MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

May 2, 1994

TO: File for o-Toluidine (CAS # 95-53-4)

FROM: Marco Bianchi

SUBJECT: Initial Risk/Secondary Risk Screening Level

The initial risk screening level (IRSL) for o-toluidine is 0.07 $\mu g/m^3$ 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, and ACGIH Guide.

o-Toluidine is used as an intermediate in dye production, rubber processing, production of pharmaceuticals (hypnotic sedatives), herbicides and print processing. The oral LD_{50} of undiluted o-toluidine in rats is 900-940 mg/kg body weight, while the oral LD_{50} values in mice, rats, and rabbits are 515, 670, and 843 mg/kg body weight, respectively, when applied in oil solutions. Toxic effects of surviving animals included methemoglobinemia, anemia, and reticulocytosis. o-Toluidine also has a moderate to strong irritating effect on the skin and eyes of rabbits. The LD_{50} for rabbits by skin application is 3.3 ml/kg body weight. The daily application by stomach tube of 225 mg/kg body weight to rats for 20 days caused mortality, cyanosis, spleen congestion with hemosiderosis and extramedullary hematopoiesis, and hypercellularity in the bone marrow.

Clinical signs of intoxication in man include methemoglobinemia, hematuria, marked irritation kidneys and bladder, and physiological and psychological disturbances. o-Toluidine is absorbed via the respiratory tract and skin. An exposure of 40 ppm in the air for 60 minutes produces severe intoxication.

NIOSH (1990) has established a PEL for o-toluidine of 9 mg/m^3 (2 ppm). The ACGIH (1993) has set a time-weighted average threshold limit value of 8.8 mg/m^3 for this chemical, giving it a "skin" designation signifying potentially significant contribution to overall exposure via cutaneous route. The ACGIH has designated it as a suspected or confirmed carcinogen based on carcinogenicity to mice and rats after oral administration produced a variety of malignant tumors. The SWQD-MDNR has determined the human oral RfD for this chemical to be 0:0009 mg/kg/day (EPBCCD, 1985),

and the human CRV oral carcinogenicity slope factor to be 0.056 $(mg/kg/day)^{-1}$.

IARC has designated o-toluidine as a group 2B carcinogen, having sufficient evidence of carcinogenicity in animals. This evidence is based on oral studies in both mice and rats having produced neoplasms at various sites in both species, particularly inducing vascular tumors such a hemangiosarcomas. Results of four oral studies considered of adequate size to allow valid assessment of tumor induction were previously reviewed by SWQD in 1982, 1985 and again in 1989. Data from each of these studies were used as input for the Global82 cancer model to derive the most conservative slope factor (q_1^*). The key study consisted of groups of 25 male CD rats, six to eight weeks old that were fed diets containing o-toluidine hydrochloride at two dose levels: 8000 mg/kg of diet for 3 months and then 4000 mg/kg of diet for a further 15 months; or 1600 mg/kg of diet for three months and then 8000 mg/kg of diet for a further 15 months. A group of 25 rats served as matched controls and a group of 111 rats as pooled controls. All animals were observed for 24 months. Statistically significant increases in tumor incidence were reported for several neoplasms. Subcutaneous fibromas and fibrosarcomas were increased: 0/16 in matched controls, 18/111 in pooled controls, 18/23 in the low-dose group, and 21/24 in the high-dose group ($P<0.025$).

Based upon the above study, an Initial Risk Screening Level is developed based on carcinogenic effects using methodology from Rule 231. The highest q_1^* value was produced by data from subcutaneous fibromas and fibrosarcomas in the male rat. A print out of the Global82 model input and output is attached.

MLE dose on 1 x 10-6 risk = 1.4009918059 E-4
95% Upper Confidence Interval = 1.351309 E-6

$$q_1^* = \frac{1.351309E\text{-}6}{1.4009918059E\text{-}4} = 9.645374E\text{-}3$$

$$q_1^* = 9.6E\text{-}3\ mg/m^3$$

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

$$T = \sqrt[3]{\frac{W_H}{W_A}} = \sqrt[3]{\frac{70}{0.51}} = 5.16$$

Adjusted q_1^*
Conversion from mg/kg to $\mu g/m^3$
IRSL and SRSL determination:

$$q_1^* = (5.2)\ x\ (9.6E\text{-}3) = 5\ x\ 10^{-2} mg/kg$$

$$5x10^{-2} mg/kg\ x\ \frac{20m3}{70kg}\ x\ \frac{1mg}{1000\mu g} = 1.4x10^{-5} \mu g/m^3$$

$$IRSL = \frac{1E\text{-}6}{1.4E\text{-}5} = 0.07\ \mu g/m^3$$

$$SRSL = \frac{1E\text{-}5}{1.4E\text{-}5} = 0.7\ \mu g/m^3$$

IRSL = 0.07 $\mu g/m^3$ based on annual averaging
SRSL = 0.7 $\mu g/m^3$ based on annual averaging

References:

ACGIH, Threshold Limit Values and Biological Exposure Indices for 1989-1990.

ACGIH, Documentation of Threshold Limit Values and Biological Exposure Indices, 5th edition, Volume I, 1987.

IARC (1982). Some aromatic amines, anthraquinones and nitroso compounds, and inorganic fluorides used in drinking-water and dental preparations. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol.27, pp. 155-175. International Agency for Research on Cancer, Lyon.

IARC (1987). Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Suppl. 7, pp. 362-363. International Agency for Research on Cancer, Lyon.

MB:ma