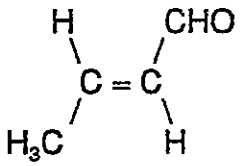
CROTONALDEHYDE

CAS: 4170-30-3

2-Butenal; Crotonic aldehyde; β-Methyl acrolein; Propylene aldehyde; trans-2-Butenal

C_4H_6O



Skin

TLV–CEILING, 0.3 ppm (0.86 mg/m³)
A3 – Animal Carcinogen

1965: TLV–TWA, 2 ppm, proposed
1967–1997: TLV–TWA, 2 ppm
1976–1986: TLV–STEL, 6 ppm
1987: TLV–STEL, deleted
1995: A3, Animal Carcinogen; proposed
1996–present: A3
1997: TLV–CEILING, 0.3 ppm; Skin; A3, Animal Carcinogen; proposed
1998: TLV–CEILING, 0.3 ppm; Skin; A3
1998: Documentation revised

Chemical and Physical Properties

Crotonaldehyde is a colorless, flammable, mobile liquid with a pungent, suffocating odor. Upon contact with air or light, this substance turns pale yellow in color. The odor threshold is reported as 0.12 ppm.[1] Chemical and physical properties include:[2]

Molecular weight: 70.09
Specific gravity: 0.8531 at 20°C
Melting point: –76.5°C
Boiling point: 104°C
Vapor pressure: 30 torr at 20°C
Vapor density: 2.41 (air = 1)
Flash point: 12.78°C, open cup
Explosive limits: upper, 15.5%; lower, 2.95% by volume in air
Solubility: in water, 18.1 g/100 g at 20°C, 19.2 g/100 g at 5°C; miscible in all proportions with most organic solvents
Conversion factors at 25°C: 1 ppm = 2.85 mg/m³; 1 mg/m³ = 0.35 ppm

Crotonaldehyde is highly flammable and a dangerous fire risk. The commercial product is the trans isomer.

Major Uses or Sources of Occupational Exposure

Crotonaldehyde is used in organic synthesis, in the manufacture of butyl alcohol and butylaldehyde, and as a warning agent in fuel gases.

Animal Studies

Acute

Topical application of crotonaldehyde to guinea pigs resulted in an LD_{50} of 26 mg/kg body-weight.[3]

Skog,[4] in comparing the toxicities of a number of lower aliphatic aldehydes, stated that crotonaldehyde produced the same signs of intoxication as acrolein. The LC_{50} for a 30-minute exposure of rats was 1500 ppm for crotonaldehyde. Pulmonary edema was observed in the rats after the fatal exposure at 1500 ppm. Rinehart[5] reported the LC_{50} for 30 minutes as 600 ppm, a value considerably less than that found by Skog.[4] Rinehart[5] considered crotonaldehyde to be a deep lung irritant, similar to phosgene and acrolein, with an acute toxicity about five times less than that of acrolein. Rinehart[5] found 100 ppm of crotonaldehyde to be a lethal concentration for rats in a 4-hour exposure. Changes in pulmonary performance resulted from single exposures at 10 ppm for 200 minutes. Rats did not survive a 10-minute exposure at 1650 ppm; effects include respiratory distress, an excitatory stage, and terminal convulsions.[5]

Crotonaldehyde was among the more potent α, β-unsaturated aldehydes to the murine respiratory tract (being only slightly less irritating than acrolein and formaldehyde).[6] Although differences in the breathing patterns between mouse strains was evident, the 10-minute respiratory depression (RD_{50}) values were similar (Swiss–Webster = 3.5 ppm; B6C3F1 mice = 4.9 ppm).[6] Ten-minute RD_{50} values for crotonaldehyde in male and female F344 rats were 23.2 and 20.5 ppm, respectively.[7] Babiuk et al.[7] concluded that the rat RD_{50} data were too variable to be utilized in evaluation potential human sensory irritation of airborne chemicals and that mice were far more responsive than rats to aldehyde-induced irritation. Schaper[8] concluded from an evaluation of 40 compounds that there was a consistent (R^2 = 0.88 to 0.90) relation between the mouse RD_{50} and the TLV. Using the highest correlation between TLV and RD_{50} for male Swiss–Webster mice (R^2 = 0.90), the TLV (0.03 × 3.5 ppm) would correspond to 0.1 ppm.[8] Steinhagen and Barrow[6] pointed out that a TLV of 2 ppm for crotonaldehyde was inconsistent with that for other aldehydes, being at least one order of magnitude too high based on the mouse RD_{50} relationship.

Carcinogenicity

The carcinogenic activities in F344 rats of crotonaldehyde and N-nitrosopyrrolidine, which is metabolized to crotonaldehyde, were compared.[9] Groups of rats were treated with either crotonaldehyde (0.6 mmol or 6.0 mmol) or N-nitrosopyrrolidine (0.6 mmol) in their drinking water for 113 or 84 weeks, respectively. At the lower concentration, crotonaldehyde induced neoplastic lesions of the liver in 9 of 27 rats; 2 rats developed hepatocellular carcinomas, and 9 rats had neoplastic nodules. Altered liver cell foci were observed in 23 of 27 rats. At the higher concentration, crotonaldehyde caused moderate to severe liver damage in 10 of 23 rats. No preneoplastic or neoplastic lesions were observed in

these rats. The remaining 13 rats of this group developed altered liver cell foci. The incidences of tumors and foci were significantly higher than those of the concurrent control group. N-Nitrosopyrrolidine induced hepatocellular carcinomas in 20 of 23 rats, liver neoplastic nodules in 16 of 23 rats, and altered liver cell foci in 23 of 23 rats.[9] Thus, crotonaldehyde appears to be a less potent hepatic carcinogen than N-nitrosopyrrolidine.

Genotoxicity Studies

Reports concerning bacterial mutagenicity of crotonaldehyde conflict. Cooper et al.[10] concluded that crotonaldehyde was not mutagenic in *Salmonella typhimurium* strain TA100. Neudecker et al.,[11] however, concluded from similar studies with the same tester strain (using extended preincubation conditions) that the compound was a direct-acting mutagen.

Crotonaldehyde was clastogenic in *Drosophila*, producing sex-linked recessive lethal mutations and reciprocal translocations.[12]

Crotonaldehyde forms DNA adducts in cultured Chinese hamster ovary (CHO) cells,[13] in rat primary hepatocytes,[14] in human fibroblasts[15] and lymphoblasts.[14] Crotonaldehyde's reaction is specific for deoxyguanosine,[16,17] and it is consistent with that observed for related low-molecular-weight α, β-unsaturated carbonyls.[18]

Pharmacokinetic/Metabolism Studies

The mechanism of crotonaldehyde-induced carcinogenesis is related to its potent DNA-protein crosslinking properties.[19] The extent of the biochemical damage induced by crotonaldehyde exposure is dependent upon the glutathione status in the target tissue, as reductions in reduced glutathione precede overt cellular toxicities. At the LD_{10}, parenteral crotonaldehyde reduced male F344 rat hepatic cytochrome P-450 and cytochrome *c* reductase activities 33% and 77%, respectively, when glutathione was depressed some 30% compared to control.[20]

Human Studies

Sim and Pattle[21] reported that 15-minute exposures at 4.1 ppm crotonaldehyde were highly irritating to the nose and upper respiratory tract and produced lacrimation in human volunteers in 30 seconds. On the other hand, Rinehart[5] found that 15 ppm for the same duration of exposure was detected as a strong but not intolerable odor, and no irritation was reported for brief exposures; brief exposures, after a few seconds at 45 ppm, proved very disagreeable with conjunctival irritation prominent. From these discrepant results, it may be that analytical differences may be a factor.

In a series of eight cases of corneal injury from industrial exposure to crotonaldehyde, healing was complete in 48 hours; the severity of exposure was not specified.[22]

TLV Recommendation

Marked discrepancies in the results of controlled inhalation trials with volunteers exposed to crotonaldehyde[5,21] have made it difficult to interpret the human irritant concentration for this compound. These discrepancies have been attributed to possible analytical errors between the two methods used.[23] Despite requests made in previous editions of this

documentation,[24] neither industrial experience nor additional controlled human trials have come to the attention of the TLV Committee. It is the judgment of the TLV Committee that the results of the mouse RD_{50} protocol[6] are more consistent with the Sim and Pattle[21] conclusion than with that published by Reinhart.[5] The mouse RD_{50} relation with TLV for related aldehydes[8] suggests that control of crotonaldehyde concentrations in workplace air to 0.1 ppm would be consistent with other irritants. It has been the practice of the TLV Committee to assign a ceiling value to rapidly-acting irritants. Crotonaldehyde is a genotoxic[11–17] animal carcinogen[9] and is assigned to the A3, animal carcinogen, category. Given that crotonaldehyde is a rapidly-acting irritant, producing lacrimation and upper respiratory tract irritation within 30 seconds of exposure at 4.1 ppm,[21] and it is equi-potent to formaldehyde in the mouse RD_{50} assay,[6] a TLV–Ceiling of 0.3 ppm is assigned, by way of analogy with the ceiling limit for formaldehyde (for which considerable data on human ocular and upper respiratory tract irritation exist; see the Formaldehyde TLV Documentation). In view of the guinea pig percutaneous LD_{50} value,[3] the skin designation is considered appropriate.

Other Recommendations

OSHA PEL: The OSHA PEL–TWA for crotonaldehyde is 2 ppm.[25] The PEL is consistent with the previously recommended ACGIH TLV. Crotonaldehyde was one of the 160 substances whose PEL was unchanged and was not evaluated during the 1989 OSHA rulemaking on air contaminants — permissible exposure limits.

NIOSH REL/IDLH: NIOSH established a REL–TWA of 2 ppm for crotonaldehyde by concurrence with the OSHA PEL [Ex 8-47, Table N3A].[26] NIOSH established an IDLH value of 50 ppm for this substance.[27]

ACGIH Rationale for TLVs that Differ from the PEL or REL: Crotonaldehyde's capacity as a rapidly-acting irritant producing lacrimation and nose and upper respiratory tract irritation in humans within 30 seconds of exposure at 4.1 ppm,[21] and the mouse RD_{50} assay data, considered equi-potent to formaldehyde,[6] warrant reduction of the TLV to a TLV–Ceiling of 0.3 ppm. The positive genotoxicity data[11–17] and the induction of neoplastic liver lesions and hepatocellular carcinomas in rats[9] are considered sufficient to assign the A3, animal carcinogen, classification.

NTP Studies: An inhalation toxicity study of crotonaldehyde in mice and rats was terminated by NTP in December 1986. A prechronic gavage study and pharmacokinetic studies have been completed, but no technical report was prepared.[28] Crotonaldehyde was positive in the *Salmonella* assays, in the *Drosophila* tests for both sex-linked recessive lethal and reciprocal translocation mutations, and in the cultured Chinese hamster ovary (CHO) cells assay for increased frequencies of both chromosomal aberrations and sister-chromatid exchanges. NTP withdrew crotonaldehyde from the mouse lymphoma assay.

Carcinogenic Classification

MAK: Group B, justifiably suspected of having carcinogenic potential.
TLV: A3, animal carcinogen.

Other Nations

Australia: 2 ppm (1990); Federal Republic of Germany: no MAK value, skin, Group B carcinogen, justifiably suspected of having carcinogenic potential (1997); United Kingdom: withdrew its limits (1997).

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