MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Ethylene glycol monoethyl ether acetate (CAS# 111-15-9)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 31, 2017

SUBJECT: Ethylene glycol monoethyl ether acetate (CAS# 111-15-9) ITSL remaining at 24-hour averaging time

The initial threshold screening level (ITSL) for ethylene glycol monoethyl ether acetate (EGEEA) is 290 µg/m^3 based on a 24-hour averaging time. The ITSL was originally established on 4/23/1998 and was set at 293 µg/m^3 based on a 24-hour averaging time. The ITSL is based on a 13 week inhalation study on male and female rats and rabbits by Barbee et al, (1984) on a related compound ethylene glycol monoethyl ether (EGEE). The critical effect of exposure to EGEE was decreased testis weight and seminiferous tubule degeneration. The ITSL has been rounded to two significant figures. As EGEEA is a reproductive toxicant, it is appropriate for the ITSL to remain at a 24-hour averaging time.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Barbee SJ, Terrill DJ, DeSousa DJ, Conaway CC. 1984. Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. Environmental Health Perspectives. 57:157-163.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 23, 1998

TO: File for Ethylene Glycol Monoethyl Ether Acetate (CAS# 111-15-9)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for ethylene glycol monoethyl ether acetate (EGEEA, also called 2-ethoxyethyl acetate) is 293 $\mu g/m^3$ based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS Online (1967 - January 7, 1998), National Library of Medicine, Health Effects Assessment Summary Tables (HEAST), and NTP Status Report. A chronic RfD was listed in HEAST as 0.3 mg/kg/day. The ACGIH and NIOSH have established occupational exposure limits (OELs) for ethylene glycol monoethyl ether acetate (EGEEA) at 27 mg/m^3 and 2.7 mg/m^3, respectively. Figure 1 shows the structure of EGEEA. The structure of a closely related compound called ethylene glycol monoethyl ether (EGEE) is depicted in Figure 2.

Figure 1. Ethylene Glycol Monoethyl Ether Acetate (Molecular Weight = 132.2g)

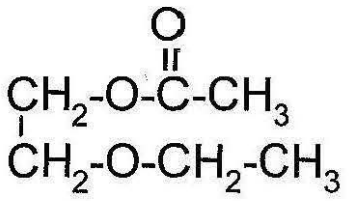
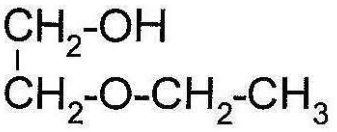


Figure 2. Ethylene Glycol Monoethyl Ether (Molecular Weight = 90.1g)



Background on NIOSH REL for EGEEA

The National Institute for Occupational Safety and Health (NIOSH) reviewed the toxicity studies available on EGEEA (NIOSH, 1991) and developed a recommended exposure limit (REL) of 2.7 mg/m^3 (0.5 ppm) for EGEEA based on a developmental study (Tyl et al., 1988). Tyl et al. (1988) dosed groups of 30 pregnant Fischer 344 rats and groups of 24 pregnant New Zealand

white rabbits by inhalation for 6 hrs/day on gestational day 6 through 15 (rats) or 6 through 18 (rabbits) at concentrations of 0, 50, 100, 200, or 300 ppm. The animals were then sacrificed on gestational day 21 (rats) or 29 (rabbits). At 100, 200 and 300 ppm maternal toxicity was observed in rabbits based on significantly decreased weight gain, reduced gravid uterine weight ($P<0.001$) and elevated absolute liver weight ($P<0.05$). In rabbits, increased incidence of totally resorbed litters was observed at 200 ppm ($P<0.05$) and 300 ppm ($P<0.001$). Rabbit fetoxicity (reduced ossification) was observed at 100, 200 and 300 ppm. In rats, significantly elevated relative liver weights were noted at 100, 200, and 300 ppm EGEEA. At 100, 200, and 300 ppm EGEEA there was an increased incidence of visceral and skeletal variations in rats. NIOSH developed a REL for EGEEA (0.5 ppm) based on the NOAEL of 50 ppm (270 mg/m^3). NIOSH first converted the animal exposure to "retained dose" then to "equivalent human exposure." NIOSH used a 100 fold uncertainty factor; 10 for interspecies variability and 10 for intraspecies variability. The same REL (0.05 ppm) was developed for the closely related compound EGEE.

Comparative Toxicity: EGEEA and EGEE

NIOSH (1991) compared the toxicity of EGEEA to that of EGEE. NIOSH (1991) stated that, "EGEEA is believed to pass through the same metabolic pathway as EGEE after hydrolysis of the ester moiety." The metabolite ethoxy acetic acid (EAA) is excreted in the urine after exposure to both EGEE and EGEEA. NIOSH stated that the, "EAA excretion in workers exposed to EGEEA vapor was similar to EAA excretion in workers exposed to EGEE." NIOSH (1991) continued,

> During exposure to EGEEA vapor, partial respiratory elimination of EGEE was observed. This finding confirmed the hypothesis that EGEEA is first converted to EGEE by esterases (Groeseneken et al., 1987).

Since EGEEA is converted to EGEE one would expect that the toxicity of both compounds would be similar.

Derivation of the RfC for EGEE

The EPA developed an RfC of 200 μg/m^3 for EGEE based on a 13 week inhalation study in male and female rats and rabbits (Barbee et al., 1984). The critical effect of exposure to EGEE was decreased testis weight and seminiferous tubule degeneration which was observed at the high dose 1485 mg/m^3 but not at the mid dose 380 mg/m^3. The doses were adjusted to the human equivalent concentration (HEC) by multiplying the exposure concentration by the days per week (5/7) and the hours per day (6/24). The $LOAEL_{HEC}$ was calculated to be 265 mg/m^3 and the $NOAEL_{HEC}$ was calculated to be 68 mg/m^3. The $NOAEL_{HEC}$ was then divided by and uncertainty factor of 300 to derive the RfC. The uncertainty factor of 300 was a composite of 10 to account for intraspecies extrapolation, 10 for the use of a subchronic study and 3 to account for interspecies extrapolation.

Derivation of the ITSL for EGEEA

It was deemed appropriate to use the ITSL for EGEE (i.e. 200 μg/m³; 24-hour averaging time) to derive the ITSL for EGEEA based on the assumption that EGEEA is converted to EGEE in vivo. Since the amount of EGEE and EGEEA are expected to have the same toxicity, a one-to-one mole ratio was used to convert the EGEE ITSL to the ITSL for EGEEA. The molecular weights of EGEE and EGEEA are 90.1 g and 132.2 g, respectively. The ITSL for EGEEA was calculated as follows:

ITSL for EGEEA = ITSL for EGEE x (Mol. weight of EGEEA)/(Mol. weight of EGEE)

ITSL for EGEEA = 200 μg/m³ x (132.2 g)/(90.1 g)

ITSL for EGEEA = 293 μg/m³ (based on a 24-hour averaging time)

The ITSL for EGEEA is 293 μg/m³ based on a 24-hour averaging time.

References

ACGIH. 1991. Threshold limit values (TLVs) and biological exposure indices (BEI) documentation. American Conference of Governmental Industrial Hygienists. Cincinnati, OH, 45240-1634.

Barbee SJ, Terrill DJ, DeSousa DJ, Conaway CC, 1984. Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. Environmental Health Perspectives. 57: 157-163.

Carpenter CP, Pozzani UC, Weil CS, Nair III JH, Keck GA, Smyth HF Jr. 1956. The toxicity of butyl cellosolve solvent. AMA Archive of Industrial Health. 14: 114-131.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E. 1987. Pulmonary adsorption and elimination of ethylene glycol monoethyl ether acetate in man. British Journal of Industrial Medicine. 44: 309-316.

NIOSH. 1991. Criteria for a recommended standard: occupational exposure to ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, and their acetates. U.S. Department of Health and Human Services, Public health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 91-119

Tyl RW, Pritts IM, France KA, Fisher LC, Tyler TR. 1988. Developmental toxicity evaluation of inhaled 2-ethoxyethanol acetate in Fischer 344 rats and New Zealand white rabbits. Fundamental and Applied Toxicology. 10:20-39.

MD:SLB
cc: Mary Lee Hultin, AQD