MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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October 16, 2017

TO: File for Propylene Glycol tert-butyl Ether (CAS No. 57018-52-7)

FROM: Mike Depa, Air Quality Division, Toxics Unit

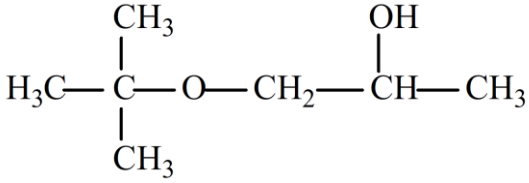
SUBJECT: Derivation of Screening Level

The Initial Risk Screening Level (IRSL) for propylene glycol tert-butyl ether (PGTBE) (also called 1-tert-butoxypropan-2-ol) is 0.7 µg/m³ with annual averaging time. The Secondary Risk Screening Level (SRSL) for propylene glycol tert-butyl ether is 7 µg/m³ with annual averaging time.

The previous Initial Threshold Screening Level (ITSL) for PGTBE of 329 µg/m³ with annual averaging time is being rescinded.

The following references and/or databases were searched in order to find data to derive a screening level: Toxic Substance Control Act Test Submissions Simple Query for TSCATS 2.0, U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), the Registry of Toxic Effects of Chemical Substances (RTECS), the California Office of Environmental Health Hazard Assessment (Cal OEHHA), National Library of Medicine's TOXNET and TOXLINE, Toxic Substance Control Act (TSCA) Test Submissions (TSCATS), EPA's Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV), European Chemicals Agency (ECHA) Risk Assessment database (REACH, 2017), Chemical Abstract Service (CAS) SciFinder database and US EPA (epa.gov). The molecular weight of PGTBE is 132.23g. The vapor pressure is 4.7 mm Hg at 20 °C (IARC, 2006). The molecular structure is shown in Figure 1.

Figure 1. Molecular Structure of Propylene Glycol Tert-Butyl Ether



Recently, the International Agency for Research on Cancer (IARC, 2017) classified PGTBE as “possibly carcinogenic to humans” (Group 2B), based on “sufficient evidence of carcinogenicity in experimental animals” and no data or “inadequate evidence” in humans. AQD has concluded that PGTBE meets the definition of a carcinogen[1] based on the results of a National Toxicology Program (NTP, 2004) study.

Summary of Two-Year Inhalation Bioassay (NTP, 2004)
Groups of 50 male and 50 female F344/N rats were exposed to 0, 75, 300, or 1,200 parts per million (ppm) PGTBE vapor 6 hours per day, 5 days per week for 104 weeks. The exposure concentrations in units of milligrams per cubic meter were converted from ppm using the molecular weight of 132.2g (see Table 1).

Table 1. Exposure Concentrations for NTP, 2014

Exposure Concentration *ppm*	Exposure Concentration *mg/m³*	Duration Adjusted* Exposure Concentration *mg/m³*
0	0	0
75	406	72.5
300	1622	290
1200	6490	1160

*for continuous exposure: 6hrs/24hr x 5days/7days

2-Year Study in Rats (NTP, 2004)
Survival of 300 ppm males was less than that of the chamber controls. Mean body weights of 1,200 ppm males and females were less than those of the chamber controls during the second year of the study. In 1,200 ppm males and females the excretion of propylene glycol mono-t-butyl ether glucuronide in urine, expressed as the metabolite to creatinine ratios, were generally significantly less than those in the groups exposed to 75 or 300 ppm.

Incidences of renal tubule hyperplasia, renal tubule hyaline droplet accumulation, papilla mineralization, and transitional epithelial hyperplasia were increased in most exposed groups of males. Marginally increased incidences of renal tubule adenoma and adenoma or carcinoma (combined) occurred in 300 and 1,200 ppm males. The severities of chronic nephropathy increased with increasing exposure concentration in males and females and were significantly increased in all exposed groups of males and in 1,200 ppm females. The incidences of hepatocellular adenoma occurred with a positive trend in male rats. The incidences of basophilic foci of the liver were significantly increased in all exposed groups of males; the incidence of clear foci of the liver was significantly increased in 1,200 ppm females. The incidences of hyaline degeneration of the olfactory epithelium in all exposed groups of males and females and the incidence of corneal mineralization in 1,200 ppm females were significantly increased.

[1] Rule 103(c)(iii): Group C – Any substance for which there is limited evidence of carcinogenicity in animals in the absence of human data and which causes a significant increase incidence of benign or malignant tumors in a single, well-conducted animal bioassay.

2-Year Study in Mice (NTP, 2004)
Groups of 50 male and 50 female B6C3F1 mice were exposed to 0, 75, 300, or 1,200 ppm propylene glycol mono-t-butyl ether vapor 6 hours per day, 5 days per week for 104 weeks. Survival of exposed groups of mice was similar to that of the chamber control groups throughout the study. Mean body weights of 1,200 ppm females were slightly less than those of the chamber control group at the end of the study. Clinical findings included ataxia, shallow breathing, and lethargy in 1,200 ppm mice during the first 6 months of the study and pale foci of the eyes in 1,200 ppm females in the last month of the study.

The incidences of hepatocellular adenoma, hepatocellular adenoma or carcinoma (combined), and hepatoblastoma occurred with positive trends in males and females, and the incidences in the 1,200 ppm groups were increased. The incidences of eosinophilic foci and multinucleated hepatocytes in 1,200 ppm males and eosinophilic foci in 1,200 ppm females were significantly increased. The incidence of mild corneal mineralization was significantly increased in 1,200 ppm females.

Genetic Toxicology (NTP, 2004)
Propylene glycol mono-t-butyl ether was mutagenic in S. typhimurium strain TA97 in the absence of liver S9 activation enzymes; negative results were obtained with strain TA97 in the presence of rat or hamster liver S9 enzymes, in strains TA98, TA100, and TA1535 with and without S9, and in strain TA1537 without S9. Propylene glycol mono-t-butyl ether did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells, with or without S9. Propylene glycol mono-t-butyl ether induced a small but significant increase in the frequency of micronucleated normochromatic erythrocytes in peripheral blood of female mice in the 3-month study; no significant increase in micronucleated normochromatic erythrocytes was seen in male mice, and percentages of polychromatic erythrocytes were similar in the exposed and chamber control groups.

Results of the 2-year Inhalation Study in Mice and Rats (NTP, 2004)
Under the conditions of this 2-year inhalation study, there was equivocal evidence of carcinogenic activity of propylene glycol mono-t-butyl ether in male F344/N rats based on marginally increased incidences of renal tubule and liver neoplasms. There was no evidence of carcinogenic activity of propylene glycol mono-t-butyl ether in female F344/N rats exposed to 75, 300, or 1,200 ppm. There was clear evidence of carcinogenic activity of propylene glycol mono-t-butyl ether in male and female B6C3F1 mice based on increased incidences of liver neoplasms.

Exposure of male rats to propylene glycol mono-t-butyl ether resulted in non-neoplastic lesions of the kidney characteristic of α2u-globulin accumulation. Exposure to propylene glycol mono-t-butyl ether resulted in non-neoplastic lesions of the liver and nose in male and female rats, the liver in male and female mice, and the eyes in female rats and mice. Kinetic and biomarker studies indicated that clearance was saturated at the 1,200 ppm exposure for both rats and mice.

Discussion
Because there were mixed results in the mutagenicity studies (as reported by NTP, 2004), it was determined that there is not enough information to conclude that PGTBE causes cancer through a mutagenic mode of action.

Derivation of the Inhalation Unit Risk
The incidences of tumors in male and female mice in the NTP (2004) study were used to derive an inhalation unit risk (IUR) using U.S. Environmental Protection Agency's (EPA's) Benchmark Dose Software (BMDS)(EPA, 2017). To calculate the IUR, the BMDS Wizard (ICF International, 2015) was used. Analysis of the incidence data found that the male mice combined hepatocellular adenoma and carcinomas[2] show the most sensitive effect of PGTBE exposure. Using the BMDS Wizard, and the dose-response data in male mice for combined hepatocellular adenoma and carcinomas, the benchmark concentration lower bound at the 10% benchmark response (BMCL10) was identified as 68.7 mg/m³. The inhalation unit risk was calculated as follows:

IUR = risk/dose
IUR = 10%/BMCL10
IUR = 0.1/68.7 mg/m³
IUR = 0.0014556 per mg/m³
IUR = 1.46E-3 per mg/m³ (rounded to 3 significant figures)
Unit conversion to µg/m³:
IUR = 1.46E-3 m³/mg x 1mg/1000µg
IUR = 1.46E-6 m³/µg (or 1.46E-6 per µg/m³)

Since the blood:gas partition coefficients for animals and humans are unknown, the dosimetric adjustment factor (DAF) is equal to one (1); therefore, the animal IUR is equal to the human IUR.

The IRSL was calculated as:
IRSL = 1E-6/IUR
IRSL = 1E-6/(1.46E-6 per µg/m³)
IRSL = 0.687 µg/m³
IRSL = 0.7 µg/m³ (rounded to 1 significant figure)
And the SRSL was calculated as:
SRSL = 1E-5/IUR
SRSL = 1E-5/(1.46E-6 per µg/m³)
SRSL = 6.87 µg/m³
SRSL = 7 µg/m³ (rounded to 1 significant figure)

The ITSL is being rescinded because it is based on older data. It may also be appropriate to utilize the updated literature review, including NTP (2004), to derive a non-cancer screening level for the protection of public health from exposures to PGTBE.

[2] 25/49, 26/48, 33/49 and 41/49 for duration adjusted (6hr/24hr x 5days/7days) doses of 0, 72.5, 290, and 1160 mg/m³, respectfully. Incidence was adjusted by subtracting deaths that occurred in animals before the first incidence of cancer, in this case day 463 in male mice.

Conclusion

The National Toxicology Program (NTP, 2004) performed a long-term inhalation study using PGTBE and found increased incidences of tumors, specifically liver tumors in male and female mice. An IRSL and SRSL of 0.7 µg/m³ and 7 µg/m³, respectively, were derived based on the increase incidence of combined hepatocellular adenoma and carcinomas in male mice from the NTP (2004) study using EPA benchmark dose software.

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