CROTONALDEHYDE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Crotonaldehyde

Chem. Abstr. Serv. Reg. No.: 4170-30-3
Chem. Abstr. Name: 2-Butenal
IUPAC Systematic Name: Crotonaldehyde
Synonyms: 2-Butenaldehyde; crotonal; crotonic aldehyde; crotylaldehyde; 1-formylpropene; β-methylacrolein; propylene aldehyde

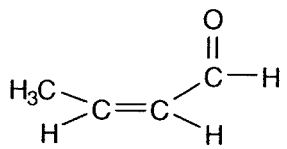
***cis* Isomer**

Chem. Abstr. Serv. Reg. No.: 15798-64-8
Chem. Abstr. Name: (Z)-2-Butenal
IUPAC Systematic Name: (Z)-Crotonaldehyde
Synonyms: *cis*-2-Butenal; *cis*-crotonaldehyde

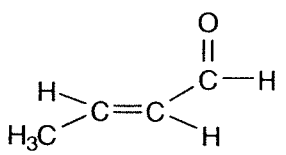
***trans* Isomer**

Chem. Abstr. Serv. Reg. No.: 123-73-9
Chem. Abstr. Name: (E)-2-Butenal
IUPAC Systematic Name: (E)-Crotonaldehyde
Synonyms: 2(E)-Butenal; *trans*-2-butenal; *trans*-2-buten-1-al; *trans*-crotonal; *trans*-crotonaldehyde

1.1.2 Structural and molecular formulae and relative molecular mass



cis



trans

C_4H_6O Relative molecular mass: 70.09

1.1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid with a pungent odour (Eastman Chemical Co., 1994)

(*b*) *Boiling-point*: 104–105 °C (Lide, 1993)

(*c*) *Melting-point*: –74 °C (Lide, 1993)

(*d*) *Density*: 0.8495 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [1457]; grating [29705]), ultraviolet [418], nuclear magnetic resonance (proton [11669]) and mass [57] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Soluble in water (150 g/L at 20 °C), acetone, benzene, diethyl ether and ethanol (Eastman Chemical Co., 1991; Lide, 1993)

(*g*) *Volatility*: Vapour pressure, 32 mm Hg [4.3 kPa] at 20 °C; relative vapour density (air = 1), 2.4 (Budavari, 1989; Eastman Chemical Co., 1994)

(*h*) *Stability*: Readily dimerizes when pure; slowly oxidizes to crotonic acid (Budavari, 1989); polymerizes to become inflammable and explosive (Eastman Chemical Co., 1994)

(*i*) *Reactivity*: Lower explosive limit, 2.15% at 24 °C; reacts violently with bases, strong oxidizing agents and polymerization initiators (Eastman Chemical Co., 1994)

(*j*) *Octanol/water partition coefficient (P)*: log P, 0.63 (United States National Library of Medicine, 1994)

(*k*) *Conversion factor*: $mg/m^3 = 2.87 \times ppm$[1]

1.1.4 Technical products and impurities

Crotonaldehyde is available commercially at a purity of 90–99%. The commercial product consists of > 95% *trans* and < 5% *cis* isomer. A typical specification for crotonaldehyde is as follows: minimal purity, 90%; maximal acidity (as crotonic acid), 0.15%; maximal water content, 8.5%; aldol, 0.1% max; butyraldehyde, 0.02% max; low-boiling-point compounds (including acetaldehyde [see IARC, 1987a] and butyraldehyde), 0.20% max; butyl alcohol, 0.15 max; and high-boiling-point compounds, 1.0% max (Blau *et al.*, 1987; Eastman Chemical Co., 1993; Spectrum Chemical Mfg Corp., 1994). The trade names for *trans*-crotonaldehyde include Topanel CA.

1.1.5 Analysis

Gas chromatography (GC) is the method most often used for the identification and determination of crotonaldehyde. Several methods have been developed for its quantitative determination in the presence of saturated aldehydes, including sulfitometric determination of double bonds and potentiometric titration with bromine in methanol (Blau *et al.*, 1987). Selected methods for the determination of crotonaldehyde in various matrices are presented in Table 1.

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[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

Table 1. Methods for the analysis of crotonaldehyde

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on sorbent coated with 2-(hydroxymethyl)piperidine on XAD-2; desorb with toluene	GC/FID & GC/MS	2 µg/sample	Eller (1994)
	Draw air through midget bubbler buffer; analyse as crotonaldehyde containing hydroxylamine/formate oxime derivative	DPP	ND	Eller (1994)
	Adsorb on glass-fibre filter coated with DNPH and phosphoric acid; extract with acetonitrile	HPLC/UV	93 µg/m^3 (0.56 mg/sample)	US Occupational Safety and Health Administration (1990)
	Draw air through midget impinger containing acidified DNPH and isooctane; extract DNPH derivatives with hexane:dichloromethane (70:30) solution; evaporate to dryness; dissolve in methanol	Reversed-phase HPLC/UV	NR	US Environmental Protection Agency (1988)
Engine exhaust	Absorb in aqueous acid solution of DNPH; extract hydrazone derivative with hexane	CGC	NR	Kachi *et al.* (1988)

GC, gas chromatography; FID, flame ionization detection; MS, mass spectrometry; DPP, differential pulse polarography; ND, not determined; DNPH, 2,4-dinitrophenylhydrazine; HPLC/UV, high-performance liquid chromatography/ultraviolet detection; NR, not reported; CGC, capillary gas chromatography

A method for identifying carbonyl compounds, including crotonaldehyde, in environmental samples involves derivatization with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride, followed by GC–mass spectrometry (Le Lacheur et al., 1993). A similar method for the determination of low-relative-molecular-mass aldehydes formed by the ozonation of drinking-water, including crotonaldehyde, involves derivatization with *O*-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine hydrochloride and analysis by high-resolution capillary GC. The limits of detection with GC–electron capture detection and GC–mass spectrometry with ion selective monitoring were 1.2 and 11.2 µg/L, respectively (Glaze *et al.*, 1989).

A method similar to that of the United States Environmental Protection Agency (1988) (see Table 1) has been described that can be used for ambient air, industrial emissions and automobile exhaust (Lodge, 1989).

Several sampling methods for the assessment of personal exposures to airborne aldehydes, including crotonaldehyde, due to emissions from methanol-fuelled vehicles were evaluated. Derivatization of aldehydes was used to enhance the integrity of the samples and to facilitate analysis. 2,4-Dinitrophenylhydrazine was found to provide better sensitivity and resolution of the hydrazones of crotonaldehyde than the other derivatization agents, (2-hydroxymethyl)-

piperidine and *N*-benzylethanolamine. Passive and active samplers containing 2,4-dinitrophenylhydrazine were also evaluated (Otson *et al.*, 1993).

Another method for the determination of acrolein and crotonaldehyde in automobile exhaust is based on bromination of their *O*-benzyloxime derivatives, followed by GC–electron capture detection (Nishikawa *et al.*, 1987).

1.2 Production and use

1.2.1 Production

The most widely used method for the production of crotonaldehyde is aldol condensation of acetaldehyde, followed by dehydration. A process involving direct oxidation of 1,3-butadiene (see IARC, 1992) to crotonaldehyde with palladium catalysis has also been reported (Baxter, 1979; Blau *et al.*, 1987).

Crotonaldehyde is produced by four companies in Japan and by one company each in China, Germany, India and the United States of America (Chemical Information Services, Inc., 1994).

1.2.2 Use

The main use of crotonaldehyde in the past was in the manufacture of *n*-butanol (Baxter, 1979), but this process has been largely displaced by the oxo process. Currently, the most extensive use of crotonaldehyde is in the manufacture of sorbic acid; crotonic acid is made commercially by oxidation of crotonaldehyde and 3-methoxybutanol by the reaction of methanol with crotonaldehyde, followed by reduction (Blau *et al.*, 1987).

Crotonaldehyde has been used as a warning agent in fuel gases, for locating breaks and leaks in pipes (Budavari, 1989). It also has been used in the preparation of rubber accelerators, in leather tanning, as an alcohol denaturant (Sax & Lewis, 1987) and as a stabilizer for tetraethyllead (see IARC, 1987b).

1.3 Occurrence

1.3.1 Natural occurrence

Crotonaldehyde occurs in emissions from the Chinese arbor vitae plant (Isidorov *et al.*, 1985) and in gases emitted from volcanoes (Graedel *et al.*, 1986). It has been detected in biogenic emissions from pine (0.19 μg/m^3) and deciduous (0.49 μg/m^3) forests in Europe and in remote, high-altitude areas with scarce vegetation (e.g. Nepal; 0.24–3.32 μg/m^3) (Ciccioli *et al.*, 1993). Crotonaldehyde also occurs naturally in many foods (Feron *et al.*, 1991). (See also section 1.3.4.)

1.3.2 Occupational exposure

The National Occupational Exposure Survey conducted between 1981 and 1983 indicated that 387 employees in the United States were potentially exposed occupationally to crotonaldehyde (United States National Institute of Occupational Safety and Health, 1994a). The

estimate is based on a survey of companies and did not involve measurements of actual exposures.

The concentrations of crotonaldehyde measured in various occupational settings in 1982–92 by the Finnish Institute of Occupational Health (1994) were all below the occupational exposure limit of 6 mg/m^3 [range unspecified] recommended in Finland. A total of 24 industries were listed, which included manufacture of electric and electronic equipment, plastic, glass and metal products, and pulp and paper.

In a bakery in Finland, crotonaldehyde was measured at 0.23 mg/m^3 near a pan used for frying doughnuts and pastries (Linnainmaa *et al.*, 1990). In a chemical plant in the United States, the concentration in general area air samples varied from not detected to 3.2 mg/m^3 and those in two personal samples were 1.9 and 2.1 mg/m^3 (Fannick, 1982). In an occupational survey at a printing and finish plant in the United States, crotonaldehyde was not detected in either area or personal samples (detection limit, 0.7–2.1 mg/m^3) (Rosensteel & Tanaka, 1976). It was detected at a concentration of 1–7 mg/m^3 in a factory producing aldehydes in Germany (Bittersohl, 1975).

1.3.3 Air

Crotonaldehyde has been detected in exhaust gases from both gasoline engines, at 0.09–1.33 ppm [0.26–3.82 mg/m^3] (Kuwata *et al.*, 1979; Nishikawa *et al.*, 1987), and diesel engines, at 0.01–0.04 ppm [0.03–0.12 mg/m^3] (Creech *et al.*, 1982; Lipari & Swarin, 1982). In a study of light-duty vehicles with catalysts and fuelled with natural gas, the emission rate of crotonaldehyde was 1.87 mg/kg fuel (Siewert *et al.*, 1993). The emission from heavy-duty engines run with natural gas was 0.12 mg/kW h [0.03 mg/MJ] and that of diesel engines 0.42 mg/kW h [0.12 mg/MJ] (Gambino *et al.*, 1993). In another study with diesel engines, the crotonaldehyde emissions were 2.8 mg/bhp h [1.04 mg/MJ] from base fuel, 1.2 mg/bhp h [0.44 mg/MJ] from fuels with ethylhexyl nitrate-containing additives and 1.0 mg/bhp h [0.37 mg/MJ] from fuels with peroxide-containing additives (Liotta, 1993).

Crotonaldehyde has been determined as an odorous constituent in aircraft emissions. In the United States, it was emitted by model jet engines operating at idling power at concentrations of 0.35–0.98 ppm [1.0–2.81 mg/m^3] (Rossi, 1992). In Japan, concentrations of 0.007–0.051 ppm [0.02–0.15 mg/m^3] were measured about 50 m behind a low-smoke combustor jet engine at idling power (Miyamoto, 1986).

Crotonaldehyde was detected in cigarette smoke at 10–228 µg/cigarette (Kuwata *et al.*, 1979; IARC, 1986), in emissions from wood-burning fireplaces at 6–116 mg/kg (Lipari *et al.*, 1984), in smoke from the burning of 5 kg of polypropylene in a 27-m^3 room at 1.1 ppm [3.16 mg/m^3] (Woolley, 1982) and in thermal degradation products of steel-protection paints at 6 mg/m^3 (Henricks-Eckerman *et al.*, 1990). It was also identified in off-gases of polyurethane foam at 40–80 °C and 90% relative humidity (Krzymien, 1989). Crotonaldehyde was released from seven of 11 samples of food packaging during heating in a microwave oven, at concentrations of 0.10–4.5 µg/in^2 [0.016–0.70 µg/cm^2] (McNeal & Hollifield, 1993).

1.3.4 Food

Crotonaldehyde was found in many fruits (e.g. apples, guavas, grapes, strawberries and tomatoes) at concentrations of < 0.01 ppm [mg/kg]; in cabbage, cauliflower, Brussels sprouts, carrots and celery leaves at concentrations of 0.02–0.1 ppm; in bread, cheese, milk, meat, fish and beer at concentrations of 0–0.04 ppm; and in wine at concentrations of 0–0.7 ppm (Feron *et al.*, 1991). It was detected in samples of various liquors at < 0.02–0.21 ppm (Miller & Danielson, 1988). It has also been identified in wheat flavour essence (McWilliams & Mackey, 1969) and in beef fat heated at 150 °C in nitrogen (Yamato *et al.*, 1970).

1.3.5 Other

Crotonaldehyde was detected qualitatively in one of 42 human milk samples from volunteers in four cities (Pellizzari *et al.*, 1982).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for the mixture of *cis* and *trans* isomers and the *trans* isomer of crotonaldehyde in several countries are given in Table 2.

2. Studies of Cancer in Humans

Bittersohl (1975) recorded cases of cancer diagnosed between 1967 and 1972 among 220 people employed in a factory for the production of aldehydes in the former German Democratic Republic. Air measurements showed concentrations of crotonaldehyde in the workroom in the range of 1–7 mg/m^3; other chemicals were also present. Nine malignant neoplasms were found in men: two squamous-cell carcinomas of the oral cavity, five squamous-cell carcinomas of the lung, one adenocarcinoma of the stomach and one adenocarcinoma of the colon. On the basis of crude comparisons with national figures, the author suspected an excess cancer risk among the employees. [The Working Group noted that the data were too sparse to be conclusive.]

3. Studies of Cancer in Experimental Animals

Oral administration

Rat: Groups of 23 and 27 male Fischer 344 rats, six weeks of age, were given 0, 0.6 or 6.0 mmol/L crotonaldehyde (purity, > 99%) in distilled drinking-water [0, 42 or 421 mg/L] for 113 weeks. Survival was similar in all groups; 17, 13 and 16 rats in the three groups survived to 110 weeks. Throughout the study, those rats receiving the high dose of crotonaldehyde had lower body weights than either the controls or those at the low dose. Gross lesions and representative samples from all major organs [unspecified] were taken for microscopic

Table 2. Occupational exposure limits for crotonaldehyde

Country	Year	Concentration (mg/m^3)	Interpretation
Australia	1991	6 (*cis* and *trans*)	TWA
Belgium	1991	5.7 (*cis* and *trans*)	TWA
Bulgaria	1993	0.5 (*cis* and *trans*)	STEL
Denmark	1991	6 (*cis* and *trans*, and *trans*)	TWA
Finland	1993	6 (*cis* and *trans*)	TWA; skin notation
		17 (*cis* and *trans*)	STEL
France	1991	6 (*trans*)	TWA
Germany	1993	None (*trans*)	TWA; justifiably suspected of having carcinogenic potential
Italy	1993	6 (*cis* and *trans*)	TWA
Netherlands	1994	6 (*cis* and *trans*)	TWA
Russian Federation	1991	0.5 (*trans*)	STEL
Switzerland	1994	6 (*trans*)	TWA; skin notation
United Kingdom	1993	6 (*trans*)	TWA
		18 (*trans*)	STEL
USA			
ACGIH	1994	5.7 (*cis* and *trans*)	TWA
NIOSH	1994	6 (*cis* and *trans*)	TWA
OSHA	1994	6 (*cis* and *trans*)	TWA

From ILO (1991); Deutsche Forschungsgemeinschaft (1993); Environmental Chemicals Data and Information Network (1993); United Kingdom Health and Safety Executive (1993); Työministeriö (1993); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Arbeidsinspectie (1994); Schweizerische Unfallversicherungsanstalt (1994); United States National Institute of Occupational Safety and Health (1994b); United States Occupational Safety and Health Administration (1994); TWA, time-weighted average; STEL, short-term exposure limit

examination; particular attention was paid to lesions in the liver, including altered liver-cell foci. Hepatocellular carcinomas were seen in 0/23 control rats, 2/27 at the low dose and 0/23 at the high dose; and neoplastic nodules were found in 0/23 controls, 9/27 at the low dose [$p = 0.01$] and 1/23 at the high dose. Altered liver-cell foci [considered by the authors to be precursors of hepatocellular neoplasms] were observed in 1/23 controls, 23/27 at the low dose ($p < 0.001$) and 13/23 at the high dose ($p < 0.001$). Liver damage, reported as moderate to severe and including fatty metamorphosis, focal liver necrosis, fibrosis and cholestasis, was seen only in 10/23 rats given the high dose [$p < 0.001$]; none of these 10 animals had preneoplastic or neoplastic lesions. With the exception of two transitional-cell papillomas of the bladder among animals receiving the low dose, no increase in the frequency of tumours was observed (Chung *et al.*, 1986a).

4. Other Data Relevant to 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

No specific information was available on the absorption and distribution of crotonaldehyde, and little information is available on its metabolism; however, it is a substrate for aldehyde dehydrogenase (Cederbaum & Dicker, 1982). It has been reported to be conjugated with glutathione with or without glutathione *S*-transferase (Boyland & Chasseaud, 1967; Maniara *et al.*, 1990; Esterbauer *et al.*, 1991; Stenberg *et al.*, 1992; Wang *et al.*, 1992); and 3-hydroxy-1-methyl- and 2-carboxyl-1-methyl-mercapturic acids have been reported in the urine of rats after exposure to crotonaldehyde (Gray & Barnsley, 1971).

4.2 Toxic effects

4.2.1 Humans

Crotonaldehyde is a potent eye, respiratory and skin irritant (Coenraads *et al.*, 1975). In humans, exposure to crotonaldehyde at 4.1 ppm [11.8 mg/m^3] for 15 min was highly irritating to the nose and upper respiratory tract, with lachrymation after 30 sec. Brief exposure to 45 ppm [129 mg/m^3] was very disagreeable, and conjunctival irritation was the predominant reaction (Rinehart, 1967). A textile worker was reported to have become sensitized to crotonaldehyde (Shmunes & Kempton, 1980).

4.2.2 Experimental systems

Crotonaldehyde causes eye, respiratory and skin irritation in animals. The concentration that reduces the respiratory rate to 50% was reported to be 3.5 ppm [10.0 mg/m^3] in mice and 23.2 ppm [66.6 mg/m^3] in rats (Steinhagen & Barrow, 1984; Babiuk *et al.*, 1985).

After crotonaldehyde was administered by gavage to male and female Fischer 344 rats and B6C3F1 mice at doses of 2.5, 5, 10, 20 or 40 mg/kg bw per day on five days per week for 13 weeks, dose-related mortality was observed in rats at doses $\geq$ 5 mg/kg bw per day, but no deaths were seen in mice. Dose-related lesions of the forestomach (hypertension, inflammation, hyperkeratosis and necrosis) were seen in rats at doses $\geq$ 10 mg/kg bw per day and in mice at 40 mg/kg bw per day. Acute inflammation of the nasal cavity was seen in rats at doses $\geq$ 5 (males) and 20 mg/kg bw per day (females) (Wolfe *et al.*, 1987).

Intraperitoneal injection to rats of crotonaldehyde at 450 μmol/kg bw [31.5 mg/kg bw] decreased cytochrome P450 levels to 67% and ethylmorphine *N*-demethylase activity to 23% of control levels within 24 h (Cooper *et al.*, 1992). [Figure 2 of the paper shows that cytochrome P450 reductase activity at 24 h was 70% of the control value but not significantly different.]

Crotonaldehyde inhibits chemotaxis and adherence of human polymorphonuclear leukocytes *in vitro* (Bridges *et al.*, 1977, 1980; Bridges, 1985). Exposure of human polymorphonuclear cells *in vitro* inhibited superoxide anion production (Witz *et al.*, 1985); this effect may be related to decreases in surface and soluble sulfhydryl groups (Witz *et al.*, 1987). Intraperitoneal treatment of mice with crotonaldehyde resulted in necrosis of the thymus and splenic atrophy (Warholm *et al.*, 1984).

The compound is ciliostatic *in vitro* (Dalhamn & Rosengren, 1971). It inhibits the activities of some enzymes *in vitro*, including cytochrome P450 (Cooper *et al.*, 1987a) and aldehyde dehydrogenase (Dicker & Cederbaum, 1984, 1986).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 Humans

No data were available to the Working Group.

4.4.2 Experimental systems (See also Table 3 and Appendices 1 and 2)

(a) DNA adducts

Crotonaldehyde binds to DNA and induces DNA–protein cross-links *in vitro*. It modifies DNA by forming cyclic 1,N^2-propanedeoxyguanosine. Both the 1- and the N^2 positions of guanine are involved in base-pairing, hence the presence of the cyclic adduct may lead to mutation (Chung *et al.*, 1986b). With a ^{32}P-postlabelling technique, authentic 1,N^2-propanedeoxyguanosine was shown to co-chromatograph with DNA of the skin of Sencar mice that had been treated topically *in vivo* with 1.4 mmol [98 mg] crotonaldehyde (Chung *et al.*, 1989). Exocyclic 1,N^2-propanodeoxyguanosine adducts detected by ^{32}P-postlabelling, however, occur *in vivo* in the absence of exposure to either crotonaldehyde or acrolein. The estimated total numbers of adducts in DNA from liver were 1.0–1.7/10^6 guanine bases for mice, 0.2–1.0 for rats and 0.3–2.0 for humans (Nath & Chung, 1994).

Not only propano-adducts but also small quantities of etheno-adducts can be detected after incubation of crotonaldehyde with deoxyadenosine or deoxyguanosine. The reaction probably involves autoxidation to an epoxide intermediate (Chen & Chung, 1994).

(b) Mutagenicity

SOS repair functions were induced in *Escherichia coli* PQ37, and a weak SOS response was obtained in *Salmonella typhimurium* TA1535/pSK1002. Crotonaldehyde induced both forward and reverse mutations in *S. typhimurium* TA100, provided that a preincubation protocol was used.

Table 3. Genetic and related effects of crotonaldehyde

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
PRB, SOS chromotest, *Escherichia coli* PQ37	–	0	53	Eder *et al.* (1992)
PRB, SOS chromotest, *Escherichia coli* PQ37	(+)[c]	0	0.00	Eder *et al.* (1993)
PRB, SOS (*umu*) induction assay, *Salmonella typhimurium* TA1535 pKS 1002	(+)	0	21	Benamira & Marnett (1992)
ECB, DNA–protein cross-linking, *Escherichia coli* HB101 pUC13, modified filter binding assay	+	0	175	Kuykendall & Bogdanffy (1992)
SAF, *Salmonella typhimurium* BA9, forward mutation, liquid assay	+[d]	0	43	Ruiz-Rubio *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	21	Neudecker *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	+	100	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation, preincubation assay	+	0	70	Neudecker *et al.* (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation, preincubation assay	–	0	75	Cooper *et al.* (1987b)
SA0, *Salmonella typhimurium* TA100, reverse mutation, preincubation assay	+[d]	+	5	Lijinsky & Andrews (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation, preincubation assay	+[e]	0	200	Eder *et al.* (1992)
SA4, *Salmonella typhimurium* TA104, reverse mutation	+	0	20	Marnett *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Lijinsky & Andrews (1980)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167	Haworth *et al.* (1983)
SAS, *Salmonella typhimurium* BA9, reverse mutation, liquid assay	+[d]		43	Ruiz-Rubio *et al.* (1984)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+		3500 inj	Woodruff *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–		4000 feed	Woodruff *et al.* (1985)
DMH, *Drosophila melanogaster*, heritable translocation	+		3500 inj	Woodruff *et al.* (1985)
URP, Unscheduled DNA synthesis, primary rat hepatocytes *in vitro*	–		7	Williams *et al.* (1989)
CGC, Chromosomal aberrations, spermatogonia treated, spermatocytes observed, mouse *in vivo*	+		300	Moutschen-Dahmen *et al.* (1976)
CGG, Chromosomal aberrations, spermatogonia treated, spermatogonia observed, mouse *in vivo*	+		300	Moutschen-Dahmen *et al.* (1976)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	0	21	Chung *et al.* (1984)
***, Binding (covalent) to nucleosides and 5′-mononucleotides *in vitro*	+	0	70	Eder & Hoffman (1992)
BVD, Binding (covalent) to DNA in mouse skin *in vivo*	+		300 top × 15	Chung *et al.* (1989)

[a] +, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; 0, not tested
[b] LED, lowest effective dose; HID, highest effective dose. In-vitro tests, mg/ml; in-vivo tests, mg/kg bw; 0,00, dose not reported
[c] Ethanol used as solvent in place of dimethyl sulfoxide
[d] Negative in plate incorporation assay
[e] Positive with and without metabolic activation with a threefold higher cell density at 35 µg/ml
***, Not included on profile

Sex-linked recessive lethal mutations and reciprocal translocations were induced in *Drosophila melanogaster* injected with crotonaldehyde. The compound did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes.

It induced chromosomal aberrations in the spermatogonia of mice after administration in the drinking-water or by injection.

5. Summary and Evaluation

5.1 Exposure data

Crotonaldehyde is produced principally as an intermediate for the production of sorbic acid. It was formerly used in large amounts in the production of *n*-butanol.

Crotonaldehyde occurs naturally in foods and is formed during the combustion of fossil fuels (including engine exhausts), wood and tobacco and in heated cooking oils. Human exposure occurs from these sources and may occur during its production and use.

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of crotonaldehyde to humans.

5.3 Animal carcinogenicity data

Crotonaldehyde was tested for carcinogenicity in one study in male rats by administration in the drinking-water. Increased incidences of hepatic neoplastic nodules and altered liver-cell foci were seen, but these were not dose-related.

5.4 Other relevant data

Crotonaldehyde is a substrate for aldehyde dehydrogenase and forms conjugates with glutathione, in the presence or absence of glutathione transferase. Mercapturic acid metabolites have been identified in urine.

Crotonaldehyde is a potent irritant, and it has been reported to interfere with immune function.

Crotonaldehyde did not induce DNA damage in rat hepatocytes *in vitro* in a single study. It was mutagenic to insects and bacteria. It bound to DNA of mouse skin *in vivo* after topical application and to DNA *in vitro* and caused formation of DNA–protein cross-links.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of crotonaldehyde.

There is *inadequate evidence* in experimental animals for the carcinogenicity of crotonaldehyde.

Overall evaluation

Crotonaldehyde *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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