# Crotonaldehyde

| CAS number: | 4170-30-3 |
| --- | --- |
| Synonyms: | 2-Butenal, crotonic aldehyde, β-methyl acrolein, propylene aldehyde, trans-2-butenal, trans-But-2-enal |
| Chemical formula: | C4H6O |

Workplace exposure standard (interim)

| TWA: | — |
| --- | --- |
| STEL: | — |
| Peak limitation: | **0.05 ppm (0.14 mg/m3)** |
| Notations: | **Sk.** |
| IDLH: | **50 ppm** |
| **Sampling** **and** **analysis**: The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

An interim peak limitation of 0.05 ppm (0.14 mg/m3) is recommended to protect for irritation of the eyes and upper respiratory tract in exposed workers.

Given the uncertainty within the data about the relevance of the outcomes of the animal carcinogenicity outcomes to humans, it is recommended that a review of additional sources be conducted at the next scheduled review.

## Discussion and conclusions

Crotonaldehyde is used in the manufacture of butanol and butylaldehyde. It is a highly reactive and a strong irritant.

Mutagenicity results are conflicting in *in vitro* and *in vivo* tests and reliable information on carcinogenic risk is not available. While malignant tumours are reported in chronic worker studies at 1–7 mg/m3 for 20 years, these data are not considered sufficiently robust because the potential bias of smoking and co‑exposure to other aldehydes was not controlled (DFG, 2018). Hepatocellular carcinomas and neoplastic nodules are reported in male rats in a 113 week oral study (crotonaldehyde in drinking water). However, this effect has unknown relevance for humans.

It is not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (ACGIH, 2018). Therefore, based on this evidence carcinogenicity is currently not considered to be a critical endpoint.

Data in humans demonstrate irritation after acute exposures (seconds to minutes) at concentrations as low as 0.17 ppm. A study in mice identified a 10 minute RD50 of 3.5 ppm (ACGIH, 2018; SCOEL, 2013). A peak limitation of 0.05 ppm is calculated based on the concentration of 0.17 ppm for acute exposure irritation in humans divided by an uncertainty factor of two and the result rounded down to 0.05 ppm. This concentration is considered to protect irritative effects and to reduce the risks of systemic effects.

## Recommendation for notations

Not classified as a 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.

A skin notation is recommended based on evidence in animals.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 2 ppm (5.7 mg/m3) | |
|  |
| ACGIH 2001 TLV-Ceiling: 0.3 ppm (0.86 mg/m3) |
| TLV-Ceiling recommended to minimise the potential for rapidly acting irritation of the eyes and upper respiratory tract.  Summary of data:  Human data:   * In volunteers, 4.1 ppm produced lacrimation in 30 sec and was highly irritating to the nose and upper respiratory tract in 15 min * Conversely, brief exposures at 15 ppm did not produce any irritation * 45 ppm for a few seconds produced conjunctival irritation * 8 industrial cases of corneal injury reported * injury healed after 48 h * no further information.   Animal data:   * LD50: 26 mg/kg (guinea pigs, dermal) * RD50: 3.5 ppm (mice, 10 min); considered equipotent with formaldehyde * 113 wk drinking water rat study induced hepatocellular carcinomas (2/27) and neoplastic nodules (9/27) in rats, significantly higher incidences than the control group * this effect has unknown relevance to humans.   Genotoxicity and mechanism   * Conflicting mutagenicity results in *Salmonella typhimurium;* not mutagenic and direct-acting mutagen outcomes in 2 different reports * Formed DNA adducts in cultured Chinese hamster ovary cells, in rat primary hepatocytes and in human fibroblasts and lymphoblast * Mechanism of carcinogenesis related to its potent DNA-protein cross-linking properties.   TLV-Ceiling based on 4.1 ppm rapid irritant effects and *via* analogy with TLV-Ceiling for formaldehyde.  Insufficient data to recommend sensitiser notations. |
| DFG 2018 Not assigned |
| No MAK assigned due to genotoxic and carcinogenic properties.  Summary of additional data:   * Considered highly reactive compound and causes mutagenic and cytotoxic effects * Covalent DNA bonding was observed in liver, lung, kidney and epidermis of mice and rats *in vivo*; binds to DNA *in vitro* * Low dermal LD50 values and evidence of rapid skin presentation warrant skin notation * No clear evidence for contact sensitisation * 9 malignant tumours in 150 aldehyde factory workers exposed to concentrations of  1–7 mg/m3 for 20 yr * smoking and exposure to other aldehydes not controlled * cannot draw dose-response relationship * Insufficient dose-response data in relation on carcinogenicity. |
| SCOEL 2013 NA |
| No health-based OEL can be derived based on current state of knowledge.  Summary of additional data:   * Irritation in humans reported after acute exposures (seconds to minutes) at 0.17–15 ppm * Crotonaldehyde-protein adducts have been found in the brains of patients with Alzheimer’s disease and in human skin * Crotonaldehyde-DNA adducts have been detected in human liver, leukocytes and mammary glands. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN NA NA |
| No report. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2016 | * Rats exposed at 1.2 mg/m3 for 3 mo demonstrated changes in motor activity and blood haemoglobin levels; non-guideline study * Due to systemic availability and genotoxicity, can play a role in human carcinogenesis. * limited information is not sufficient to warrant hazard classification * Based on the critical systemic long-term (mutagenicity), systemic acute and local health effects, the chemicals could pose an unreasonable risk to workers if not adequately controlled. |
| IARC |  | 1997 | * Inadequate evidence in humans and animals for carcinogenicity. |

### 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 | NA |
| HCIS | NA |
| NICNAS | NA |
| EU Annex | NA |
| ECHA | NA |
| ACGIH | Carcinogenicity – A3, Skin |
| DFG | Carcinogenicity – 3B, H (skin) |
| SCOEL | NA |
| HCOTN | NA |
| IARC | Carcinogenicity – Group 3 |
| 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? | Yes |
| --- | --- |

## Additional information

| Molecular weight: | 70.09 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = Number mg/m3; 1 mg/m3 = Number 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) (2018) Crotonaldehyde – MAK value documentation.

International Agency for Research on Cancer (IARC) (1995) Volume 63, Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. IARC Monographs on the evaluation of the carcinogenic risk to humans.

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

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – crotonaldehyde.