Benzyl Alcohol

Document History
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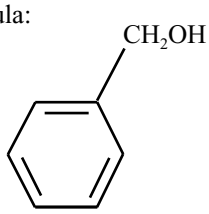
I. IDENTIFICATION

Chemical Name: Benzyl Alcohol
Synonyms: α-Hydroxy Toluene; Phenylmethanol; Phenylcarbinol
CAS Number: 100-51-6
Molecular Formula: C_7H_8O
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–6]

Physical State and Appearance: Colorless liquid
Odor Description: Faint aromatic
Odor Threshold: 5.5 ppm
Molecular Weight: 108.13
Conversion Factors: 1.0 ppm = 4.42 mg/m^3
1.0 mg/m^3 = 0.23 ppm
Melting Point: -15.3°C (4.5°F)
Boiling Point: 205°C (401°F) at 760 mm Hg
Vapor Pressure: ~0.1 mm Hg at 25°C (77°F)
Saturated Vapor Concentration: ~150 ppm at 25°C (77°F)
Flammability Limits: LEL: Not Available
Flash Point: (closed cup) 104°C (220°F)
Autoignition Temperature: 436°C (816°F)
Specific Gravity: 1.05 at 25°C (77°F)
Solubility in Water: Moderate
Stability: Stable
Reactivity and Incompatibilities: Incompatible with acids and strong oxidizers
Partition Coefficient ($K_{o/w}$): 1.1

III. USES

Used in flavors and perfumes, photographic developers, solvent for inks and dyes, antimicrobial preservative for drugs, and as a chemical intermediate.[2,4]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

Rats: LD_{50} = 1,230–3,100 mg/kg[7–10]

Symptoms reported included lethargy, depression, ataxia, coma & abnormal excitability.[8,9] Another study indicated rapid breathing and "peculiar gait" in animals dosed at sub lethal levels (down to 670 mg/kg).[7]

Rats: LD_{10} = 550 mg/kg[11]

Mice: LD_{50} = 1,580 mg/kg[8]

Symptoms reported included depression[8]

2. *Eye Irritation*

Rabbits: Instillation of undiluted benzyl alcohol (amount not specified) is reported to cause "severe response characterized by marked irritation of the conjunctive membranes and cloudiness of the cornea."[4]

Rabbits: Instillation of benzyl alcohol using the method developed by Carpenter and Smyth resulted in eye injury graded as 8 on a scale of 10. This score is described as "Excess of 5% solution gives injury up to 5.0 points [of a 20 point maximum] (15% solution gives over 5.0)."[10]

3. *Skin Absorption*

Rabbits: LD_{50} = 2,000 mg/kg (method not described)[6]

4. *Skin Irritation*

Rabbits: Irritation score of 4 on a 10-point scale reported for undiluted material. The application was apparently not occluded. The observation and scoring was performed 24 hours after application of the material.

This score is described as "slight erythema."[10]

Mice: Severe irritation resulted from application of 10% aqueous solution, occluded for 24 hours.[6]

5. Skin Sensitization

Guinea Pigs: One of 10 reported as sensitized.[1]

Guinea Pigs: No sensitization was reported to have occurred in a standard test.[6]

[Note: The actual data are not available on these two reports of sensitization tests]

6. Inhalation Toxicity

Rats: Inhalation of "saturated" vapor for 2 hours resulted in no fatalities.[10] Note that this would probably have been in excess of 100 ppm but less than 200 ppm.

Rats: Three of six rats died within 14 days following 8-hour inhalation exposure to nominal concentration of 2,000 ppm; vapor/aerosol mixture.[10]

Rats: Male rats were exposed to aerosol/vapor combinations for various times to evaluate acute inhalation toxicity:

Number of Rats	Hours Exposed	Nominal Concentration (mg/m^3)
2	4	1,100
4	8	830
4	8	450
2	8	3,110
2	4	9,060

The study notes considerable condensation in the generation apparatus at the two highest nominal concentrations, and no visible aerosol in the exposure chamber. Thus, the authors conclude that actual concentrations were considerably less than the nominal concentrations for these two highest nominal exposure groups, perhaps no more than a saturated atmosphere.

During exposure, the animals were described as being flushed and sluggish, with labored breathing.

Following the exposure, the animals were observed for 10 to 12 days. None of the animals died during exposure or the observation period. After a slight initial weight loss, the animals all later appeared normal. Gross and microscopic examination after the observation period revealed no pathological changes attributable to benzyl alcohol.[7]

Rat LC_{50}: Groups of male rats were exposed for either one 6-hour period (5 animals per group) or three 6-hour periods on successive days (4 rats per group). Nominal concentrations were 0, 175, 350, 750, or 1500 mg/m^3. The authors observed aerosol formation in the exposure chamber at concentrations of 750 and 1500 mg/m^3, which is consistent with the calculated saturated vapor concentration of approximately 660 mg/m^3 at ambient temperature. The derived LC_{50} for the single exposure groups was 1,059 mg/m^3, while that for three exposures was calculated as 1,119 mg/m^3. These were determined by the authors to be not statistically significantly different. Deaths that occurred were all in the high dose groups and were all in the first 1 to 3 days immediately after exposure. High dose animals were observed to have general weakness and ataxia/hind limb paralysis. The only effect observed at 750 mg/m^3 (170 ppm) was nasal discoloration in 2 of 4 animals. A concentration of 350 mg/m^3 (equivalent to about 80 ppm) was the NOAEL under the conditions of the test.[12]

7. Other Toxicity

a. Intraperitoneal

Rats or Guinea Pigs: LD_{50} = 400-800 mg/kg[4]

b. Intravenous

Experiments with dogs, mice, and rats to evaluate relative toxicity for use as an antimicrobial preservative indicated that both the concentration and rate of injection have a very marked effect on the toxicity.[13]

B. Subacute Toxicity

Six male rats were dosed by gavage, 5 days per week for 2 consecutive weeks, at a level of 450 mg/kg-day. Three of the rats were sacrificed and examined after the tenth treatment. The remaining three were sacrificed after an additional 10 days of observation. The animals had a slight weight loss during treatment, and those observed afterwards had slightly reduced weight gain. There were no other outward signs of toxicity noted. Organ weights were all normal and no pathological changes were observed.[7]

In another oral toxicity study with rats, groups of 10 (5 of each sex) were dosed via gavage at 0, 125, 250, 500, 1000, or 2000 mg/kg-day. Twelve doses were given over a 16-day period. All of the rats in the highest dose group died and half of those dosed at 1000 mg/kg-day also died. However, all animals in the other dose groups survived treatment. At both 1000 and 2000 mg/kg-day, the animals were lethargic and were observed to have blood around the mouth and nose and had subcutaneous hemorrhages. Rough hair coats were observed in the male animals at and above 500 mg/kg-day and also in the females at and above 250 mg/kg-day. No other adverse effects were observed.[14]

In an oral toxicity study with mice, groups of 10 (five of each sex) were dosed via gavage at 0, 125, 250, 500, 1000, or 2000 mg/kg-day. Twelve doses were given over a 16-day period. All of the mice from the highest dose group died and three of the 10 dosed at 1000 mg/kg-day also died. There were single deaths in other groups, but these were attributed to the gavage technique. All others survived the treatment. At both 1000 and 2000 mg/kg-day, the animals were found to have blood in the bladder upon necropsy. Rough hair coats and lethargy were observed in the male animals at and above 500 mg/kg-day and also in the females at and above 1000 mg/kg-day. No other adverse effects were observed.[14]

In a range-finding study in preparation for a reproductive study, groups of 10 mice were dosed by gavage at 0, 160, 325, 645, 1300, or 2595 mg/kg-day for 8 days, followed by 8 days of observation. All of the high-dose animals died after the first day and 8 of 10 animals in the 1300 mg/kg-day group died during the course of treatment. The animals in the two highest-dose groups exhibited symptoms including hunched posture, tremors, piloerection, prostration, ataxia, and dyspnea, and the surviving animals in the 1300 mg/kg-day group had reduced weight gain.[15]

In an inhalation study, six rats were exposed to an average of 248 ppm (calculated average from range of 216–270 ppm) benzyl alcohol for 4 hours per day, 5 days per week, for 2 weeks. There were two control groups of 6 rats each. One control group was subjected to the same handling regimen as the exposed animals, but without any test compound (the exposure chamber involved exposure to dried air at 32ºC (90ºF)). The second control group was kept in the same room as the other animals but was not placed in an exposure chamber. Half the animals in each group were sacrificed and examined after the final exposure period. The remaining rats were observed for an additional 10 days. There was a slightly reduced weight gain in the exposed animals and the first control group, which the authors attributed to heat stress. There were no other clinical differences. Organ weight measurements and pathology indicated no treatment-related effects.[7]

C. Subchronic Toxicity

In a 13-week oral feeding study, groups of rats, 20 per group (10 of each sex), were dosed at 0, 50, 100, 200, 400, or 800 mg/kg-day. The high-dose animals exhibited signs of neurotoxicity, including staggering, lethargy, and labored breathing and had reduced weight gain in comparison to the controls. Five of the 10 high-dose male rats exhibited blood around the nose and mouth after 8 weeks on study. Upon histopathological examination, the high-dose animals were found to have necrosis of the hippocampus and the high-dose male rats also had skeletal muscle necrosis, nephrosis of the kidney and thymic congestion, hemorrhage and atrophy. The NOAEL for rats in this study was 400 mg/kg-day.[14]

In a 13-week oral feeding study, conducted concurrently with the one immediately above, groups of mice, 20 per group, 10 of each sex, were dosed at 0, 50, 100, 200, 400, or 800 mg/kg-day. Four of 20 at the high dose and two of 20 in the 400 mg/kg-day group died during the study. A few animals in the other dose groups also died, but the authors attributed these deaths to the gavage technique rather than toxicity. The high-dose animals exhibited staggering, but only in the first 2 weeks on study. Both the 400 mg/kg-day and 800 mg/kg-day groups exhibited reduced weight gain in comparison to the controls. None of the dosed groups were found to have any significant differences from controls upon histopathological examination. The NOAEL for mice in this study was 200 mg/kg-day.[14]

D. Chronic Toxicity/Carcinogenicity

A 2-year oral study was conducted under direction of the National Toxicology Program to evaluate the carcinogenic potential of benzyl alcohol. Groups of 50 rats, 25 of each sex, were dosed, via gavage, at 0, 200, or 400 mg/kg-day for 103 weeks, while groups of mice were similarly dosed at 0, 100 or 200 mg/kg-day. There was no evidence of carcinogenicity. There was no effect on body weight gain in any group, and survival of male rats and of both male and female mice was unaffected. Survival rates of female rats were significantly reduced — by 50% — in both the 200 mg/kg-day and 400 mg/kg-day groups, but the

authors attribute this primarily to errors in the gavage procedures rather than toxicity. There were no apparent compound-related non-neoplastic effects observed. There were, however, dose-dependent reduced numbers of certain naturally occurring tumors in the exposed animals when compared to the controls. This included reduced incidence of pituitary gland neoplasms in female rats and reduced incidence of harderian gland adenomas in male mice. The NOAEL was determined to be 200 mg/kg-day in mice and 400 mg/kg-day in rats, although the reduced survival rate of female rats confounds the study to some degree.[14]

E. Reproductive/Developmental Toxicity

In a preliminary study, groups of mice (4 per group) were dosed via gavage on days 6–15 of gestation at 0, 200, 380, 720, 1370 or 2605 mg/kg-day. Animals in the two highest dose groups exhibited numerous signs of neurotoxicity, including unsteady gait, languid behavior, hunched posture, tremors, rapid and labored respirations, and hyperactivity. All four mice in the high-dose group died on the second day of treatment. Two mice in the 1370 mg/kg-day group died on the fourth day of treatment. One mouse in the 380 mg/kg-day group died from causes unrelated to toxicity. Reduced weight gain was observed in the two highest dose groups. All surviving animals were sacrificed and examined on day 17 of gestation. All four animals in the 200 mg/kg-day group had viable fetuses. Two of three mice in the 380 mg/kg-day group and three of four in the 720 mg/kg-day group also had viable fetuses. Fetuses in the other surviving mice had been resorbed. In the follow-up study, groups of four mice were dosed at either 0 or 550 mg/kg-day on days 6–15 of gestation. All were allowed to deliver and were observed for 3 days post-partum. No statistically significant effect was seen on maternal mortality although one of the 50 died after exhibiting symptoms including languid behavior and labored breathing. There was no effect on weight gain and no other signs of toxicity were observed. No effect was seen on pups per litter, post-partum survival, or pup weight gain. The authors concluded that 550 mg/kg-day was a NOAEL in this study.[11]

In a separate reproductive study, groups of 50 mice were exposed via gavage to either 0 or 750 mg/kg-day on days 7-14 of gestation. Eighteen of the 50 exposed mice died during treatment and one other died on day 15 of gestation. Surviving animals were permitted to deliver and were observed for 3 days post-partum. Reduced maternal and pup weight gains were observed in the exposed group. There was no effect on gestation index, total number of resorptions, length of gestation, pups per litter, or pup survival. The authors concluded that the study demonstrated a LOAEL of 750 mg/kg-day.[15]

F. Genotoxicity/Mutagenicity

Benzyl alcohol has been found to be negative in several Ames assays, both with and without S-9 metabolic activation. These included the *S. typhimurium* strains TA-97, 98, 100, 1535, and 1537.[16,17]

When tested in the L5178Y Mouse Lymphoma Cell Mutation test, benzyl alcohol was negative with S-9 metabolic activation. The same laboratory conducted four trials without S-9 activation, and concluded that one was positive, one negative, and two inconclusive.[18]

When tested for ability to induce chromosome aberrations in the Chinese Hamster Ovary cell test, benzyl alcohol was found to be equivocal, weakly positive, or positive in different trials. It was found to be weakly positive when evaluated for inducing sister chromatid exchanges in a Chinese Hamster Ovary cell assay.[19]

Benzyl alcohol has been uniformly negative in various *in vivo* assays for genotoxicity/mutagenicity, including *Drosophila melanogaster* sex-linked recessive lethal mutation, Mouse micronucleus and Mouse hepatocyte replicative DNA synthesis tests.[19]

G. Metabolism/Pharmacokinetics

In rabbits or rats, benzyl alcohol is rapidly metabolized to benzoic acid, which is subsequently conjugated to and excreted as hippuric acid.[20,21]

When injected intravenously in dogs at 50-100 mg/kg, the plasma concentration half-life was determined to be 1.5 hours.[13]

V. HUMAN USE AND EXPERIENCE

Observations in humans confirm that humans also rapidly metabolize benzyl alcohol to hippuric acid.[22]

Since benzyl alcohol is used as an antimicrobial preservative in injectable drugs, there have been a number of anecdotal reports regarding effects in humans via this route of exposure. Doses in the range of 99–405 mg/kg-day have been reported to be associated with the deaths of several premature infants who received benzyl alcohol as a component of intravenous medications. The Centers for Disease Control recommended doses of up to 4.5 mg/kg-day as safe for neonates. An intravenous dose of approximately 180 mg/kg-day was reported as probably contributing to

death in the treatment of a seriously ill 5-year-old child. There is also a report implicating an intravenous dose of 90 mg/kg as contributing to fatal hemolysis in a patient receiving chemotherapy, however, the author indicates this may have been complicated by the presence of sickle-cell trait in the patient.[23–25]

As part of an indoor air quality study, humans were exposed to the volatiles released from heating flooring materials, of which the predominant component was benzyl alcohol. Each of three subjects was exposed to a different concentration for a 30-minute period on 4 successive days. Two of the exposures for each subject were at non-detectable concentrations, while the other two ranged from 59 to 119 micrograms per cubic meter (13–27 ppb). There was no relationship between subjective response and concentration.[26]

Upon review of benzyl alcohol as a food additive, the European Commission's Scientific Committee on Food classified it as safe for daily intake by the general population at up to 5 mg/kg.[27]

VI. RATIONALE

No clinical signs of toxicity were observed in rats exposed 6 hours/day for 3 days at concentrations of 350 mg/m^3 (about 80 ppm) as vapor, and only minimal effects (discoloration around the nose of some animals) were observed for a mixed vapor/aerosol concentration of 750 mg/m^3 (170 ppm). In another inhalation study, rats exposed to an average concentration of about 250 ppm for 4 hours/day, 5 days per week, for 2 weeks suffered no treatment-related effects.

Subchronic and chronic gavage studies indicate no effect levels in mice and rats by the oral route of 200 mg/kg-day for mice and 400 mg/kg-day for rats. A person weighing 50 kg and breathing 8 cubic meters of air over an 8 hour period would have to be exposed to an airborne concentration of about 1,250 mg/m^3 (about 300 ppm) to receive a dose of 200 mg/kg-day.

The limited reproductive studies available have indicated a NOAEL of 550 mg/kg-day.

On balance, benzyl alcohol does not appear to be genotoxic or mutagenic.

Although there have been no published reports relating ocular or respiratory irritation from airborne exposures, it is presumed, based on contact-type acute testing in animals, that benzyl alcohol has some potential to cause such irritation.

An OEL of 10 ppm should be adequate to prevent any potential irritation while providing a substantial margin of safety below what would be expected to cause any systemic effects. Exposure at this level, if completely absorbed, would result in workplace doses in the same range as approved for the general population, or even sensitive individuals such as neonates, through food additive and medicinal use.

VII. RECOMMENDED OEL

10 ppm (44 mg/m^3) as an 8-hour time-weighted average

VIII. REFERENCES

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