# Vinyl cyclohexene dioxide

| CAS number: | 106-87-6 |
| --- | --- |
| Synonyms: | 4-Vinylcyclohexene diepoxide,  1,2-epoxy-4-(epoxyethyl)-cyclohexane,  3-oxiranyl-7-oxabicyclo[4.1,0] heptane, VCD |
| Chemical formula: | C8H12O2 |

Workplace exposure standard (retained)

| TWA: | **10 ppm (57 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc. 2, Sk.** |
| IDLH: | **—** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 10 ppm (57 mg/m3) is recommended to minimise the potential for adverse effects on male and female reproductive tracts in exposed workers.

## Discussion and conclusions

No specific Australian use, import, or manufacturing information for vinyl cyclohexane dioxide (VCD) is identified (NICNAS, 2016). International use includes as a reactive diluent for other diepoxides, producing epoxy resins for coatings, adhesives and inks and formulating encapsulants for various electrical applications.

The critical effects of exposure are adverse effects on male and female reproductive tracts. Carcinogenic potential is observed in animal studies but its relevance in humans *via* inhalation is unknown.

No relevant data are identified in humans. The target organs of VCD in rat and mouse are those of the reproductive system. VCD is carcinogenic in rodents. Following chronic dermal application, VCD induces benign and malignant skin tumours in male and female rats and mice. It also induces ovarian and lung tumours in female mice (ACGIH, 2018; NICNAS, 2016). Mutagenicity is demonstrated in both *in vitro* and *in vivo*. The evidence in rodents suggest that carcinogenicity may act through a mutagenic mechanism and DFG (1999) note it is a proven genotoxic carcinogen (ACGIH, 2018; HCOTN, 2008). However, the relevance of the cancers reported in animals for humans is unclear and there is a lack of data available to confirm this effect in humans through the inhalational route.

There is lack of evidence that this chemical is used or generated in Australian workplaces. Although, there is evidence for potential for carcinogenic outcomes in rodents, there is no evidence of carcinogenic potential in humans by inhalation. The current SWA TWA of 10 ppm (57 mg/m3) is recommended to be retained to protect for adverse effects in exposed workers.

## Recommendation for notations

Classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Given the evidence in experimental animals for carcinogenicity and the mutagenic potential, a review of this classification is recommended.

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended based on dermal uptake evidence and severity of effects in animals.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 10 ppm (57 mg/m3) | |
|  |
| ACGIH 2001 TLV-TWA: 0.1 ppm (0.57 mg/m3) |
| TLV-TWA recommended to minimise the potential for adverse effects on male and female reproductive tracts and cancer, reported among experimental animals.  Summary of data:   * Direct-acting mutagen: * demonstrated induction of tumours in animals both locally and distant from site of administration * No quantitative derivation of TLV-TWA; assumed to be derived by analogy to 4-vinyl cyclohexene (VCH) (TLV-TWA 0.1 ppm).   Human data:   * Mild to moderate skin irritant; occasional instances of marked skin irritation reported among exposed workers: * 1 case of severe vesiculation of skin of both feet when worker wore shoes previously contaminated with VCD * 1 case of allergic contact dermatitis in an electron microscopist within 3 mo of occupational exposure.   Animal data:   * LD50 of680 mg/kg (rabbits, dermal) * LC50 of 800 ppm (rats, 4 h); respiratory tract irritation and acute pulmonary congestion during exposure * Topical administration of VCD in acetone conducted 5 d/wk for 105 wk to groups of 60 rats of each sex at 0, 15, or 30 mg/animal; groups of 60 mice of each sex administered 0, 2.5, 5, or 10 mg/animal 5 d/wk for 103 wk: * treatment acutely necrotising, causing local ulceration * mice developed sebaceous gland hyperplasia, acanthosis and localised hyperkeratosis * caused all treated female mice marked ovarian atrophy and dose–related tubular hyperplasia * significant increase in squamous cell and basal cell papillomas and carcinomas of skin in male and female rats * increase in squamous cell carcinomas of skin in male mice and squamous cell carcinomas of skin and ovarian granulosa cell neoplasms in female mice * increased incidence of lung neoplasms in female mice considered to result from metastasis of ovarian cancer to the lung * increase in alveolar/bronchiolar adenoma and carcinoma (no further information) * Oocyte destruction in rats occurred after repeated oral intubation of 10-80 mg/kg over 30 d; no further information * Exposure reduced primordial and primary follicle oocytes in immature and mature rats; no further information * Male mice given parenteral VCD at 320 mg/kg/d for 30 d; followed by additional daily treatments for 5–30 d (no further information): * elevated plasma follicle stimulating hormone levels * significant reductions in testis and seminal vesicle weights * necrosis in the germinal epithelium   Genotoxicity   * Mutagenic in presence or absence of mammalian microsomal metabolic activation in *S. typhimurium* strains TA98, TA100 and TA1535; activity in strain TA1537 dependent on exogenous microsomal bioactivation * Direct-acting mutagen in cultured Chinese hamster V79 cells * Direct sister-chromatid exchange and chromosomal aberrations in cultured Chinese hamster ovary cells.   Insufficient data to recommend a sensitiser notation or TLV-STEL. |
| DFG 1990 Not assigned |
| MAK not assigned due to genotoxic potential.  Summary of additional data:   * An alkylating diepoxide and thus a direct mutagen in *in vitro* test systems * Dermal application to animals induced local carcinomas and tumours in ovaries and lungs in female mice (cited by ACGIH, 2018). |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2008 Not assigned |
| Evaluation of carcinogenicity and genotoxicity.  Summary of additional data:   * No data on genotoxicity and carcinogenicity in humans available * Refers to dermal study in rodents cited by ACGIH (2001) * Produces DNA adducts *in vivo* (female mice; topical application; 17–225 μmol/mouse; 1/d for 3 d); adduct levels far below levels generally found for highly potent carcinogens at comparable doses, such as benzo[a]pyrene * Increased levels of DNA adducts *in vitro* and *in vivo* * Considered a genotoxic compound that acts by a stochastic mechanism * Regarding ovarian carcinogenicity, it might exert its effect by acting as a promotor * Did not find indications that observations in animals and the proposed carcinogenic mechanism, would not occur in humans. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2016 | * No additional data * The critical health effects include systemic long-term effects (carcinogenicity, mutagenicity and reproductive toxicity) and systemic acute effects (acute toxicity from oral, dermal and inhalation exposure). |
| IARC |  | 1994 | * No additional data * Inadequate evidence in humans for carcinogenicity * Sufficient evidence in experimental animals for carcinogenicity * Concludes possibly carcinogenic to humans. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Yes |
| --- | --- |
| Is the chemical carcinogenic with a mutagenic mechanism of action? | Insufficient data |
| **Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.** | |

## Notations

| Source | Notations |
| --- | --- |
| SWA | Carc. 2, Skin |
| HCIS | Carcinogenicity – category 2 |
| NICNAS | Carc. Cat 3, Skin |
| EU Annex | Carcinogenicity – category 2, |
| ECHA | Carc. 2 |
| ACGIH | Carcinogenicity – A3, Skin |
| DFG | — |
| SCOEL | NA |
| HCOTN | Carcinogenicity – category 2 |
| IARC | Carcinogenicity – Group 2B |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
| --- |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | Adverse effects in human case study: |  |  |  |  | | Dermal LD50 ≤1000 mg/kg: | yes | 3.00 |  |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  |  | | Dermal LD50/Inhalation LD50 <10: |  |  |  |  | | *In vivo* dermal absorption rate >10%: |  |  |  |  | | Estimated dermal exposure at WES >10%: |  |  |  |  | |  |  | 3 | **consider assigning a skin notation** | | |

### IDLH

| Is there a suitable IDLH value available? | No |
| --- | --- |

## Additional information

| Molecular weight: | 140.17 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 5.73 mg/m3; 1 mg/m3 = 0.17 ppm |
| This chemical is used as a pesticide: |  |
| This chemical is a biological product: |  |
| This chemical is a by-product of a process: |  |
| A biological exposure index has been recommended by these agencies: | ACGIH  DFG  SCOEL |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (1990) 4-Vinyl-1-cyclohexene dioxide – MAK value documentation.

European Chemicals Agency (ECHA) (2019) Vinyl cyclohexene dioxide – REACH assessment.

Health Council of the Netherlands (HCOTN) (2008) 4-Vinylcyclohexene diepoxide. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2008/03OSH.

International Agency for Research on Cancer (IARC) (1994) 4-Vinylcyclohexene diepoxide. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) Epoxidised cycloaliphatic olefins: Human health tier II assessment – IMAP report.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).