MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

January 18, 1994

TO: File for Melamine (CAS #108-78-1)

FROM: Marco Bianchi

SUBJECT: Initial Risk/Secondary Risk Screening Level

The initial risk screening level (IRSL) for melamine is 1.5 $\mu g/m^3$ based on an annual averaging time.

The following references or databases were searched to identify data to determine the 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 #245 -Carcinogenesis Bioassay of Melamine.

After reviewing the above references it was determined, the NTP report provided the best short and long term studies with which to derive a screening level. Both sexes of F344/N rats and B6C3F1 mice were used in single dose, fourteen day, 13-week, and 2-year studies. The LD50 values for the oral single dose studies were 3,161 mg/kg and 3,828 mg/kg for male and female rats, respectively. Comparable LD50 values were observed in male mice at 3,296 mg/kg, but female mice exhibited more than a 2-fold increase at 7,014 mg/kg. The fourteen day studies showed the beginnings of melamine dose-related effects by the formation of a hard crystalline solid found in the urinary bladders of both sexes of rats and mice. Additionally, some of the male rats had pale and pitted kidneys. The 13-week feed studies showed similar results. Male and female rats contained stones in their urinary bladders, while histopathologic examination revealed diffuse epithelial hyperplasia in both sexes. Both male and female mice also had urinary bladder stones, in addition to bladder ulceration and ulcerative cystitis. These short-term studies led to the 2-year NTP bioassay, which showed a manifestation of male urinary bladder carcinomas due to melamine exposure.

The NTP bioassay, Carcinogenesis Bioassay of Melamine in 344/N Rats and B6C3F1 Mice (Feed Study) was published in March, 1983. The NTP determinations for this study concluded that, melamine was carcinogenic for male F344/N rats, causing transitional-cell carcinomas in the urinary bladder. With one exception, urinary bladder stones were observed in male rats that

had transitional-cell carcinomas. Melamine was not carcinogenic for female F344/N rats or for B6C3F1 mice of either sex.

Mutagenicity data indicated that melamine was negative in all short-term assays which included; Ames testing, with and without activation; Drosophila melanogaster; sister chromatid exchanges in Chinese hamster ovary cells; and unscheduled DNA synthesis in rat hepatocyte primary culture.

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 the data from urinary bladder carcinomas in male rats. Doses were adjusted from oral to inhalation doses, and the number of animals per group were adjusted to include only those rats 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 = 0.6551901467
95% Upper Confidence Interval = 2.700395 x 10-4

$$q_1^* = \frac{2.700395E\text{-}4}{0.6551901467} = 4.1E\text{-}4\ (animal)$$

Animal to human conversion:

$$q_1^*(human) = (4.1E\text{-}4)\ \sqrt[3]{70kg/0.4kg} = 2.3E\text{-}3\ (mg/kg/day)^{-1}$$

$$(oral\ dose)$$

Oral to inhalation dose:

$$2.3E\text{-}3\ (mg/kg/day)^{-1}\ x\ \frac{20m^3}{70kg} = 6.6E\text{-}4\ mg/m^3$$

Milligram to microgram conversion:

$$6.6E\text{-}4\ mg/m^3\ x\ 1E\text{-}3 = 6.6E\text{-}7\ \mu g/m^3$$

IRSL and SRSL determination:

$$IRSL = \frac{1E\text{-}6}{6.6E\text{-}7} = 1.5\ \mu g/m^3$$

$$SRSL = \frac{1E\text{-}5}{6.6E\text{-}7} = 15\ \mu g/m^3$$

IRSL = 1.5 $\mu g/m^3$ based on annual averaging
SRSL = 15 $\mu g/m^3$ based on annual averaging

References:

U.S. Department of Health and Human Services, (March) 1983, National Toxicology Program, Technical Report Series No. 245, Carcinogenesis Bioassay of Melamine in F344/N Rats and B6C3F1 Mice (Feed Study).

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