MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

February 23, 1988

TO: Cathy Simon, AQD

FROM: Gary Butterfield, SWQD

SUBJECT: p-toluidine, and 3-chloro-p-toluidine

The following justifications should provide you with sufficient information to develop acceptable air concentrations (AAC) for p-toluidine (CAS # 106-49-0) and 3-chloro-p-toluidine (CAS # 95-74-9).

p-toluidine

There were no inhalation studies available on this material, either acute or longer duration. The ACGIH has established a TWA-TLV of 2 ppm (9 mg/cu.m). There was no available study of adequate quality to provide a NOAEL. In the ACGIH documentation of the TLV, there was mention of a four week feeding study conducted at Industrial Bio-Test Laboratories. However, this study was not found in the published literature reviewed. In addition, some work done at IBT is of questionable quality. For these reasons this study was not used to develop a NOAEL. A lifetime feeding study conducted by Weisburger, et al 1978 found evidence of carcinogenicity in mice. Although rats were also tested in this bioassay, there was no increased incidence of tumors in rats. Both male and female mice had statistically significant increases in hepatomas when compared to the pooled controls. The incidence in male mice was 7/99, 8/17, and 9/18 for the control, 75 mg/kg and 150 mg/kg dose groups respectively. The incidence in female mice was 1/102, 2/21 and 3/17. The dosage was calculated from the data reported by the authors. The time weighted average of 6 months at 1000 and 2000 ppm followed by 12 months of 500 and 1000 ppm. This results in TWA dosage of 666 ppm and 1333 ppm. The dose was then converted to mg/kg by use of 0.13 for feed consumption expressed as a fraction of body weight. This resulted in conversion to 87 and 170 mg/kg. A 3 month observation period followed the 18 month dosing period. The doses were converted to a "Study Average Dose" by multiplying by 18/21. This results in dosages of 75 and 150 mg/kg. The cancer risk value for p-toluidine was calculated by use of linearized multistage model, Global 82, at a risk of one out of a million. In calculation of the potency, the body weight for mice was assumed to be 30g. The potency for male mice (0.11 d/kg/mg) is larger than the females potency and therefore was used in calculation of dose. The dose for one in a million risk was found to be 9.45×10^{-6} mg/kg/d. For a 70 kg person breathing 20 cu.m/d, the acceptable air concentration to receive that dose is then calculated to be 33 ng/cu.m. No details on survival, food consumption or body weights were given in this article. However, the authors mention adjusting the doses to match the body weights. The authors are very well

known in the world of carcinogenicity bioassays. This article is also widely referenced in other literature as the study providing evidence of carcinogenicity for p-toluidine. Although minimal details were given in this article, there is sufficient statistical indication of carcinogenicity in mice. There is adequate information provided to calculate a cancer risk value.

In attempts to support the classification as a carcinogen, mutagenicity assays were reviwed. A review of mutagenicity assays finds conflicting results for p-toluidine in assays detecting DNA damage/repair. In the studies reviewed there were positive references for DNA strand breaking, unschelded DNA synthesis, and inhibition of DNA synthesis. However, there also were negative assays in DNA strand breakage, and the Pol A assay. Studies detecting gene mutations were negative.

Several oral LD50's for birds were reported by Schaffer, et al 1983. These studies are of little value for calculation of AAC as the body weights and respiration rate for these species are unknown.

Although the CAS-on-line search was conducted for 1980-1988, references from those articles and references from secondary literature resulted in a rather extensive literature review including pre-1980 studies.

References

- ACGIH. 1986. Documentation of the threshold limit values. 5th Ed.
- Industrial Bio-Test Laboratories, Inc. Bio-FAX 31-4/1973.
- Schafer, E.W. Jr., et al. 1983. The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild and domestic birds. Arch Environ Contam Toxicol 12:355-382.
- Weisburger, E.K., et al. 1978. Testing of twenty-one environmental aromatic amines or derivatives for long term toxicity or carcinogenicity. J Environ Path Toxicol 2:325-356.

3-chloro-p-toluidine

There were no inhalation studies available for this material, either acute or longer duration. A subacute and a chronic study were conducted for NTP. These were both feeding studies. So few details of the 4 week, subacute study were described a NOAEL cannot be identified. No carcinogenic effects were observed in the chronic bioassay for either rats or mice. However, the chronic bioassay indicates there was non-carcinogenic effects in rats at the high doese (165 mg/kg). The body weight was depressed. There was a substantial increase in fibrosis of the spleenic capsule seen at incidences of 0/20, 1/47 and 24/50 for males and 0/19, 3/49 and 34/50 for females at doses of zero, 82 mg/kg, 165 mg/kg respectively. There also was increased incidence in fatty metamorphosis of the liver occurring in 2/20, 5/47 and 35/50 of males; and 0/18, 4/50 and 34/50 of females for each respective dose groups. Dose levels were converted to mg/kg by use of the factor 0.05 for food consumption expressed as a percent of bodyweight. Unfortunately statistical analysis of these non-carcinogenic effects were not performed. Therefore, the low dose cannot be used as a NOAEL without doubt of the low dose being statistically different from the controls. If 82 mg/kg is used as a

NOAEL in calculation of an AAC the following results. The male rats * weighed 400 gm at 50 wks and females weighed 225 gms. If an ungertainty factor of 100 is assumed, this will result in an AAC of 1.4 mg/m^3. If 82 mg/kg is considered to be an LOAEL than AAC would be reduced to 0.14 mg/m^3.

An alternate method of obtaining an AAC would be based on the LD50 of 655 mg/kg as reported by Apostolou & Peoples 1971. The rats weighed 80-130 gm in this study. Assuming a weight of 100 g the calculated breating volume would be 0.97 cu.m/d. This results in a AAC of 2.0 ug/m^3. A CAS-on-line search was conducted from vol. 66 to Feb. 1988.

References

NTP-NCI:1978. Bioassay of 3-chloro-p-toluidine for possible carcinogenicity. NCI-CG-TR-145.

Apostolou, A. and S.A. Peoples. 1971. Toxicity of the avicide 2-chloro-4-acetotoluidine in Rats: a comparison with its nonacetylated 3-chloro-p-toluidine. Toxicol Appl. Pharmacol 18:517-521.

* These calculations don't consider that exposure duration was less than study duration

3/1/88

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

March 2, 1988

TO: File

FROM: Catherine Simon

SUBJECT: 3-Chloro-p-toluidine (CAS No. 95-74-9)

Based upon the memo from Gary Butterfield to Cathy Simon, dated February 23, 1988, the recommended acceptable ambient concentration (AAC) for 3-chloro-p-toluidine, to be used in permit reviews for new sources is 2.0 ug/m^3. In determining allowable stack concentrations, this value should be modeled as an annual average concentration.

In determining an AAC for 3-chloro-p-toluidine, the rat data from the NTP study was not used for the following reasons:

1. The lowest dose tested may be an effect level.

2. Mice exhibited depressed body weights at dose levels lower than the lowest dose used in the rat study.

3. This compound is extremely toxic to birds, with oral LD50s as low as 1 mg/kg, compared to an oral rat LD50 of 655 mg/kg. Since methods have not been developed to determine safe exposure levels for birds, a conservative AAC calculated from an oral rat LD50 is more likely to provide adequate protection to avian wildlife.

CAS:mh