MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Ethylene glycol monomethyl ether acetate (CAS# 110-49-6)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 30, 2017

SUBJECT: Ethylene glycol monomethyl ether acetate (CAS# 110-49-6) ITSL remaining at 24-hour averaging time

The initial threshold screening level (ITSL) for ethylene glycol monomethyl ether acetate (EGMEA) will remain at 31 µg/m^3 based on a 24-hour averaging time. The ITSL was originally established on 11/6/2002 and was set at 31 µg/m^3 based on a 24-hour averaging time. The ITSL is based on a 13 week inhalation study on rats and rabbits by Miller et al. (1983) on a related compound ethylene glycol monomethyl ether (EGME). The critical effect of EGMEA is decreased testis weight and degenerative changes in the germinal epithelia. As EGMEA 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.

Miller R, Ayres J, Young J, and McKenna M. 1983. Ethylene glycol monomethyl ether. I. Subchronic vapor inhalation study with rats and rabbits. Fundamental and Applied Toxicology. 3(1): 49-54.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

October 23, 1998

TO: File for Ethylene Glycol Monomethyl Ether Acetate (CAS No. 110-49-6)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for ethylene glycol monomethyl ether acetate (EGMEA) is 31 $\mu g/m^3$ based on a 24-hour averaging time. The critical effect of EGMEA is decreased testis weight and degenerative changes in the germinal epithelia.

The following references or databases were searched to identify data to determine the ITSL: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, MDEQ's Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) On-line (1967-February 28, 1996), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program (NTP) Status Report. Review of these sources found that EPA has not established a Reference Concentration (RfC) or Reference Dose (RfD) for EGMEA. The NIOSH Recommended Exposure Limit (REL) for EGMEA is 0.5 mg/m^3 and the ACGIH TLV is 22 mg/m^3. The molecular weight of EGMEA is 118.1 g. The vapor pressure of EGMEA is 2.0 to 37. mm Hg (@ 25°C). EGMEA is also called 2-methoxyethyl acetate and methyl cellosolve acetate.

Overview of EGMEA Toxicity and Other Relevant Information

Ethylene glycol ethers are widely used as industrial solvents for resins, lacquers and dyes. The critical health effect of ethylene glycol monomethyl ether (EGME, CAS No. 109-86-4) and its acetate, ethylene glycol monomethyl ether acetate (EGMEA), is testicular atrophy. Reproductive and developmental effects (fetal malformations and decreased fetal body weight) have also been observed. Other effects include blood (erythrocyte fragility), central nervous system and hematopoietic system effects. Toxicity data on EGME was used to develop occupational exposure limits (OELs) for EGMEA based on the presumption that EGMEA is metabolized to EGME. The ITSL for EGME is 20 $\mu g/m^3$ (24-hour average) which was based on the EPA RfC. Other ethylene glycol ethers have been evaluated for there toxicity. The OEL for ethylene glycol mono*ethyl* ether acetate (EGEEA) was developed from the toxicity data on ethylene glycol mono ethyl ether (EGEE). Similarly the ITSL for EGEEA (CAS No. 111-15-9) was based on the RfC

for EGEE (CAS No. 110-80-5) [see the memo to the chemical file for EGEEA for more information].

Toxicity Studies

In a human study, a 21-year old woman was exposed to EGMEA by dermal contact and probably by inhalation in the course of two pregnancies (Bolt et al., 1990). She cleaned glassware and other equipment used in the laboratory using EGMEA as a solvent for at least four hours a day. Gloves were usually used but not always. The following malformations were observed in both children: perineal hypospadia (a failure of closure of the urethral groove), micropenis, and pronounced bifid type of scrotum. Extensive laboratory examinations reveal no other abnormalities. The authors stated that a high percutaneous absorption of EGMEA in man is well known.

Groups of six female rats (strain not specified) were exposed to various concentrations of vapors for 4 hours and an erythrocyte osmotic freagility est was performed immediately after exposure (Carpenter et al., 1956). The means of the intital hemoysis values were compared with preexposure means by the use of the t-test and a fiducial limit of $p = 0.05$. The lowest concentration causing significant osmotic fragility of the erythrocytes was 32 ppm EGMEA (155 mg/m^3). The highest concentration causeing no freagiliy was 16 ppm (77 mg/m^3).

Groups of 6 male albino Sherman rats (90 - 120 g) were given a single-dose by stomach tube of 0.1, 1 or 10 g EGMEA/kg body weight and observed for 14-days (Smith et al., 1948). Regarding the LD50 and the range of doses used the authors stated, "It is recognized that the resulting value is an extremely rough approximation and we call it an 'R.F. LD50.'" The "R.F." stands for range-finding. The R.F LD50 was determined to be 3.39 g/kg (no statistical analysis was presented). In the same report a vapor inhaltion study was performed where the vapor concentration was estimed from the settings of a proportioning pump and flowmeter rather than being determined analytically. A group of 6 male Sherman rats were exposed to 7000 ppm (33,826 mg/m^3) for 4 hours. Two of 6 rats died over the 14-day observation period.

A Group of 6 male or female Sherman rats were exposed to 8,000 ppm (38,652 mg/m^3) EGMEA for 4 hours and observed for 14 days (Carpenter et al., 1949). The rats that died numbered 2/6, 3/6, or 4/6. No other toxicological findings were reported.

In another acute oral LD50 study performed by Smyth et al. (1941) the LD50 in male Wistar rats was determined to be 3.93 (3.29-4.69) and the LD50 in male and female guinea pigs (strain not specified) was determined to be 1.25 g/kg (1.08-1.45). Groups of 10 animals were used for these tests, but the dose levels and method of LD50 was not given.

In an acute inhalation study, a group of 5 male and 5 female rats (strain not specified) were exposed for 6 hours to saturated vapor concentrations' (approx. 12,700 mg/m^3) of EGMEA and observed for 14 days (Bushy Run, 1984). There were no deaths. There were no signs of inhalation toxicity observed and gross pathologic examination revealed no remarkable lesions. No other information was reported.

In a immunosupression study groups of 6 male F344 rats were dosed by gavage with 0, 50, 100, 200, or 400 mg/kg/day EGMEA for 2 days following immunization with 20 μg trinitrophenyl-lipopolysaccharide (TNP-LPS) (Smialowicz et al., 1992). The day after the second dose was given the rats were challenged with TNP-LPS and various measures of plaque forming cells (PFC) were made. The number of PFC and the number of PFC per spleen were significantly decreased ($p < 0.01$) at all dose levels compared to the control. The number of cells per spleen and serum hemagglutination titers were decreased at the 200 and 400 mg/kg dose levels ($p < 0.01$). The study also looked at the effects of ethylene glycol (EG) and ethylene glycol monomethyl ether (EGME) in the same system at the same dose levels. EG caused no significant difference in any endpoint compared to controls. The effects of EGMEA on antibody response were virtually identical to those of EGME. A LOAEL of 50 mg/kg was identified from this study based on suppressed antibody response (decreased PFC).

In a developmental toxicity study 49 pregnant CD-1 mice were dosed by gavage with 1225 mg/kg/day EGMEA on gestational day 6-13 (Hardin et al., 1987). The dose level of 1225 mg/kg/day was pre-determined to be the LD10 then used for this study (details of study not reported). There were no maternal deaths; however, there were 0/31 viable litters ($p < 0.05$). No other data was presented. The dose of 1225 mg/kg was determined to be a developmental frank effect level (FEL).

Groups of 5 male JCL-ICR mice (6 weeks of age) were dosed by gastric intubation with 62.5, 125, 250, 500, 1000 or 2000 mg/kg EGMEA 5 days a week for 5 weeks (Nagano et al., 1984). The summary presented here is composed of both the English translation found in Environmental Health Perspectives (Nagano et al. 1984) and a summary by NIOSH (1991) taken from the original Japanese study first published in 1979 by Nagano and colleagues. In animals given EGMEA, a dose-dependent decrease in testicular weight was observed. When dose was measured in mmol/kg the decrease in testicular weight was identical for EGMEA, ethylene glycol dimethyl ether (EGDME) and ethylene glycol monomethyl ether (EGME also called 2 methoxyethanol). At the 62.5 mg/kg dose, testicular weight was approximately 87% of control testicular weight (not significantly different form controls). Nagano et al. stated that histopathology revealed a dose-related atrophy of the seminiferous epithelium. Nagano et al. also stated that there was a significant decrease in red blood cell count, packed cell volume and/or hemoglobin content at the higher dose levels (significance level and dose levels were not given). A LOAEL of 500 mg/kg was identified from this study based on testicular atrophy.

Metabolism of EGMEA

Groups of 3 female Sprague-Dawley rats inhaled 800 ppm EGMEA for 2 hours after which blood samples were taken (Romer et al., 1985). The blood concentration of EGME after exposure to EGMEA was measured at 0.8 ± 0.15 mmol/l.

In another metabolic study, carboxylesterase activity was measured in vitro in the nasal mucosa, liver, kidney, lung and blood of mice (Stott et al., 1985). EGMEA was metabolized *in vitro* to EGME in all tissues. In the same study, the nasal mucosa of male and female mice, male rats,

male and female rabbits and female dogs was analyzed for carboxylesterase activity using EGMEA as substrate. All animals metabolized EGMEA to EGME. There were no sex differences in carboxylesterase activity.

Discussion

The NIOSH REL and the ACGIH TLV for EGMEA were developed from toxicity studies using EGME. Regarding the use of EGME toxicity data NIOSH (1991) stated

> The toxic effects caused by EGMEA are likely to be similar to those caused by EGME because EGMEA is metabolized to EGME and then to the active metabolite. Therefore, it is reasonable to use the NOAELs for EGME to extrapolate NOAELs for EGMEA.

A developmental study by Hanley et al. (1984) was used to develop the NIOSH RELs for EGME and EGMEA. In this study, groups of pregnant mice, rats and rabbits were exposed via inhalation to 0, 3, 10 or 50 ppm EGME (~9, 31 and 156 mg/m^3, respectively) during the gestation period (Hanley et al., 1984). Decreased maternal weight gain was observed in the mice at 50 ppm. There were significant increases in the incidences of minor skeletal variations in the rats at 50 ppm. In the rabbits there was reduced maternal body weight gain increased absolute liver with, increased resorption rate, reduced mean fetal body weights, and increased incidence of skeletal and visceral malformations at 50 ppm. From this study NIOSH identified a NOAEL of 10 ppm EGME (31 mg/m^3). NIOSH used a 100 fold uncertainty factor (10 for interspecies extrapolation and 10 for intraspecies extrapolation). The NIOSH REL for EGME and EGMEA is 0.1 ppm (0.3 mg/m^3 for EGME and 0.5 mg/m^3 for EGMEA).

As mentioned above the inhalation RfC for EGME is 20 μg/m^3. The RfC is based on a subchronic inhalation study by Miller et al. (1983). In this study, groups of New Zealand white rabbits (5/sex/dose) and Sprague-Dawley rats (10/sex/dose) were exposed to 0, 30, 100 of 300 ppm EGME (0, 91, 311 or 934 mg/m^3) for 6 hours per day, 5 days per week for 13 weeks. RABBITS: Effects reported in both sexes of rabbits exposed to 300 ppm included reduced body weight, hematological changes (pancytopenia), lymphoid tissue atrophy (thymus) and a significant decrease in testicular weight with small flaccid testes in the males. A slight to moderate decrease in testes size was also reported in 2/5 and 4/5 male rabbits exposed to 30 and 100 ppm, respectively. Microscopic lesions included degenerative changes in the germinal epithelium of the testes in 3/3, 3/5 and 1/5 male rabbits exposed to 300, 100 and 30 ppm, respectively. The decrease in testes weight was considered to be concentration dependent in the male rabbits. No effects on the reproductive organs of the female rabbits were found. Thymus weights were significantly decreased in both sexes exposed to 300 ppm ethylene glycol monomethyl ether. Based upon the testicular effects in rabbits a NOAEL of 30 ppm (human equivalent concentration = 17 mg/m^3) and a LOAEL of 100 ppm (human equivalent concentration = 56 mg/m^3) was identified. RATS: The authors reported a significant decrease in body weight in the male rats exposed to 300 ppm and in the females exposed to 100 ppm or more. Effects reported in both sexes of rats exposed to 300 ppm included hematological changes (pancytopenia), lymphoid tissue atrophy, a decrease in liver weight, and changes in clinical chemistry parameters. In the 300 ppm groups (male and female rats) the mean values for total

serum protein, albumin and globulins were lower than the control value. A significant decrease in testicular weight and small flaccid testes were also reported in the male rats exposed to 300 ppm. Microscopic examination showed moderate to severe degeneration of the germinal epithelium in the seminiferous tubules at the highest exposure. There were no microscopic changes in the testes in the animals exposed to 100 ppm or 30 ppm ethylene glycol monomethyl ether (EGME). The authors found no effects in the reproductive organs of the female rats. In rats, the LOAEL for degenerative effects on the testes is 300 ppm (human equivalent concentration =167 mg/m^3), and the NOAEL was 100 ppm (human equivalent concentration = 56 mg/m^3).

Derivation of the ITSL for EGMEA

Based on the assumption that EGMEA is converted to EGME in vivo the ITSL for EGME was used to derive the ITSL for EGMEA. Since the amount of EGME and EGMEA are expected to have the same toxicity, a one-to-one mole ratio was used to convert the EGME ITSL to the ITSL for EGMEA. The molecular weights of EGME and EGMEA are 76.1 g and 118.1 g, respectively. The ITSL for EGMEA was calculated as follows:

ITSL for EGMEA = ITSL for EGME x (Mol. weight of EGMEA)/(Mol. weight of EGME)

ITSL for EGMEA = 20 μg/m^3 x (118.1 g)/(76.1 g)

ITSL for EGMEA = 31 μg/m^3

The initial threshold screening level (ITSL) for ethylene glycol monomethyl ether acetate (EGMEA) is is 31 μg/m^3 based on a 24-hour averaging time.

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