MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

May 10, 2000

TO: File for 2-Ethyl-1,3-Hexanediol (CAS No. 94-96-2)

FROM: Michael Depa, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for 2-ethyl-1,3-hexanediol (EHD) is 30 µg/m³ based on an annual averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. EPA Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967- May 29, 1999), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) or reference dose (RfD) for EHD. There were no occupational limits available for EHD. The molecular weight of EHD is 146.26g. Vapor pressure is < 0.01 mmHg at 20ºC.

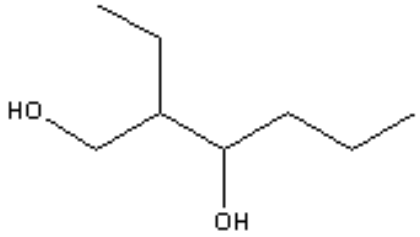

Figure 1. Molecular Structure of 2-ethyl-1,3-hexanediol (EHD)

Animal Toxicity Studies

The toxicity of EHD was previously reviewed by the Michigan Department of Environmental Quality, Air Quality Division in a document called “AQD Interim Chemical Evaluation” (AQD, 1994). Toxicity studies that were not reviewed in the previous document are described below.

The acute rat LD50 was reported as 2.71 (2.52 – 2.93) g/kg (Smyth et al., 1951). A study by Ballantyne et al. (1985) reported that the acute LD50 in rats was 9.86 ml/kg in male rats and 4.92 ml/kg in female rats. In an acute inhalation study, the rat LC50 was reported as greater than 3.8 mg/l (Ballantyne et al., 1985).

In a 90 day oral toxicity study, groups of rats (number and strain unspecified) were exposed to 0.2, 0.48, or 0.7 g/kg/day EHD. The maximum daily dose having no effect was reported to be 0.48 g/kg, animals dosed at 0.7 g/kg experienced reduced growth. No mention of: control rats, histopathology, organ weight, gross pathology, body weight, clinical observations, hematology, clinical chemistry or purity of compound administered. This study was deemed insufficient in quality for determining a screening level.

In an developmental toxicity study., groups eight of time-pregnant CD female rats received 0, 500, 1000, 2000 or 4000 mg/kg EHD by gavage on days 6 through days 15 of gestation (Kodak, 1988). Clinical signs associated with toxicity consisted of weakness, respiratory difficulty, gait disturbances, nasal discharge, porphyrin tears, and unkempt haircoats in the 2000 and 4000 mg/kg dose groups. In addition, hypothermia, partially closed eyes, excessive tearing, and piloerection were seen in the 4000 mg/kg animals. No clinical abnormalities were seen at the 0, 500 or 1000 mg/kg dose levels. Mean body weight gains and feed consumption were reduced at all dose levels during the first three days of treatment. Mean body weight gains were also reduced at all dose levels when calculated for the entire treatment period (days 6-16 of gestation). Mean relative liver weight was significantly increased for the 2000 mg/kg dams. Gross pathologic changes were seen only in the dams that died or were euthanized and included, necrosis of the glandular gastric mucosa, excessive mucus in the cecum, and atrophy of the thymus and adipose tissue. No necropsy lesions were noted in the 500 or 1000 mg/kg dams. Mean corpora lutea, implantation sites, viable fetuses per litter, and pre-implantation losses did not differ among the EHD-treated groups and the controls. Post-implantation losses (early resorptions) were statistically increased for the 2000 mg/kg EHD. These malformations included rudimentary (filamentous)tails, missing tails, and abnormal curvature of the hindliimbs. In addition, incidences of arthrogryposis, shortened trunk (lumbar region), and unbilical hernia were seen at the 2000 mg/kg dose level. Malformations noted at 500 or 1000 mg/kg were restricted to rudimentary tails in one fetus at 500 mg/kg and two fetuses from different litters in the 1000 mg/kg dose group. Hematomas (a developmental variation) were seen on nine fetuses from four 2000 mg/kg litters. The incidence of this variation was statistically significant. Thus, preliminary data indicate the EHD produces maternal toxicity and lethality at oral doses of 2000 or 4000 mg/kg. Significant fetal toxicity and teratogenicity were evident at a maternally toxic dose (2000 mg/kg), while only one fetus in the 500 mg/kg group and two fetuses in the 1000 mg/kg group had malformations. The developmental no-observed-adverse-effect-level (NOAEL) was determined to be 1000 mg/kg, whereas the lowest-observed-adverse-effect-level (LOAEL) was determined to be 2000 mg/kg based on increased incidence of hematomas in fetuses.

In a four week oral toxicity study, groups of 5 male and 5 female rats (strain not specified) were exposed to 0, 100, 300 or 1000 mg/kg/day, five days per week over a 29 day period (Kodak, 1989). No mortality of abnormal clinical signs were observed during the study. Though not statistically significant, mean body weights were slightly reduced for the 300 and 1000 mg/kg males and slightly higher for the 100 mg/kg males at the end of the treatment period when compared to controls. The 100 and 1000 mg/kg male and the 1000 mg/kg female consumed slightly more feed compared to the controls. Hematologic changes consisted of higher white blood cell counts for both sexes at all dose levels, but the differences were statistically different from the controls only for females at the 300 mg/kg and 1000 mg/kg dose level. Platelet counts were reduced only in the 1000 mg/kg females. No other differences from controls were observed for other hematologic parameters. No treatment-related changes in clinical chemistry parameters were observed for either sex at any dose level. Organ weight changes were restricted to increased relative liver and spleen weights for the 1000 mg/kg males. The authors stated that since liver enzyme tests were normal and no histopathology was seen in either the liver or splenic tissue, the changes in organ weights are probably adaptive in nature rather than due to a direct toxic effect. No treatment-related organ weight changes were observed for the 100 and 300 mg/kg males and females. No treatment-related gross or histopathologic lesions were seen in any of the tissues examined. The 100 mg/kg dose group was deemed a NOAEL. The LOAEL of 300 mg/kg was based on statistically increased white blood cell count in female rats.

Derivation of the Screening Level

Since there was no information indicating that the oral to inhalation route extrapolation was inappropriate, the 4 week oral toxicity study was used to develop a screening level (Kodak, 1989). The critical effect was increased white blood cells. Normally a subchronic study would be chosen over a 4 week study, however, the subchronic study was poorly reported (no mention of control animals, histopathology, etc.) and determined to be unacceptable to use to derive the ITSL. The 7-day equation in Rule 232(1)(e) was used to calculate the ITSL. The duration of the study was greater

than 7 days, however, there is no other equation available, therefore, the ITSL was calculated as follows:

$$ITSL = \frac{NOAEL\ (mg/kg/day)}{35 \times 100} \times \frac{W_a}{I_a} \times \frac{a}{b}$$

Where W_a is the body weight of the experimental animal in kg,
I_a is the inhalation rate of the experimental animal in m^3/day,
b is the absorption efficiency by the oral route of exposure, and
c is the absorption efficiency by the inhalation route of exposure.

According to EPA (1988) the body weight of the rat (stain and sex not given) is 0.395 kg and the inhalation rate is 0.373 m³. Since there is no information available on the oral or inhalation absorption efficiency, the default ratio of 1 was used. The ITSL then becomes:

$$ITSL = \frac{100\ mg/kg/day}{35 \times 100} \times \frac{0.395\ kg}{0.373\ m^3} \times \frac{1}{1}$$

$$ITSL = 0.0286\ mg/kg/day \times 1.059\ kg/m^3$$

$$ITSL = 0.030\ mg/m^3$$

$$ITSL = 30\ \mu g/m^3$$

The initial threshold screening level for 2-ethyl-1,3-hexanediol is 30 µg/m³ based on an annual averaging time [Rule 232(2)(c)].

REFERENCES

AQD. 1994. AQD Interim Chemical Evaluation for of 2-ethyl-1,3-hexanediol. Dated: April 12, 1994. DJO, Daniel O'Brien.

EPA. 1988 Recommendations for and documentation of biological values for use in risk assessment. PB 88-179874.

Kodak, 1988. Acute toxicity and developmental toxicity probe study of 2-ethyl-1,3-hexanediol with attachments and cover letter dated 121988. EPA, Office of Toxic Substances, EPA/OTS 88-890000024 (microfiche).

Kodak, 1989. A four week oral study of 2-ethyl-1,3-hexanediol in the rat. EPA, Office of Toxic Substances, EPA/OTS 89-890000193 (microfiche).