MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

January 28, 1994

TO: File for Allyl Glycidyl Ether (106-92-3)

FROM: Marco Bianchi

SUBJECT: Initial Risk/Secondary Risk Screening Level

The initial risk screening level (IRSL) for allyl glycidyl ether (AGE) is 0.1 $\mu g/m^3$ 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 #376 - Toxicology and Carcinogenesis Studies of Allyl Glycidyl Ether.

RTECS listed both LD_{50} and LC_{50} studies by Hine et al., 1956. In these studies, administration of AGE to rats and mice produced depression and dyspnea within 20 minutes; death occurred within 4 hours to 5 days after dosing. The oral LD50 for mice is 390 mg/kg and for rats, 1600 mg/kg. The inhalation exposure LC50 is 270 ppm for mice (4 hour exposure) and 670 ppm for rats (8 hour exposure).

The ACGIH listed an OEL of 5 ppm (23 mg/m3), while NIOSH listed an OEL of 10 ppm (45 mg/m3) in the 1985 edition of the pocket guide. The NIOSH OEL has since been changed to 5 ppm in the 1990 edition of the pocket guide. Worker related health effects from exposure to AGE included primary irritation and occasional sensitization. According to the ACGIH, a TLV of 5 ppm is believed to be sufficiently low to prevent primary irritation but may not protect against sensitization in all workers. A calculated OEL based on a screening level of 230 $\mu g/m^3$ would seem acceptable had it not been for a NTP inhalation bioassay completed in 1990. This study showed evidence of carcinogenicity of the nasal epithelium in both laboratory rats and mice, and produced a cancer screening level of 0.1 $\mu g/m^3$. It would therefore seem inappropriate to base a screening level on the OEL, when this number is over 120 times higher (time-adjusted) than the NTP-based screening level.

The NTP report provided both short and long term studies with which to evaluate AGE. Both sexes of Osborne-Mendel rats and B6C3F1 mice were used in 14-day, 8-week reproductive, 13-week and 2-year inhalation studies. All studies, except for the reproductive study, revealed that allyl

glycidyl ether affects the nasal turbinates of rats and mice due to inhalation exposure. In the 14-day study, both rats and mice had signs of respiratory distress, lacrimation, rhinorrhea, and mild squamous metaplasia of the nasal turbinate epithelium at 200 ppm and 100 ppm respectively. The subsequent 13-week study confirmed the 14-day results with squamous metaplasia of the turbinate epithelium for rats and mice at the lowest dose of 4 ppm and 1 ppm, respectively. Results from the 8-week reproduction studies showed impaired reproductive performance at overtly toxic concentrations (200 ppm) for males, but not for females. No increase in malformed fetuses was observed. These short term studies led to the 2-year NTP inhalation bioassay, which showed a manifestation of adenomas of the respiratory epithelium in both sexes of rats and mice.

The NTP bioassay, Toxicology and Carcinogenesis Studies of Allyl Glycidyl Ether in Osborne-Mendel Rats and B6C3F1 Mice (inhalation studies) was published in January, 1990. The NTP determination concluded that there was equivocal evidence of carcinogenic activity of allyl glycidyl ether for male rats based on the presence of one papillary adenoma of respiratory epithelial origin, one squamous cell carcinoma of respiratory epithelial origin, and one poorly differentiated adenocarcinoma of olfactory epithelial origin of the nasal passage at 10 ppm. There was some evidence of carcinogenic activity for male B6C3F1 mice, based on the presence of three adenomas of the respiratory epithelium, dysplasia in four males , and focal basal cell hyperplasia of the respiratory epithelium in the nasal passages of seven males at 10 ppm. There was equivocal evidence of carcinogenic activity for female mice, based on the presence of one adenoma of the respiratory epithelium and focal basal cell hyperplasia of the respiratory epithelium in seven females exposed to 10 ppm. Finally, there was no evidence of carcinogenic activity for female rats.

Mutagenicity data indicated that allyl glycidyl ether was positive for Salmonella typhimurium base-substitution strains with or without metabolic activation, but negative for frame-shift strains with or without metabolic activation. In cytogenetic tests using Chinese hamster ovary cells, this chemical induced highly significant increases in sister chromatid exchanges and chromosomal aberrations both with and without activation.

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 nasal epithelial adenomas in either male rats, or 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 = 3.5870855818 E-2
95% Upper Confidence Interval = 3.587466 E-4

$$q_1^* = \frac{3.587466E\text{-}4}{3.5870855818E\text{-}2} = 1E\text{-}2$$

$$q_1^* = 1E\text{-}2\ mg/m^3$$

Milligram to microgram conversion:

$$1E\text{-}2\ mg/m^3\ x\ 1E\text{-}3 = 1E\text{-}5\ \mu g/m^3$$

IRSL and SRSL determination:

$$IRSL = \frac{1E\text{-}6}{1E\text{-}5} = 0.1\ \mu g/m^3$$

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

IRSL = 0.1 $\mu g/m^3$ based on annual averaging
SRSL = 1 $\mu g/m^3$ based on annual averaging

References:

1. U.S. Department of Health and Human Services, (June) 1990, National Toxicology Program, Technical Report Series No. 376, Toxicology and Carcinogenesis Studies of Allyl Glycidyl Ether in Osborne-Menedl Rats and B6C3F1 Mice (Inhalation Studies).

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