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SUBJECT: PROPOSED ACTION LEVELS FOR 1,2,4-TRIMETHYLBENZENE AND 1,3,5-TRIMETHYLBENZENE

Staff of the Office of Environmental Health Hazard Assessment (OEHHA) have reviewed your Department's proposed action level of 330 µg/L for both 1,2,4-trimethylbenzene (1,2,4-TMB) (CASRN 95-63-6) and 1,3,5-trimethylbenzene (1,3,5-TMB) (CASRN 108-67-8). OEHHA concurs with these action levels.

Introduction:

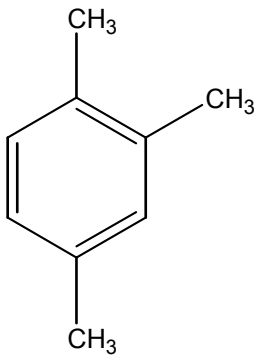
1,2,4-trimethylbenzene (Figure 1a), also known as pseudocumene, is a volatile aromatic hydrocarbon liquid (Henry's Law constant = 6.16×10^{-3} atm-m^3/mole) used in United States commerce in the manufacture of trimellitic anhydride, dyes, and pharmaceuticals and as a solvent and paint thinner. 1,2,4-TMB is a major component (typically 40 percent) of a petroleum refinery distillation fraction known as the C9 aromatic fraction (U.S. EPA, 1994) and is found in gasoline, coal tar oil, and some mineral oils. It is also formed during processing of crude oil, especially catalytic cracking and reforming (HSDB, 2001). 1,2,4-TMB is isolated by only one

refinery in the U.S. but it is estimated that total production is greater than ten million pounds per year (U.S. EPA, 1994). It is released into the environment as road runoff and in urban storm water (U.S. Geological Survey, 1999).

1,3,5-trimethylbenzene (Figure 1b), commonly known as mesitylene, is also a volatile aromatic hydrocarbon liquid (Henry's Law constant = 8.77×10^{-3} atm-m^3/mole) used as a dyestuff intermediate, solvent, paint thinner, and a UV oxidation stabilizer for plastics. It is released directly into the environment as a component of gasoline and by emission from gasoline-powered vehicles, municipal waste treatment plants, and coal-fired power stations (Hazardous Substances Data Bank, 2000).

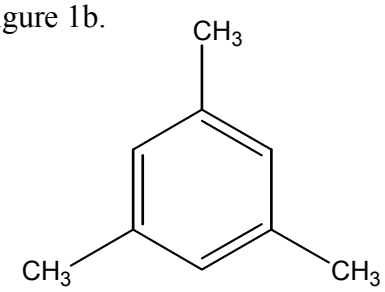
Considering the Henry's Law constants of both compounds, they are expected to volatilize from surface waters into the air with an estimated half-life for a model river and model lake of three hours and four days, respectively (HSDB, 2000). They have been found in groundwater, drinking water, surface waters, rain, and snow in numerous countries. The chemicals have been reported in Wisconsin groundwater in 1997 at a level of 3.9 mg/L (ppm) for 1,3,5-TMB and 5.8 mg/L for 1,2,4-TMB (Wisconsin Department of Natural Resources, 2000).

Figure 1a.



1,2,4-trimethylbenzene

Figure 1b.



1,3,5-trimethylbenzene

Both compounds are on the U.S. Environmental Protection Agency Method 524.2 analyte list for monitoring in groundwater, surface water, and drinking water and, in California, are considered unregulated chemicals requiring monitoring (Title 22, California Code of Regulations §64450).

The routes of exposure to 1,2,4-TMB and 1,3,5-TMB are inhalation of ambient air, ingestion of food and drinking water, and dermal contact with vapors, food and other products.

These chemicals can cause eye, skin, and mucous membrane irritation. However, their prevalence in the California subsurface environment is apparently rare, with only four detections of 1,2,4-TMB in California water supplies among 9582 tests and three detections of 1,3,5-TMB in 9581 tests from 1984-1998 (S. Book, personal communication). This is not necessarily the case in other areas, however. In 1998, Wisconsin detected 1,2,4-TMB in 152 groundwater wells out of a total of 1851 wells, with a high measurement of 5800 µg/L and a mean of 54 µg/L. 1,3,5-TMB was found in 114 wells of 1862 tested, with a high of 1200 µg/L and a mean of 26 µg/L (Wisconsin Department of Natural Resources, 2000).

The human toxicity data is limited to an occupational inhalation exposure study (Bättig *et al*., 1958). Workers in a Swiss transportation plant painting shop were exposed to a solvent consisting of 97.5 percent aromatic hydrocarbons (1,2,4-TMB>50 percent, 1,3,5-TMB>30 percent, 1,2,3-TMB plus various methylethylbenzenes). Exposure levels were in the range of 10-60 ppm (49-295 mg/m^3). The solvent had been used for about ten years but the length of these worker's exposures was not reported. The workers reported CNS symptoms (vertigo, headaches, and drowsiness) more often than controls (70 percent versus 30 percent), who were recruited from a different section of the plant. The incidence of CNS symptoms in the workers compared to controls was significantly higher as determined by a Fisher's exact test ($p<0.05$). Other effects that did not reach statistical significance were chronic asthma-like bronchitis (30 percent of solvent workers and 10 percent of controls), anemia with <4.5 million erythrocytes per mm^3 usually combined with normal hemoglobin (50 percent and 20 percent), and alterations in blood clotting (30 percent compared to 10 percent). There are no reports of human oral toxicity studies in the literature.

The animal oral toxicity data for 1,2,4- and 1,3,5-TMB have recently been reviewed (NCEA, 1999).

1,3,5-TMB Toxicity Studies: Two studies of 1,3,5-TMB are cited but one only has one dose level in addition to controls. A subchronic study conducted by IIT Research Institute (IITRI, 1995) forms the basis of the U. S. EPA National Center for Environmental Assessment (NCEA) reference dose (RfD) calculation for both 1,3,5- and 1,2 4-TMB. Groups of 10 male and 10 female Sprague-Dawley rats were administered via gavage 0, 50, 200, or 600 mg/kg 1,3,5-TMB in corn oil 5 days/week for 90 days. Adjustment of the doses for daily exposures (7 days/wk) resulted in calculated equivalent doses of 0, 36, 143, and 429 mg/kg-day. Additional groups of 10/sex were administered 600 mg/kg 1,3,5-TMB 5 days/week for 90 days and then held 28 days without treatment for recovery, prior to sacrifice. Physical examinations, clinical observations, opthamological examinations, body weights, food consumption, hematological and clinical chemistry, organ weights, and gross and histopathology were assessed.

Physical examination: Abnormal clinical observations consisted of discolored and/or wet inguinal fur and salivation in the highest dose group of both sexes.

Body weight changes: A non-significant decrease in cumulative body weight gain (11 percent lower than controls) was observed for the high dose males.

Clinical chemistry: Clinical chemistry parameters were ascertained at 30 days post-dosing and at the end of the 28-day recovery period. At the 30-day time point, statistically significantly affected parameters in treated animals versus controls consisted of increased albumin levels and albumin/globulin ratio, decreased globulin and cholesterol levels in high dose males (429 mg/kg-day); decreased cholesterol levels in mid dose males (143 mg/kg-day); and decreased blood urea nitrogen levels in high dose females (429 mg/kg-day). At the termination of dosing, significantly affected parameters occurred only in the high dose group. These consisted of increased alkaline phosphatase and phosphorus levels and decreased glucose levels in high dose males, and increased cholesterol and phosphorus levels and decreased sodium and chloride levels in high dose females. The 30-day differences were not considered treatment-related since they were not present post-dosing. The post-dosing differences, with the exception of increased serum phosphorus levels, were either within normal parameters or due to high values in two individual animals and were not statistically significant. The increased serum phosphorus levels were considered treatment-related but the recovery group did show some decrease (data not given) from the high dose and vehicle controls at the end of the 90-day dosing period. The lowest-observed-adverse-effect level (LOAEL) for this study is therefore considered to be 429 mg/kg-day, based on the increased serum phosphorus levels in high-dose males and females.

Hematology: A significant increase in mean monocyte levels was observed in the 143 and 429 mg/kg-day male groups. The authors did not consider this treatment-related, although they provided no explanation for this conclusion.

Organ weights: Mean absolute liver weight was significantly increased in the high dose females compared to vehicle controls. Mean relative kidney weight was significantly increased in high dose males and mean relative liver weight was significantly increased in both high dose males and females. In the recovery animals, both the relative kidney weight in males and the relative liver weight in males and females were decreased from those of the high dose animals at the end of the 90-day dosing period. The authors attribute the increased liver weights to induction of microsomal enzyme pathways in an attempt to metabolize the test substance.

1,2,4-TMB Toxicity Studies: Two studies are cited by NCEA but are considered inadequate for derivation of a RfD. In the first study (Borriston Laboratories, Inc., 1984) only nephropathology was evaluated. The second study (Maltoni *et al.*, 1997) was a carcinogenicity study that demonstrated only decreased survival (slight for female Sprague-Dawley rats and

intermediate for males) using only 0 and 800 mg/kg, 4-days/week gavage dosing in 1 ml olive oil for 104 weeks. Because there was only one treatment dose, no food or water consumption data or body weight data were given, and no statistical analysis of the necropsy data was provided, this study is considered insufficient. NCEA considers the survival data to demonstrate a LOAEL of 800 mg/kg for 1,2,4-TMB in this study.

NCEA (1999) concludes that the IITRI study is adequate to derive a no-observed-adverse-effect level (NOAEL) of 143 mg/kg-day and a LOAEL of 429 mg/kg-day for 1,3,5-TMB. They further conclude that the metabolism and disposition of 1,3,5-TMB and 1,2,4-TMB are quite similar. They both yield dimethylhippuric acids in rats administered a single oral dose, and inhalation toxicokinetic studies in humans show similar elimination kinetics and metabolism. Therefore, NCEA recommends deriving an RfD for 1,2,4-TMB by analogy to 1,3,5-TMB. OEHHA concurs in this evaluation.

Calculation of Action Levels:

A public health protective concentration (C) for 1,2,4-TMB and 1,3,5-TMB in drinking water can be derived from the equation:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times DWC} = \frac{(143\ mg/kg\text{-}day)(70\ kg)(0.2)}{(3{,}000)(2\ L/day)} = 0.334\ mg/L \cong 330\ \mu g/L$$

where:

NOAEL = no-observed-adverse-effect level (143 mg/kg-day, based on increased serum phosphorus levels in rats at the next higher dose of 429 mg/kg-day),
BW = adult body weight (default of 70 kg),
RSC = relative source contribution (default of 20 percent, or 0.2),
UF = combined uncertainty factor (comprised of 10 for interspecies extrapolation, 10 for extrapolation from a subchronic to a chronic study, 10 for human variability, and 3 for database deficiencies), and
DWC = adult drinking water consumption (default of 2 L/day).

Based on the health protective concentration calculated, OEHHA recommends and supports an action level of 330 ppb (µg/L) for both 1,2,4-trimethylbenzene and 1,3,5-trimethylbenzene in drinking water.

Should you have any questions about this review, please contact me at (510) 622-3168 or Dr. Robert Haas at (510) 622-3172.

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