MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

September 21, 1993

TO: File for N,N-dimethylaniline (CAS # 121-69-7)

FROM: Robert Sills, Surface Water Quality Division

SUBJECT: Screening Level Development

A review of the available literature on the toxicity of N, N-dimethylaniline indicates ample basis for ITSL development. An occupational guideline of 5 ppm (25 mg/m^3) as a TWA is provided by ACGIH (1991) and OSHA/NIOSH (U.S. DHHS, 1990). The basis for these occupational limits is the minimization of neurotoxic effects and anoxia due to the formation of methemoglobin. The level of 5 ppm was derived primarily from the limited human data on N,N-dimethylaniline, and the more extensive human data on aniline (ACGIH 1991). EPA (1987) derived an oral RfD of 2 $\mu g/kg$-d for N,N-dimethylaniline, based on a mouse subchronic gavage bioassay which provided a LOAEL of 22 mg/kg-d for effects on the spleen, and a UF of 10,000. EPA (1987) noted the occupational limit of 5 ppm (converted to an equivalent oral dose of 0.6 mg/kg-d) but did not use this for RfD development due to uncertainties in route-to-route extrapolation and the reliance on data for the analogous compound, aniline, in deriving the occupational limits. However, N,N-dimethylaniline also presents a carcinogenicity hazard. ACGIH (1991) noted that in view of the positive findings in an NTP (1989) bioassay, positive cytogenicity results, and structural similarity to the carcinogenic anilines, dimethylaniline is under review by the TLV committee.

In the rat portion of the NTP (1989) study, Fischer 344/N rats were given a lifespan dose of N,N-dimethylaniline. Dosage levels of 0, 3 or 30 mg/kg suspended in corn oil were administered by gavage to groups of 50 males and 50 females. The compound was administered for 5 days/week for 103 weeks. Vehicle controls received corn oil only. Statistical methods were used to analyze tumor incidence data: life table tests, incidental tumor analysis, and Fisher Exact/Cochran-Armitage trend analysis. In this two year study, the spleen was the expected site of chemical-related effects. Sarcoma of the spleen was seen in 3/50 high dose male rats and an osteosarcoma was seen in another high dose male rat. No dose-related statistically increased incidence was seen in female rats. The 4/50 incidence of splenic tumors (sarcoma and osteosarcoma) were not statistically significant ($p = 0.061$) but are biologically significant in two respects: 1) absence in concurrent controls (0/49) and rare spontaneous incidence in historical controls (3/2081) and 2) the histomorphological differences (NTP, 1989; Abdo, K. 1990; Haseman, J. 1990).

Also, NTP (1989) presents a review of tumorigenic activity of structurally related compounds, indicating a pattern of splenic tumor induction. NTP (1989) also discusses the ability of N,N-dimethylaniline to cause clastogenic effects in cultured mammalian cells, particularly in the presence of exogenous enzyme induction. Along with the rat study, B6C3F1 mice were exposed to 0, 15 or 30 mg/kg (males and females) by gavage 5 days/week in corn oil for the two year duration of the study. There was no evidence of carcinogenic activity of N,N-dimethylaniline for male B6C3F1 mice given 15 or 30 mg/kg body weight by gavage for two years. There was equivocal evidence of carcinogenic activity for female mice, based on an increased incidence of squamous cell papillomas of the forestomach. There were no squamous cell carcinomas identified in the stomach of female mice, suggesting that these papillomas might not be progressive according to the study authors.

Due to the biological significance of splenic tumors (sarcoma and osteosarcoma) the 4/50 incidence was utilized in the calculation of a potency factor. An adjustment was made in NTP (1989) data to eliminate animals not sufficiently at risk (examined prior to week 82 when the first of these tumors appeared). Application of the linearized multistage model was performed to derive a q_1^* value of 4.13×10^{-2} $(mg/kg/day)^{-1}$ (global 82), based on the incidence of splenic tumors in male rats.

An update CAS search to September 1993 revealed no carcinogenicity studies via the inhalation route of exposure, and no oral carcinogenicity bioassays other than NTP (1989).

The IRSL and SRSL are derived as follows:

$$q_1^* \ (\mu g/m^3) = 4.13 \times 10^{-2} \ (mg/kg\text{-}day) \times \frac{20 \ m^3}{70 \ kg} \times \frac{1 \ mg}{1000 \ \mu g} \times \frac{a}{b}$$

$$assuming \ a=b, \ q_1^* (\mu g/m^3) = 1.18 \times 10^{-5} \ (\mu g/m^3)^{-1}$$

$$IRSL = \frac{1 \times 10^{-6}}{1.18 \times 10^{-5} \ (\mu g/m^3)^{-1}} = 0.085 \ \mu g/m^3, \ annual \ averaging$$

$$SRSL = \frac{1 \times 10^{-5}}{1.18 \times 10^{-5} (\mu g/m^3)^{-1}} = 0.85 \ \mu g/m^3, \ annual \ averaging$$

REFERENCES

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