MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 16, 2002

TO: Crontonaldehyde File (CAS# 4170-30-3)

FROM: Marco Bianchi, Air Quality Division, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for crotonaldehyde is 9 µg/m³ based on a 1-hr averaging time. The following references or databases were searched to identify data to determine the ITSL/IRSL: IRIS-online, HEAST, NTP Management Status Report online, RTECS, EPB-CCD, EPB library, CAS-onIine, NLM-online, IARC-online, NIOSH Pocket Guide, and ACGIH Guide.

According to the American Conference of Governmental Industrial Hygienists (ACGIH) documentation (1998), crotonaldehyde is a colorless, flammable, mobile liquid with a pungent, suffocating odor. The odor threshold is 0.12 ppm. The ACGIH adopted a short-term-exposure limit (STEL), or ceiling level in 1998 of 0.3 ppm (0.86 mg/m³). This value replaced a Threshold Limit Value (TLV) recommendation of 2 ppm (5.7 mg/m³) for crotonaldehyde based on the irritancy of acrolein. Since that time, new information has become available to revise TLV to the current STEL value.

The literature review of this chemical found marked discrepancies in the results of animal and human studies. The ACGIH documentation stated that Skog (1950), reported an LC50 for a 30-minute exposure of rats at 1500 ppm for crotonaldehyde. Pulmonary edema was observed in the rats after fatal exposures at 1500 ppm. However, Rinehart (1967), reported the LC50 for 30 minutes as 600 ppm, a value considerably less 1500 ppm. Rinehart 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 found 100 ppm of crotonaldehyde to be a lethal concentration for rats for a 4-hour exposure. Changes in pulmonary performance resulted from single exposures at 10 ppm for 200 minutes. Rats did not survive exposure at 1650 ppm for 10 minutes; effects include respiratory distress, an excitatory stage, and terminal convulsions.

Crotonaldehyde was among the more potent α,β-unsaturated aldehydes to the murine respiratory tract (being only slightly less irritating than acrolein and formaldehyde).

Although differences in the breathing patterns between the mouse strains was evident, the 10-minute respiratory depression (RD50) values were similar (Swiss-Webster = 3.5 ppm; B6C3F1 mice = 4.9 ppm). Ten-minute RD values for crotonaldehyde in male and female F344 rats were 23.2 and 20.5 ppm, respectively. Babiuk et al. concluded that the rat RD50 data were too variable to be utilized in evaluating potential human sensory irritation of airborne chemicals and that mice were far more responsive than rats to aldehyde-induced irritation. Schaper concluded from an evaluation of 40 compounds that there was a consistent (R2 = 0.88 to 0.90) relation between the mouse R050 and TLV. Using the highest correlation between the TLV and RD50 for male Swiss-Webster mice (R2 = 0.90), the TLV (0.03 x 3.5 ppm) would correspond to 0.1 ppm. Steinhagen and Barrow 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 relationship.

Crotonaldehyde has also shown limited carcinogenic activity in rats. Although the EPA weight- of-evidence has classified this compound as a possible human carcinogen (Classification C), only one animal carcinogenicity study is available. It is limited by the use of only one sex of one species. Additionally, fewer tumors were observed in the high dose group than in the low-dose group. In this study, crotonaldehyde 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. 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 pre-neoplastic or neoplastic lesions were observed in these rats. The remaining 13 rats of this group developed altered liver cell foci. The incidence of tumors and foci were significantly higher than those of the concurrent control group. However the decreased incidence of neoplastic and pre-neoplastic lesions at the higher dose was not explained.

The mechanism of crotonaldehyde-induced carcinogenesis is related to its potent DNA protein crosslinking properties. 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 LD10, parenteral crotonaldehyde reduced male F344 rat hepatic cyctochrome P-450 and cytochrome c reductase activities 33% and 77%, respectively, when glutathione was depressed some 30% compared to control.

As was similar in the acute studies, there are conflicting reports concerning bacterial mutagenicity of crotonaldehyde. Cooper et al. concluded that crotonaldehyde was not mutagenic in Salmonella typhimurium strain TA 100. Neudecker et al., however, concluded from similar studies with the same tester strain (using extended pie-incubation conditions) that the compound was a direct-acting mutagen. Crotonaldehyde was clastogenic in Drosophila, producing sex-linked recessive lethal mutations and reciprocal translocations. This compound also forms DNA adducts in cultured Chinese hamster ovary cells, in rat primary hepatocytes, in human fibroblasts and lymphoblasts.

Crotonaldehyde's reaction is specific for deoxyguanosine, and it is consistent with that observed for related low-molecular-weight R-unsaturated carbonyls.

In human studies, Sim and Pattle (1957) reported that 15-minute exposures to crotonaldehyde at 4.1 ppm were highly irritating to the nose and upper respiratory tract, and produced lacrimation in human volunteers in 30 seconds. On the other hand, Rinehart found 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. Analytical differences may be a factor in these study discrepancies. 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.

In addition to the ACGIH documentation for crotonaldehyde, other toxicity information obtained for this chemical evaluation was limited to studies obtained from TSCA 8(e) submissions. One submission by Kodak (1965) described crotonaldehyde toxicity in a health hazard summary. Crotonaldehyde vapor causes eye, mucous membrane and lung irritation. The lethal concentration LC50 for a 30 min. exposure in rats is 1400 ppm. Most deaths occurred from lung injury 6-24 hrs after exposure. The maximum duration of exposure to vapor concentrations near saturation at which no deaths occurred in rats is 1-min. In rats exposed for 6 hrs. to a calculated crotonaldehyde vapor of 130-160 ppm, 5 out of 6 rats died 24-48 firs post-exposure. Exposures for 6 firs to 35-100 ppm caused 0/6 deaths in rats. In animals, given single doses of crotonaldehyde by mouth, injection, or skin applications the effects are severe irritation. Moderate toxicity is observed in single dose administration by mouth to rats: the LD50 being determined at 0.16 gm/kg and 0.3 gm/kg. The liquid caused severe eye injury and skin burns when held in contact with the skin. Men exposed experimentally for 10 minutes to 4 ppm of vapor experienced transient eye and upper respiratory tract irritation. In summary, the major effects of crotonaldehyde are eye and respiratory tract irritation from vapor exposure; skin irritation and eye bums from liquid contact. At low concentrations the vapor causes prompt transient symptoms of eye and respiratory tract irritation. In another Kodak TSCA 8(e) submission (1961), a 6-hr LC50 was listed at <0.48 mg/L but >0.16-0.28 mg/L; however, only three rats were exposed for each experiment, each having differing exposure times. test chamber air-flows, and post-exposure observation times.

During this chemical review process, a National Toxicology Program (NTP) 13-week rat gavage study abstract of crotonaldehyde was also discovered. An attempt was made to obtain the complete study, but the NTP Management Report stated that a technical report was not prepared for this 13-week study. The abstract stated that crotonaldehyde was administered for 13 weeks via gavage in corn oil to F344 rats and B6C3F1 mice (10/sex/group) at dose levels of 0, 2.5, 5, 10, 20, and 40 mg/kg. Compound related mortality was observed in rats of both sexes at 5, 10, 20, and 40 mg/kg, while all mice survived to termination. Mean body weights were significantly decreased for the 40 mg/kg male rats at termination. Compound-related gross necropsy lesions observed in male and female rats at 20 and 40 mg/kg were thickened

forestomach or nodules. No compound-related gross necropsy lesions were noted for the mice. Microscopic lesions were observed in the stomach of the mice and rats and in the nasal cavity of the rats. Stomach lesions in the mice included hyperplasia of the epithelial lining of the forestomach in most of the 40 mg/kg males and females and chronic active inflammation of the forestomach in two 40 mg/kg males. Stomach lesions in the rats included hyperplasia of the forestomach epithelium in the males and females at 10, 20, and 40 mg/kg. Nasal lesions in the rats consisted of acute inflammation in the males as low as 20 mg/kg and females as low as 5 mg/kg.

In summary, crotonaldehyde is a rapidly-acting irritant producing lacrimation and nose and upper respiratory tract irritation in humans. It was found to induce neoplastic liver lesions and hepatocellular carcinomas in rats; however, only one sex of one test specie was used in the bioassay. Fewer tumors and altered liver foci were found in the high dose group than in the low-dose group making this data questionable for use in cancer risk-based modeling. Likewise, data from the 13-week subchronic study is questionable to be used to develop an RfD, since it was only presented in an abstract format. According to the AQD Rules governing ITSL derivations, data derived from an OEL takes precedence over data derived from other studies, provided the studies are not adequate to derive an RfC or RfD. This leaves the ACGIH STEL value to be used to derive ITSL. The STEL recommendation from the ACGIH stated that the marked discrepancies in the results of controlled inhalation trials with volunteers exposed to crotonaldehyde 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. It is the judgment of the TLV Committee that the results of the mouse RD50 protocol are more consistent with the Sim and Paille conclusion than with that published by Reinhart. The mouse RD50 relation with the TLV for related aldehydes 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. 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 exists.

The ITSL was determined as follows:

ACGIH STEL = 0.3 ppm or 0.86 mg/m^3

0.86 $mg/m^3 \div 100 = 0.0086\ mg/m^3$

0.0086 $mg/m^3 \times 1000\ \mu g/mg = 8.6\ \mu g/m^3$

The ITSL for crotonaldehyde = 9 $\mu g/m^3$ based on a 1-hr. averaging time.

References:

1. Documentation of Threshold Limit Values and Biological Exposure Indices Supplemental. 1998. Crotonaldehyde. American Conference of Governmental Industrial Hygienists (ACGIH), 6th Edition Supplemental.

2. Chung Fung-Lung et al. 1986. Induction of liver tumors in F344 rats by crotonaldehyde. Cancer Research 46, 1285-1289

3. TSCA 8(e) submittal. 1992. Initial submission: Summary of range-finding tests on crotonaldehyde with cover letter dated 09/08/92. Mellon Institute of Industrial Research, University of Pittsburgh. TSCA document # 88-920009348.

4. TSCA 8(e) submittal. 1992. Initial submission: Acute inhalation toxicity study of 2-butenol (crotonaldehyde) in rats with cover letter dated 09/21/92. Eastman Kodak Company. TSCA document # 88-9200 10705.

5. Wolfe G. W. et al. 1987. Thirteen week subchronic toxicity study of crotonaldehyde (CA) in F344 rats and B6C3FI mice (Abstract). Toxicology, 7, 209.