4-VINYLCYCLOHEXENE DIEPOXIDE

This substance was considered by a previous Working Group, in February 1976 (IARC, 1976), under the name 1-epoxyethyl-3,4-epoxycyclohexane. Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

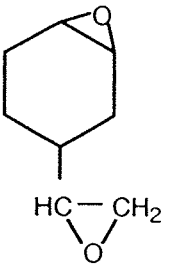
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 106-87-6
Replaced CAS Reg. No.: 25550-49-6
Chem. Abstr. Name: 3-Oxiranyl-7-oxabicyclo[4.1.0]heptane
IUPAC Systematic Name: 3-(Epoxyethyl)-7-oxabicyclo[4.1.0]heptane
Synonyms:1,2-Epoxy-4-(epoxyethyl)cyclohexane; 1-(epoxyethyl)-3,4-epoxycyclohexane; 3-(1,2-epoxyethyl)-7-oxabicyclo[4.1.0]heptane; vinylcyclohexene diepoxide; 4-vinyl-1-cyclohexene diepoxide; 4-vinyl-1,2-cyclohexene diepoxide; 4-vinylcyclohexene dioxide; 1-vinyl-3-cyclohexene dioxide; 4-vinyl-1-cyclohexene dioxide

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_8H_{12}O_2$ Relative molecular mass: 140.18

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (American Conference of Governmental Industrial Hygienists, 1986)
(*b*) *Boiling-point*: 227 °C (Lide, 1991)

(*c*) *Melting-point*: –108.9 °C (freezing-point) (American Conference of Governmental Industrial Hygienists, 1986)
(*d*) *Density*: 1.0986 at 20 °C/20 °C (Lide, 1991)
(*e*) *Spectroscopy data*: Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported (Weast & Astle, 1985; US National Toxicology Program, 1989).
(*f*) *Solubility*: Soluble in water (Lide, 1991)
(*g*) *Volatility*: 0.1 mm Hg [13 Pa] at 20 °C (American Conference of Governmental Industrial Hygienists, 1986)
(*h*) *Conversion factor*: $mg/m^3 = 5.73 \times ppm$[a]

1.1.4 *Technical products and impurities*

No data were available to the Working Group.

1.1.5 *Analysis*

No data were available to the Working Group.

1.2 Production and use

1.2.1 *Production*

4-Vinylcyclohexene diepoxide is manufactured by epoxidation of 4-vinylcyclohexene with peroxyacetic acid in an inert solvent (Wallace, 1964). Production of 4-vinylcyclohexene diepoxide provides a commercial outlet for 4-vinylcyclohexene (see monograph, p. 347) recovered as a by-product during production of vinylnorbornene (Chemical Manufacturers Association, 1991).

1.2.2 *Use*

4-Vinylcyclohexene diepoxide is used as a reactive diluent for other diepoxides and for epoxy resins derived from bisphenol A and epichlorohydrin (Union Carbide Corp., 1964). One of the applications is in embedding biological tissues in epoxy polymer for electron microscopy (Fluka Chemika-BioChemika, 1993).

1.3 Occurrence

1.3.1 *Natural occurrence*

4-Vinylcyclohexene diepoxide is not known to occur as a natural product.

1.3.2 *Occupational exposure*

Little information exists on the number of workers who may be exposed to 4-vinylcyclohexene diepoxide. The National Occupational Exposure Survey conducted by the National

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[a]Calculated from: mg/m^3 = (molecular weight/24.45)×ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

Institute for Occupational Safety and Health between 1981 and 1983 indicated that 6200 US employees were potentially exposed to a product containing 4-vinylcyclohexene diepoxide (US National Institute for Occupational Safety and Health, 1993). The estimate is based on a survey of US companies and did not involve measurements of actual exposures. Industry sectors in which potential exposure was identified include electrical lighting and wiring equipment manufacture, use, manufacture and maintenance of aircraft, missiles and space vehicles, and manufacture of measurement and control devices. Exposures in these sectors probably reflect the use of epoxy resins and glues.

There are no published data on exposure to 4-vinylcyclohexene diepoxide. Exposures may occur during manufacture of 4-vinylcyclohexene diepoxide from 4-vinylcyclohexene or in production and use of epoxy-based polyglycols and resins. Laboratory workers may be exposed during preparation of epoxy resin tissue embedding agents for electron microscopy (Ringo *et al.*, 1982).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for 4-vinylcyclohexene diepoxide in 12 countries are presented in Table 1.

Table 1. Occupational exposure limits and guidelines for 4-vinylcycohexene diepoxide

Country	Year	Concentration (mg/m^3)	Interpretation
Argentina	1991	60	TWA; potential carcinogen; skin
Australia	1983	40	TWA; suspected human carcinogen; skin
Belgium	1984	60	TWA; probable human carcinogen; skin
Canada	1986	60	TWA
Denmark	1988	60	TWA
Finland	1989	60	TWA; suspected human carcinogen
		120	STEL
Germany	1993	None	Animal carcinogen
Mexico	1984	60	TWA
Netherlands	1986	60	TWA
Switzerland	1987	60	TWA; potential carcinogen
United Kingdom	1992	60	TWA; maximum exposure limit; under review
USA			
ACGIH	1994	57	TWA; suspected human carcinogen; skin
NIOSH	1992	60	Potential carcinogen

From Arbejdstilsynet (1988); US National Institute for Occupational Safety and health (1992); American Conference of Governmental Industrial Hygienists (1993); Deutsche Forschungsgemeinschaft (1993); ILO (1993); Työministeriö (1993); UNEP (1993)

TWA, time-weighted average; STEL, short-term exposure limit; skin, absorption through the skin may be a significant source of exposure.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Skin application

3.1.1 *Mouse*

A group of 20 male albino mice [strain and age unspecified] received a daily skin application of 16 mg of a commercial sample (contaminated with water-insoluble material) of 4-vinylcyclohexene diepoxide in acetone on five days a week for 12 months. The last mouse died 21 months after the start of the treatment. Skin tumours occurred in 11/20 mice; nine were reported to be squamous-cell carcinomas and/or sarcomas (Hendry *et al.*, 1951). [The Working Group noted that no data on controls were provided.]

A group of 30 male Swiss ICR/Ha mice, eight weeks old, received skin applications of a 10% solution of 4-vinylcyclohexene diepoxide [purity unspecified] in benzene three times per week for life. The mean survival for the group was 326 days. Skin tumours occurred in 14 mice; nine were squamous-cell carcinomas. In a group of 150 controls painted with benzene, skin tumours occurred in 11 mice; one was a squamous-cell carcinoma. Of 207 untreated mice, 13 had skin tumours, one of which was a squamous-cell carcinoma [$p < 0.001$] (Van Duuren *et al.*, 1963). [The Working Group noted the carcinogenic potential of the vehicle.]

A group of 30–40 [exact number unspecified] C3H mice [sex unspecified], 13 weeks old, received skin applications of a 10% solution of 4-vinylcyclohexene diepoxide [purity unspecified] in acetone three times per week for 21 months. Of 18 mice that survived for 12 or more months, three developed skin tumours; one tumour was malignant (Weil *et al.*, 1963). [The Working Group noted the limited reporting and that no data on controls were provided.]

Groups of 60 male and 60 female B6C3F1 mice, eight to nine weeks old, each received daily skin applications of 0 (control), 2.5, 5 or 10 mg 4-vinylcyclohexene diepoxide (purity, approximately 97%) in 0.1 ml acetone on five days per week for 103 weeks. High-dose females were treated for only 85 weeks because of toxicity, and all high-dose male mice had died by week 83. At 15 months, 10 mice from each group were killed and examined; all other survivors were killed at 113 weeks of age, except for 12 high-dose females which were killed at 93 weeks. Survival at the end of the experiment was 38/50, 35/50, 4/50 and 30/50, 31/50, 15/50 for the control, low- and mid-dose groups of males and females, respectively. There was a significant increase in the incidence of squamous-cell carcinoma of the skin in males (control, 0/50; low-dose, 14/50; mid-dose, 39/50; high-dose, 42/50) and females (0/50, 6/50, 37/50, 41/50, respectively) ($p < 0.001$; logistic regression trend tests). Treatment-related non-neoplastic lesions of the skin in mice of each sex included necrotizing inflammation, hyperkeratosis and acanthosis. In female mice, there were significant increases in the incidences of granulosa-cell tumours (control, 0/50; low-dose, 0/49; mid-dose, 7/49;

high-dose, 12/50) and benign mixed tumours (0/50, 0/49, 11/49, 6/50, respectively) of the ovary ($p < 0.001$, logistic regression trend tests). Non-neoplastic lesions in the ovary included a treatment-related increase in follicular atrophy and tubular hyperplasia. The incidence of alveolar–bronchiolar adenoma or carcinoma of the lung was significantly increased in mid-dose females (control, 4/50; low-dose, 9/50; mid-dose, 11/50; high-dose, 7/50; $p = 0.032$, logistic regression test) (US National Toxicology Program, 1989; Chhabra *et al.*, 1990a).

3.1.2 *Rat*

Groups of 60 male and 60 female Fischer 344/N rats, seven to eight weeks old, received daily skin applications of 0 (control), 15 or 30 mg/animal 4-vinylcyclohexene diepoxide (purity, approximately 97%) in 0.3 ml acetone on five days per week for 105 weeks. At 15 months, 10 rats from each group were killed; all other survivors were killed at 114 weeks of age. Body weights were reduced (9–14%) in the high-dose male and female rats in comparison with controls. Survival was reduced in all groups of males (control, 7/50; low-dose, 8/50; high-dose, 4/50) and was significantly reduced ($p = 0.005$; life-table test) in high-dose females (27/50, 23/50, 15/50, respectively). There was a significant increase ($p < 0.001$; logistic regression trend test) in the incidence of squamous-cell carcinoma of the skin in treated males (control, 0/50; low-dose, 33/50; high-dose, 36/50) and females (0/50, 16/50, 34/50, respectively). The incidence of squamous-cell papillomas was increased in male rats (control, 0/50; low-dose, 3/50; high-dose, 6/50; $p = 0.015$, logistic regression, pair-wise comparison of high-dose to controls); that of basal-cell adenoma or basal-cell carcinoma was increased in males (0/50, 1/50, 6/50, respectively; $p = 0.011$, logistic regression pair-wise comparison); and that of basal-cell carcinoma was increased in females (0/50, 3/50, 4/50, respectively; $p = 0.015$, logistic regression trend test). Treatment-related non-neoplastic lesions of the skin in rats of each sex included sebaceous gland hypertrophy and acanthosis (US National Toxicology Program, 1989; Chhabra *et al.*, 1990a).

4. Other Data Relevant for an Evaluation of Carcinogenicity and Its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The metabolism of 4-vinylcyclohexene diepoxide includes hydrolysis of the epoxide groups to the respective glycols or conjugation with glutathione. Enzymatic formation of 4-epoxyethylcyclohexane-1,2-diol, 4-dihydroxyethyl-1,2-epoxycyclohexane and 4-dihydroxyethylcyclohexane-1,2-diol by epoxide hydrolase in rabbit liver microsomes showed V_{max} values of 4.7, 10.2 and 1.1 nmol/mg protein per min, respectively. The enzymatic rates of

hydrolysis of 4-epoxyethylcyclohexane-1,2-diol and 4-dihydroxyethyl-1,2-epoxycyclohexane to the tetrol had V_{max} values of 10.0 and 7.6 nmol/mg protein per min, respectively. Non-enzymatic hydrolysis was less important (Watabe & Sawahata, 1976).

Elimination of 4-vinylcyclohexene diepoxide occurred mainly via the urine. The tetrol was the major metabolite in rat urine, whereas the major metabolites in mouse urine appear to be polar conjugates (Salyers *et al.*, 1993).

4.2 Toxic effects

4.2.1 *Humans*

A case report described allergic contact dermatitis in a female electron microscopist. Sensitization was detected three months after she started using 4-vinylcyclohexene diepoxide in the laboratory. Disposable latex and polyvinyl chloride gloves were found to be permeable to 4-vinylcyclohexene diepoxide, so that dermatitis was elicited after sensitization (Dannaker, 1988).

4.2.2 *Experimental systems*

4-Vinylcyclohexene diepoxide exerts both local and systemic toxicity. Fourteen-day dermal exposure of male B6C3F1 mice to 10 mg/mouse per day resulted in epidermal hyperplasia and hyperkeratosis. At 20 mg/mouse per day, 80% died. Fischer 344 rats tolerated five times higher concentrations of the compound per skin surface area (US National Toxicology Program, 1989).

Groups of 10 female and 10 female Fischer 344 rats were treated with skin applications of 0.1 ml 4-vinylcyclohexene diepoxide in acetone (3.75–60 mg/rat per day) on five days per week for 13 weeks. As part of the same study, groups of 10 male and 10 female B6C3F1 mice were treated similarly but with doses of 0.625–10 mg/mouse per day. Rats given the highest dose had reduced body weight gain and compound dose-related redness and ulceration at the application site, diffuse sebaceous gland hyperplasia, and acanthosis and hyperkeratosis of the stratified squamous epithelium. Thymus weights were reduced in male rats. Mice showed acanthosis of the stratified squamous epithelium at the application site. Liver and kidney weights were increased in both male and female mice. In a 13-week gavage study with doses of 62.5–1000 mg/kg bw on five days per week, mice showed forestomach hyperplasia and hyperkeratosis; ovarian atrophy was seen in females and degeneration of the germinal epithelium in testis of males at dose levels of $\geq$ 250 mg/kg. In rats, hyperplasia and hyperkeratosis of the forestomach were recorded at $\geq$ 125 mg/kg, and renal tubular-cell degeneration and/or regeneration was recorded at $\geq$ 500 mg/kg (Chhabra *et al.*, 1990b).

Liver and kidney (weight increase), thymus (weight decrease) and bone marrow (hypoplasia) were additional target tissues for the toxicity of 4-vinylcyclohexene diepoxide. Most of the effects showed a strongly nonlinear dose–response relationship. In a comparative study of the ovarian toxicity of 4-vinylcyclohexene diepoxide and some related compounds over 30 days, doses required to reduce the small oocyte counts were 0.2 and 0.4 mmol/kg per day for B6C3F1 mice and Fischer 344 rats, respectively. These values are much lower and closer for the two species than the corresponding values for 4-vinylcyclohexene, which were 2.7 and > 7.4 (highest dose given) mmol/kg per day (Smith *et al.*, 1990).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

4.4 Genetic and related effects (see also Table 2 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

4-Vinylcyclohexene diepoxide was mutagenic to *Salmonella typhimurium* and to *Saccharomyces cerevisiae*. It also caused gene conversion and mitotic crossing-over in *S. cerevisiae*.

Micronuclei were induced by the compound in cells of two plant species, *Allium cepa* and *Vicia faba*.

4-Vinylcyclohexene diepoxide induced mutations at both the *hprt* and *tk* loci in cultured mammalian cells. In rodent cell lines, it induced sister chromatid exchange and chromosomal aberrations; micronuclei were not induced by a single high dose.

4-Epoxyethylcyclohexane-1,2-diol, tested in a single study, was not mutagenic to *Salmonella typhimurium*. In the same study, micronuclei but not mutations were induced at a single dose in cultured mammalian cells.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

4-Vinylcyclohexene diepoxide is produced by epoxidation of 4-vinylcyclohexene with peroxyacetic acid. It is used as a reactive diluent for other diepoxides and for epoxy resins. No data are available on levels of occupational exposure to 4-vinylcyclohexene diepoxide.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

4-Vinylcyclohexene diepoxide was tested for carcinogenicity by skin application in three studies in mice and in one study in rats. Skin application of 4-vinylcyclohexene diepoxide produced benign and malignant skin tumours in all studies in mice and in the study in rats. In one study in mice, it also increased the incidences of ovarian and lung tumours in females.

5.4 Other relevant data

4-Vinylcyclohexene diepoxide can be absorbed through the skin of rodents. Higher concentrations tend to be found in the ovary rather than in other organs, and virtually all

Table 2. Genetic and related effects of 4-vinylcyclohexene diepoxide

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	550.0000	Murray & Cummins (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation (spot test)	+	0	5000.0000	Wade *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	0	125.0000	El-Tantawy & Hammock (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	700.0000	Watabe *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	1050.0000	Frantz & Sinsheimer (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	140[c]	Turchi *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	50.0000	Mortelmans *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	0.0000	Ringo *et al.* (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	125.0000	El-Tantawy & Hammock (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	1050.0000	Frantz & Sinsheimer (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	170.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	0	500.0000	El-Tantawy & Hammock (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	?	(+)	1700.0000	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation (spot test)	+	0	5000.0000	Wade *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	0	500.0000	El-Tantawy & Hammock (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	500.0000	Mortelmans *et al.* (1986)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	+	0	3500.0000	Bronzetti *et al.* (1980)
SCH, *Saccharomyces cerevisiae* D7, mitotic crossing-over	+	0	3500.0000	Bronzetti *et al.* (1980)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	+	0	3500.0000	Bronzetti *et al.* (1980)
PLI, *Allium cepa*, micronucleus formation	+	0	700.0000	Ronchi *et al.* (1986)
PLI, *Vicia faba*, micronucleus formation	+	0	1400.0000	Ronchi *et al.* (1986)
G9H, Gene mutation, Chinese hamster V79 lung cells, *hprt* locus	+	0	140.0000	Gervasi *et al.* (1981)
G9H, Gene mutation, Chinese hamster V79 lung cells, *hprt* locus	+	0	700.0000	Turchi *et al.* (1981)
G5T, Gene mutation, mouse lymphoma L5178 cells, *tk* locus	+	0	25.0000	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary cells	+	+	3.7300	US National Toxicology Program (1989)
MIA, Micronucleus formation, Chinese hamster V79 lung cells	-	0	280.0000	Turchi *et al.* (1981)

Table 2 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster ovary cells	+	+	37.8000	US National Toxicology Program (1989)
4-Epoxyethyl cyclohexane-1,2-diol				
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	1600.0000[c]	Turchi *et al.* (1981)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	-	0	3200.0000	Turchi *et al.* (1981)
MIA, Micronucleus formation, Chinese hamster V79 lung cells	+	0	320.0000	Turchi *et al.* (1981)

[a] +, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable responses in several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
[c] Overnight incubation with the bacteria before plating, 0.1 ml/sample; negative in standard plate test

elimination occurs via the urine. Its metabolism involves hydration to a mixture of glycols and conjugation with glutathione.

4-Vinylcyclohexene diepoxide is locally toxic and, when given orally, causes ovarian degeneration in both mice and rats and testicular degeneration in mice, as well as lesser effects in other organs.

No data were available on the genetic and related effects of 4-vinylcyclohexene diepoxide in humans.

4-Vinylcyclohexene diepoxide induced gene mutation, sister chromatid exchange and chromosomal aberrations but not micronuclei in mammalian cells *in vitro*. It was mutagenic in bacteria and caused gene conversion and mitotic crossing-over in *Saccharomyces cerevisiae*.

A metabolite of 4-vinylcyclohexene diepoxide, 4-epoxyethylcyclohexane-1,2-diol, was not mutagenic to *Salmonella typhimurium*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 4-vinylcylcohexene diepoxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 4-vinylcyclohexene diepoxide.

Overall evaluation

4-Vinylcyclohexene diepoxide *is possibly carcinogenic to humans (Group 2B).*

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[1]For definition of the italicized terms, see Preamble, pp. 27–30.

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