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Response to Public Comments for Ethylene Glycol (CAS No. 107-21-1)

Summary:

Based on public comments, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) has reviewed the Initial Threshold Screening Level (ITSL) for ethylene glycol. Oral studies recommended by the commenter provided little relevant new information regarding the inhalation effects of ethylene glycol. However, conclusions from these studies as well as physiologically-based pharmacokinetic studies further confirmed the usefulness of the Wills et al. (1974) study as the basis for the ITSL. Because of this review, the AQD is changing the ITSL to 2,000 µg/m³ with a 24-hr averaging time based on methodology used by the Agency of Toxic Substances and Disease Registry (ATSDR) in their derivation of a minimal risk level (MRL) for ethylene glycol. The previous ITSL of 1,000 µg/m³ with 1-hr averaging time is being rescinded.

Background:

Revisions to the Air Pollution Control Rules[1] were promulgated December 22, 2016. Subsequently, the AQD published toxic air contaminant screening levels and their basis as 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.

[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).

Comments and Responses:

Comment:
The commenter disagrees with the interpretation of the Wills et al (1974) study made by the American Conference of Governmental Industrial Hygienist (ACGIH) TLV Committee. The commenter submitted references concerning ethylene glycol toxicity that were published since the 1998 AQD ITSL justification memorandum was established. The commenter requests that AQD consider this new data to derive a robust ITSL.

Response:
An updated literature review was performed which included a search of the following databases: The following references and databases were searched to identify data for screening level derivation: United States Environmental Protection Agency's (EPA) 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, SciFinder, EPA School Air Toxics Benchmarks, EPA National Air Toxics Assessment Benchmarks, World Health Organization Air Quality Guidelines, and European Chemicals Agency Registered Substances Dossiers.

The commenter states, "[I]n submitting the attached comments on the proposed TLVs, [we] disagreed with the interpretation of the Wills study." The commenter did not specify the points of disagreement. It is not known if the commenter disagrees with the ACGIH TLV committee's interpretation of the Wills study or if the commenter disagrees with the AQD's interpretation of the Wills study. The AQD contacted the commenter for more information on this statement, but has not received clarification.

Of the studies identified by the commenter, the majority were conducted via oral administration. Since portal of entry effects have been described in a well-conducted controlled, human study (Wills et al., 1974), oral studies were deemed inappropriate for ITSL derivation. Both the Wills et al. (1974) study and this conclusion were cited in a few of the studies provided by the commenter. It was determined that the Wills et al. (1974) study was the best study with which to derive an acute ITSL. Regarding published health-based screening levels for inhalation exposure, the AQD reviewed

reports by agencies including the ACGIH, the California Office of Environmental Health Hazard Assessment (OEHHA), Agency for Toxic Substances and Disease Registry (ATSDR), and the Texas Commission on Environmental Quality (TCEQ), as well as others. All agreed that the portal of entry effects described by Wills et al. (1974) and Coon et al. (1970) show that the respiratory tract is the most sensitive organ affected by acute and long-term inhalation exposure to ethylene glycol. Because of potential portal of entry effects; i.e., significant differences in effects observed between the oral and inhalation routes of exposure, it is not appropriate to use oral studies to derive an inhalation screening level for ethylene glycol.

Controlled human studies are some of the best research sources for acute screening level derivation. The 1974 Wills et al. study is an example of this, where this study has been used by all the agencies listed in Table 2 in their health benchmark derivations to protect against toxic effects from ethylene glycol inhalation. There have been additional controlled inhalation studies in people, and these studies further support the Wills et al. (1974) study. These are the Carstens et al. (2003) study and the Upadhyay et al. (2008) study where 2 and 4, respectively, male volunteers were exposed to approximately 25 to 30 mg/m^3 ethylene glycol for 4 hours. The original publications were not obtained, but based on a summary from TCEQ, no adverse effects were reported at these exposure concentrations (TCEQ, 2016).

In the Wills et al. study (1974), 19-20 male volunteers were exposed to ethylene glycol, while 14 other volunteers were kept under similar conditions but not exposed to ethylene glycol. The low, high, and weekly mean concentrations were reported for the first four weeks of exposure. For the last two days of exposure, the low, high and mean ethylene glycol concentrations were reported. Physical exams as well as psychological tests were reported to be performed before the exposure, 2 weeks after the exposure began and at the end of the exposure. Blood samples were collected before the study began, and every 2-4 days during the exposure. Urine samples were collected daily. Wills et al. noted, “Considering each single test or all tests collectively…there was no difference between the control and the exposed groups.”

There are noted limitations to this study. For one, the study was carried out in a prison with volunteer inmates, which brings up ethical questions and considerations. Details about the results for the physical examinations were not provided, and it is unclear how similar this population is to the general population.

Derivation of acute ITSL

The acute ITSL of 2,000 $\mu g/m^3$ with a 24-hour averaging time is derived (see Equation 1 below) from information reported in the Wills et al. (1974) study, in concurrence with the ATSDR MRL.

In the Wills et al. (1974) study, the concentrations of ethylene glycol varied. The authors initially hypothesized that:

> "[W]e felt we could begin to expose a few human volunteers for a short duration of almost continuous exposure to a concentration of aerosolized ethylene glycol of around 30 mg/m^3 without endangering them. If indeed, no ill effects were suffered, we would then increase gradually the level of exposure."

Ethylene glycol concentrations were incrementally raised to concentrations as high as 308 mg/m^3 while the exposed group was taking a meal break. It was reported that at 140 mg/m^3, the irritation became significant; at 188 mg/m^3, ethylene glycol was irritating but tolerable for 15 minutes; at 244 mg/m^3, ethylene glycol was intolerable for more than 1-2 minutes; and at 308 mg/m^3, ethylene glycol was intolerable for more than 1-2 breaths (Wills et al., 1974).

ATSDR considered the exposure within the first 2 weeks, 23 mg/m^3 (average of 29 and 17 mg/m^3), to be the no-observed-adverse-effect-level (NOAEL). The lowest-observed-adverse-effect-level (LOAEL) was identified as 140 mg/m^3 based on respiratory irritation. An uncertainty factor (UF) of 10 was used for intraspecies variability. Duration extrapolation to continuous exposure was deemed unnecessary as the response is concentration-dependent and not duration-dependent (ATSDR, 2010). Also, for this reason, a chronic ITSL was determined not to be necessary, as limiting each 24-hr period to a concentration of 2,000 µg/m^3 would be protective of irritation effects over the long-term. In contrast to the occupational exposure limits (the TLV and the acute SMAC), the screening levels developed by the AQD, as well as the ATSDR acute inhalation MRL are designed to protect the general population, including sensitive individuals. As a result, the ATSDR MRL is more suitable to adopt as the acute ITSL as compared to the occupational exposure limits listed in Table 2. In deriving the ITSL from the Wills et al. (1974) study, the AQD concurred with the methodology used by the ATSDR. Furthermore, ATSDR's methodology was deemed more appropriate than that of the TCEQ, because:

1) the ATSDR MRL was derived from a NOAEL while the TCEQ ReV was derived from a LOAEL; and
2) TCEQ methodology used a database uncertainty factor that is not appropriate in this case, because of the robustness of the toxicity database for ethylene glycol.

Equation 1. Derivation of Acute ITSL based on AQD Rule 233 (1)

$$\text{Acute } ITSL = \frac{POD}{UF_H} \times \frac{hours\ exposed}{averaging\ time}$$

Where

POD=point of departure=NOAEL=23 mg/m^3
UF is 10 for human variability.
The hours exposed/averaging time adjustment to continuous exposure was deemed unnecessary because the irritation effects are expected to be concentration-related not duration-related.

$$\text{Acute } ITSL = \frac{23\ mg/m^3}{10} = 2.3\frac{mg}{m^3}x\frac{10^3\mu g}{mg} = 2300\ \frac{\mu g}{m^3} \approx 2000\frac{\mu g}{m^3}$$

A 24-hour averaging time was applied to the ITSL since daily averages were collected during the study.

Summary and Conclusions:

As oral studies, most of the studies identified by the commenter were largely not relevant for ITSL derivation since portal of entry effects had been identified in both human and animal inhalation studies. Based on an updated literature review, the ITSL of 2,000 µg/m^3 with 24-hour averaging time is being established. The previous ITSL of 1,000 µg/m^3 with 1-hr averaging time is being rescinded.

The primary AQD reviewer for these comments was Keisha Williams, AQD Toxics Unit toxicologist. The secondary (peer) reviewer was Mike Depa, AQD Toxics Unit toxicologist.

References:

ACGIH. 2017. Documentation of the Threshold Limit Values and Biological Exposure Indices-Ethylene Glycol. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ATSDR. 2010. Toxicological profile for ethylene glycol. U.S. Department of Health and Human Services.

Carstens, J., Csanády, G. A., Faller, T. H., Filser, J. G. 2003. Human inhalation exposure to ethylene glycol. *Archives of toxicology,* 77(8), 425-432.

Coon, R. A., Jones, R. A., Jenkins, L. J., Siegel, J. 1970. Animal inhalation studies on ammonia, ethylene glycol, formaldehyde, dimethylamine, and ethanol. *Toxicology and applied Pharmacology*, 16(3), 646-655.

MDEQ. 1998. Memo from Michael Depa to File for Ethylene Glycol (CAS#107-21-1). Subject: Initial Threshold Screening Level for Ethylene Glycol. October 20, 1998.

OEHHA. 2008. Chronic Toxicology Summary: Ethylene Glycol. Pp. 234-239 in Appendix D.3 Chronic RELs and toxicity summaries using the previous version of the Hot Spots Risk Assessment Guidelines (OEHHA 1999), Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Air Toxicology and Epidemiology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA: [online]. Available: https://oehha.ca.gov/media/downloads/crnr/appendixd3final.pdf [accessed September 13, 2017].

TCEQ. 2016. Development Support Document, Ethylene Glycol, CAS registry number: 107-21-1. https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/final/feb16/EG.pdf (accessed September 13, 2017). Toxicology Division, Chief Engineer's Office.

Upadhyay, S., Carstens, J., Klein, D., Faller, T. H., Halbach, S., Kirchinger, W., Kessler, W., Csanády, G. A., Filser, J. G. 2008. Inhalation and epidermal exposure of volunteers to ethylene glycol: kinetics of absorption, urinary excretion, and metabolism to glycolate and oxalate. *Toxicology letters*, 178(2), 131-141.

Wills, J.H., Coulston, F., Harris, E.S., McChesney, E.W., Russell, J.C., Serrone, D.M. 1974. Inhalation of aerosolized ethylene glycol by man. *Clinical Toxicology*, 7(5), 463-476.

Wong, K.L. 1996. Ethylene glycol. Pp. 232-270 in Spacecraft maximum allowable concentrations for airborne contaminants, Vol. 3. Washington, DC: National Academy Press.

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