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Response to Public Comments for Propylene Glycol tert-Butyl Ether (CAS No. 57018-52-7)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the current toxicity information available for propylene glycol tert-butyl ether (PGTBE). The AQD agrees that the screening level is based on older toxicological information and needs to be updated. The National Toxicology Program (NTP) performed a two-year inhalation study with PGTBE in mice and rats and found increased incidences of tumors in mice. AQD disagrees with the commenter that the maximum tolerated dose was exceeded in the NTP study. The validity of NTP's statement that hepatoblastomas are "very rare tumors" was considered by AQD as immaterial, since a quantitative risk assessment using this tumor type was not used as the basis for the inhalation unit risk estimate. AQD based the inhalation unit risk for PGTBE on the increased incidences of hepatocellular adenomas or carcinomas as seen in male mice in the NTP study. Based on this data, AQD derived an Initial Risk Screening Level (IRSL) and Secondary Risk Screening Level (SRSL) for PGTBE of 0.7 and 7 µg/m³, respectively, both with annual averaging time. The current Initial Threshold Screening Level (ITSL) of 329 µg/m³ is being rescinded.

Background:

Revisions to the Air Pollution Control Rules[1] were promulgated December 22, 2016. Subsequently, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) published toxic air contaminant screening levels and their basis as

[1] 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).

required by Rule 230(1). Pursuant to Rule 230(2), the AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14, 2017. The AQD must respond to these comments within 180 days; the latest date for response is October 11, 2017.

Comments and Responses:

Comment: The ITSL document for PGTBE needs to be updated with new information.

Response: A full literature review of toxicity information on PGTBE was completed by AQD. The National Toxicology Program (NTP, 2004) published several inhalation studies in mice and rats that varied the dosages and duration of exposure to PGTBE. Additionally, the NTP (2004) assessed the genetic toxicology of PGTBE, and stated:

> Propylene glycol mono-*t*-butyl ether, tested over a concentration range of 100 to 10,000 µg/plate, 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, and in strains TA98, TA100, and TA1535 with and without S9 (Table E1). Propylene glycol mono-*t*-butyl ether was also nonmutagenic in TA1537 in the absence of S9; it was not tested with S9. Propylene glycol mono-*t*-butyl ether did not induce SCEs [sister-chromatin exchanges] (NTP, 2004)

PGTBE was positive in the Mouse Peripheral Blood Micronucleus Test (NTP, 2004). The increased formation of micronuclei is usually an indication of increased DNA damage or mutation. It is characteristically found in cancer cells, or cells that have been exposed to increased risk factors.

NTP (2004) concluded:

> 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 nonneoplastic 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.

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[2] based on the results of a National Toxicology Program study.

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

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). AQD used the BMDS Wizard (ICF International, 2015) which streamlines data entry and option file creation, and implements logic to compare and analyze modeling results. Analysis of the incidence data found that the male mice combined hepatocellular adenoma and carcinomas[3] show the most sensitive effect of PGTBE exposure. Using the BMDS Wizard, and the dose-response data 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)

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)

[2] 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.
[3] 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.

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.

Comment: A cancer bioassay with PGTBE concluded that there was clear evidence of carcinogenic activity in male and female mice based on increased incidences of liver neoplasms. However, the high dose level in the bioassay exceeded the Maximum Tolerated Dose (MTD), calling into question the validity of any conclusions based on the high dose group. There is no significant increase in the incidence of combined malignant and benign liver tumors or the incidence of hepatoblastoma at concentrations that do not exceed the MTD.

Response: The AQD disagrees with the commenter that the maximum tolerated dose (MTD) was exceeded in the NTP, 2004 study for the following reasons:

1) Both sexes of rats and mice had 10% or less decreased body weight compared to control animals at the high dose at the end of the study.
2) Animal survival rates of female rats and male and female mice were not decreased compared to controls. Male rat survival at termination of the study was approximately 19% less than control rats: 22 of 50 animals (44% survival rate) in high dose male rats vs. 27 of 50 animals (54% survival rate) in control male rats. The cancer evidence classification and unit risk estimate are based on the tumor finding in mice, not rats.

Furthermore, even if the high-dose group in male mice was dropped for modeling purposes, there appears to be an upward trend in the incidences of combined hepatocellular adenomas or carcinomas in male mice in the control, low-dose and mid-dose groups of 25/49, 26/48 and 33/49, respectively (after adjusting for animals that died before the first incidence of tumor). Since the high dose was deemed as not exceeding MTD, the high dose was not dropped for modeling purposes.

Comment: The National Toxicology Program (NTP) describes hepatoblastomas as “very rare tumors with an extremely low spontaneous incidence in mice.” However, the historical control database does not appear to include studies that were conducted during the same time frame during which the propylene glycol tert-butyl ether bioassay was conducted, may not be from male mice from the same laboratory, and varies considerably from study to study. These findings raise significant questions about the validity and reliability of the conclusion that there was an increased incidence of a rare malignant tumor due to treatment with propylene glycol tert-butyl ether.

Response: AQD reviewed the information presented by the commenter. The use of the phrase “very rare” by NTP does not materially affect the derivation of an inhalation unit risk for PGTBE. A mode of action for carcinogenesis could not be determined based on the available information. AQD compared the incidence of tumors observed in control animals to the dosed animals. Endpoints within a study that appear to be relevant to the exposure are considered for modeling. This AQD policy helps ensure that no endpoints with the potential of having the most sensitive effect for risk assessment applications, usually having the lowest BMDL, are excluded from the

analysis. AQD modeled the hepatoblastoma dose-response data and found that it was not the most potent tumorigenic effect of PGTBE. AQD's policy in this regard agrees with EPA's guidance for carcinogenic risk assessment (EPA, 2005):

> In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity.

Summary and Conclusions:

AQD reviewed the latest research on the toxicity of PGTBE and found that the ITSL is outdated and no longer considered protective for potential long-term effects from exposure to PGTBE. The National Toxicology Program 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/m^3 and 7 µg/m^3, respectively, were derived based on the data from the NTP study using EPA benchmark dose software. AQD examined whether the high dose group from the NTP study exceeded the maximum tolerated dose, and determined that the evidence does not support this claim. AQD also examined the question about NTP concluding that hepatoblastomas are "very rare". It was determined that whether the "very rare" statement is accurate or not has no bearing on the use of heptoblastoma incidence rates for the purpose of quantitating cancer risk from exposure to PGTBE.

The primary AQD reviewer for these comments was Mike Depa, AQD Toxics Unit Toxicologist. The secondary (peer) reviewer was Robert Sills, AQD Toxics Unit Supervisor.

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