MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Phenol (CAS No. 108-95-2)

FROM: Cathy Simon, Air Quality Division

DATE: November 7, 2012

SUBJECT: Screening Levels for Phenol

The initial threshold screening level (ITSL) for phenol is 190 µg/m^3 based on an 8-hour averaging time. Background information, supporting data, and the basis for this screening are provided below.

Background

In 1992, the Air Quality Division (AQD) of the Michigan Department of Natural Resources (MDNR) established interim ITSLs for phenol of 600 µg/m^3 (1-hour averaging time) and 2100 µg/m^3 (24-hour averaging time). The data and interim ITSLs for phenol were re-evaluated in 1995 by the AQD, and a final ITSL of 600 µg/m^3 (1-hour averaging time) was established for this compound (MDNR, 1995).

The US Environmental Protection Agency (EPA), Office of Air Quality Planning and Standards (OAQPS) has adopted a chronic toxicity value of 200 µg/m^3 for phenol (EPA, 2012a). This value is based upon the chronic reference exposure level for phenol derived by the California Environmental Protection Agency (Cal/EPA, 2000). The EPA OAQPS has used this chronic toxicity value to evaluate the health impacts from emissions of phenol as part of the National Air Toxics Assessment program (EPA, 2011), and from levels of phenol measured in the ambient air near schools (EPA, 2009).

A review was undertaken to evaluate the basis for the different health benchmark values for phenol used by the AQD and the EPA, and update the existing ITSL as appropriate. This evaluation did not include an independent review of all relevant scientific literature, but relied primarily on reviews done by various organizations such as the National Toxicology Program (NTP), Agency for Toxics Substances and Disease Registry (ATSDR), International Agency for Research on Cancer (IARC), EPA, and Cal/EPA. Information from these and other sources, as well as the findings of the evaluation are presented below.

Review of the ITSL

The National Institute of Occupational Safety and Health (NIOSH) has established a recommended exposure level (REL) for phenol of 5 ppm (19 mg/m^3) on a time weighted average (TWA) basis, and a ceiling limit of 15.6 ppm (60 mg/m^3) (NIOSH, 2012). The current ITSL was derived by dividing the NIOSH REL ceiling limit by 100, to obtain a value of 600 µg/m^3 based on a 1-hour averaging time, pursuant to Rule 232(1)(c) and 232(2)(a) of the Michigan Air Pollution Control Rules (MDNR, 1995).

The chronic reference exposure level of 200 µg/m^3 (0.05 ppm) established by the Cal/EPA is based upon a study by Sandage (1961) in which mice, Sprague Dawley rats and rhesus monkeys were exposed continuously by inhalation for 90 days to 5 ppm of phenol (Cal/EPA, 2000). The original study by Sandage was not available for review; however, according to Cal/EPA, the 5 ppm dose level was considered a no observable adverse effect level (NOAEL). This NOAEL was also considered a human equivalent concentration (HEC) by Cal/EPA, and the chronic reference exposure level was derived by dividing the HEC by a total uncertainty factor (UF) of 100. The UF of 100 was composed of a subchronic UF of 3, an interspecies UF of 3, and an intraspecies UF of 10.

In the *Toxicological Review of Phenol*, the EPA evaluated the available scientific literature on the health effects due to exposure to phenol and found that the data were inadequate to derive an inhalation reference concentration (RfC) (EPA, 2002). A screening level review of the toxicological data for phenol conducted in August 2003 by an EPA contractor did not identify any new studies that would allow development of an RfC. As a result, no inhalation RfC is currently listed on the EPA's Integrated Risk Information System (IRIS) database (EPA, 2012b).

The study by Sandage (1961) upon which Cal/EPA based their chronic reference exposure level was also reviewed by the EPA (2002). In their review of this study, the EPA reported additional details, including that the number of animals tested consisted of 10 male rhesus monkeys, 50 male Sprague Dawley rats, and 100 male albino mice. Additionally, the EPA identified the exposure concentration as 4.72 ppm (18.2 mg/m^3). A major difference in interpretation of this study between the two agencies is that the EPA identified the single dose tested as a lowest observable effect level (LOAEL), whereas CAL/EPA identified it as a NOAEL. The EPA's rationale for their interpretation is as follows:

> The authors considered the histopathology findings "essentially negative" and did not provide any description of the observed lesions or the number of animals examined histopathologically. Liver and kidney pathology was observed in 30% and 20%, respectively, of the monkeys (compared with 0% of the controls). However, the authors did not consider these changes to be significant, and they noted that 6/7 reports of pathology in monkeys were considered "minimal or doubtful." Liver and kidney pathology was also reported in 20% of phenol-exposed rats (compared with 0% of the controls) and lung pathology was reported in 20% of the phenol-exposed mice (compared with 6% of the controls). The incidences of liver and kidney pathology in the rat and lung pathology in the mouse were statistically significant in a Fisher's exact test done for this assessment. Although the incidence of lung pathology was not affected in monkeys and rats, a relatively high incidence of lung pathology in the control animals (30% and 65%, respectively) decreased the sensitivity of the evaluation. No other significant pathological changes were reported in the test animals.
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> Although the authors concluded that there was no evidence that phenol exposure resulted in significant damage, there is some indication of liver, kidney, and lung pathology in this study, but the inadequate reporting precludes the determination of whether there was a treatment-related effect. For the purposes of this assessment, the single exposure level tested, 18.2 mg/m^3, should be considered a free-standing LOAEL, although it might be considered a minimal LOAEL if additional histopathology data were available. The LOAEL (HEC) for the kidney and liver lesions is also 18.2 mg/m^3. In the absence of additional information on the nature of the lung lesions, the LOAEL (HEC) for the lung cannot be determined (EPA, 2002, page 59).

In addition to the inadequate documentation of histopathology results in the Sandage (1961) study, other shortcomings identified by the EPA included problems with generating and monitoring exposure levels. As a result, the EPA concluded that this study could not be used for derivation of an inhalation RfC because it did not meet the criterion of a "…well conducted subchronic inhalation study that has adequately evaluated a comprehensive array of endpoints, including the respiratory tract…" (EPA, 2002).

Considering the uncertainty regarding whether the single dose used in the Sandage (1961) study is a LOAEL or NOAEL, as well as other problems identified with this study by the EPA, the use of the Cal/EPA chronic reference exposure level is not appropriate to use for derivation of the ITSL. As previously stated, no other human or animal data were identified by the EPA that could be used in the derivation of an inhalation RfC. The ATSDR has also evaluated the available data for phenol, including the Sandage (1961) study, and concluded that no acute, intermediate, or chronic duration inhalation minimal risk levels could be derived for this compound (ATSDR, 2008).

The hierarchy of methods for deriving the ITSL provided in Rule 232 of Michigan Air Pollution Control Rules, calls for use of an inhalation RfC first if one is available. Lacking an inhalation RfC, Rule 232(1)(b) specifies that an oral reference dose (RfD) should be used to derive the ITSL, if data are not available to indicate that extrapolation from the oral route to inhalation route is inappropriate.

While the EPA has established an oral RfD for phenol of 0.3 mg/kg/day (EPA, 2012), it has also concluded that "a route-to-route extrapolation is not appropriate, because phenol can be a direct-contact irritant, and so portal of entry effects are a potential concern" (EPA, 2002). In addition to the concern for portal of entry effects, the toxicokinetics of phenol raises additional concerns regarding the extrapolation of oral to inhalation data. While phenol is readily absorbed via the oral and inhalation routes of exposure, differences exist regarding portal-of-entry metabolism. Data are available that show the lung, liver, and gut all have ability to metabolize phenol; however significant differences exist with regard to the capacity and affinity for metabolism. The EPA found that "because portal-of-entry conjugation is more efficient following ingestion rather than following inhalation of phenol, it is not surprising that the systemic toxicity (i.e. liver and kidney effects) of a given absorbed dose may be higher for inhaled phenol" (EPA, 2002, p. 87). The EPA's review of the data also indicates uncertainty regarding whether the toxic effects of phenol are due to the parent compound or its metabolites. Considering all of the above information, the available data indicate that extrapolation from the oral route to inhalation route is inappropriate and the ITSL should not be derived from the oral RfD.

Rule 232(1)(c) specifies the use of an occupational exposure level (OEL) to derive the ITSL when an inhalation RfC is not available and it is not appropriate to use the oral RfD. Available OELs for phenol include a time weighted average (TWA) Threshold Limit Value (TLV) of 5 ppm (19 mg/m^3) established by the American Conference of Governmental Industrial Hygienists (ACGIH), and a recommended exposure level (REL) of 5 ppm (TWA) and ceiling limit of 15.6 ppm (60 mg/m^3) established by NIOSH.

The rationale for the ACGIH TLV and NIOSH REL of 5 ppm has a stronger scientific basis than the rationale for the NIOSH ceiling liming of 15.6 ppm. NIOSH states that the basis for the ceiling limit is to avoid irritation and minimize exposure to large amounts of phenol (NIOSH, 1976). The references cited for this recommendation include an oral ingestion case study from 1869, and two studies involving dermal application of phenol, one from 1943 and one from

1961. No inhalation studies are referenced with regards to the recommendation for the ceiling limit.

The primary study cited as a basis for the ACGIH TLV of 5 ppm is a study by Piotrowski (1971) in which 8 human volunteers (7 men and 1 woman) were exposed to phenol vapor by inhalation (6 – 20 mg/m^3) and through skin contact (5, 10, and 25 mg/m^3) (ACGIH, 1994). For the inhalation exposure, subjects inhaled vapors through a face mask to avoid absorption through the skin. For the dermal exposure experiments, subjects were placed in an exposure chamber and received fresh air from outside the chamber so no phenol could be absorbed through the lungs. The inhalation exposure experiments lasted for 8 hours with two breaks of 30 minutes, while the dermal exposure experiments were for 6 hours with one break in the middle. The primary purpose of this study was to evaluate absorption of phenol vapor through the lungs and skin, and excretion of phenol in the urine. While Piotrowski (1971) did not report on whether any adverse effects were experienced by any of the exposed subjects, it appears that ACGIH assumed that the highest exposure was without effects (ACGIH, 1994). The Cal/EPA also used the Piotrowski (1971) study to derive an acute inhalation reference exposure level and assumed that the highest concentration was a NOAEL (Cal/EPA, 2008). In support of this assumption, Cal/EPA (2008) cites a study by Ruth (1986) that reports an irritation threshold of 47 ppm. Based on all available data, the assumption of no observable adverse effects occurring after an 8-hour inhalation exposure of up to 20 mg/m^3 of phenol seems reasonable.

Considering the above information, the ITSL will be derived from the ACGIH TLV and NIOSH TWA recommended exposure level of 5 ppm (19 mg/m^3), pursuant to Rule 232(1)(c) as follows:

$$\text{ITSL} = \frac{OEL}{100} = \frac{19\ mg/m^3}{100}$$

$$\text{ITSL} = 0.19\ \text{mg/m}^3 = 190\ \mu\text{g/m}^3$$

The previous ITSL of 600 µg/m^3 was derived from the NIOSH ceiling limit of 60 mg/m^3. The NIOSH ceiling limit was selected over the NIOSH REL or ACGIH TLV because it provided a lower ITSL taking into account the associated averaging times (MDNR, 1995). In 1995 when the previous ITSL was established, the scaling factor used for converting from a one hour averaging time to an eight hour averaging time was about 0.25. Using a more recent screening dispersion model (SCREEN 3), results in a scaling factor of 0.7 for this conversion. Based on the scaling factor of 0.7, an ITSL of 190 µg/m^3 with an 8-hour averaging time would be more restrictive than an ITSL of 600 µg/m^3 with a 1-hour averaging time.

The use of the ACGIH TLV and NIOSH REL of 5 ppm was selected for derivation of the current ITSL because its rationale has a stronger scientific basis than that for the NIOSH ceiling limit of 15.6 ppm. It is also consistent with the language of Rule 232(1)(c) that states the ITSL shall be based on the lowest OEL. In summary, the ITSL for phenol is 190 µg/m^3, with an averaging time of 8 hours, as per Rule 232(1)(c) and Rule 232(2)(a).

Review of Carcinogenicity Data

Phenol has been tested for carcinogenicity in one chronic lifetime animal bioassay in which male and female F344 rats and B6C3F1 mice were exposed to 2500 or 5000 ppm in the drinking water for 103 weeks (NCI, 1980). The NCI concluded that under the conditions of this bioassay, phenol was not carcinogenic for either rats or mice. The NCI did note however, that

the incidence of leukemia or lymphoma was significantly increased in the low dose male rats, but because this effect was not seen in the high dose rats, no association with exposure to phenol could be established (NCI, 1980).

The International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity data for phenol and found that there is inadequate evidence for the carcinogenicity of phenol in humans and experimental animals. The IARC's overall evaluation is that "phenol is not classifiable as to its carcinogenicity to humans (Group 3)" (IARC, 1999).

The US EPA has also evaluated the available data for phenol and concluded that it is not adequate to assess the carcinogenic potential of phenol (EPA, 2002). The EPA's rationale for this conclusion is as follows:

> Although phenol was negative in oral bioassays conducted in rats and mice (NCI, 1980), questions remain regarding its carcinogenic potential in light of the positive results in initiation/promotion assays (albeit at exposures typically above the MTD), the increases in leukemia in low-dose male rats in the oral bioassay, and the observation of gene mutations in mammalian cells in vivo and micronuclei in vivo following i.p. dosing. No inhalation studies of sufficient duration to assess phenol carcinogenicity have been conducted. Dermal carcinogenicity or initiation/promotion studies with phenol at exposures below the MTD have not been conducted. The carcinogenic potential of phenol via inhalation exposure has not been evaluated at all. Under the draft revised *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes *are inadequate for an assessment of human carcinogenic potential*. Under the current guidelines (U.S. EPA, 1986a), phenol falls in Category D: not classifiable as to human carcinogenicity (EPA, 2002, page 94).

Phenol does not meet the definition of carcinogen in Rule 103(c) of the Michigan Air Pollution Control Rules, and therefore, it is not appropriate to derive an initial risk screening level or secondary risk screening level.

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