MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 24, 2005

TO: File for Cresol – mixed isomers (CAS #1319-77-3)

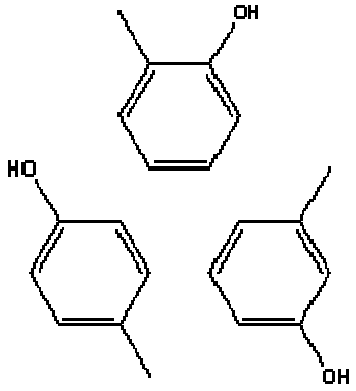
FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for Cresol has been derived (100 ug/m^3 based on an 8-hour averaging time), but due to the potential for particulate matter release from the solid state, the National Ambient Air Quality Standard for particulate matter (NAAQS PM) was emphasized.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2005), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration for Cresol, but has established a reference dose for Cresol. The molecular weight of Cresol is 324.4 g. The molecular structure of Cresol is shown in Figure 1.

Figure 1



Background

Cresol is a mixture of the o- (95-48-7), m- (108-39-4), and p- (106-44-5) isomers of the monomethyl derivative of phenol. Also known as cresylic acid, cresols may be found as colorless solids or as yellowish liquids with a “sweet, tarry odor” depending on the purity

of the mixtures and/or the isomer composition of the mixture (ChemFinder.com, 2005). The vapor pressure at 25˚C ranges from 0.11 mmHg to 0.29 mmHg (ACGIH, 2001). Commercial cresols are usually contaminated with small amounts of phenols and xylenols. The typical percent composition of a USA-distribution technical grade cresol breaks down to "about 20% o-cresol, 40% m-cresol, 30% p-cresol, and 10% phenol and xylenols" (WHO, 1995).

Cresols are found in a number of substances. It is used in a variety of solvents and disinfectants and as constituents of fragrances, coal tar, dyes, resins, antioxidants, and pesticides (WHO, 1995; NTP, 1992). Cresols are also found "naturally in human and animal tissues, fluids, and urine" as tyrosine, an amino acid, can form cresol (US ATSDR, 1992).

Animal Toxicity

A short-term toxicity study was conducted by Uzhdavini et al. (1972) exposing mice to o-cresol (aerosol and vapor mixture) 2 hours/day, 6 days/week for one month (WHO, 1995). The mice were exposed to concentrations ranging from 26 mg/m^3 to 76 mg/m^3. At the start of exposure, clinical signs of respiratory irritation were followed by hypoactivity that, then, lasted the entire study. Microscopic examination of the lungs revealed signs of edema, cellular proliferation, and small hemorrhages, all of which indicated that cresol was an irritant. Other adverse effects noted included the degeneration of many vital organs, such as the heart, liver, and kidney.

A more recent short-term study was conducted by NTP (1992). For 28 days, groups of five F344/N rats and groups of five B6C3F1 mice were exposed to o-, m-, p-, or m-/p-cresol (60:40 mixture). Each group was fed concentrations of 0, 300, 1000, 3000, 10000, or 30000 mg/kg in their diets (ad libitum). Feed consumption, compared to that of control, was reduced only for the first week of cresol exposure; consumption was similar to control following the first week of the study. Clinical signs of toxicity included hunched posture, rough hair coat, and thin appearance. Several organs were increased in weight, relative to the decreased body weight, but only the liver and kidney had increased weight relative to brain weight. Rats and mice exposed to o-cresol and m-cresol did not develop any gross or microscopic lesions, except for evidence of uterine atrophy at the high-dose exposure. When exposed, however, to p-cresol or m-/p-cresol, histopathologic evaluation revealed a number of adverse effects: hyperplasia of the respiratory epithelium in the nasal cavity, increased colloid within thyroid follicles, mild hyperplasia, and hyperkeratosis of the esophageal epithelium and forestomach, and mild bone marrow hypocellularity. Based on the study's results, NOAELs were established for all of the isomers as well as the m-/p-cresol mixture. For o-, m-, and m-/p-cresols, the NOAEL was established at 3000 mg/kg and for p-cresol, it was set at 1000 mg/kg. US NTP (1992) also conducted a 13-week study that tested the effects of o-cresol and m-/p-cresol in groups of twenty F344/N rats and ten B6C3F1 mice. Many of the results were consistent with those from the 28-day short-term study. Based on the 13-week study, a NOAEL of 1250 mg/kg and 625 mg/kg were determined for o-cresol and m-/p-cresols exposures, respectively.

In a four-month study, Uzhdavini et al. (1972) evaluated the effects of o-cresol vapor in rats (WHO, 1995). A number of effects were observed in an unknown number of rats after exposure to an average vapor concentration of 9 mg/m^3 o-cresol: "accelerated loss of conditioned defensive reflex, leukocytosis, decreased erythroid/myeloid ratio in the bone marrow, increased duration of hexanol narcosis [indicative of liver function impairment], and morphological changes in respiratory tissues" (WHO, 1995).

Human Toxicity

Cresol toxicity has been observed in human cases whether by accidental or intentional ingestion or by occupational dermal exposure. The results of these acute exposure cases support the designation of the blood, kidneys, liver, and central nervous system as the primary target organs. There is some indication that special subpopulations may be more susceptible to the toxic effects of cresols. Although this has not been fully established, individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, those with decreased immune function capacity, and the very young infant population may be at a greater risk with cresol exposure. (ATSDR, 1992)

Uzhdavini et al. (1972) conducted a study on ten human subjects focusing on the inhalation effects of o-cresol exposure (ATSDR, 1992). Eight of the ten subjects, after exposure to 6 mg/m^3 (1.4 ppm) o-cresol "complained of mucosal irritation symptoms including dryness, nasal constriction, and throat irritation" (ATSDR, 1992).

An occupational study was conducted on seven workers, who were exposed 1.5 to 3 years to unknown concentrations of cresol vapor. They complained of headaches that were usually accompanied by nausea and vomiting. Four of the seven workers presented high blood pressure, impaired kidney function, blood calcium imbalance, and noticeable muscle tremors. (ACGIH, 2001)

Discussion

EPA found inadequate information to derive a reference concentration (RfC) value, but EPA has established reference dose (RfD) values for two of the three isomers (ortho- and meta-cresol) (IRIS, 2005a-b). Both were based on NOAELs of 50 mg/kg-day where the critical effect observed was decreased body weights and neurotoxicity. The two 90-day oral subchronic neurotoxicity studies in rats conducted by EPA (1986, 1987) resulted in a RfD of 0.05 mg/kg-day (IRIS, 2005a-b). This value is equal to the minimal risk levels (MRLs) ATSDR has set for each isomer form of cresol (ATSDR, 1992).

OSHA has developed a permissible exposure limit (PEL) for cresol of 22 mg per cubic meter of air (22 mg/m^3), or 5 ppm, for 8 hours/day, 40 hours/week. ACGIH established a threshold limit value time-weighted average (TLV-TWA) that is consistent with OSHA's value of 22 mg/m^3 (5 ppm). ACGIH's basis included the similarity of the toxicity of phenol to that of cresol. NIOSH (1997), however, set the recommended exposure limit (REL) at 10 mg/m^3, or 2.3 ppm. NIOSH's basis included study results indicating adverse effects below cresol exposures below 20 mg/m^3 (NIOSH, 1978).

The resulting NOAEL values from the NTP study (1992) were 1000 mg/kg and 3000 mg/kg from the 28-day studies and 625 mg/kg and 1250 mg/kg from the 13-week studies. Since the EPA RfD value was based on a lower NOAEL concentration of 50 mg/kg-day compared to the lowest NOAEL of 625 mg/kg-day from the NTP study, using the NTP results would be inappropriate. The RfD, however, is based on oral studies while the NIOSH REL is based on inhalation studies and occupational studies. Thus, it is more appropriate to use the REL value of 10 mg/m^3 to derive an initial threshold screening level (ITSL).

The physical property of cresol must also be taken into consideration. Due to its variability of its physical state (i.e., solid or liquid depending on the cresol mixture), there is potential for cresol in the solid form to contribute to particulate matter levels in the ambient air. The following calculated ITSL can not be used if it is a value greater than the National Ambient Air Quality Standard for particulate matter (NAAQS PM).

Derivations of Screening Level

Using the occupational exposure level value of 10 mg/m^3, the ITSL can be calculated as promulgated in Rule 232(1)(c).

$$ITSL = \frac{OEL}{100}$$

$$ITSL = \frac{10\ mg/m^3}{100}$$

$$ITSL = 0.10\ mg/m^3 = 100\ ug/m^3$$

Therefore, the ITSL for cresol (1319-77-3) is 100 ug/m^3 based on an 8-hour averaging time.

In addition to background particulate matter levels, the calculated ITSL above may be greater than the National Ambient Air Quality Standard for particulate matter (NAAQS PM) (Table 1).

Table 1. National Ambient Air Quality Standard for Particulate Matter

	PM10	**PM2.5**
annual	50 ug/m^3	15 ug/m^3
24-hour	150 ug/m^3	65 ug/m^3

It is considered inappropriate to set an ITSL for a chemical emitted as particulate matter that is greater than the NAAQS, especially considering the lack of chronic inhalation toxicity data for this compound. Although this ITSL is not greater than the NAAQS PM (standing) alone, the NAAQS PM must still be considered due to potential additive effects from background particulate matter levels. Therefore, as longs as the ambient impact of cresol combined with the background particulate matter concentration is less than NAAQS PM for both PM10 and PM2.5, then adverse health effects would not be expected to occur, and compliance with health-based screening level requirements of the air toxic rules is satisfied.

References

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