lower value than the NOAEL chosen for the 1997 PHG of 125 mg/kg-day, from a subchronic study in F-344 rats that was part of the same NTP (1985) studies.

In the 1997 PHG, OEHHA had rejected the mouse kidney endpoint for risk assessment because concurrent experiments conducted by NTP showed incidences as high for this effect among other control animal populations as for those in the high-dose group exposed to 1,2-dichlorobenzene. In addition, single acute doses of 1,2-dichlorobenzene up to 600 mg/kg caused liver but not kidney damage in mice in the study of Ban *et al.* (1998). Thus, the significance or robustness of the renal endpoint remains unclear.

Other recent studies on 1,2-dichlorobenzene toxicity have addressed the mechanism of hepatotoxicity. Studies of the biochemical correlates of strain-dependent hepatotoxicity in rats (Gunawardhana and Sipes, 1991; Kulkarni *et al*., 1999; Younis *et al*., 2000, 2003) have helped explain the critical effects of 1,2-dichlorobenzene in hepatocytes. In addition, Hissink *et al.* (1997) developed a physiologically based pharmacokinetic (PBPK) model for 1,2-dichlorobenzene that they suggested would be useful as "a quantitative tool for evaluating human risk for two different toxicity scenarios, namely covalent binding of reactive metabolites and depletion of GSH" with regard to liver toxicity. The cross-species extrapolation was based on their earlier study comparing 1,2-dichlorobenzene metabolism in rat and human liver microsomes (Hissink *et al*., 1996), suggesting that humans should be

much less sensitive. However, in our opinion, the uncertainties regarding hepatotoxicity mechanisms as well as in the parameters of human liver metabolism are not yet well-enough established to utilize these data in our risk assessment.

The ATSDR divided its $BMDL_{10}$ by an uncertainty factor of 100 (10 for interspecies extrapolation, and 10 for human variability) to derive the MRL. Our previous risk estimate used an uncertainty factor of 1,000, with the extra 10-fold related to the fact that our calculation was based on a subchronic study rather than chronic exposure. In addition, our current preference is to use drinking water consumption rates based on the 95th percentile consumption estimates calculated by U.S. EPA (2004) rather than the earlier default rate of 2 L/day.

If we were to calculate a health-protective concentration using the ATSDR $BMDL_{10}$ approach and a higher drinking water consumption rate, the value would be about double the current PHG of 0.6 mg/L. Keeping the same liver toxicity endpoint and using the higher drinking water consumption rate would decrease the value by about a third. However, neither change seems critical, since this chemical has relatively low-toxicity and is rarely found at significant levels in drinking water.

In conclusion, we have considered several new studies, the revised interpretation of the NTP (1985) mouse data provided by ATSDR (2006), and our new approach to drinking water consumption rates. We conclude that incorporating these new data and interpretations does not provide an adequate rationale for revision of our earlier PHG. Therefore a complete update and revision of the PHG document is considered to be unnecessary.

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