MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: 4-Nitrophenol file (CAS # 100-02-7)

FROM: Gary Butterfield

SUBJECT: Screening level development for 4-nitrophenol

DATE: March 8, 2007

4-Nitrophenol is also known as p-nitrophenol or 4-hydroxynitrobenzene. This is a solid, crystalline material at ambient temperatures. The melting point is 113C. The boiling point is 297C. The vapor pressure is 0.0003 mmHg at 30C. It is moderately soluble in cold water. 4-Nitrophenol is used to manufacture drugs, fungicides, and dyes. This material is included in the list of EPA's hazardous air pollutants (HAPs), and is a high production volume chemical.

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 (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 - September 2006), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line searches were conducted on September 19, 2006. There were two inhalation toxicity studies identified during the literature searches. An unpublished 4-week rat study reported by Hazleton (1983), and an acute and 2-week study reported by Smith et al (1988). There also was a 13-week oral exposure study conducted by Hazleton (1989).

4-Nitrophenol has been identified by the EPA as being one of the 188 HAPs. This material is included in the list of IRIS chemicals. However, there is no RfC, or RfD values calculated in IRIS by the EPA.

The acute inhalation study by Smith et al reported no deaths occurring when six male rats were exposed to 4.7 mg/L of p-nitrophenol sodium salt, which converts to 4033 mg/m^3 of p-nitrophenol. In this acute study, four of the six rats at this dose level had corneal opacity

observed following exposure, which went away in all but one rat during the 14-day recovery/observation period.

There were actually two 2-week studies reported by Smith et al. In the first one, groups of 10 male Crl:CD rats were head-only exposed to 0, 0.34 mg/L with MMAD of 4.6 u, or 2.47 mg/L with MMAD of 7.5 u of p-nitrophenol sodium salt, which converts to p-nitrophenol exposure of 0, 292 or 2119 mg/m^3. In the second 2-week study, groups of 10 male Crl:CD rats were head-only exposed to lower concentrations of 0.03 mg/L with MMAD of 4.0 u and 0.13 mg/L with MMAD of 4.8 u of p-nitrophenol sodium salt, which converts to 26 and 112 mg/m^3 of p-nitrophenol. The exposures in both these two weeks studies lasted for 6 hours a day, 5 days a week for a total of 10 exposures. Groups of rats were held for a 14-day recovery period to assess exposure longer term effects. The NOAEL level from these studies was reported to be 26 mg/m^3, the lowest exposure level. There was a dose-related increase in methemoglobin at the 112 mg/m^3 and higher dose levels, which tended to resolve at the lower doses following the recovery period. The findings of increased methemoglobin with nitrophenol exposure are not completely unexpected as other amino- and nitro- aromatic compounds are known inducers of methemoglobin.

The longest exposure with p-nitrophenol that was located was an unpublished 13-week rat gavage study by Hazleton (1989). Although the full study was not available, there are adequate summaries of the findings of this study reported by ATSDR (1992), WHO (2000), and the EPA (2002). In this study, groups of 20 male and 20 female Sprague-Dawley rats were gavaged with p-nitrophenol dissolved in water at daily doses of 0, 25, 70 or 140 mg/kg. There were premature deaths observed at the highest two dose levels – one male and one female at 70 mg/kg, and 15 males and six females at 140 mg/kg. The NOAEL of 25 mg/kg, based on those premature deaths, was identified be ATSDR and WHO. This study also reported uncertain methemoglobin monitoring, high values in the control rats, which lead the authors and ATSDR to conclude that there were likely problems with analytical methods. The methemoglobin monitoring, if done correctly, is likely to be a much more sensitive endpoint than premature deaths for the purpose of establishing the NOAEL. Because this study had questionable methemoglobin results, this study was considered to be unsuitable for setting the ITSL even though it was for a longer exposure duration.

In the Hazleton (1983) 4-week study, groups of 15 male and 15 female Sprague-Dawley rats were exposed whole body for 6 hours a day, 5 days a week to concentrations of 0, 1.09, 5.27 or 29.2 mg/m^3 aerosols with MMAD of ~6 u. This study was conducted according to OECD Guideline 412 "Repeated dose inhalation toxicity in 28 or 14 day study." The high-dose rats had 11 of 30 with anterior capsular cataracts, and three additional rats with corneal keratitis sicca. The NOAEL for cataract formation is reported to be 5.27 mg/m^3. This study also reported changes in methemoglobin levels, but these effects were not consistent or dose-related. The inconsistent and not-dose-related effect led ATSDR and WHO to the conclusion that methemoglobin effects should not be used to identify a NOAEL in this study. However, the cataract NOAEL is also a fairly sensitive effect, and it can be concluded that this study is the best available study to be used as the basis in screening level determination.

The NOAEL for cataract formation of 5.27 mg/m3 from Hazleton (1983) provides the best available basis for setting the ITSL. The screening level can be set using the equation from R232(1)(d), as follows.

$$\text{ITSL} = \frac{5.27\ \text{mg/m3}}{20 \times 100} \times \frac{6}{24} = 0.7\ \text{ug/m3}$$ with annual averaging

It should be noted that the 35-fold uncertainty factor from the equation in R232(1)(d), for a 7-day study, was changed to a 20-fold factor in this calculation because the study is of a longer duration, a 4-week study.

References:

ATDSR. 1992. Toxicological profiles for nitrophenols, 2-nitrophenol, 4-nitrophenol.

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EPA. 2006. IRIS on-line.

Hazleton. 1983. Subacute dust inhalation toxicity study in rats, p-nitrophenol. (HLA # 82-242) EPA OTS doc # 0520433.

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Smith et al. 1988. Acute and repeated dose inhalation toxicity of paranitrophenol sodium salt in rats. Drug Chem Toxicol 11:319-327.

WHO. 2000. Concise international chemical assessment document (CICAD) # 20 – mono-nitrophenols.

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