MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

May 2, 1994

TO: File for Benzaldehyde (CAS # 100-52-7)

FROM: Marco Bianchi

SUBJECT: Initial Risk/Secondary Risk Screening Level

The initial risk screening level (IRSL) for benzaldehyde is 0.4 $\mu g/m^3$ based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL/IRSL: IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide, ACGIH Guide, and the NTP #378 - Toxicology and Carcinogenesis Studies of Benzaldehyde.

Benzaldehyde is a natural constituent of several species of plants and insects. It is found in several essential oils such as hyacinth, citronella, orris, cinnamon, and sassafras. It has also been identified in the defensive excretions of harvester ants and millipedes. Humans are generally exposed to benzaldehyde through foodstuffs and according to one estimate, the adult ingestion rate of this compound is 48.2 mg/day.

Benzaldehyde has been described as being a narcotic to humans at high concentrations. In two case studies, the first of which, one woman committed suicide by consuming an oral dose of 50-60 ml of the compound, while the second, a man was revived from near death after consuming an oral dose of 40 ml of o-hydroxybenzaldehyde. It is estimated that an oral dose of 600-900 mg/kg of benzaldehyde would probably be lethal to humans in the absence of prompt treatment.

Animal studies have shown that benzaldehyde has caused moderate irritation when applied directly to the skin or eyes of rabbits exposed to 500 mg per day. Oral LD_{50} values were reported to be 1,000 mg/kg in guinea pigs and 1,300 mg/kg in rats. In short-term studies, benzaldehyde fed to male rats at 1,000 ppm for 28 weeks and to female rats at 10,000 ppm for 16 weeks reportedly produced no macroscopic or microscopic effects.

The EPA has established an oral RfD for benzaldehyde at 0.1 mg/kg-day based on a rat and mouse subchronic oral gavage study by Kluwe et al (1983). Groups of 10 mice of each sex were dosed with 0, 75, 150, 300, 600 or 1200 mg/kg/day benzaldehyde, and groups of 10 rats of each sex with 0, 50, 100, 200, 400, or 800 mg/kg/day benzaldehyde, 5 days/week for 13

weeks. Administration of 600 mg/kg/day in mice caused renal tubular necrosis, and administration of 400 mg/kg/day to rats resulted in forestomach hyperplasia and hyperkeratosis. A rat NOEL of 200 mg/kg/day resulted in the listed RfD of 0.1 mg/kg-day. A calculated ITSL based on this RfD would result in a value of 350 $\mu g/m^3$. This number would be acceptable had it not been for a NTP bioassay completed in 1990. This study showed evidence of squamous cell papillomas in the forestomach of male and female mice, producing a cancer screening level of 0.4 $\mu g/m^3$. It would therefore seem inappropriate to base a screening level on the RfD, when this number is over 80 times higher (time-adjusted) than the NTP-based screening level.

The NTP report provided both short and long term studies with which to evaluate benzaldehyde. Both sexes of F344/N rats and B6C3F1 mice were used in 16-day, 13-week and 2-year oral gavage studies. The acute and subchronic studies yielded different outcomes than did the bioassay study. In the 16-day study, all rats and mice that received ≥ 1,600 mg/kg died by days 2 and 3, respectively. No compound-related gross lesions were observed in the remaining lower dose groups for both rats and mice. The subsequent 13-week study revealed compound-related lesions in rats at 800 mg/kg. In the brain these lesions included degeneration and necrosis of the cerebellum and necrosis of the neurons in the hippocampus. Hyperplasia and/or hyperkeratosis of the forestomach, characterized by a mild-to-moderate thickening of the squamous epithelium, occurred in both males and females at 800 mg/kg. For mice, 9/10 and 1/10 females that received 1,200 mg/kg died during the first week. The only other compound related effect was a mild-to-moderate renal tubule degeneration that occurred in all 10 males that received 1,200 mg/kg and in 1 male that received 600 mg/kg. These short-term studies led to the 2-year NTP oral bioassay, which showed a manifestation of squamous cell papillomas in the forestomach of both sexes of mice. Interestingly, dosed rats developed hyperplasia and/or hyperkeratosis during short-term toxicity testing, but exhibited no increase over controls in the bioassay; whereas dosed mice exhibited no hyperplasia of the forestomach during subchronic testing, but developed hyperplasia of the forestomach which led to squamous cell papillomas in this organ.

The NTP bioassay, Toxicology and Carcinogenesis Studies of Benzaldehyde in F344/N Rats and B6C3F1 Mice (gavage studies) was published in March, 1990. The NTP determination concluded that there was no evidence of carcinogenic activity of benzaldehyde for male or female F344/N rats receiving 200 or 400 mg/kg-day.

There was some evidence of carcinogenic activity of benzaldehyde for male and female B6C3F1 mice, as indicated by increased incidence of squamous cell papillomas and hyperplasia of the forestomach. Female rats and male and female mice might have been able to tolerate higher doses.

Mutagenicity data indicated that benzaldehyde was negative in six strains of Salmonella typhimurium and did not induce chromosome aberrations in CHO cells with or without metabolic activation. Benzaldehyde induced

increases in trifluorothymadine-resistant mouse lymphoma cells without metabolic activation, and increased sister chromatid exchange in CHO cells with and without metabolic activation. Sex-linked recessive lethal mutations were not induced in the germ cells of adult male D. malanogaster administered benzaldehyde by feeding or by injection.

Based on the NTP bioassay, an Initial Risk Screening Level is developed based on carcinogenic effects using the methodology from Rule 231. The highest q_1^* value was produced by data from squamous cell papillomas of the forestomach in male and female mice. The number of animals per group were adjusted to include only those animals surviving until the time of the first tumor appearance. A printout of the Global82 model input and output is attached.

MLE dose on 1 x 10-6 risk = 2.4109844257 E-3 (female)
95% Upper Confidence Interval = 1.581886 E-6 (female)

$$q_1^* = \frac{1.581865E\text{-}6}{2.4109844257E\text{-}3} = 0.00066$$

$$q_1^* = 6.6E\text{-}4\ mg/m^3$$

Interspecie Scaling Factor:
W_H= body weight of human adult
W_A= body weight of test specie

$$T = \sqrt[3]{\frac{W_H}{W_A}} = \sqrt[3]{\frac{70}{0.035}} = 12.6$$

Adjusted q_1^*

$$q_1^* = (12.6)\ x\ (6.6E\text{-}4) = 8.3\ x\ 10^{-3} mg/kg$$

Conversion from mg/kg to $\mu g/m^3$

$$8.7x10^{-3} mg/kg\ x\ \frac{20m3}{70kg}\ x\ \frac{1mg}{1000\mu g} = 2.5x10^{-6} \mu g/m^3$$

IRSL and SRSL determination:

$$IRSL = \frac{1E\text{-}6}{2.4E\text{-}6} = 0.4\ \mu g/m^3$$

$$SRSL = \frac{1E\text{-}5}{2.4E\text{-}6} = 4\ \mu g/m^3$$

IRSL = 0.4 $\mu g/m^3$ based on annual averaging
SRSL = 4 $\mu g/m^3$ based on annual averaging

References:

1. U.S. Department of Health and Human Services, (March) 1990, National Toxicology Program, Technical Report Series No. 378, Toxicology and Carcinogenesis Studies of Benzaldehyde in F344/N Rats and B6C3F1 Mice (Gavage Studies).

2. EPA IRIS Database, 1994.

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