MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Tripropylene Glycol Methyl Ether-TPGME (CAS # 25498-49-1)

FROM: Keisha Williams, Air Quality Division

SUBJECT: Updated Screening Level Review

DATE: October 18, 2017

The initial threshold screening level (ITSL) for exposure to tripropylene glycol methyl ether (TPGME) is 20 µg/m^3 (annual averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1232 (1) (d)[1]. The ITSL established on December 14, 2000 is being rescinded based on this updated review.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 Arbeitsplatz-konzentrationen) 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

TPGME (Figure 1) is used as a solvent and a coupling agent (Dow, 2015). Chemical properties are listed in Table 1.

[1] 336.1232. 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 for TPGME

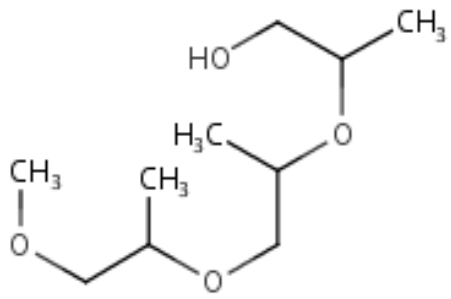

Table 1. Chemical and physical properties of TPGME

Molecular weight: 206.282 grams/mole
Melting point: -110° F
Boiling point: 468° F at 760 mm Hg
Vapor pressure: 3 Pa at 20° C
Physical state: liquid
Color: colorless
Odor: mild, ethereal

Reference: National Center for Biotechnology Information, https://pubchem.ncbi.nlm.nih.gov/compound/25054

There is limited information about TPGME-specific toxicity. With this updated review, a teratology study by Breckenridge et al. (1985) was recommended for review from a commenter (MDEQ, 2017).

In the Breckenridge et al. (1985) study, Sprague-Dawley female rats were exposed to 0, 0.1, 0.29, or 1.02 mg/L (or 0, 100, 290, or 1020 mg/m^3) on gestation days 6-15 for 6 hours per day via a whole-body inhalation exposure system. Clinical examinations for mortality and morbidity occurred daily, and body weights were collected on days 0, 6, 9, 12, 15, 18, and 20 of gestation. After the final exposure necropsies were performed: livers, lungs, kidneys, brains, and gravid uteri were weighed; abnormal tissues were collected for microscopic examination; “the number of corpora lutea, the number and position of early…, middle…, and late resorptions and the numbers of live and dead fetuses were recorded”; and fetuses were weighed and necropsied (Breckenridge et al., 1985). Statistical analysis was performed to determine statistically significant difference between exposure groups and the control group. The authors did not find fetal toxicity, but they did find maternal toxicity with muzzle staining at the highest concentration of 1.02 mg/L (1020 mg/m^3). Therefore, the lowest-observed-adverse-effect-level (LOAEL) was identified as 1020 mg/m^3 based on adverse clinical observations (muzzle staining). A no-observed-adverse-effect-level (NOAEL) of 0.1 mg/L (290 mg/m^3) was also identified.

Compared to the key study previously used to derive the ITSL, adverse effects identified in the Breckenridge study were found at the same level identified as the NOAEL in the Miller et al. (1985) study (MDEQ, 2000; MDEQ, 2004). As a result, the Breckenridge et al. study is preferred

above the Miller et al. study as more sensitive adverse effects were identified in the Breckenridge et al. study.

The ITSL is calculated pursuant to Rule 232(1)(d) as follows:

$$ITSL = \frac{NOAEL}{35x100} x \frac{hrs\ exposed\ per\ day}{24\ hrs\ per\ day}$$

Where:
NOAEL = 290 mg/m³, and hours exposed per day is 6.

$$\text{ITSL} = \frac{290\ \text{mg/m}^3}{35\text{x}100} \text{x} \frac{6\ \text{hrs per day}}{24\ \text{hrs per day}} = \ 0.0207\ \text{mg/m}^3$$

ITSL = 0.0207 mg/m³ x 1000µg/mg (unit conversion) = 20.7 µg/m³
ITSL = 20 µg/m³ (rounding to 1 significant figure)

Pursuant to Rule 232(2)(c), the ITSL is assigned an annual averaging time. Therefore, the ITSL is 20 µg/m³, with annual averaging time.

References

Breckenridge, C., Collins, C., Robinson, K., Lulham, G., Hamelin, N., Osborne, B., Procter, B.G. 1985. A teratological study of inhaled Dowanol TPM in the albino rat. Bio-Research Laboratories Ltd. Confidential report of the Dow Chemical Company, August 2, 1985.

Dow. 2015. Product Safety Assessment. Form No. 233-00406-MM-1115X. Dow Company.

Miller, R.R., Lomax, L.G., Calhoun, L.L. 1985. Tripropylene glycol monomethyl ether (TPGME): 2-week Aerosol Inhalation Toxicity Study in Rats and Mice. Unpublished Report-The Dow Chemical Company.

MDEQ, 2000. Memorandum. To: File for tripropylene glycol methyl ether. From: Marco Bianchi (AQD Toxicologist). Date: December 14, 2000. Subject: Initial Threshold Screening Level.

MDEQ, 2004. Memorandum. To: File for Propanol, 3-(3-(3-methoxypropoxy)propoxy)-. From: Maggie Sadoff (AQD Toxicologist). Date: April 9, 2004. Subject: Update of Screening Level.

MDEQ, 2017. Response to Public Comments for Tripropylene Glycol Methyl Ether (CAS No. 25498-49-1). Date: October 10, 2017.

National Center for Biotechnology Information. PubChem Compound Database; CID=25054, https://pubchem.ncbi.nlm.nih.gov/compound/25054 (accessed October 18, 2017).

REACH. 2017. [2-(2-methoxymethylethoxy)methylethoxy]propanol Registration Dossier. European Chemical Agency (ECHA). Accessed 7-26-17. https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13199

KW:lh

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 1, 2004

TO: File for Propanol, 3-(3-(3-methoxy propoxy)propoxy)- or Glycol Ether (CAS #25498-49-1)

FROM: Maggie Sadoff

RE: Update of screening level

An ITSL of 11 µg/m^3, annual averaging time, was set in December of 2000. This chemical was re-evaluated for any new information pertaining to carcinogenicity or reproductive/ developmental toxicity but no information was found.

No further evaluation for this chemical was conducted.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

December 14, 2000

TO: File for Tripropylene Glycol Methyl Ether - TPGME (25498-49-1)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for tripropylene glycol methyl ether is 11 ug/m^3 based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS-online, HEAST, NTP Management Status Report-online, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC-online, NIOSH Pocket Guide, ACGIH Guide, and Patty's Industrial Hygiene and Toxicology.

Tripropylene glycol methyl ether is a mixture of eight isomeric forms. Although general toxicologic information is found for this isomeric mixture, specific information for each isomer was difficult to obtain. A detailed database search was conducted for TPGME (25498-49-1), but information was limited to one proprietary rat and mouse aerosol study by Dow Chemical Company. In this study, five Fischer 344 rats/sex/group, and five B6C3F1 mice/sex/group were exposed to an aerosol at 0.15, 0.36, or 1.01 mg/l, 6 hr/day for 9 days. There were no exposure-related effects on body weights or the weights of brain, heart, kidneys, thymus, and testes, and no changes in hematology, clinical chemistry parameters or urinalyses (rats). An increase in liver weight in both species and both sexes was the only consistent exposure-related effect; the liver weights of male mice were significantly increased at all three exposure concentrations, whereas there were no effects on the liver weights of female mice or male or female rats in the low (0.15 mg/l) exposure group.

There were no treatment-related gross or histopathologic changes in the liver, or any other organ or tissue, in either rats or mice, except for minimal changes in tinctorial properties (increased eosinophilia) in peripheral regions of hepatic lobules of male mice in the high exposure group. The tinctorial staining changes and the increased liver weights were considered by the study investigators to be an adaptive response rather than a degenerative one.

From the study results, Dow interpreted changes in liver weights lacking histopathologic effects as adaptive. Although there is scientific debate on interpretation of organ weight changes, statistically significant weight changes in organs that follow a dose-response relationship strongly suggests a potential for future toxic effects to exposed animals. Presently, uncertainty

exits in the scientific community as to whether a change in liver weight is a clear indication of potential adverse effects if there are no other morphologic changes indicating toxicity. This is because the liver is a major site of chemical metabolism, and a temporary increase in liver size and weight may occur from a chemical exposure due to an increase in liver function. This condition may return to normal after the chemical has been metabolized. Several experts from EPA (Annie Jarabek, Henry Spencer, and Gary Foureman - personal communication) were contacted on this subject. In their professional judgment they generally consider compound related changes in liver weights, but not other organ weights, as adaptive in nature provided no other adverse effects have been observed. In making such a determination, however, they also consider other relevant studies and structure activity relationships. For example, necrogenic or frank liver effects found in an acute study for a compound may be suggestive that liver weight effects only seen in a subacute or chronic study could progress to more significant effects.

Considering all available information, the weight-of-evidence suggests changes in liver weights seen in this 9-day study are not adverse effects. Therefore, the NOAEL for this study is 150 mg/l. The NOAEL will be used to determine an ITSL by Rule 232(1)(d).

The ITSL was determined as follows:

LOAEL = 0.15 mg/l.
Uncertainty factor = 10; LOAEL to NOAEL conversion

Conversion of mg/l to mg/m^3

0.15 mg/l x 1,000 1/m^3 = 150 mg/m^3

$$\text{ITSL} = \frac{\text{LOAEL}}{35 \times 100} \times \frac{\text{hrs exposed per day}}{24 \text{ hrs per day}}$$

$$\text{ITSL} = \frac{150 \text{ mg/m}^3}{35 \times 100} \times \frac{6 \text{ hrs per day}}{24 \text{ hrs per day}} = 0.0107 \text{ mg/m}^3$$

Conversion of mg/m^3 to ug/m^3

0.0107mg/m^3 x 1000 = 10.7 µg/m^3

The ITSL for tripropylene glycol methyl ether 11 µg/m^3 based on an annual averaging.

References:

1. Miller RR, et al., 1985. Tripropylene glycol methyl ethers: 2-week aerosol Inhalation study in rats and mice. Unpublished Report - The Dow Chemical Company.