Proposition 65 Maximum Allowable Daily Level (MADL) for Reproductive Toxicity for Benzene

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Office of Environmental Health Hazard Assessment (OEHHA)
Reproductive and Cancer Hazard Assessment Section

Summary

The maximum allowable daily level (MADL) for benzene exposure by the inhalation route is **49 µg/day** and by the oral route is **24 µg/day**. Dermal exposures leading to an absorbed dose of 24 µg/day should be considered the maximum allowable for Proposition 65 purposes. These values were derived as described below, based on a developmental toxicity study in mice conducted by Keller and Snyder (1988).

Background

This report describes the derivation of a maximum allowable daily level (MADL) for benzene (CAS # 71-43-28), a chemical listed under Proposition 65 as known to the State to cause reproductive toxicity, effective December 26, 1997. Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. Procedures for the development of Proposition 65 MADLs are provided in regulation (Title 22, California Code of Regulations [22 CCR], Sections 12801 and 12803).

The Proposition 65 listing of benzene was based on a finding by the Developmental and Reproductive Toxicant (DART) Identification Committee, the Proposition 65 state's qualified experts for reproductive toxicity, that the chemical had been clearly shown by scientifically valid testing according to generally accepted principles to cause developmental and male reproductive toxicity. As part of its deliberations, the Committee reviewed the document "Evidence on Developmental and Reproductive Toxicity of Benzene" (OEHHA, 1997), a comprehensive review of the scientific literature on the adverse reproductive effects of benzene. This review serves as the primary reference for MADL development.

As defined in regulations, MADLs are derived from No Observable Effect Levels (NOELs) or Lowest Observable Effect Levels (LOELs) (22 CCR Sections 12801 and 12803). The values discussed below are the highest exposure level at which no effect was observed, or the lowest exposure level at which an adverse effect was observed, under the specific conditions of the study in question. Where multiple reproductive effects provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity, the reproductive effect for which studies produce the lowest

NOEL is utilized for the determination of the NOEL (22 CCR Section 12803(a)(1)). Accordingly, only a single MADL is being developed, based on the effect producing the lowest NOEL.

Study Selection

Relevant studies were reviewed in the document "Evidence on Developmental and Reproductive Toxicity of Benzene" (OEHHA 1997), utilized by the DART Identification Committee. An update of the literature search conducted for that document identified additional human and animal studies of interest that were also reviewed and considered for the establishment of the MADL. These studies are identified in the Appendix.

The NOEL is based on the most sensitive study deemed to be of sufficient quality (22 CCR Section 12803(a)(4)). Human studies were not judged to have adequate exposure assessment for the identification of a NOEL. NOELs from studies of male reproductive toxicity of benzene were substantially higher than those for developmental toxicity. From all the available animal studies the most sensitive study was a developmental toxicity study in mice using endpoints reflecting altered hematopoiesis (blood cell formation) (Keller and Snyder, 1988). Exposures were by inhalation at 0, 5, 10 and 20 ppm benzene concentrations in air, 6 h/day, during gestation days 6 to 15. The LOEL for developmental hematopoietic effects was 5 ppm based on a significantly reduced relative number of early nucleated red cells in a sample of nucleated cells from the peripheral blood of 2-day old neonates that had been exposed to benzene *in utero*.

MADL Calculation

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (22 CCR Section 12803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (22 CCR Section 12803(b)). For developmental toxicity, the assumed body weight of the pregnant woman is 58 kg.

Because the Keller and Snyder study provided a LOEL rather than a NOEL, a NOEL for purposes of assessment was calculated by dividing the LOEL of 5 ppm by 10, resulting in a NOEL of 0.5 ppm (22 CCR Section 12803(a)(7)).

The following calculations were performed to derive the MADL for benzene:

Conversion of air concentration in ppm to mg/m^3 using a molecular weight for benzene of 78.11 daltons and a partial molar volume (i.e., the volume occupied by one mole of an ideal gas) of 24.45 at 25°C.

$(0.5 \text{ ppm} \times 78.11) \div 24.45 = 1.6 \text{ mg/m}^3$

Conversion of air concentration for 6 hour (h) exposure to a 24 h day:

$1.6\ mg/m^3 \times (6\ h \div 24\ h) = 0.40\ mg/m^3$

Calculation of NOEL dose for 30 g mouse with an inhalation rate of 0.063 m^3/day (Bond et al. 1986, Depledge 1985)

$(0.40\ mg/m^3 \times 0.063\ m^3/day) \div (0.030\ kg) = 0.84\ mg/kg/day$

Calculation of NOEL dose for a 58 kg woman:

$0.84\ mg/kg/\ day \times 58\ kg = 48.7\ mg/day$, or 49 mg/day after rounding

The MADL is derived by dividing the NOEL by one thousand (22 CCR Section 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL.

MADL $_{inhalation}$ = 49 mg/day ÷ 1000 = **49 µg/day**

Benzene absorption is route dependent, with oral exposures resulting in approximately twice as much absorption as by the inhalation route (OEHHA, 2000). Studies of rates of absorption among humans and animals to low levels of benzene (e.g., <10 ppm) suggest 100% absorption by the oral route and 50% absorption by the inhalation route (OEHHA, 2000), thus an equivalent MADL for oral daily intake is:

MADL $_{oral}$ = 48.7 µg/day ÷ 2 = **24 µg/day**, after rounding

Similarly, dermal exposure leading to an absorbed dose of 24 µg/day should be the maximum allowable for purposes of Proposition 65.

References

Bond JA, Dahl AR, Henderson RF, Dutcher JS, Mauderly JL, Birnbaum LS (1986). Species differences in the disposition of inhaled butadiene. *Toxicol Appl Pharmacol* **84**: 617-627.

Depledge MH (1985). Respiration and lung function in the mouse, *Mus musculus* (with a note on mass exponents and respiratory variables). *Respir Physiol* **60**: 83-94.

Keller KA, Snyder CA (1988). Mice exposed in utero to 20 ppm benzene exhibit altered numbers of recognizable hematopoietic cells up to seven weeks after exposure. *Fundam Appl Toxicol* **10**: 224-232.

OEHHA (1997). Office of Environmental Health Hazard Assessment. Evidence on Developmental and Reproductive Toxicity of Benzene. Reproductive and Cancer Hazard

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OEHHA (2000). Office of Environmental Health Hazard Assessment. Public Health Goal for Benzene in Drinking Water. OEHHA, California Environmental Protection Agency, Oakland, California. Draft, February, 2000 (Appendix C). Available at URL: http://www.oehha.ca.gov/water/phg/pdf/benzene.pdf

Appendix

Additional references reviewed since publication of "Evidence on Developmental and Reproductive Toxicity of Benzene" (OEHHA 1997)

The following studies were identified in a literature search conducted to identify relevant literature published subsequent to the development of the OEHHA (1997) review. They were reviewed along with the studies in OEHHA (1997) to evaluate the most appropriate basis for derivation of a MADL.

Abraham NG (1996). Hematopoietic effects of benzene inhalation assessed by long-term bone marrow culture. *Environ Health Perspect* **104**(Suppl6):1277-1282.

Ahmad S, Agrawal R, Agrawal DK, Rao GS (2000). Bioreactivity of glutathionyl with implications to benzene toxicity. *Toxicology* **150**:31-39.

Chen D, Cho S, Chen C, *et al*. (2000). Exposure to benzene, occupational stress, and reduced birth weight. *Occup Environ Med* **57**:661-667.

Corti M, Snyder CA (1998). Gender- and age-specific cytotoxic susceptibility to benzene metabolites in vitro. *Toxicol Sci* **41**:42-48.

Farris GM, Robinson SN, Gaido KW, Wong BA, Wong VA, Hahn WP, Shah RS (1997). Benzene-induced hematotoxicity and bone marrow compensation in B6C3F1 mice. *Fund Appl Toxicol* **36**:119-129.

Farris GM, Robinson SN, Wong BA, Wong VA, Hahn WP, Shah R (1997). Effects of benzene on splenic, thymic, and femoral lymphocytes in mice. *Toxicology* **118**:137-148.

Nordlinder R, Jarvholm B (1997). Environmental exposure to gasoline and leukemia in children and young adults–an ecology study. *Int Arch Occup Environ Health* **70**(1):57-60.

Snyder R (2000). Recent developments in the understanding of benzene toxicity and leukemogenesis. *Drug Chem Toxicol* **23**(1):13-25.

Thurston SW, Ryan L, Christiani DC, *et al*. (2000). Petrochemical exposure and menstrual disturbances. *Am J Ind Med* **38**:555-564.

Wang X, Chen D, Niu T, Wang Z, Wang L, Ryan L, Smith T, Christiani DC, Zuckerman B, Xu X (2000). Genetic susceptibility to benzene and shortened gestation: evidence of gene-environment interaction. *Am J Epidemiol* **152**(8):693-700.

Xu X, Cho S, Sammel M, *et al*. (1998). Association of petrochemical exposure with spontaneous abortion. *Occup Environ Med* **55**:31-36.