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MEMORANDUM

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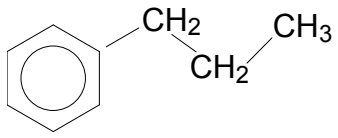
DATE: October 27, 2000

SUBJECT: PROPOSED ACTION LEVEL FOR n-PROPYLBENZENE

Staff of the Office of Environmental Health Hazard Assessment (OEHHA) have reviewed your Department's proposed action level of 30 µg/L for n-propylbenzene. The proposed action level for n-propylbenzene was derived by analogy based on structural similarities to another alkyl aromatic hydrocarbon, ethylbenzene, and is based on non-carcinogenic effects (hepatotoxicity) observed in experimental animal studies. However, recent data which was not accounted for in the development of OEHHA's public health goal (PHG) for ethylbenzene (on which the n-propylbenzene Action Level is based), show ethylbenzene to be an animal carcinogen (IARC, 2000). It is not clear at this time whether n-propylbenzene could be expected to have carcinogenic effects (neoplasms in kidneys and testes of Fischer rats, and in lungs of male and liver of female B6C3F1 mice) similar to those found with ethylbenzene. Based on this uncertainty, we do not agree with the Department of Health Services (DHS) proposal to base the Action Level for n-propylbenzene on toxic effects of ethylbenzene, either from the earlier OEHHA evaluation, or including the ethylbenzene carcinogenicity study of Chan et al. (1998). As the n-propylbenzene toxicological data is insufficient to derive an action level, it is OEHHA's recommendation that the Action Level for n-propylbenzene be based on another structural analog, cumene, for which there is appropriate subchronic oral toxicity data. This results in a proposed Action Level of 260 µg/L.

n-Propylbenzene (isocumene, CAS No.103-65-1, see Figure 1) is a member of the alkyl aromatic family of hydrocarbons, which also includes toluene (methylbenzene), xylenes, ethylbenzene, and cumene. n-Propylbenzene occurs as a natural constituent in petroleum and bituminous coal. It is used in the manufacture of cumene and methylstyrene, and in textile dyeing and printing. It is released to the atmosphere in emissions from combustion sources, and from solvent evaporation, landfill leaching, and the use of asphalt. n-Propylbenzene has been qualitatively detected in various wastewaters from the following industries: petroleum refining, textile mills, auto and other industries, plastics manufacturing, and publicly owned treatment works (Bursey and Pellizzari, 1982). The general population is continually exposed to low concentrations of n-propylbenzene through inhalation, since it occurs ubiquitously in the atmosphere. It is very slightly soluble in water, 0.06 g/L (Merck, 1989). n-Propylbenzene has a measured Henry's Law constant of 0.0105 atm-cu m/mole at 25 ^{o}C, indicating that volatilization from environmental waters can be rapid (Lyman, 1982). Based upon a vapor pressure of 3.42 mm Hg at 25^{o}C, n-propylbenzene is expected to exist almost entirely in the vapor-phase in the ambient atmosphere (Daubert and Danner, 1989).

Figure 1, n –Propylbenzene



There is little human toxicology data available regarding n-propylbenzene, and no oral exposure studies in humans were found in the literature. There is a paucity of data concerning oral exposures in animal studies. Two different oral LD_{50}s for n-propylbenzene in rats have been reported, 6.04 g/kg (RTECS, 1993), and 7.5 g/kg (NAS, 1977). NAS (1977) reported an LD_{50} of 5.2 g/kg for n-propylbenzene in mice. The oral LD_{Lo} in rats is reported to be 4.3 g/kg n-propylbenzene, in which 2/10 rats died (RTECS, 1992).

The National Academy of Sciences (NAS, 1977) summarized the results of a six-month oral study with n-propylbenzene in rabbits. Unfortunately, the actual research article cannot be located for review.

> "Gerarde and Ahlstrom (1966a) fed groups of 15 rabbits 0.25 or 2.5 mg/kg/day propylbenzene for 6 months. There was a 7% decrease in the red-cell count in the group fed 2.5 mg/kg/day that was not significant. Hemosiderin was deposited in the spleens of the high-dosage animals, indicating red cell destruction. Individual animals exhibited mild protein dystrophy of the liver and kidneys. Leukocytes were increased in both dosage

groups, although the increase was not significant. The test animals did not differ from the controls in general appearance, body weight, organ weight, and protein function of the liver."

Gerarde (1956) exposed groups of male rats (40/group) to 1.0 ml/kg-day of either benzene, propylbenzene, ethylbenzene, toluene, or butylbenzene in olive oil s.c. for a two-week period. The control group received olive oil only. Ten animals were killed at weekly intervals from each group during the exposure period and at ten-day intervals during the three-week recovery period. Blood was taken from the tail for leukocyte counts. Because of the similarity in response, the four alkylbenzene-treated groups were discussed collectively. Gross observations showed diminished motor activity, owing to central nervous system depression, but the growth curve did not differ significantly from that of the controls. Mortality was 5 percent. The hematocrit in the alkylbenzene treated animals was normal. The femoral marrow nucleated cell count was normal or slightly elevated relative to the controls, and the peripheral leukocyte count was slightly elevated during the two-week exposure period, but normal during the recovery period. Total femoral marrow nucleic acids were slightly higher than the controls but this may have been the result of an inflammatory response to the injected materials. In contrast with the benzene–treated animals, there was no involution of the thymus gland and the spleen weight was normal or slightly increased. All other tissues were normal on gross and microscopic examination.

The metabolic pathways of n-propylbenzene are, by and large, known and do not appear to involve any highly reactive species. Biotransformation of the alkyl side chain yields benzoic acid, which when conjugated with glycine, is excreted in the urine as hippuric acid (Parmeggiani, 1983). Certain mono-n-alkyl derivatives, such as n-propylbenzene and ethylbenzene, also undergo ring hydroxylation to form phenols, which are then eliminated in the urine as conjugates of sulfuric acid (Gerarde, 1960). Gerarde and Ahlstrom (1966b) conducted toxicologic studies on a number of the mono-n-alkyl derivatives in male albino rats and found notable metabolic differences in the urinary sulfate ratio (an increase in urinary organic sulfate is indicative of phenol formation). The data show that as the alkyl side chain lengthens, the degree of ring hydroxylation seems to increase, and the time required to restore the value of inorganic/total (I/T) to normal (in rats exposed orally) is prolonged. With toluene and ethylbenzene, the urinary sulfate ratio returned to normal within 72 hours, whereas in the case of n-propylbenzene, the ratio I/T remained below normal 72 hours after dosing.

Other authors have also described differences between hydrocarbon structure and induction of liver cytochrome P450. Yuan et al. (1995) found that small changes in hydrocarbon size or isomeric structure influenced RNA levels for specific P450 isozymes. Rats were treated with daily injections of benzene, toluene, ethylbenzene, n-propylbenzene, m-xylene, or p-xylene for three days and the effects on specific RNA levels were examined. A significant elevation in cytochrome 2B2 mRNA was observed after exposure to the larger aromatic

hydrocarbons,ethylbenzene and m-xylene. And, despite the depression of cytochrome 2C11 levels by several hydrocarbons, the 2C11 mRNA was only suppressed by ethylbenzene.

Carcinogenicity/Mutagenicity

No adequate data exist with which to determine the carcinogenic and mutagenic potential of n-propylbenzene.

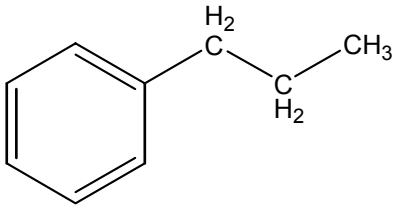
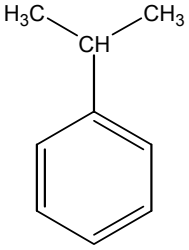
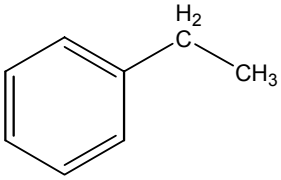
Developmental/Reproductive Data

No studies were found with which to evaluate the developmental, reproductive, or teratogenic effects of n-propylbenzene.

Structural analogs

Table 1 outlines some of the chemical/toxicological characteristics of several of the alkylbenzenes.

Table 1.

Alkylbenzene	N-propylbenzene	Cumene	Ethylbenzene
			
Vapor Pressure	3.42 mm Hg @ 25° C	4.5 mm Hg @25 °C	9.6 mm Hg at 25°C
LD_{50} (rats)	6.04 g/kg	2.91g/kg 1.4 g/kg	5.46 g/kg; 3.5 g/kg
LD_{50} (mice)	None	None	2.3 g/kg
*RD_{50} (mice)	1530 ppm	2,490 ppm	4,060 ppm
Hematotoxic	Unknown	No	No
Teratogenic	Unknown	Unknown	Fetotoxic/teratogenic
Carcinogenicity (IARC)	Unknown	Class D	Class 2B

*RD_{50} = the concentration of a chemical required to depress the respiratory rate by 50 percent due to sensory irritation of the respiratory tract.

Action Level Derivation

The information provided in the NRC (1977) summary of the Gerarde and Ahlstrom (1966) paper lacks sufficient detail for risk assessment purposes, and therefore cannot be used to derive an Action Level for n-propylbenzene. Insufficient toxicological and pharmacokinetic information is available to elucidate similarities/differences of action among alkyl benzene structural analogs.

The proposed n-propylbenzene Action Level of 30 µg/L proposed by DHS is derived from OEHHA's Public Health Goal (PHG) for ethylbenzene, a structural analog. The National Toxicology Program (NTP, 1996) study cited in the development of the PHG provides evidence of hepatotoxicity in mice exposed to 250 ppm ethylbenzene in air for two years. A no-observed-adverse-effect-level (NOAEL) for hepatotoxicity was determined to be 75 ppm from the NTP study, corresponding to a daily dose of 49 mg/kg. The PHG calculation is based on non-carcinogenic effects observed in experimental studies. There now exists positive animal bioassay data for the carcinogenicity of ethylbenzene in air (Chan et al., 1998). In contrast, no data exist with which to evaluate the carcinogenicity of n-propylbenzene. Therefore, it is OEHHA's recommendation that the Action Level for n-propylbenzene be based on another structural analog, cumene, for which there is subchronic oral toxicity data.

From Table 1, it can be seen that both ethylbenzene and cumene (isopropyl benzene) are more acutely toxic via the oral route than n-propylbenzene. Nielsen and Alarie (1982) have found that the potency of the alkylbenzenes to depress the respiratory rate by 50 percent (RD_{50}) increases with chain length. In this regard, n-propylbenzene is the most toxic, with an RD_{50} of 1,530 ppm, followed by cumene (2,490 ppm) and then ethylbenzene (4,060 ppm). Based on their respective vapor pressures, all three of the alkylbenzenes listed, n-propylbenzene, cumene, and ethylbenzene, would be expected to exist almost entirely in the vapor-phase in the ambient atmosphere, and volatilization from environmental waters would be rapid (Lyman, 1982).

No adequate data exist on the carcinogenic potential of either cumene or n-propylbenzene. The U.S. Environmental Protection Agency (U.S. EPA) has assigned cumene the carcinogen category D (not classifiable), indicating inadequate or no human and animal data. Cumene has not been shown to be mutagenic in a number of genotoxicity studies (Florin et al., 1980; Gulf Life Sciences Center, 1985a; Lawlor and Wagner, 1987; Yang, 1987). A micronucleus assay performed in mice administered up to 1 g/kg cumene by gavage was negative (Gulf Life Sciences Center, 1985b). No multigeneration reproductive study exists for cumene either by the oral or inhalation route. U.S. EPA concluded that since there was no evidence of developmental toxicity in rats or rabbits, or effects on reproductive organs or spermatogenesis in a 13–week rat inhalation exposure even at maternally-toxic exposure levels (Darmer et al., 1997), no additional developmental/reproductive studies would be required for cumene. However, there are no data

regarding cumene exposure prior to mating, from conception through implantation, or during late gestation, parturition, or lactation.

The Division of Drinking Water's proposed action level of 770 µg/L for cumene (isopropylbenzene) is based on U.S. EPA's oral reference dose (RfD), and is derived from the Wolf et al. (1956) subchronic study in which female rats (10/group) were administered 139 doses of cumene at 154, 462, or 769 mg/kg-day over a 194 day (six to seven months) period by gavage. The LOAEL (ADJ) for this study, based on adjustment for the stated dosing schedule of 139 doses/194 days, was identified as 331 mg/kg-day. The critical effect seen at this dose level is an increase in kidney weights. No renal histopathology was observed or reported. The low dose in this study (154 mg/kg x 139/194 days = 110 mg/kg-day), in which no observable adverse effects were noted, was designated as the NOAEL (ADJ). Overall, little quantitative data (i.e. percent changes in organ weights, total number animals affected/total number of exposed animals) are presented.

While n-propylbenzene was not one of the compounds tested in the Wolf et al. (1956) study, of the alkylbenzenes tested, only ethylbenzene (and benzene) caused histopathological changes. These were characterized by cloudy swelling of the parenchymal cells of the liver and cloudy swelling of the tubular epithelium in the kidney. The other test materials (e.g. cumene) caused significant increases in the average weights of the liver and or kidney only.

The Wolf et al. (1956) study did not observe or report behavioral effects (the only significant effect observed in this study is a description of dose-related increases in average renal weights), although pharmacologically the alkylbenzenes are classified as central nervous system depressants. A later study by the Chemical Manufacturers Association (CMA, 1989) did observe and report behavioral effects in their study on alkylbenzenes and no adverse behavioral effects were observed at a dose level of 33 mg/kg-day cumene. n-Propylbenzene was not tested in this study.

Unfortunately, the CMA (1989) study cannot be used to derive a LOAEL as only one dose level was tested. Therefore, OEHHA concurs with the Division of Drinking Water's use of the Wolf et al. 1956 study as the principal study for cumene. For the n-propylbenzene action level derivation then, application of a 3,000-fold safety factor to the Wolf et al. (1956) NOAEL (ADJ) of 110 mg/kg-day is deemed adequate to protect against any potential toxic effects in humans. This includes uncertainty factors of 10 each for interspecies and intraspecies differences, a factor of 3 for extrapolation from six months to chronic duration, and 10 for the many database deficiencies.

A public health protective concentration (C) for n-propylbenzene of 260 µg/L is derived from the following equation:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times DWC} = \frac{110\ mg/kg\text{-}day \times 70\ kg \times 0.2}{3{,}000 \times 2\ L/day} = 260\ \mu g/L$$

Where:

NOAEL = no-observed-sdverse-rffect-level
BW = body weight (adult)
RSC = relative source contribution
UF = uncertainty factor
DWC = drinking water consumption (adult)

Based on the health protective concentration calculated, OEHHA recommends and supports an action level of 260 µg/L for n-propylbenzene in drinking water.

Should you have any questions about this review, please contact me at (510) 622-3168 or Ms. Moira Sullivan at (510) 622-3213.

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