MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Propylene glycol monomethyl ether acetate (CAS # 108-65-6)

FROM: Keisha Williams, Air Quality Division

DATE: October 10, 2017

SUBJECT: Screening Level Update

The initial threshold screening level (ITSL) for acute exposure to propylene glycol monomethyl ether acetate (PGMEA) is 5,400 µg/m^3 (1-hour averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1229(2)(b)[1]. An ITSL of 3,000 µg/m^3 (annual averaging time) established on January 25, 2017, is rescinded based on an updated review.

The following references and databases were searched to identify data for screening level derivation: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances, the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, MDEQ Library, International Agency for Research on Cancer Monographs, National Library of Medicine, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Toxic Substances Control Act Test Submissions database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration Permissible Exposure Limits, Spacecraft Maximum Allowable Concentrations, Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profiles, California Office of Environmental Health Hazard Assessment's Reference Exposure Levels, Texas Commission on Environmental Quality Effects Screening Levels, Maximum Workplace Concentrations (Maximale Arbeitsplatzkonzentrationen) for Germany, EPA School Air Toxics Benchmarks, EPA National Air Toxics Assessment Benchmarks, World Health Organization Air Quality Guidelines, and European Chemicals Agency Registered Substances Dossiers.

Background Information

PGMEA (Figure 1) is used as a solvent (NIOSH, 1990), and in similar applications to the closely related chemical, propylene glycol monomethyl ether (PGME). Chemical properties are listed in Table 1.

[1] 336.1229. Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994. PA 451, as amended (NREPA).

Figure 1. Chemical structure of PGMEA

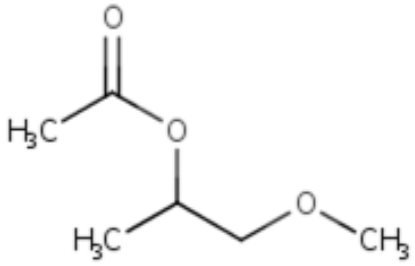

Table 1. Chemical and physical properties of PGMEA

Molecular weight: 132.159 grams/mole
Boiling point: 146°C
Vapor pressure: 0.5 kPa at 20°C
Physical state: liquid
Color: colorless
Odor: sweet, ether-like

Reference: National Center for Biotechnology Information, https://pubchem.ncbi.nlm.nih.gov/compound/7946

The toxicity of PGMEA has been noted to be similar to the toxicity of PGME. The toxicity of PGME has been reviewed and described in the PGME ITSL derivation (MDEQ, 2017). One notable exception is that PGMEA is expected to be more acutely toxic, as the acetate dissociates from the rest of the molecule and produces acetic acid (Miller et al., 1984). This dissociation was described in an animal inhalation study; and a potential ITSL was derived from this study (see Equation 1 and Equation 2).

Male and female Fischer 344 rats and B6C3F1 mice (N=5 for each exposure group) were exposed to 0, 300, 1000, or 3000 ppm (0, 1.62, 5.39, or 16.18 mg/L) PGMEA for 6 hours/day for 9 days (intermittently) (Miller et al., 1984). Mortality and morbidity were evaluated. Body weights were collected before the first exposure, and before every 3 exposures, as well as immediately before necropsy. Samples were collected to evaluate clinical hematology, chemistry analyses, and urinalyses immediately before necropsy. Organ weights were collected. Nasal tissues, lungs, liver, kidneys, thymus and bone marrow were collected for microscopic analysis. Statistical analysis was performed to evaluate whether there were statistically significant differences between groups. Among the exposure-related responses: “the mean (+/- SD) relative liver weight (g/100 g body wt) of female rats in the 3000 ppm group (3.79 +/- 0.13) was significantly higher than that of controls (3.59 +/- 0.07), possibly as a result of exposure to the test material…slight renal changes were also observed histologically in all five male rats in the 3000 ppm exposure group and in one of five male rats at the 1000 ppm…A second histologically detectable effect in rats which appeared to be related to exposure to the test material was slight-to-moderate degeneration of the olfactory epithelium in the nasal cavities of three of five males and one of five females in the 3000-ppm-exposure group…The only histopathologic changes in mice which were attributable to exposure to vapors of PGMEA occurred in the nasal cavities. Degeneration of the olfactory epithelium, similar to that described for rats, was present to some degree in all male and female mice in the 300-, 1000-, and 3000-ppm exposure groups” (Miller et al., 1984).

The critical effect was degeneration of the olfactory epithelium in mice, where the lowest-observable-adverse-effect-level (LOAEL) was 300 ppm. A no-observable-adverse-effect-level was not identified. While the Miller et al. (1984) study noted, "this acute degenerative change occurred in a dose-related manner and was generally more severe and more extensive in animals exposed to 3000 ppm. However, even at 300 ppm, slight changes were generally present…" (Miller et al., 1984), the publication does not describe the olfactory degeneration in enough detail to apply Benchmark Dose Modeling. As a result, the point of departure (POD) will be the LOAEL.

Equation 1.

$$POD_{HEC} = POD_A \; x \; DAF$$

Where:
-POD_A = Point of Departure from animal study, which is the LOAEL 300 ppm (1.62 mg/liter or 1,620 mg/m^3)

-POD_{HEC} = Point of Departure for human equivalent concentration

-DAF is the dosimetric adjustment factor, which is 1 for a category 1 gas with portal of entry effects

$$POD_{HEC} = 1620 \frac{mg}{m^3} \; x \; 1 = 1620 \; mg/m^3$$

Equation 2.

$$Potential \; ITSL = \frac{POD_{HEC}}{UF_H x \; UF_A x UF_L} \; x \; \frac{hours \; exposed}{AT}$$

Where:
-The combined uncertainty factor for human variability (UF_H) and extrapolation from an animal study (UF_A) is 10: (UF_H is ≈ 3 since portal of entry effects are not expected to vary significantly across the range of individuals in the general population and UF_A is ≈ 3 since dosimetric adjustment was used to determine the POD_{HEC}) and an uncertainty factor to account for the extrapolation from a LOAEL to a NOAEL (UF_L) is 10.

The hours exposed/averaging time was set equal to 1, since the irritancy effects are expected to be concentration-dependent and not duration-dependent.

$$Potential \; ITSL = \frac{1620 \frac{mg}{m^3}}{10 \; x \; 10} = \; 16.2 \frac{mg}{m^3} \; x \; \frac{10^3 \mu g}{mg} = 16200 \; \frac{\mu g}{m^3}$$

However, since a LOAEL and not a NOAEL was identified in the Miller et al. (1984) study, the PGME ITSL of 3,700 µg/m^3 (1-hour averaging time) (MDEQ, 2017) was considered. The PGME ITSL is based on a controlled human study (ACGIH, 2013) where a NOAEL was identified. The ITSL derived for PGME is still health-protective when considering molecular weight adjustments, so the PGME ITSL of 3,700 µg/m^3 (1-hour averaging time) with molecular weight adjustment will be adopted for PGMEA (Equation 3).

Equation 3.

$$ITSL_{PGMEA} = ITSL_{PGME}\ x\ \frac{molecular\ weight\ of\ PGMEA}{molecular\ weight\ of\ PGME}$$

$$ITSL_{PGMEA} = 3700\ \frac{\mu g}{m^3}\ x \frac{132.159\ grams/mole}{90.122\ grams/mole} = 5425.848 \frac{\mu g}{m^3} \approx 5400\ \frac{\mu g}{m^3}$$

Therefore, the acute ITSL is 5,400 µg/m^3, 1-hour averaging time.

References

ACGIH. 2013. 1-Methoxy-2-propanol. CAS Number: 107-98-2. Documentation of the Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Johanson, G. 1990. NEG and NIOSH basis for an occupational health standard: propylene glycol ethers and their acetates.

MDEQ. 2017. Memo from Keisha Williams to File for Propylene glycol monomethyl ether (CAS # 107-98-2). Subject: Screening Level Update. October 4, 2017.

Miller, R.R., Hermann, E.A., Young, J.T., Calhoun, L.L., Kastl, P.E. 1984. Propylene glycol monomethyl ether acetate (PGMEA) metabolism, disposition, and short-term vapor inhalation toxicity studies. Toxicology and Applied Pharmacology. 75: 521-530.

National Center for Biotechnology Information. PubChem Compound Database. Accessed October 4, 2017. CID=7946, https://pubchem.ncbi.nlm.nih.gov/compound/7946

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MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Propylene glycol monomethyl ether acetate (CAS# 108-65-6)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 25, 2017

SUBJECT: Propylene glycol monomethyl ether acetate (CAS# 108-65-6) ITSL change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for propylene glycol monomethyl ether acetate (PGMEA) is 3000 µg/m^3 based on an annual averaging time. The ITSL was originally established on 4/16/1992 and was set at 3000 µg/m^3 based a 24-hour averaging time. The ITSL is based on an EPA (1991) reference concentration (RfC) for a related compound, polyethylene glycol monomethyl ether (PGME) RfC of 2000 µg/m^3, which was derived from a 13-week inhalation study by Landry et al., (1983). Fischer 344 rats (10/sex/dose) and New Zealand White rabbits (7/sex/dose) were exposed to 0, 300, 1000, or 3000 ppm (0, 1106, 3686, or 11060 mg/m^3) for 6 hours/day, 5 days/week, for 13 weeks. The critical effect was mild reversible sedation. EPA calculated the no observed adverse effect level (NOAEL) human equivalent concentration (HEC) at 658 mg/m^3. PGME molecular weight of 90.14 g/mol is lighter than PGMEA which has a molecular weight of 132.18 g/mol. After the weight was adjusted to the adjusted RfC was 3000 µg/m^3. The current file review concludes that the averaging time may appropriately be set at annual, as the key study is a subchronic inhalation study. Therefore, the averaging time is being changed from 24 hours to annual.

References:

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

EPA. 1991. Integrated Risk Information System. Propylene glycol monomethyl ether (PCME); CASRN 107-98-2. Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=404

Landry TD, Gushow TS, and Yano BL. 1983. Propylene glycol monomethyl ether: A 13-week inhalation study in rats and rabbits. Fund. Appl. Toxicol. 3:627-630.

Michigan Department of Natural Resources

Interoffice Communication

April 16, 1992

To : Propylene Glycol Monomethyl Ether Acetate File

From : Gary Butterfield

Subject : AAC for Propylene Glycol Monomethyl Ether Acetate (CAS # 108-65-6)

EPA has developed a RfC for propylene glycol monomethyl ether (CAS # 107-98-2) or PGME, a compound very closely related to propylene glycol monomethyl ether acetate or PGMEA. EPA's RfC of 2 mg/m3, for PGME is based on Landry et al (1983). In this 13 week study a NOAEL of 1000 ppm (or 3687 mg/m3) was identified for sedation or narcosis (considered to be an adverse effect) on the rats and rabbits.

The RfC for PGME was calculated by EPA as follows :
RfC = [(3687 mg/m3)x(6/24)x(5/7)x(1.00)]/300 = 2 mg/m3/d

Adjustment for using the acetate form can be made as follows :
PGME NOAEL of 1000 ppm is equivalent to 5410 mg/m3 PGMEA.
RfC = [(5410 mg/m3)x(6/24)x(5/7)x(1.00)]/300 = 3 mg/m3/d

It is appropriate to use the PGME RfC data for a PGMEA RfC because of the following reasons. Authors have identified similar systemic toxic effects of PGME and PGMEA, Stott and McKenna (1984), Miller et al (1984). Both propylene glycol ethers are metabolized to innocuous conjugates, Morgott and Nolan (1987). PGMEA can also be expected to initially be hydrolyzed to PGME and acetic acid during metabolism. As acetate is a normal physiologic component, at anticipated concentrations it is not expected to add any additional toxicity to that of PGME. For these reasons, it is considered appropriate to use the adjusted EPA PGME RfC for PGMEA's AAC of 3 mg/m3 with 24 averaging.

<u>References</u>:

EPA. 1992. IRIS.

Landry et al. 1983. Fund Appl Toxicol 3:627-630. (as cited in IRIS)

Miller et al. 1984. Toxicol Appl Pharmacol 75:521-530. (as cited in IRIS)

Morgott and Nolan. 1987. Toxicol Appl Pharmacol 89:19-28. (as cited in IRIS)

Stott and McKenna. 1984. (as cited in IRIS)

PGMEA Mol wt : 132.18
PGME Mol wt . 90.14