Crotonaldehyde; CASRN 123-73-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Crotonaldehyde

File First On-Line 06/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	06/01/1991*

*A comprehensive review of toxicological studies was completed (07/27/05) - please see section II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Crotonaldehyde
CASRN — 123-73-9
Primary Synonym — Trans-2-butenal

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Crotonaldehyde
CASRN — 123-73-9
Primary Synonym — Trans-2-butenal

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Crotonaldehyde
CASRN — 123-73-9
Primary Synonym — Trans-2-butenal
Last Revised — 06/01/1991

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen

Basis — Based on no human data and an increased incidence of hepatocellular carcinomas and hepatic neoplastic nodules (combined) in male F344 rats. The possible carcinogenicity of crotonaldehyde is supported by genotoxic activity and the expected reactivity of croton oil and

aldehyde. Crotonaldehyde is also a suspected metabolite of N-nitrosopyrrolidine, a probable human carcinogen.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Only one animal carcinogenicity study of crotonaldehyde is available; it is limited by the use of only one sex of one species. In addition, fewer tumors were observed in the high-dose group than in the low- dose group.

Crotonaldehyde (>99% pure, in 85% aqueous solution) was administered to male F344 rats (23-27/group) ad libitum in the drinking water at 0, 0.6 or 6.0 mM (0, 42 or 421 mg/L, respectively) for 113 weeks (Chung et al., 1986). Survival rates of the dosed groups did not differ significantly from controls (approximately 63%). In the high-dose group there was approximately a 10% decrease in body weight starting at about week 8, suggesting an MTD had been reached. There was a statistically significant increase in the incidence of hepatocellular neoplasms (including neoplastic nodules and hepatocellular carcinomas) in the low-dose group. The incidences were 0/23, 9/27 (33%) and 1/23 (4%) in the control, low- and high-dose groups, respectively. The incidences of hepatocellular carcinomas alone were 0/23, 2/27 and 0/23, respectively. The incidence of enzyme-altered liver foci, which are considered precursors of neoplasms, was 1/23 (4%), 23/27 (85%) and 13/23 (57%) in the control, low- and high-dose groups, respectively. The increased incidences in both the low- and high-dose groups were statistically significant relative to controls; the incidences of enzyme altered liver foci also showed a statistically significant positive trend with dose (Wymer and Rice, 1991). The decreased incidence of neoplastic and preneoplastic lesions at the higher dose was not explained. Bladder tumors, an unusual finding, were noted in 2/27 rats in the low-dose group, but not in controls or in the high-dose group.

II.A.4. Supporting Data for Carcinogenicity

The results of Salmonella mutagenicity assays are variable, possibly due to the use of different methods. Liquid suspension methods indicate that crotonaldehyde is mutagenic (Neudecker et al., 1981; Lutz et al., 1982; Ruiz- Rubio et al., 1984; Lijinsky and Andrews, 1980), while the results of plate incorporation studies were negative (Simmon et al., 1977; Florin et al., 1980; Cooper et al., 1987, 1988). Crotonaldehyde was negative for mitotic recombination in Saccharomyces cerevisiae strain D3 (Simmon et al., 1977).

Crotonaldehyde induced chromosome aberrations and SCE in CHO cells (Galloway et al., 1987). Crotonaldehyde (without metabolic activation) has been shown in vitro to react with the deoxyguanosine nucleotide of DNA to form 1,N2-propanodeoxyguanosine, a 1,N2-cyclic guanine adduct (Chung et al., 1984). Crotonaldehyde was administered in the food (0 or 4000 ppm) or by injection (0 or 3500 ppm) to adult male Drosophila melanogaster (Woodruff et al., 1985). The injected animals showed a significant increase over controls in the percent lethals (0.36% vs. 0.05%) and in reciprocal translocations. There was no difference in the sex-linked lethal mutations in the animals that received the substance in their food.

Crotonaldehyde is a possible metabolite of N-nitrosopyrrolidine, which has been classified B2, a probable human carcinogen (Gray and Barnsky, 1971).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1989

The 1989 Health and Environmental Effects Document for Crotonaldehyde has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 03/07/1991

Verification Date — 03/07/1991

A comprehensive review of toxicological studies published through July 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for Crotonaldehyde and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Crotonaldehyde
CASRN — 123-73-9
Primary Synonym — Trans-2-butenal

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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Wymer, L. and G. Rice. 1991. U.S. EPA, Cincinnati, OH. Memorandum to R. Schoeny, U.S. EPA, Cincinnati, OH, May 20. Statistical significance of the reported incidences of hepatocellular neoplasms and enzyme altered liver foci in F344 rats in Chung et al., 1986.

VII. Revision History

Substance Name — Crotonaldehyde
CASRN — 123-73-9
Primary Synonym — Trans-2-butenal

Date	Section	Description
06/01/1991	II.	Carcinogenicity assessment on-line
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.
08/15/2005	II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — Crotonaldehyde
CASRN — 123-73-9
Primary Synonym — Trans-2-butenal
Last Revised — 06/01/1991

- 123-73-9
- C4-H6-O
- CROTONALDEHYDE, (E)-
- ETHYLENE GLYCOL, DIPROPIONATE
- 1,2-ETHANEDIOL, DIPROPANOATE
- 2-Butenal, (E)-
- (E)-2-Butenal
- ALDEHYDE CROTONIQUE [French]
- beta-METHYL ACROLEIN
- Crotenaldehyde
- Crotonal
- Crotonaldehyde
- Crotonic aldehyde
- E-2-BUTENAL
- Ethylene dipropionate
- Ethylene propionate
- NCI-C56279
- Propylene aldehyde
- RCRA WASTE NUMBER U053
- Topanel
- Topanel CA
- TRANS-CROTONALDEHYDE
- trans-2-BUTENAL
- 2-BUTENAL (TRANS)