1,2-EPOXYBUTANE

Document History
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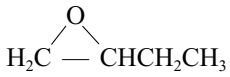
I. IDENTIFICATION[1,2]

Chemical Name: 1,2-Epoxybutane
Synonyms: Butylene oxide; 1-butene oxide; α-butylene oxide; 1,2-butene oxide; 1,2-butylene oxide; epoxybutane; BO; ethyl ethylene oxide, 2-ethyloxirane
CAS Number: 106–88–7
Molecular Formula: C_4H_8O
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1-4]

Physical State: Clear, colorless liquid
Molecular Weight: 72.12
Conversion Factors: 1 ppm = 2.95 mg/m^3
1 mg/m^3 = 0.339 ppm
Boiling Point: 62.0–64.5°C (144–147°F) at 760 mmHg
Vapor Pressure: 140 mmHg at 20°C (68°F)
Saturated Vapor Concentration: 184,000 ppm (18%) at 20°C (68°F)
Odor Description and Threshold: Sweet, disagreeable; 0.06 ppm
Flammability Limits: 3.1%–25.1% by volume in air
Flash Point: -26°C (-15°F) (closed cup)
Specific Gravity: 0.826 at 25°C (77°F)
Solubility in Water: ≈8.24% (w/w) at 25°C (77°F)
Stability: Relatively stable
Reactivity and Incompatibilities: Butylene oxide may react violently with materials having a reactive hydrogen, especially if catalyzed by acids, alkalis, or certain salts; it may polymerize exothermically.

III. USES AND VOLUME

Butylene oxide is used for the production of butylene glycol and its ester and ether derivatives. It is used to make butanolamines, surface-active agents, and gasoline additives. It is also used as an acid scavenger and stabilizer for chlorinated solvents.[1]

IV. TOXICOLOGY DATA

A. Acute Toxicity

1. Oral Toxicity

Rats: LD_{50} = 500 mg/kg (30% mixed isomers in corn oil)[1]
LD_{50} = 1000–2000 mg/kg[4-5]
LD_{50} = 630–1580 mg/kg (mixed isomers)[4]

2. Eye Toxicity

Rabbits: Moderate conjunctival irritation, slight transient corneal injury.[4] Score of 4/10 (scoring as described by Smyth & Carpenter, 1954)[5]

3. Skin Toxicity

a. Irritation

Rabbits: Prolonged and repeated exposure of intact skin resulted in scaling and redness. A single, prolonged exposure of mixed isomer resulted in blistering and necrosis (exposure concentration not cited).[4] No irritation (0.01 mL undiluted, uncovered, 24 hr).[5]

b. Absorption

Rabbits: LD_{50} = 2.1 mL/kg (1740 mg/kg) (wrapped)[5]

c. Sensitization

Butylene oxide did not cause skin sensitization in the guinea pig using a method involving four, 48-hour topical induction doses of 0.1 ml, with Freunds adjuvant injected intradermally adjacent to the third application, and topical challenge with 0.1 ml after resting for 2 weeks.[4]

4. Inhalation

Rat: LC_{Lo} (4-hr) = 4000 ppm (nominal)[5]
LC_{100} (4-hr) = 8000 ppm (nominal)[5]
LC_{100} (4-hr) = 6550 ppm[6]

Mice: LC_{50} (4-hr) = 944 ppm[6] (males)
LC_{50} (4-hr) = 1123 ppm[6] (females)

Rats, guinea pigs, and rabbits were reported to tolerate a 7-hr exposure to 400 ppm.[1]

Rats, exposed to saturated concentrations of butylene oxide (184,000 ppm) showed anesthetic effects within minutes. Exposures lasting 12 min were lethal; 6-min exposures caused some delayed deaths, all of which were caused from secondary pneumonia.[1]

B. Mutagenicity

Butylene oxide has exhibited mutagenicity in a wide range of species in a number of studies. Mutations (base-pair substitutions) were reported, usually above 500 µg/plate, in *Salmonella typhimurium* strains TA100, TA100-FR1, TA1530, and TA1535, with and without S9 metabolic activation.[6]

In tests with *Escherichia coli*, butylene oxide exhibited strain-specific mutagenic activity that was sometimes dependent on S9 activation.[6]

Butylene oxide also has been mutagenic in tests with *Schizosaccharomyces pombe, Saccharomyces cerevissiae, Klebsiella pneumoniae,* and *Neurospora crassa*.[6]

In two *Drosophila* sex-linked, recessive lethal assays, equivocal results have been reported. In one study there was no increase in lethal mutations after exposure to 1000 ppm for 7 hr. Inductions of lethal mutations, however, were reported in another study after injection of 117–233 mM solution of BO.[6]

The relative mutagenic potency of ethylene oxide (EO), propylene oxide (PO) and butylene oxide (BO) in the *Drosophila* forward mutation induction (recessive lethal mutations) assay showed the following relationship: EO>PO>BO.[7] The lowest concentrations showing positive results after 24 hour exposures were 2, 16 and 1,000 ppm, respectively.

In mouse L5178Y lymphoma assays, BO caused gene mutations with and without S9 activation.[6]

In Chinese hamster ovary cells, butylene oxide produced a dose-related increase in sister chromatid exchanges and chromosmal aberrations with and without S9 activation. Chromosomal aberrations in the assay without S9 activation only occurred at doses that were toxic to the cells, hence the assay was judged weakly positive.[6]

Unscheduled DNA synthesis studies were negative in human fibroblast cells and rat hepatocytes in culture without S9 activation.[6]

In vivo mammalian studies also were negative. No sperm abnormalities were reported in mice after exposure at up to 1000 ppm of BO for 7 hr/day, for 5 days. No dominant lethal mutations were observed in rats after similar exposures.[6]

Based on a weight-of-evidence evaluation of the data provided above, butylene oxide should be considered a genotoxic material.

C. Metabolism and Pharmacokinetics

In inhalation and gavage studies with rats, butylene oxide is reported to be extensively metabolized and eliminated. After acute exposures to 400, 1000, or 2000 ppm, a dose-related depletion of nonprotein sulfhydryl groups in liver and kidney tissue was observed. Steady-state uptake rates were reported as 0.0433 mg/kg/min at 50 ppm and 0.720 mg/kg/min at 1000 ppm. It appears that the physical and biological processes involved in absorption, metabolism, and elimination of butylene oxide are essentially linear (i.e., not metabolically saturated) over the exposure range of 50 to 1000 ppm.[4]

When rats were administered a single dose (route unspecified) of 137 mg/kg of butylene oxide, 11% of the original dose was excreted in the urine as 2-hydroxybutyl-mercapturic acid. In rabbits 4% of the original dose of 180 mg/kg was excreted as 2-hydroxbutyl-mercapturic acid.[8]

Butylene oxide reacted much more slowly than ethylene oxide and propylene oxide with glutathione transferase, a detoxication enzyme.[9] The authors concluded that this observation was consistent with the lower chemical reactivity of butylene oxide compared to the other two epoxides. Propylene oxide was metabolized at a rate 1.5–2.0 times that of ethylene oxide and the metabolism of butylene oxide could not be distinguished from the analytical background (i.e., PO>EO>>BO).

D. Developmental Toxicity

Developmental and reproductive studies were conducted with rats and rabbits exposed in stainless steel dynamic inhalation chambers to 250 or 1000 ppm of butylene oxide.[10-12] Wistar rats (N = 30–36 per group) were exposed to filtered air or butylene oxide (250 or 1000 ppm) for 7 hr/day, 5 day/week, for 3 weeks prior to mating. After

mating the animals were exposed to either filtered air or butylene oxide (250 or 1000 ppm) on gestation days 1–19. No significant effects were observed on reproduction or development. Rabbits (N = 15–23 per group) were inseminated artificially and exposed 7 hr/day to filtered air or butylene oxide (250 or 1000 ppm) for 24 days of gestation. Butylene oxide was extremely toxic to pregnant rabbits with increased mortality occurring in both dose groups. Mortality (12% at 250 ppm and 58% at 1000 ppm) was related to the development of suppurative pneumonia. Suggestive evidence (although not statistically significant) of embryofetal toxicity seen only in two litters from surviving animals in the 1000 ppm group and was considered to be related to maternal toxicity.

E. Subacute Toxicity

In a 9-day study, groups of 5 mice and 5 rats of each sex were exposed for 6 hr/day, 5 days/week, to 0, 400, 800, or 1600 ppm of butylene oxide. The 1600 ppm concentration was lethal to mice, while all rats survived this exposure without obvious signs of distress. Reduced body weight gain was seen in both species at all exposures. Inflammatory and degenerative changes of the nasal turbinates were observed in both species in the 800 and 1600 ppm groups.[13]

In a 2-week study, groups of 5 mice and 5 rats of each sex were exposed for 6 hr/day, 5 days/week, to 0, 400, 800, 1600, 3200, or 6400 ppm of butylene oxide. The 6400 and 3200 ppm concentrations were lethal to rats while all exposures of 1600 ppm and higher were lethal to mice. Reduced body weight gain was seen in rats in the 1600 and 800 ppm group and in mice in the 800 ppm group. Erratic movements and piloerection were observed in rats in the 1600 ppm group. Moderate multifocal pulmonary hemorrhage was observed in most rats exposed to 1600 ppm. In mice, moderate nephrosis was observed in some of the 1600 ppm group, while mild to moderate nephrosis was observed in some of the 800 ppm group. No adverse findings were reported at 400 ppm.[6]

The overall no-observed-adverse-effect level (NOAEL) in subacute inhalation studies was 400 ppm.

F. Subchronic Toxicity

In a 13-week study, groups of 15 mice and 15 rats of each sex were exposed for 6 hr/day, 5 days/week to 0, 75, 150, or 600 ppm of butylene oxide. No treatment-related mortality occurred. Slight decreases in body weight were apparent in both species exposed to 600 ppm. Lesions of the nasal mucosa also were observed in both species exposed to 600 ppm. There were no histopathologic effects observed in any of the animals exposed to 75 or 150 ppm.[13]

In a 13-week study, groups of 10 mice and 10 rats of each sex were exposed for 6 hr/day 5 days/week, to 50, 100, 200, 400, or 800 ppm of butylene oxide. The 800 ppm concentration was lethal to mice, with renal tubular necrosis observed in most animals. Inflammation of the nasal cavity was seen in all rats exposed to 800 ppm, but not at any lower concentrations. Inflammation of the nasal turbinates was observed in all mice exposed to 200 ppm or higher.[6]

Thus, the overall NOAEL in subchronic inhalation studies was 150 ppm.

G. Chronic Toxicity and Carcinogenicity

A 2-year carcinogenicity study was conducted by exposing groups of 50 animals per species and sex to butylene oxide by inhalation 6 hr/day, 5 days/week. Rats were exposed at concentrations of 0, 200, or 400 ppm for 103 weeks, and mice were exposed at concentrations of 0, 50, or 100 ppm for 102 weeks.[6,14]

The NTP[6] concluded there was "clear evidence" of carcinogenic activity for male rats as shown by the increased incidence of alveolar/bronchiolar adenomas or carcinomas (0/50, control; 2/50, 200 ppm; 5/49, 400 ppm) and of papillary adenomas of the nasal cavity (0/50, control; 0/50, 200 ppm; 7/50, 400 ppm). At the time of this study, the historical incidence of nasal cavity tumors and alveolar/bronchiolar adenomas and carcinomas in control male rats was 0.1%, 1.75%, and 1.41%, respectively. There was "equivocal evidence" for carcinogenic activity for female rats as shown by the presence of papillary adenomas of the nasal cavity (0/50, control; 0/50, 200 ppm; 2/50, 400 ppm). Within the respiratory system there was also an increased, concentration-related, incidence in a number of non-neoplastic lesions of the nasal cavity including inflammation, epithelial and adenomatous hyperplasia, and squamous metaplasia of the respiratory epithelium, atrophy of the olfactory epithelium, and hyperostosis (hypertrophy of bone).

There was no evidence of carcinogenic activity for male or female mice at either 50 or 100 ppm. Concentration-related increases in the incidence of non-neoplastic lesions of the nasal cavity were observed in exposed mice. These lesions included suppurative and chronic inflammation; epithelial hyperplasia; erosion and regeneration; squamous metaplasia; atrophy of the sensory epithelium; hyperplasia of the nasal gland; and inflammation

and hyperplasia of the nasolacrimal duct.[6] Since these non-neoplastic effects were observed at the lowest concentration tested the LOAEL for this study is 50 ppm.

To evaluate the carcinogenicity by skin contact, 0.1 ml of a 10% solution of butylene oxide in acetone (dose = 10 mg BO) was applied three times per week for 540 days to the clipped skin of ICR/Ha Swiss mice (N = 30). No skin tumors were observed.[15]

H. Other

The carcinogenicity of related compounds also has been investigated in similar studies. The NTP concluded that propylene oxide showed evidence of carcinogenic activity with neoplasms of the nasal cavity in both species and sexes at an exposure concentration of 400 ppm.[6] Ethylene oxide (EtO) showed evidence of carcinogenic activity with neoplasms of the lung or other organs in both sexes of mice at exposure concentrations of 50 and 100 ppm.[6] In another study EtO also showed evidence of carcinogenicity in rats with mononuclear cell leukemia in females at 10 ppm and both sexes at 33 and 100 ppm. Males also showed peritoneal mesothelioma at these latter dose levels.[6]

Both butylene oxide and propylene oxide produced neurotoxic effects in rats in an experimental model of ethylene oxide-induced axonal neuropathy.[16]

V. HUMAN USE AND EXPERIENCE

No data were available on the potential adverse effects of butylene oxide when handled as the pure material. There was a single case-report of neurotoxic effects in a 19-year-old worker exposed to an industrial solvent containing 1-bromopropane as the main component, but it also contained butylene oxide, 1,3-dioxolone, nitromethane and other components.[17] The author hypothesized that the neurotoxic effects were likely due to 1-bromopropane because it produced similar findings in rats. Ethylene oxide has been shown to produce neurotoxic effects in workers.[18]

VI. RATIONALE

Butylene oxide does not exhibit a high level of acute toxicity; however, it is moderately irritating to the eyes and slightly irritating to the skin. In subchronic studies no effects were observed at 150 ppm, but in chronic studies histological evidence of respiratory irritation was observed at the lowest dose levels of 50 ppm in mice and 200 ppm in rats. No significant adverse effects on reproductive or developmental toxicity were noted in rats or rabbits. The most significant potential adverse effect appears to be its potential to cause cancer. This effect is also a concern with the structurally similar compounds ethylene oxide and propylene oxide.

Butylene oxide was carcinogenic in rats at concentrations of 200 and 400 ppm, producing an increased incidence of nasal adenomas and alveolar/bronchiolar carcinomas. It was not carcinogenic in mice at 100 ppm, the highest level tested. The carcinogenic effects in rats occurred at concentrations that also produced recurrent degenerative/regenerative effects in the nasal cavity. These non-neoplastic changes were observed at concentrations as low as 50 ppm (LOAEL). *In vitro* genotoxicity studies have demonstrated the genotoxic potential of BO, which is not unexpected for this alkylating agent. Mechanistically, the increased cell turnover in the presence of mutagenic pressure may have enhanced the production of tumors. The *in vivo* mammalian genotoxicity tests and dermal carcinogenicity study were negative. The reason that no tumorigenic response was seen in mice, despite the chronic nasal irritation, is unknown.

In comparison, ethylene oxide was carcinogenic in the lung and other organs in two species at lower dose levels than those used for BO, with effects noted at a dose of 50 ppm for mice, and 10 ppm in female rats. The current threshold limit value (TLV®) for ethylene oxide is 1 ppm[19] and the OSHA PEL is 1 ppm with an excursion limit of 5 ppm.[19] Propylene oxide was carcinogenic in the nasal cavities of mice and rats at 400 ppm and has a TLV® of 20 ppm.[16]

An OEL guide of 2 ppm as an 8-hr TWA should minimize the risk of cancer and provide adequate protection against possible irritation of the respiratory tract.

VII. RECOMMENDED OEL

8-hr time-weighted average (TWA): 2 ppm (5.9 mg/m^3).

VIII. REFERENCES

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