# 4-Vinyl Cyclohexene

| CAS number: | 100-40-3 |
| --- | --- |
| Synonyms: | 4-Ethenylcyclohexene, VCH; 1-Vinylcyclohexene-3,  4-Vinyl-1-cyclohexene, 4-Vinylcyclohex-1-ene |
| Chemical formula: | C8H12 |

Workplace exposure standard (new)

| TWA: | **­—** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc. 2** |
| IDLH: | **—** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

## Given the limited data available from the primary sources and its carcinogenic potential in animals, a TWA is not recommended in the interim. It is recommended that a broader evaluation be conducted at the next scheduled review.

## Discussion and conclusions

4-Vinyl cyclohexene (VCH) is used as an intermediate in the manufacture of other chemicals such as polyolefins, flame retardants, fragrances and solvents. No specific Australian use, import, or manufacturing information has been identified.

Critical effects of exposure are reproductive effects including testicular degeneration and ovarian atrophy, and ovarian neoplasms and other cancers.

There are limited human studies available. Rubber workers exposed to VCH at 271 to 542 ppm, with peaks of 677 ppm, are reported to suffer from keratitis, rhinitis, headache, hypotonia, leukopenia, neutrophilia, lymphocytosis and impairment of pigment and carbohydrate metabolism.

Ovarian atrophy and testicular degeneration in mice, with a NOAEC of 250 ppm reported in a 13‑week inhalation study in rats and mice (ACGIH, 2018). The numbers of uncommon ovarian neoplasms and ovarian pathologies increases significantly among female mice in a two‑year oral gavage study in rats and mice. Slight but significantly increased incidence of tumours reported at various locations in both male mice and male rats and slight increase in female rats (ACGIH, 2018). Several sources consider VCH carcinogenic based on evidence in rats and mice, with possible relevance to humans. There are no human cancer studies available and VCH has negative results in genotoxicity studies. However, metabolites of VCH are genotoxic (ACGIH, 2018; HCOTN, 2008; NICNAS, 2016). NICNAS (2016) propose a non-genotoxic mode of action for ovarian carcinogenicity in animals. There are inconsistent data and decisions about the carcinogenic and genotoxic potential of VCH and it is unclear if a non-threshold mechanism for cancer is a critical effect in recommending a TWA.

Given the limited available relevant toxicological data and its carcinogenic potential in animals as well as the fact that no specific Australian use, import or manufacturing information has been identified, a TWA is not recommended in the interim.

Given the limited data available from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review.

## Recommendation for notations

Classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

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

There are insufficient data to recommend a skin notation.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA NA NA | |
| No report |
| ACGIH 2001 TLV-TWA: 0.1 ppm (0.44 mg/m3) |
| TLV-TWA recommended to minimise potential for reproductive effects including testicular degeneration and ovarian atrophy and generation of ovarian neoplasms and other cancers, as reported in rodents.  Summary of data:   * ACGIH concluded that it is not a direct-acting carcinogen because it requires metabolic activation to elicit the carcinogenesis * TLV-TWA based on lack of mutagenicity in standard short-term tests, finding of VCH-induced cancer in mice and clear evidence for VCH-1,2-epoxide induced carcinogenesis in rats and mice; no quantitative derivation specifics provided.   Human data:   * Russian rubber workers inhaling mean concentrations of 271–542 ppm (with peak concentrations to 677 ppm) reported to suffer from keratitis, rhinitis, headache, hypotonia, leukopenia, neutrophilia, lymphocytosis, and "impairment of pigment and carbohydrate metabolism” * Reports the highest concentrations of occupational personal measurements from a range of industries was in polymer operators and supervisors in styrene/butadiene (5.1–5.3 ppm) and in process and maintenance during vinylnorborene operations (4.9–5.3 ppm) * Not clear whether exposure has any relationship to elevated cancer risk associated with rubber industry (no further details).   Animal data:   * LC50 of 6,095 ppm (rats, inhalation) * Skin irritation after application of undiluted VCH to shaved rabbit skin rated moderate * Administration (stock solution 0.01% butylated hydroxytoluene) by gavage in corn oil at 0, 300, 600, 1,250, 2,500, or 5,000 mg/kg/d for 14 d to groups of 5 male and 5 female rats and mice: * CNS depression, tremors and gastrointestinal distress reported and all animals died at doses of 1250 mg/kg/d or more * all mice dosed with 2,500 or 5,000 mg/kg died. Tremors and inactivity observed in the mice that died * no compound-related gross or histologic changes observed * Groups of B6C3F1/CrIBR male and female mice and CDBR rats exposed 6 h/d at 0, 50, 250, or 1,000 ppm (mice) or 0, 250, 1,000, or 1,500 ppm (rats) by inhalation for total 65 exposures over 13 wk: * although exact cause of death could not be identified, treatment-related tremors, followed by death of all male mice inhaling 1,000 ppm, occurred by day 12, and 50% of female mice also died at that time * while inhaling, rats and mice appeared lethargic with, but no deaths reported * male rats developed hyaline droplet renal degeneration. Increased liver weights reported in both sexes * ovarian atrophy and testicular degeneration occurred in mice * based on ovarian/testicular pathology associated with inhaled VCH, the lowest sub‑chronic NOAEC was 250 ppm (species not provided) * Application of 45 mg in 50% benzene to the shaved dorsal skin of 30 mice, 3 d/wk for 54 wk resulted in extensive skin damage: * produced one squamous cell carcinoma a result attributed by the authors to trace concentrations of VCH hydroperoxide, a known animal carcinogen * similar skin-painting bioassay or IP injection with VCH metabolite VCH-1,2- diepoxide produced squamous cell carcinomas and sarcomas or peritoneal sarcomas, respectively, confirming earlier dermal and parenteral VCH-1,2- diepoxide studies in rodents * VCH (> 98% pure) administered by oral gavage in corn oil 5 d/wk for 2 yr at 0, 200, or 400 mg/kg/d to groups of 50 rats and mice of each sex. Following was reported: * high incidence of mortality among rats compromised the study * marginally suggestive increases in squamous cell papillomas or carcinomas in male rat skin observed * among mice, acute inflammation and epithelial hyperplasia of forestomach with assorted histopathologic changes (lung congestion, splenic red pulp atrophy, adrenal gland congestion) not necessarily dose-dependent observed * mortality among high-dose male mice confounded interpretation of the scattered instances of lymphomas and cancers of the lung * suggestion that increased numbers of adrenal gland adenomas (found only in high-dose female mice) may have been related to oral intubation * numbers of uncommon ovarian neoplasms and ovarian pathologies increased significantly among VCH-treated mice * No inhalation studies in relation to carcinogenicity * Reports that IARC found dermal studies confounded by carcinogenic contaminants and a known carcinogen was utilised as the vehicle and oral gavage studies in rats and male mice judged inadequate; but concluded there was sufficient evidence for the carcinogenicity of VCH in animals.   Genotoxicity   * VCH not mutagenic in *S. typhimurium* TA100, TA1535, TA1537, or TA98, either in the presence or absence of a metabolic activating system * In one study *S. typhimurium*, only VCH-diepoxide showed mutagenic response; expanded studies with *S. typhimurium* tester strains TA100, TA1535, TA98, or TA1537; a positive response observed only in TA100 or TA1535 * In point mutation studies with V79 cells, a significant increase in mutation frequency observed only with VCH-diepoxide.   Insufficient evidence to recommend a skin or sensitiser notation of TLV-STEL. |
| DFG 1997 Not assigned |
| No MAK assigned due to potential carcinogenicity in animals  Summary of additional data:   * No useful toxicological data in humans * Clearly carcinogenic in the female mouse after chronic oral administration; in male mouse and the male and female rat the incidence of tumours at various locations was slightly, but significantly increased (Cited by ACGIH, 2018) * Negative results in studies of genotoxic effects of VCH to date * Metabolites (vinylcyclohexene monoepoxide and diepoxide) found to be genotoxic; therefore, genotoxic mechanism assumed by DFG for carcinogenic effects in animals. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA 2009 TWA: 1 ppm |
| No report identified. |
| HCOTN 2008 Not assigned |
| Evaluation of data on carcinogenicity and genotoxicity for classification.  Summary of additional data:   * No data on genotoxicity and carcinogenicity of humans available * No carcinogenicity data available on inhalation exposure in animals * Refers to oral study in rats and mice cited by ACGIH (2018) as carcinogenetic evidence * Metabolite 4-vinylcyclohexene diepoxide is genotoxic and acts by a stochastic mechanism; plausible that 4-vinylcyclohexene is genotoxic * No indication that observations in animals, and proposed carcinogenic mechanism would not occur in humans * HCOTN recommends VCH should be considered carcinogenic to humans and be considered a genotoxic agent that acts by a stochastic mechanism. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2016 | * Based on evidence in rats and mice, considered carcinogenic, warranting hazard classification * Non-genotoxic mode of action proposed for ovarian carcinogenicity and is considered relevant to humans. |
| IARC |  | 1994 | * Possibly carcinogenic to humans (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animals. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Insufficient data |
| --- | --- |
| 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 | NA |
| HCIS | Carcinogenicity – category 2 |
| NICNAS | NA |
| EU Annex | NA |
| ECHA | NA |
| ACGIH | Carcinogenicity – A3 |
| DFG | Carcinogenicity – 2 |
| 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 |
| --- |
| Insufficient evidence to recommend a skin notation. |

### IDLH

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

## Additional information

| Molecular weight: | 108.18 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 4.42 mg/m3; 1 mg/m3 = 0.23 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 on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2000) 4-Vinylcyclohexene – MAK value documentation.

European Chemicals Agency (ECHA) (2019) 4-Vinyl Cyclohexene – REACH assessment.

Health Council of the Netherlands (HCOTN) (2008) 4-Vinylcyclohexene. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2008/04OSH.

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

NICNAS (2016) Cyclohexene, 4-ethenyl-: Human health tier II assessment.