MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 16, 1999

TO: File for ethylene glycol mono-2-ethylhexyl ether [EGEHE] (1559-35-9)

FROM: Dan O'Brien, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for EGEHE is 37 µg/m^3 based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files; EPA's Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST); American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Booklet; National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards and Registry of Toxic Effects of Chemical Substances (RTECS); National Toxicology Program (NTP) World Wide Website (WWW), MDEQ Library; International Agency for Research on Cancer (IARC) WWW; Chemical Abstract Service (CAS) On-line and National Library of Medicine (NLM) Toxline (1967–April 14, 1999), Chemical Evaluation Search And Retrieval System (CESARS), Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary.

No specific information on the uses of EGEHE was noted in our searches, but it seems likely that, similar to other glycol ethers, it is employed primarily as a solvent. Ethylene-based glycol ethers are used primarily by the coatings industry, where their relatively slow rate of evaporation is particularly useful. Other uses include inks, cleaners, chemical intermediates, process solvents, brake fluids and deicers (Gingell *et al.*, 1994).

Available toxicological data for EGEHE were limited to two sources. The first, a range-finding toxicity study by Smyth et al. (1954), reports a Lethal Dose 50 (LD_{50}) of 3.08g/kg with 95% confidence limits of (2.49, 3.81)g. Those same authors listed the maximum exposure period to EGEHE vapor which was survived without animal deaths as eight hours (the maximum tested) for exposure concentrations "approaching saturation". Using rough calculations based on vapor pressure, this exposure concentration is likely to have been $\approx$ 1125 mg/m^3. Smyth et al. (1954) also note a dermal LD_{50} of 2.12 (1.26-3.56) ml/kg in rabbits, and found the agent to be caustic to both skin and eyes in irritation tests.

The other toxicological data for the chemical were derived from a collection of unpublished studies from Eastman Kodak submitted to U.S. EPA (Krasavage and Vlaovic, 1982). The collection consists of an acute oral LD_{50} study in rats and mice, an acute dermal LD_{50} study in rabbits, and a six week repeat dose gavage study in rats. In the acute oral LD_{50} study, EGEHE was 1.5 to 2 times more toxic in fed (as opposed to fasted) animals. LD_{50}s (with 95% CIs) were 7832 (5585, 10,997) mg/kg in fasted rats and 7308 (5203, 10,266) mg/kg in fasted mice, vs. 5149 (3480, 7689) mg/kg in fed rats and 3898 (2506, 6055) mg/kg in fed mice. The considerable deviation from the lethal doses reported by Smyth et al. (1954) is interesting, although as Krasavage and Vlaovic note, "comparison of the toxicity between the various ethers (over time) is difficult because of inter and intra-laboratory variations".

In the six week gavage study, EGEHE of > 99% purity was dosed undiluted once daily, 5 days/week for six weeks to male albino caesarean-derived rats with an average body weight of 235.7 g. Ten animals were assigned randomly to each of four exposure groups: control, 957 mg/kg, 1914 mg/kg and 3828 mg/kg (intended to represent 0, 1/8, ¼ and ½ of the LD_{50}, respectively). Animals were housed individually with *ad libitum* access to rodent chow and water. Parameters evaluated on all rats included clinical signs, body weights, feed consumption and gross and histopathology on a full complement of 31 tissues. Hematology[1], serology[2], and organ weights[3] were obtained from those rats surviving to termination. Blood samples were obtained just prior to necropsy. Rats that died spontaneously were subjected to necropsy as soon as possible; moribund animals were asphyxiated with CO_2 and necropsied. Animals surviving to the end to the study were also sacrificed with CO_2.

Rats in the high dose group all died prior to the end of the study; the median day of death was 3 with a range of 2 to 33 days. There were no deaths in either of the other exposed groups. Clinical signs were reported in the high and intermediate dose rats. The only high dose rat to survive longer than four days had an unkempt hair coat, moderate weakness, and urinary signs (hematuria and distended bladder) after 20 days on study. In addition, what appeared to be urinary incontinence was also reported in the intermediate dose rats. High dose rats experienced statistically significant ($p \leq 0.05$) decreases in body weight gain and feed consumption compared to controls; rats in the other two dose groups had lower body weight gains than controls, but these reductions were non-significant. Mean terminal body weights in all exposed groups were significantly reduced compared to controls. With respect to the results of hematology and serology tests, hemoglobin concentrations were significantly decreased compared to control values

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[1]Hemoglobin concentration, hematocrit, red blood cell count, red cell indices, and total and relative white cell counts.
[2]Glutamic oxalacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, lactic dehydrogenase, urea nitrogen, creatinine and glucose.
[3]Liver, kidneys, heart, testes, brain and spleen.

in both the intermediate and low dose groups, while absolute white blood cell counts were significantly increased in the low dose group. A significantly decreased mean blood glucose in the intermediate dose group was the only serological change noted. Absolute and relative (to body weight) liver weights were significantly increased compared to controls in both the low and intermediate dose groups, as were relative kidney and testes weights. Relative heart weights differed significantly from controls in both dose groups as well, although illegibility of the study copy available for our review prevented determination of the direction of the weight deviation. Absolute brain weights were significantly decreased in the intermediate dose group. Gross hematuria was noted in the urinary bladders of 3 of the high dose rats at necropsy, while in the intermediate group, 3 rats had grossly enlarged livers, and 1 rat had an enlarged kidney. There were no gross lesions in the low dose group. Histopathological lesions were noted in all dose groups; they included:

- Degenerated epididymal spermatocytes (2/10 rats, high dose)
- Diffuse thymic hemorrhage (5/10, high dose)
- Gastric hyperkeratosis and acanthosis, (all rats, all doses)
- Hepatocytomegaly (5/10, intermed.; 1/10, low dose)
- Anisokaryosis of liver cells (3/10, high; 7/10, intermed.; 10/10, low dose)
- Lack of liver cytoplasmic basophilia (7/10, intermed.; 5/10, low dose)
- Splenic congestion (3/10, high; 9/10, intermed. dose)
- Renal proximal convoluted tubule cells, hyaline droplet degeneration (7/10, high; 10/10, intermed.; 10/10, low dose; 10/10, controls)

While the authors did not specifically state what they considered to be adverse effect levels, it is clear that adverse effects (decreased hemoglobin, body weight changes, liver weight and histopathologic changes) that showed evidence of a dose response relationship occurred even at the lowest dose level. Thus, a no observed adverse effect level was not identified in this study, and the lowest exposure level studied (957 mg/kg-day) is considered a lowest observed adverse effect level (LOAEL).

In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal inhalation studies which can be used to derive a Reference Concentration (RfC). Such data were not found in our searches; indeed no inhalation studies of any kind were located. When adequate data for RfC calculation are not available, next preference is given to oral data for calculation of a Reference Dose (RfD) if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. With respect to EGEHE, no chronic oral data are available. Since no Occupational Exposure Limits (OELs) are available for this compound, nor any short term inhalation data, the next most appropriate basis for a screening level would be subacute/subchronic repeated dose oral data. The six week repeated dose gavage study of Krasavage and Vlaovic (1982)

fits in this category. The LOAEL from that study (957 mg/kg-day) is used here in the absence of a NOAEL.

ITSL Derivation: Applying section R 336.1232, rule 232(1)(e) of Act 451, as amended:

$$\text{ITSL} = \frac{\text{LOAEL (mg/kg} - \text{day)}}{35 \times 100 \times \text{UF}} \times \frac{W_A}{I_A} \times \frac{b}{a}$$

where:

W_A = Mean terminal body weight[4] of a male rat in the low dose group from Krasavage and Vlaovic (1982)
I_A = Daily inhalation rate of a strain-unspecified male rat (default value from MDEQ, 1996 and EPA, 1988)
b = Absorption efficiency by the oral route of exposure
a = Absorption efficiency by the inhalation route of exposure

The factor of 35 in this equation is a safety factor to account for using a NOAEL from a seven day exposure period to estimate a NOAEL for a lifetime exposure, as outlined by the MATPC (1989). Since the exposure period in Krasavage and Vlaovic (1982) was 42 days, this safety factor is reduced from 35 to 20, consistent with EPA methodology. The Uncertainty Factor (UF) is intended to account for the uncertainty of extrapolation from a NOAEL to an LOAEL, and can take on any value between 1 and 10. Given the multiple dose-related effects noted even at the lowest dose tested in Krasavage and Vlaovic (1982), as well as the fact that no threshold for toxicity was identified in the study, this UF is assigned its full value of 10. A ratio term of 5/7 is incorporated into the equation in this case to adjust for the intermittent dosing schedule (5 out of 7 days/week).

So,

$$\text{ITSL} = \frac{957\text{mg/kg}-\text{day}}{20 \times 100 \times 10} \times \frac{0.362\text{kg}}{(0.916\text{m}^3/\text{kg}-\text{day} \times 0.362\text{kg}} \times \frac{1}{1} \times \frac{5\,\text{days}}{7\,\text{days}}$$

$$= 0.048 \text{ mg/kg-day} \times (0.916 \text{ m}^3\text{/kg-day})^{-1} \times 1 \times 0.714$$

[4]Terminal body weight is used, since animals were not sufficiently mature at sacrifice for a plateau of body weights to have been attained.

$$= 0.0374\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}}$$

$$= 37.4\ \mu\text{g/m}^3 \approx \mathbf{37\ \mu g/m^3}$$

with (*b/a*) taking on the default value of 1 in the absence of data to the contrary.

Per 232(2)(c), an **annual averaging** time applies.

REFERENCES

EPA (1988). Recommendations For and Documentation of Biological Values For Use in Risk Assessment. Cincinnati, OH: Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Document # PB88-179874, EPA Report # EPA/600/6-87/008, 200+ pp. (2/1988).

Gingell R, Boatman RJ, Bus JS, Cawley TJ, Knaak JB, Krasavage WJ, Skoulis NP, Stack CR and Tyler TR (1994). A. Ethers of the ethylene glycols. *In*: Patty's Industrial Hygiene and Toxicology, 4th Ed. (Clayton GD and Clayton FE, Eds.), Volume II, Part D, Chapter Thirty One: Glycol Ethers and other Selected Glycol Derivatives. John Wiley and Sons, Inc., New York, p. 2762.

Krasavage WJ and Vlaovic, MS (1982). Initial submission: Letter from Eastman Kodak Company to U.S. EPA regarding toxicity studies of nine glycol ethers with attachments and cover letter dated 092882. Submitted to U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC. EPA Document #88-920008915, 152 pp.

MATPC (1989). Final Report of the Michigan Air Toxics Policy Committee (MATPC): A Proposed Strategy for Processing Air Quality Permit Applications for New Emission Sources of Toxic Air Pollutants. Michigan Department of Natural Resources, 9/14/89, p. 31.

Michigan Department of Environmental Quality (MDEQ), (1996). Default animal data for risk assessment (as based on U.S. EPA, 1988, Recommendations for and documentation of biological values for use in risk assessment, EPA Document # PB 88-179874).

Smyth HF, Carpenter CP, Weil CS, Pozzani UC (1954). Range-finding toxicity data. List V. *AMA Arch Indus Hyg Occup Med* **10**:61-68.

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