MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for 1,3-Dichlorobenzene file (CAS # 541-73-1)

FROM: Gary Butterfield

SUBJECT: Screening level for 1,3-Dichlorobenzene

DATE: August 4, 2006

1,3-Dichlorobenzene is a liquid at ambient temperatures. This material has a molecular weight of 147 g/mol. The melting point is -24C. The boiling point is 173C. The vapor pressure is reported to be 4.9 mmHg at 39C.

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 - May 2006), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches were conducted on May 9, 2006. Several short term exposure studies and one 90-day study were located in the literature search. The short-term studies included: a single dose study looking for hepatoxic effects, Umemura et al (1996); a 9-day gavage study looking for drug metabolism and urinary products, Poland et al (1971); a 10-day gavage study as a preliminary study to the 90-day gavage study McCauley et al (1995).

EPA announced July 11, 2006 in the federal register the availability of a draft Toxicological Review document for dichlorobenzenes for the upcoming IRIS entries. The Toxicological Review did not establish an RfD or RfC for 1,3-dichlorobenzene as does the old IRIS entry, but did discuss the available sub-chronic data (McCauley et al) and why it was insufficient for calculating a RfD.

In the single dose gavage study by Umemura et al (1996), groups of 5 male B6C3F1 mice were given doses of 120, 200 or 300 mg/kg.

In the 9-day gavage study reported by Poland et al (1971) female Sherman rats were given doses of 800 mg/kg. Liver enzyme activity, urinary porphyrin were evaluated for changes following being dosed.

As a preliminary study to the 90-day study, a 10-day gavage study was conducted by McCauley et aI (1995), groups of 10 male and 10 female Sprague-Dawley rats were gavaged with 0, 37, 147, 368 or 735 mg/kg in corn oil. At 735 mg/kg there was decreased body weights. In both the high doses there was increased liver weight, increased serum cholesterol, hepatocellular centrolobular degeneration observed.

The 90-day gavage study reported by McCauley et al (1995), groups of 10 male and 10 female Sprague-Dawley rats were gavaged with 0, 9, 37, 147 or 588 mg/kg in corn oil for 90 consecutive days. The body weights were decreased at the highest dose. At the highest two doses liver and kidney weights were increased, with liver, thyroid, pituitary, and kidney histological lesions. Serum cholesterol and serum calcium levels were increased in all doses in male rats, and in the highest three doses in females. Although these changes can be considered to not be an adverse effect, but a biological reaction to the other organ changes. Even at the lowest dose there were pathologic changes in the thyroid and pituitary. The thyroid reduction of follicular colloidal density in the male rats was considered by EPA (2006) to be the most critical effect of this study observed at even the 9 mg/kg dose level. The incidence of thyroid pathology was reported to be 2/10, 8/10, 10/10, 8/9, 8/8 for the controls to high dose male rats. The authors reported the LOAEL to be 9 mg/kg.

Unfortunately, EPA (2006) also goes on to say this study is not adequate to calculate an RfD because the total UF is too great, due to application of the database uncertainty factor. This EPA (2006) document also determined that BMD modeling was not appropriate due to the inconsistent dose response, even dropping highest doses from modeling.

This 90-day study provides the best available longer term toxicity information upon which to base the screening level. The inhalation screening level will be determined from the 90-day oral study assuming that there are no differences in absorption or effects between oral and inhalation routes of administration. The ITSL will be calculated using the R232(1)(e) equation. This method of ITSL determination is considered appropriate after EPA (2006) decided that an RfD calculation was not possible due to many uncertainties. The ITSL is calculated as follows:

LOAEL = 9 mg/kg

R232(1)(e) 7 day study equation

ITSL = LOAEL/(35x100xUF) x wt/inhal x (oral absorb/(inhal absorb)

ITSL = (9 mg/kg)/(10x100x3) x 1kg/0.9m^3 x 1/1 = 3 µg/m^3 annual average

The 35 fold uncertainty factor from R232(1)(e) in the above calculation was changed to a factor of 10, because this was a 90-day study rather than 7-day. A factor of 3 for the LOAEL to NOAEL uncertainty factor was used because the low doses had mild to moderate severity of thyroid histopathology, while the higher doses had moderate to marked severity. The default rat inhalation rate ($0.9 m^3/kg$) was used in the calculation. The oral and inhalation absorption efficiencies are not known, so 100% for each route was assumed.

References

EPA. 2006. Toxicological review of dichlororbenzenes — final review draft. EPA/635/R-03/01 5 as announced 71FR39113.

McCauley et al. 1995. Toxicity studies of 1 ,3-dichlorobenzene in Sprague-Dawley rats, Drug and Chemical Toxicology 18: 201-221

Poland et al. 1971. A reciprocal relationship between the induction of gamma-aminolevulinic acid synthetase and drug metabolism produced by m-dichlorobenzene. Biochem Pharmacol 20:1281-1290.

Umemura et al. 1996. Isomer-specific acute toxicity and cell proliferation in livers of B6C3F1 mice exposed to dichiorobenzene. Toxicol Appi Pharmacol 137: 268-274.

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