MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for diglycol amine (CAS# 929-06-6)

FROM: Keisha Williams, Air Quality Division

DATE: July 15, 2024

SUBJECT: Screening level derivation for diglycol amine (CAS# 929-06-6)

The acute initial threshold screening level for diglycol amine (CAS# 929-06-6) is 9 µg/m^3 (8-hour averaging time) based on the Michigan Department of Environment, Great Lakes, and Energy (EGLE), Air Quality Division (AQD), Rule 336.1232 (1) (c) and (2) (a). The chronic initial threshold screening level is 0.2 µg/m^3, annual averaging time based on EGLE-AQD Rule 336.1232(1)(a) and (2)(b).

The following references or databases were searched to identify data to determine the screening level: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS); 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; Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels, International Agency for Research on Cancer (IARC) Monographs; Health Effects Assessment Summary Tables (HEAST); National Toxicology Program (NTP) Status Report, EPA Superfund Provisional Peer Reviewed Toxicity Values; EPA Acute Exposure Guideline Levels (AEGLs) for Airborne Chemicals; EPA High Production Volume Database; United States Department of Labor Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs); Spacecraft Maximum Allowable Concentrations (SMACs); California Office of Environmental Health Hazard Assessments Reference Exposure Levels; Texas Commission on Environmental Quality (TCEQ) Effects Screening Levels (ESLs); European Chemicals Agency Registered Substances Dossiers; Chemical Abstract Service (CAS) Online search (search date: April 8, 2016); TSCA database; ACToR database, NLM/TOXLINE database; HAZARDOUS SUBSTANCES DATA BANK (HSDB); Chemical Safety Program Protective Action Criteria; the Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) files; and Deutsche Forschungsgemeinschaft maximale Arbeitsplatz-Konzentration (MAK) values, where maximale Arbeitsplatz-Konzentration translates to maximum workplace concentration in English.

Background Information

Diglycol amine is also referred to as 2-(2-aminoethoxy)ethanol. It has been used as an emulsifying agent for metal-working fluids, in the production of detergents, and in the removal of hydrogen sulfide and carbon dioxide from natural and refinery gases (MAK Collection, 2014). See Figure 1 for the chemical structure. At room temperature, diglycol amine is a colorless liquid with a fishlike odor (Pubchem). Chemical properties are listed in Table 1.

Figure 1. Chemical structure for diglycol amine

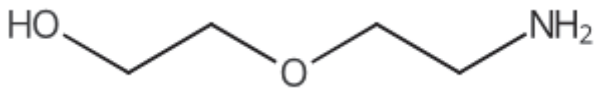


Table 1. Chemical properties of diglycol amine

Molecular weight: 105.14 grams/mole (Pubchem)
Melting point: -12.5 °C (Pubchem)
Boiling point: 222.5-223.8°C at 1013 hPa (ECHA, 2023)
Vapor pressure: 0.5 hPa at 58.5°C (ECHA, 2023)

Few health benchmarks were found for diglycol amine. TCEQ has developed interim health effects screening levels for long-term exposure at 38 µg/m^3 and for short-term exposure at 380 µg/m^3 (TAMIS). There is a German occupational exposure level (OEL) at 0.87 mg/m^3, 8-hour time-weighted average (MAK Collection, 2014).

No inhalation toxicity data was found for human exposure.

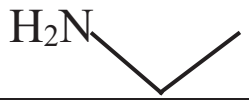
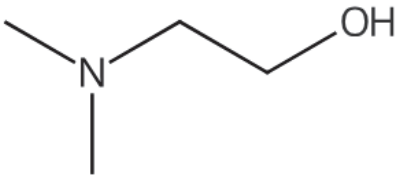
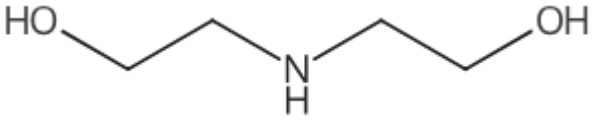
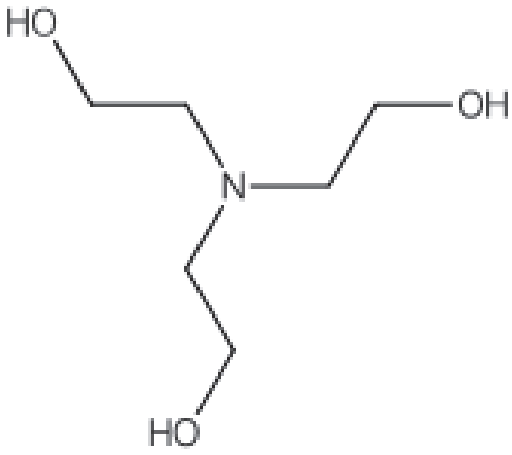
The MAK value documentation summarizes skin sensitization data based on patch tests in both case studies and occupational exposure studies (MAK Collection, 2014). Diglycol amine has been shown to be a skin sensitizer and in one of the worker studies, up to 6.6% of workers tested were positive for reactions to a 1% preparation of diglycol amine in Vaseline.

As compared to the effects observed in humans, the MAK value documentation notes that in guinea pigs, a study on skin sensitization was negative.

Summaries of one inhalation study in rats was found (MAK Collection, 2014; OECD SIDS, 2014; ECHA, 2023). The study was conducted according to OECD Test Guideline 422 (Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test), where male and female Wistar rats (N=10 per dose group) were exposed to 0, 4, 16, or 40 mg/m^3 for 6 hours per day, 7 days per week, for 29 days for males and 46-48 days for females. The median mass aerodynamic diameter (MMAD) was not detectable-0.8, 2.6-3.0, or 1.9-2.6 at the low, mid, and high dose, respectively. A no observable adverse effect concentration was observed at 4 mg/m^3. After 14 days of exposure, rats in the F0 generation were mated. As compared to the control group, increased squamous metaplasia was observed in the larynx of male rats at the mid dose. As compared to the control group, increased squamous metaplasia was observed at the highest dose in both genders. Similarly, there was dose-dependent increases in chronic inflammation in the larynx of both genders. There was no noted effect in the nose.

Although the toxicity database on diglycol amine is limited with only one repeat dose inhalation study, similarly structured alkanolamines and primary amines as a group have been shown to be corrosive with eye, lung, and skin irritation as the critical effect (see Table 2). These portal of entry effects are expected to occur because of the alkaline properties of these toxic air contaminants (TACs) (OECD, 2014). Given the potential for portal of entry effects, extrapolation from oral studies is inappropriate.

Table 2. AQD TACs with similar structures and toxicological properties to diglycol amine with irritation observed as the critical effect to protect against with acute exposures

Name (CAS#)	Structure	ITSLs
Ethylamine (CAS# 75-04-7)		92 µg/m^3, 8-hour AT (MDEQ, 1998)
Monoethanolamine (CAS# 141-43-5)		80 µg/m^3, 8-hour AT (MDEQ, 2013)
Dimethylethanolamine (CAS# 108-01-0)		5.2 µg/m^3, annual AT; 220 µg/m^3, 8-hour AT (MDEQ, 2013)
Diethanolamine (CAS# 111-42-2)		0.2 µg/m^3, annual AT; 10 µg/m^3, 8-hour AT (EGLE, 2022)
Triethanolamine (CAS# 102-71-6)		50 µg/m^3, 8-hour AT (MDEQ, 1997)

It is important to note, similar to diglycol amine, most of these TACs have very limited toxicity databases. The TAC with the most toxicity studies, diethanolamine (CAS# 111-42-2), has respiratory irritation as a critical effect, along with liver and kidney effects. Furthermore, diethanolamine has been shown to be a carcinogen via dermal exposure in male and female

mice (but not rats) with not enough information to derive an initial risk screening level for inhalation exposure. Taken together, it will be important to review the basis of the ITSL as more information becomes available for both diglycol amine and structurally similar TACs.

No carcinogenicity studies were identified, so diglycol amine is not classifiable as a carcinogen based on lack of information. However, summaries of *in vivo* and *in vitro* genotoxicity studies are presented in the dossier (ECHA, 2023). All of the studies gave negative results for genotoxicity, indicating that diglycol amine is not likely to be genotoxic.

Derivation of Acute Screening Level

The MAK documentation presented rat inhalation toxicity data as the basis for their occupational exposure limit. Specifically, the basis for the MAK was identified as a rat inhalation study consisting of exposure to diglycol amine at 0, 4, 16, or 40 mg/m^3 for 6 hours/day, 7 days/week for 29 days in male rats and 46-48 days in female rats. The study found no effects at 4 mg/m³. A lowest observable adverse effect level was identified at 16 mg/m^3 based on squamous cell metaplasia and inflammation in the larynx. The MAK of 0.87 mg/m³ for 8-hr exposure period was developed to protect against respiratory effects with acute exposure. Therefore, an acute ITSL will be derived per Rule 336.1232 (1) (c) using the MAK value as shown in Equation 1.

Equation 1.

$$ITSL = \frac{OEL}{100}$$

where

OEL is the occupational exposure level, the MAK value,

$$ITSL = \frac{0.87\ mg/m^3}{100}\ x\ \frac{1000\ \mu g}{mg} = 8.7\frac{\mu g}{m^3} \approx 9\ \frac{\mu g}{m^3}, 8\ hr\ averaging\ time$$

Derivation of Chronic Screening Level

Given the hierarchy of data used to develop screening levels, the acute and subacute chemical-specific data available for diglycol amine, as well as other aspects of the limited database for diglycol amine, preference was initially given to deriving an acute screening level alone. Based on public comments, more research was done to determine if there is enough information to derive a screening level that would be protective of health effects from chronic exposure.

Based on Rule 232(d), a potential chronic screening level could be derived for diglycol amine as shown I Equation 2.

Equation 2.

$$potential\ chronic\ ITSL = \frac{NOAEL}{35\ x\ 100} x \frac{hours\ exposed\ per\ day}{24\ hours\ per\ day}$$

Where

The rats were exposed for 6 hours per day

$$potential\ chronic\ ITSL = \frac{4\frac{mg}{m^3}}{35\ x\ 100} x \frac{6\ hours\ exposed\ per\ day}{24\ hours\ per\ day} x \frac{10^3 \mu g}{mg} = 0.2857$$
$$\approx 0.3\ \frac{\mu g}{m^3}, \qquad annual\ averaging\ time$$

There are strengths and limitations to using a chronic screening level derived in this manner. In terms of strengths, this screening level is based on a diglycol amine, chemical-specific research study. On the other hand, this chronic screening level is based on a subacute study, which would not typically be used for the derivation of a screening level that protects against long-term exposure (EPA, 2022). Deriving an acute screening level that protects against the acute effects observed in this subacute inhalation study is sounder and has less measures of uncertainty than the extrapolation needed to derive a chronic screening level from the same information. In this specific case, since Rule 232(d) is typically meant to be used with a 7-day inhalation study, use of the full uncertainty factor of 35 for duration extrapolation may be overly conservative as the subacute study is based on exposure durations up to 48 days. Lastly, deriving a chronic screening level from the same study and critical effect used to derive the acute screening level is not well supported as the acute screening level is expected to provide enough health protection against potential health effects observed in this study. As a result, this potential chronic screening level will not be used.

Given the larger toxicity database for some of the other, similar chemicals that also have screening levels, both the chemical structure and critical effect similarities were reviewed to see if one of their chronic screening level(s) could be adopted. As shown in Table 2, there were two potential candidates, diethanolamine (CAS# 111-42-2) and dimethylethanolamine (CAS# 108-01-0). While the critical effects for all three TACs may be generally described as irritation, the upper respiratory tract-related irritation observed after acute, diglycol amine exposure is more similar to the upper respiratory tract-related irritation observed with chronic, diethanolamine exposure compared to the ocular irritation observed with dimethylethanolamine (EPA, 2012; EGLE, 2022; MAK, 2014; MDEQ, 2013). Furthermore, the chronic ITSL for diethanolamine is within one order of a magnitude to the potential chronic ITSL derived from the diglycol amine-specific study. While, as previously noted, there is concern that the chemical-specific potential chronic ITSL is overly conservative, it is also important to note that each of the acute ITSLs for diglycol amine and diethanolamine are also within one order of a magnitude to each other. Conversely, both the chronic ITSL for diethanolamine is more than a magnitude less than the chronic ITSL for dimethylethanolamine, and the acute ITSLs for diethanolamine and diglycol amine are more than a magnitude less than the acute ITSL for dimethylethanolamine. Taken together, it the diethanolamine chronic ITSL will be adopted as the chronic ITSL for diglycol amine and these TACs should be regulated under the same hazard index when they are co-emitted.

Briefly, the diethanolamine chronic ITSL is adopted from the diethanolamine United States Environmental Protection Agency (USEPA) Provisional Peer-Reviewed Toxicity Value (PPRTV) for chronic exposure (EPA, 2012; EGLE, 2022). The PPRTV was developed from an approximately 90-day inhalation exposure study in rats (Gamer et al., 2008). At 3 mg/m^3, the most sensitive health effect observed in the study was increased squamous metaplasia in the upper respiratory tract, specifically in the epiglottis and in the larynx. Benchmark Dose Software and safety factors were used to estimate a concentration that is not expected to cause the most sensitive health effect. The USEPA performed modeling on the data using Benchmark Dose (BMD) Software to determine the benchmark concentration confidence limit corresponding to a 10% response and adjusted to a human equivalent concentration ($BMCL_{HEC10}$) of 0.63 mg/m^3. A

total uncertainty factor of 3000 was then applied to derive a provisional reference concentration of 0.2 µg/m^3, where the individual uncertainty factors are 3 for interspecies extrapolation, 10 for lack of developmental studies, 10 for intraspecies extrapolation, and 10 for subchronic to chronic extrapolation.

Therefore, the acute ITSL for diglycol amine (CAS# 929-06-6) is 9 µg/m^3, 8-hour averaging time and the chronic ITSL for diglycol amine is 0.2 µg/m^3, annual averaging time.

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