MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

September 2, 1993

TO: File for m-aminophenol (CAS No. 591-27-5)

FROM: Robert Sills, Surface Water Quality Division

SUBJECT: Screening Level Derivation

An occupational exposure level from ACGIH or NIOSH is not available for m-aminophenol, nor is an IRIS RfD or RfC available. These and other references do not identify m-aminophenol as a human or animal carcinogen. Database searches (NTIS and CAS online) also did not reveal any human or animal carcinogenicity studies.

The HEAST (1992) reference does report an oral RfD, as provided by EPA (1985). Per HEAST (1992), the chronic RfD is 0.07 mg/kg/d, derived from a 13 week rat feed-exposure study NOAEL of 1300 ppm and a composite UF of 1000. The critical effect was altered weight of whole body and thyroid (Re et al., 1984).

A review of the available literature via CAS online reveals that the database is quite limited. The study by Re et al. (1984) is clearly the best available study for risk assessment, including screening level derivation. Other available studies include human dermal studies, short-term oral or injection data, and screening studies for carcinogenic potential.

The study by Re et al. (1984) was a combined subchronic and reproduction/development bioassay. Groups of 35 female Sprague-Dawley rats/group received m-aminophenol at dietary levels of 0, 0.1, 0.25 and 1% for 13 weeks. Growth and food intake were monitored throughout the study. Ten animals per group were then sacrificed and necropsied. The remaining 25 animals per group remained on test diet, and were mated to untreated males beginning during week 14 of the study. Each female was sacrificed on day 20 of gestation, followed by examination of the uterus, ovaries, resorptions and fetuses. The two highest exposure levels resulted in statistically significant body weight suppression, with a magnitude of roughly 5% (at 0.25%) and 21% (at 1%). A hemolytic effect was apparent at the 1% exposure level, as indicated by reduced RBC counts and hemoglobin levels, an increase in mean corpuscular volume, and the accumulation of iron positive pigment in the liver, kidneys and spleen. The absolute and relative weights of the thyroids of the groups treated at 0.1 (due to the lack of histopathologic changes in the thyroid at the 0.1% dose, this was not deemed an adverse effect) and 0.25% were significantly less than the

control values, while the 1.0% treatment resulted in significantly higher relative thyroid weights. The histomorphologic appearance of the thyroid was consistent with hyperactivity (increased epithelial cell height and a reduction in the size of the follicles) for the animals receiving m-aminophenol at 0.25 or 1.0% in the diet. There was no evidence of embryo toxicity, teratogenicity, or reduced fertility.

Based on statistically significant body weight suppression and altered histology of the thyroid at 0.25 and 1.0%, the NOAEL for this study is 0.1% in the diet. This dietary exposure may be converted to a daily dose rate in mg/kg/d from the actual measured dietary level of 0.13%, and the documented mean weekly body weight for the group and the weekly mean food consumption data. This analysis, performed for each week 1-13, indicates that the average weekly dose ranged from 146 mg/kg/d during week 1 to 90 mg/kg/d during week 12. The arithmetic and geometric mean doses are calculated as 112 and 111 mg/kg/d, respectively. The ITSL is most appropriately derived from the geometric mean study NOAEL of 111 mg/kg/d.

It may, however, be noted that the RfD in HEAST (1992) was derived from this same exposure group and a NOAEL of 70 mg/kg/d. A review of the source of this RfD (EPA, 1985) reveals that the NOAEL at 0.13% m-aminophenol in the diet was converted to 65 mg/kg/d by assuming that a rat eats a daily amount of food equal to 5% of its body weight. For the present analysis, the use of this default assumption in lieu of study-specific animal weight and food intake data does not appear justified. EPA (1985) applied a composite UF of 1000, with the same rationale described below for the present analysis, resulting in a chronic RfD of 0.065 mg/kg/day. This was reported in HEAST (1992) as 0.07 mg/kg/d, presumably due to rounding-off. Therefore, the ITSL is most appropriately derived from a NOAEL calculated to be 111 mg/kg/d, notwithstanding the different NOAEL calculation of EPA (1985) utilizing a default assumption.

The NOAEL of 111 mg/kg/d is divided by a composite UF of 1000 (10x for each inter- and intraspecies extrapolation and 10x for subchronic-to-chronic conversion) to derive the RfD of 0.111 mg/kg/d.

Data are not available to indicate that oral route to inhalation route extrapolation is inappropriate. Re et al. (1984) note that the rate of absorption from the rat gut is not known. The literature review by EPA (1985) reveals evidence of extensive GI absorption following oral administration to rabbits, followed by rapid elimination via the urine as metabolites. Inhalation pharmacokinetics data were completely lacking (EPA, 1985).

$$ITSL = oral\ RfD \times \frac{70\ kg}{20\ m^3} = 0.111\ mg/kg/d \times \frac{70\ kg}{20\ m^3} = 0.3885\ mg/m^3 = 390\ \mu g/m$$

based on 24 hour averaging

REFERENCES

EPA. 1985. Health and Environmental Effects Profile for Aminophenols. NTIS Number: PB88-173612.

HEAST. 1992. Health Effects Assessment Summary Tables. NTIS No. PB92-921199.

Re, T.A. et al. 1984. Results of teratogenicity testing of m-aminophenol in Sprague-Dawley rats. Fundamental and Applied Toxicology 4:98-104.

m-aminophenol CAS No. 591-27-5
Re et al., 1984 0.1% = 1000 ppm = 1000 µg/g food = 1 mg/g food*
NOAEL = 0.1% in diet

CONVERSION to mg/kg/d dose

A. Pre-mating Period (week)	B. Mean Food Cons/Wk (gms)	C. Daily Dose (mg)* (B/7)	D. Mean Weekly Body Wt (kg)	E. Daily Dose (mg/kg/d) (C/D)	Daily Dose via Actual Measured Diet Levels (E*1.3)
1	117.9	16.8	0.1506	112	146
2	128.3	18.3	0.1727	106	138
3	126.6	18.1	0.1886	95.9	125
4	130.3	18.6	0.2052	90.7	118
5	134.8	19.2	0.2128	90.5	118
6	136.8	19.5	0.222	88	114
7	138.1	19.7	0.2323	84.9	110
8	136.0	19.4	0.2409	80.6	105
9	135.9	19.4	0.2485	78.1	102
10	137.3	19.6	0.2534	77.4	101
11	129.5	18.5	0.2548	72.6	94
12	125.4	17.9	0.2574	69.6	90
13	132.9	19.0	0.2619	72.5	94

$$Arith.\ Avg. = \frac{1457}{13} = 112\ mg/kg/d$$

$$Geo.\ mean = \sqrt[13]{3.78E{+}26} = 111\ mg/kg/d$$

RS:ma