MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Benzyl Alcohol (CAS # 100-51-6)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: March 6, 2023

SUBJECT: Screening Level for Benzyl Alcohol (CAS # 100-51-6)

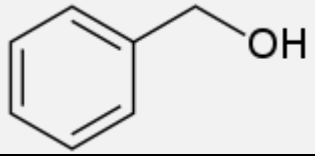
Summary

The initial threshold screening level (ITSL) for benzyl alcohol is 400 µg/m^3 (annual averaging time).

Uses and Physical Chemical Properties

Benzyl alcohol is an aromatic alcohol which is used: as a topical anesthetic; as a preservative in medicinal products; for curing epoxy resins; as a solvent in waterborne coatings; in paint strippers; in cosmetics; as a preservative and flavor in food; and as an active ingredient in a lotion for treating head lice (MAK, 2018).

Table 1. Physical/Chemical Properties of Benzyl alcohol

Structure	
CAS Number	100-51-6
Synonyms	A-cresol; α-toluenol; α-hydroxytoluene; α-hydroxyphenylmethane; phenylcarbinol; benzenemethanol; benzyl hydroxide
Appearance/Odor	Colorless oily liquid with a mild floral odor
Odor Threshold	5.5 ppm
Molecular Weight	108.140 g/mol
Melting Point	-15.2 °C
Boiling Point	205.3 °C
Flash Point	93 °C (closed cup); 105 °C (open cup)
Autoignition Temperature	436 °C

Solubility: Water	42,900 g/L @ 25 °C
Density	1.0419 g/cm^3 @ 24 °C
Vapor Density (Air = 1)	3.72
Vapor Pressure	0.094 mm Hg at @ 25°C
Log Kow	1.10
Henry's Law Constant	3.37x10^{-7} atm-m^3 /mole at 25°C

Literature Search

The literature was searched to find relevant data to assess the toxicity of 1,1-dichloroethylene. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched 11/2/2022), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

Key Study

The ITSL is derived from an EPA Provisional Peer-Reviewed Toxicity Value (PPRTV) chronic provisional reference dose (p-RfD) for oral exposure of 0.1 mg/kg-day. The chronic p-RfD is based on the chronic NTP (1989a) study in mice. NTP (1989a) performed a 2-year study in 50 F344/N rats (50 per sex per dose) to concentrations of 0, 200, or 400 mg/kg and groups of 50 B6C3F$_1$ mice (50 per sex per dose) to concentrations of 0, 100, or 200 mg/kg of technical grade benzyl alcohol (99% pure) dissolved in corn oil administered by gavage 5 days/week for 103 weeks.

"Survival of the benzyl alcohol treated female rats was significantly lower than controls after Week 50 in high-dose animals and, after Week 71, in low-dose animals (NTP, 1989a). Many of the deaths were attributed to gavage error (1, 17, and 13 in the control, low-, and high-dose groups, respectively); however, there was an apparent dose-response trend in nonaccidental deaths in females (13/50, 16/50, and 20/50, respectively, at 0, 200, and 400 mg/kg-day). Because of the high incidence of gavage-related deaths, it is not clear if the apparent increase in nonaccidental mortality in treated female rats was related to benzyl alcohol toxicity. In males, an apparent dose-related increase in gavage-related deaths was observed (4/50, 8/50, and 14/50 at 0, 200, and 400 mg/kg-day, respectively); however, survival curves in males were similar in both treated groups compared with controls. No effects on body weight or incidences of clinical signs of toxicity were observed" (EPA, 2009). "High-dose male rats were observed with a higher incidence of epithelial hyperplasia in the forestomach than controls (0/48, 0/19, and 4/50 at 0, 200, and 400 mg/kg-day, respectively) (NTP, 1989a)" (EPA, 2009). "Increased incidences of microscopic lesions of the respiratory tract, larynx, and lungs were also observed in treated rats; however, these effects appear to have been caused by gavage error or by reflux of the gavage material and aspiration into the lungs due to the anesthetic properties of the test substance. High-dose rats were also observed with an increased incidence of cataracts and retinal atrophy, but this was attributed to those animals being housed in cages on the top racks,

permitting greater exposure to fluorescent lighting. The data from this study indicate that there were no toxic effects that were associated with benzyl alcohol administration to male or female rats at any dose; therefore, the NOAEL in rats observed in this study is 400 mg/kg-day, and a clear LOAEL is not established. There is some uncertainty, however, as meaningful interpretation of the mortality data is not possible due to the high rate of gavage errors – particularly in females. Thus, the data cannot be used for dose-response assessments" (EPA, 2009).

"In mice, no effects on survival, clinical signs of toxicity, or body weight were observed (NTP, 1989a). High-dose male and female mice had an increased incidence of corpora amylacea (incidence of 15/49, 21/48, and 22/50 in males, and 14/50, 15/48, 25/50 in females in the control, low-, and high-dose groups, respectively). The lesion was described as consisting of 'one or several small foci of mineralization in the thalamus' and was noted to be a common, spontaneously occurring lesion. Inspection of 2-year studies published in 1989 by the National Toxicology Program indicates that the incidences of corpora amylacea in the 2-year benzyl alcohol study in mice were within the vehicle control incidence of brain mineralization in mice in these studies (NTP, 1989b, c). Therefore, it does not appear that this lesion was likely related to benzyl alcohol treatment. There was also an increased incidence (p=0.044 by the life table and incidental tumor tests) in adrenal cortex adenomas in high-dose male mice (adjusted terminal rates of 0/33, 0/30, and 3/35 in the control, low-, and high-dose groups respectively). The incidence at the high dose, however, was within the historical control incidence and was, therefore, not attributed to benzyl alcohol treatment. Overall, no treatment-related effects were observed in this study at any dose. Therefore, the NOAEL in mice is 200 mg/kg-day (143 mg/kg-day when adjusted for a 5 day/week dosing schedule), the highest dose tested, and a LOAEL is not achieved" (EPA, 2009).

"In the chronic studies (NTP, 1989a), benzyl alcohol…study featured comprehensive histopathological examination of the test animals. No effects, other than increased incidence of corpora amylacea, were clearly related to benzyl alcohol administration in either species. The NOAEL in rats and mice was 400 and 200 mg/kg-day, respectively, the highest dose tested in both species. The rat study, however, experienced a high incidence of accidental deaths, precluding a meaningful interpretation of the mortality data in this study" (EPA, 2009).

"The chronic NTP (1989a) study in mice provides a suitable basis for derivation of a chronic p-RfD for benzyl alcohol. This study provides a NOAEL of 200 mg/kg-day for effects on survival, growth, and tissue histopathology; a LOAEL is not identified. The mouse chronic study reported mineralization of thalamus in female mice and adenomas in adrenal cortex in high-dose males; these were within historical control incidence, and were therefore, not attributed to benzyl alcohol treatment. This mouse study has been chosen over the similar rat study, with a NOAEL of 400 mg/kg-day, as the critical study because the rat study is compromised by a high number of accidental deaths, precluding a meaningful interpretation of the mortality data from this study. The NOAEL in mice of 200 mg/kg-day has been adjusted to a continuous exposure basis (200 mg/kg-day x 5 days/7 days = 143 mg/kg-day) and divided by a composite UF of 1000 (10 for interspecies extrapolation; 10 for human variability; and 10 for database deficiencies, which includes the lack of adequately conducted reproductive, developmental, and neurological toxicity tests). A chronic p-RfD is derived as follows" (EPA, 2009):

$$Chronic\ p-RfD = \frac{NOAEL}{UF} = \frac{143\ {}^{mg}/_{kg-day}}{1000} = 0.1\ {}^{mg}/_{kg-day}$$

Derivation of ITSL

Under Rule 232(1)(b) an ITSL can be derived from an oral reference dose using the following equation:

$$ITSL = Oral\ RfD \times \frac{70\ kg}{20\ m^3} = 0.1\ {}^{mg}/_{kg-day} \times \frac{70\ kg}{20\ m^3} = 0.35\ {}^{mg}/_{m^3} = 350\ {}^{\mu g}/_{m^3}$$
$$\cong 400\ {}^{\mu g}/_{m^3}$$

According to Rule 232(2)(b) an annual averaging time should be used. Therefore, the ITSL for benzyl alcohol is 400 µg/m^3 based on an annual averaging time.

References

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environment, Great Lakes, and Energy.

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MAK. 2018. Benzyl alcohol/ phenylmethanol. [MAK Value Documentation, 2018]. The MAK Collection for Occupational Health and Safety, Vol 3, No. 9: 1075-1110. Available online at: The MAK-Collection for Occupational Health and Safety | Major Reference Works (wiley.com)

NTP. 1989a. US National Toxicology Program: Toxicology and Carcinogenesis Studies of Benzyl Alcohol (CAS No. 100-51-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 343. NIH Publication No. 89-2599. Available online at: Abstract for TR-343 (nih.gov)

NTP. 1989b. NTP Technical Report on Toxicology and Carcinogenesis Studies of N, N-Dimethylaniline (CAS No. 121-69-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 360. NIH Publication No. 90-2815.

NTP. 1989c. NTP Technical Report on Toxicology and Carcinogenesis Studies of Dichlorvos (CAS No. 62-73-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 342. NIH Publication No. 89-2598.

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