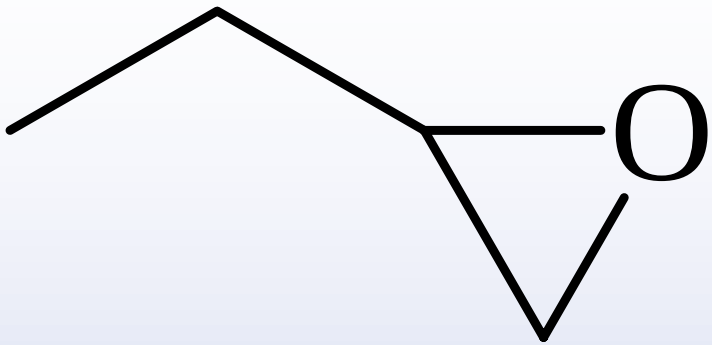
1,2-Epoxybutane



Molecular Weight: 72.1 CAS Reg. No.: 106-88-7

Use and Occurrence of 1,2-Epoxybutane

- Stabilizer for chlorinated hydrocarbons
- Chemical intermediate for glycol ethers and other compounds
- High Production Volume chemical (U.S. EPA)
  - 10 to 50 million pounds produced annually nationally
  - 260,000 employees estimated to be exposed

Carcinogenicity of 1,2-Epoxybutane

- Carcinogenicity in humans
  - No human data identified
- Carcinogenicity in experimental animals
  - Long-term inhalation studies in male and female rats and mice
  - Combined exposure studies in mice
  - Long-term skin painting studies in mice

Tumors in Male F344/N Rats Exposed to 1,2-Epoxybutane Six Hours Per Day, Five Days Per Week, for Two Years (NTP, 1988)

Tumor Site and Type		Exposure Level (ppm)			Trend Test[a]
		0	200	400	
Nasal cavity	Papillary adenomas	0/50	0/50	7/50[b]	0.0010
Lung	Alveolar / bronchiolar adenomas	0/50	1/50	1/49	n.s.
	Alveolar / bronchiolar carcinomas	0/50	1/50	4/49[b]	0.017
	Combined alveolar / bronchiolar adenomas and carcinomas	0/50	2/50	5/49[b]	0.0061

[a] Poly-3 Trend Test p-value (n.s. = not significant, $p > 0.10$).

[b] Statistically significant increase in incidence above controls by pairwise Poly-3 Test ($p \leq 0.05$).

Tumors in Female F344/N Rats Exposed to 1,2-Epoxybutane Six Hours Per Day, Five Days Per Week, for Two Years (NTP, 1988)

Tumor Site and Type		Exposure Level (ppm)			Trend Test [a]
		0	200	400	
Nasal cavity	Papillary adenomas	0/50	0/50	2/50 [b]	0.045
Thyroid gland	Follicular cell adenomas	0/45	0/48	2/48 [b]	0.044
	Follicular cell carcinomas	0/45	1/48	1/48	n.s.
	Combined follicular cell adenomas or carcinomas	0/45	1/48	3/48 [b]	0.077

[a] Poly-3 Trend Test p-value (n.s. = not significant, $p > 0.10$).

[b] Marginally significant increase in incidence above controls by pairwise Poly-3 Test ($0.05 < p \leq 0.1$).

Long-term Inhalation Studies in Mice (NTP, 1988)

- No significant increases in tumor incidence
- Survival decreases
  - Males: high-dose < low-dose
  - Females: high-dose < low-dose, controls
- Non-cancer effects on the nasal cavity
  - Extensive inflammation, erosion, regeneration, epithelial hyperplasia, and squamous metaplasia in both sexes

Combined Exposures: Long-term Gavage Studies in Mice (Henschler *et al.*, 1984)

- Study design (n=50)
  - Male and female Swiss mice
  - Oral gavage with amine base-stabilized TCE, 1,2-epoxybutane-stabilized TCE, or corn oil
  - Treated 18 months, then observed for 6 months
- Squamous cell carcinomas of the forestomach observed in 1,2-epoxybutane-stabilized TCE treated mice: 3/49 male mice, 1/48 female mice.
- No squamous cell carcinomas of the forestomach in control or amine-stabilized TCE treated mice.

Skin Painting Study in Mice (Van Duuren *et al*., 1967)

- Study design
  - Female Swiss mice (n=30)
  - 100 mg of 10% 1,2-epoxybutane solution in acetone
  - 3 times/week for 77 weeks, sacrifice at 85 weeks
- No significant increases in tumor incidence

Genotoxicity of 1,2-Epoxybutane: Non-Mammalian Systems

- Bacterial systems
  - Positive: *Salmonella* reverse mutation assays
    - Base substitution *vs.* frameshift mutation
    - Generally not influenced by metabolic activation
  - Positive: *Escherichia coli* reverse mutation and differential toxicity assays
  - Positive: *Klebsiella pneumoniae* forward mutation assay
- Fungal systems
  - Positive: *Saccharomyces cerevisiae* D3 (homozygosis)
  - Positive: *Schizosaccharomyces pombe*
  - Positive: *Neurospora crassa* (reverse mutation)

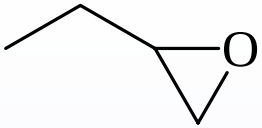
Genotoxicity of 1,2-Epoxybutane Mammalian *In Vitro* Systems

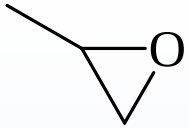
- Rat
  - Negative: unscheduled DNA synthesis in hepatocytes
  - Positive: cell transformation in embryo cells
- Mouse
  - Positive: L5178Y lymphoma cells (*hprt* and *tk* loci)
  - Negative: cell transformation in 3T3 fibroblasts
- Hamster
  - Positive: sister chromatid exchange and chromosomal aberrations in CHO cells and V79 cells (SCE only)
  - Positive: clonal and focus assays in embryo cells

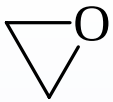
Genotoxicity of 1,2-Epoxybutane (cont.)

- Mammalian *in vivo* systems
  - Negative: dominant lethal mutations in mice (inhalation exposure)
  - Negative: covalent binding to DNA in mice (skin application)
- Other *in vivo systems*
  - Positive: eye mosaic, sex-linked recessive lethal mutation, and reciprocal translocation assays in *Drosophila*

Structure-Activity Comparisons







1,2-Epoxybutane	Propylene Oxide	Ethylene Oxide
Rats: Nasal cavity adenomas, lung carcinomas	Rats: Nasal cavity hemangiomas or hemangiocarcinomas Mice: Nasal turbinate papillary adenomas	Humans: Lymphatic, hematopoietic, and breast cancer Rats: Tumors of the lung, hematopoietic system, harderian gland, mammary gland, uterus Mice: Tumors of the hematopoietic system, brain, mesothelium

Potential Mechanism of Carcinogenicity

- Genotoxicity

Summary of Evidence

- Animal evidence
  - Nasal adenomas in rats
    - Significant number in males; Small number in females
    - Rare tumor type
  - Lung carcinomas in male rats
- Supporting evidence
  - Extensive evidence of genotoxicity
  - Structural similarity to compounds known to cause cancer

Authoritative Body Activity

- IARC (1989; 1999)
  - — Group 2B: “possibly carcinogenic to humans” (1999)
    - “limited evidence in experimental animals”
    - no human data
    - “1,2-epoxybutane is a direct-acting alkylating agent which is mutagenic in a range of systems”
  - — Change from 1989 classification in Group 3 (“not classifiable”)