MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Diethanolamine (CAS # 111-42-2)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: December 5, 2022

SUBJECT: Screening Level for Diethanolamine (CAS # 111-42-2)

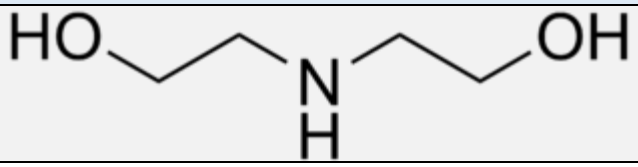
Summary

The initial threshold screening level (ITSL) for diethanolamine (DEA) is 0.2 µg/m^3 (annual averaging time) and an acute ITSL for diethanolamine is 10 µg/m^3 (8-hour averaging time).

Uses and Physical Chemical Properties

Diethanolamine is an organic amine that is used: as a chemical intermediate and as a corrosive inhibitor and surface-active agent in metal working fluids, cutting oils, fuels, paints, and inks; as a dispersing agent for agricultural chemicals; as an absorbent for acidic gases; and in consumer products, such as shampoos, soaps, detergents, cosmetics, and pharmaceuticals (EPA, 2012; PubChem, 2022).

Table 1. Physical/Chemical Properties of Diethanolamine

Structure	
CAS Number	111-42-2
Synonyms	DEA; DEOA; 2,2'-Iminodiethanol; diolamine; or 2-(2-hydroxyethylamino)ethanol
Appearance/Odor	Oily, colorless liquid or solid white crystals with a slight rotten fish odor
Odor Threshold	0.27 ppm
Molecular Weight	105.14 g/mol
Melting Point	27.9 °C
Boiling Point	268.8 °C @ 760 mmHg

Flash Point	134 °C (open cup); 152 °C (closed cup)
Autoignition Temperature	662 °C
pH (of 0.1N aqueous solution)	0.1
Solubility: Water	1000 mg/mL @ 20 °C
Density	1.0966 g/cm^3
Relative Vapor Density	3.65 (Air = 1)
Vapor Pressure	2.8 x 10-4 mm Hg at 25°C
Log Kow	-1.43
Henry's Law Constant	3.87 x 10-11 atm-m^3 /mole at 25°C

Literature Search

The literature was searched to find relevant data to assess the toxicity of DEA. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched 8/19/2022), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

Key Study for Chronic ITSL

The ITSL is derived from an EPA Provision Peer-Reviewed Toxicity Value (PPRTV) chronic provisional reference concentration (p-RfC) for inhalation exposure of 2 x 10^{-4} mg/m^3. The p-RfC is based on a rat inhalation study performed by Gamer et al., (2008). "In two peer-reviewed nose-only inhalation studies, Gamer et al. [2008] exposed Wistar rats to concentrations of 0, 15, 150, or 400 mg/m^3 *n* = 13/sex/dose group; (hereafter referred to as Study 1) or 0, 1.5, 3, or 8 mg/m^3 *n* = 10/sex/dose group; (hereafter referred to as Study 2) diethanolamine (purity >99%) 6 hours per day for a total of 65 exposures over a time period of 99 days (90-day study; as specified by the study authors). The corresponding adjusted continuous exposure concentrations are 0, 2.5, 24.6, and 65.7 mg/m^3 for Study 1 and 0, 0.25, 0.49, and 1.3 mg/m^3 for Study 2" (EPA, 2012). "Study 1 specifically investigated neurotoxicity; thus, authors administered comprehensive neurofunctional test in 10 rats/sex. This functional observational batter (FOB) test included observations for sensory and motor functions and was performed before the exposure and then four times (once a month) during the study. Tests covered responses to visual, auditory, olfactory, and touch stimuli, and neuromotor

alterations (e.g., pain perception). Motor activity was tested on the same day as the FOB…" (EPA, 2012).

"There were no deaths in Study 1. Clinical effects included a diethanolamine-related decrease in body weight in males exposed to 400 mg/m^3 (equivalent HEC of 181.3 mg/m^3) compared to control animals" (EPA, 2012). "The authors observed significant ($p < 0.01$) decreases in red blood cells, hemoglobin, hematocrit, and mean corpuscular volume ($p < 0.05$) in both sexes of rats exposed to 400 mg/m^3 (equivalent HEC of 181.3 mg/m^3 and 181.7 mg/m^3 for male and female rats, respectively) diethanolamine. At 150 and 400 mg/m^3 (equivalent HEC of 67.9 and 181.3 mg/m^3 for female rats) diethanolamine, there were slight, significant (level not reported) increases in serum alkaline phosphatase for both sexes and a decrease in serum alanine aminotransferase in males only. Serum levels of calcium, total protein, albumin, and globulin were increased in females of the mid- and high-exposure groups…" (EPA, 2012). "There was a significant (level not reported) increase in blood in the urine in both sexes at the high concentration. Males exposed to 150 and 400 mg/m^3 (corresponding HEC of 67.9 and 181.3 mg/m^3) diethanolamine also experienced significant (level not reported) increases in renal tubular epithelial cells and occasional granular casts" (EPA, 2012). "Organ examinations revealed significant ($p < 0.05$ or $p < 0.01$) increases in weights of the liver and kidneys in males and females at the highest concentration. Females exposed to 24.6 mg/m^3 (corresponding HEC of 68.1 mg/m^3) also experienced significant increases ($p < 0.01$) in the weights of both these organs, and males exposed to the mid-dose experienced significant ($p < 0.05$) increases in kidney weight…" (EPA, 2012). "The relative brain weight was statistically significantly ($p < 0.05$) increased in high-dose males, which is consistent with reduced body weight. The study authors noted gross lesions of the epithelium of the glandular stomach in females at the intermediate and high concentrations. These findings included focal squamous metaplasia of the ventral laryngeal epithelium at the base of the epiglottis at all concentrations and a diethanolamine-dependent increase in laryngeal squamous hyperplasia and the incidence and severity of laryngeal and tracheal inflammation at the mid- and high-concentrations…" (EPA, 2012). "Based on these results, a $LOAEL_{ADJ}$ of 2.5 mg/m^3 is identified in Study 1 for respiratory effects in male and female rats (corresponding $LOAEL_{HECs}$ of 5.6 mg/m^3 and 4.8 mg/m^3 for male and female rats, respectively). A NOAEL cannot be identified" (EPA, 2012).

In Study 2, "no clinical effects were seen. There were no significant differences in body weight or relative organ weight for males at any concentration compared to the control" (EPA, 2012). "Effects in the larynx at the high concentration were similar to those seen in the first study. This finding was not seen in the low concentration group in Study 1, indicating variability of populations. The authors noted a significant ($p < 0.05$) increase in liver weight in female rats exposed to 8 mg/m^3 (corresponding HEC of 2.93 mg/m^3)" (EPA, 2012). "Squamous metaplasia of the laryngeal epithelium at the base of the epiglottis…and the larynx…and submucosal inflammation were seen in both sexes. Squamous metaplasia (without inflammatory cell infiltration) was found in 3/10 male rats exposed to 3 mg/m^3 (corresponding HEC of 1.11 mg/m^3) diethanolamine, and some inflammatory cell infiltration was seen in control animals" (EPA, 2012).

"The study authors concluded that diethanolamine is toxic to the upper respiratory tract, as evidenced by epithelial effects in the larynx. Diethanolamine also affected hematology, clinical chemistry, and urinalysis parameters, which corresponded to increases in liver and kidney weights and lesions in the kidneys. Results from Studies 1 and 2 indicate that the respiratory tract (in particular, the trachio-bronchiolar region) is more sensitive to diethanolamine via inhalation exposure" (EPA, 2012). "Based on these results, a $LOAEL_{ADJ}$ of 0.49 mg/m^3 (corresponding to a $LOAEL_{HEC}$ of 2.15 mg/m^3 for respiratory effects due to increased incidences of squamous metaplasia in the epiglottis…and in the larynx…in male rats and a $NOAEL_{ADJ}$ of 0.36 mg/m^3 (corresponding to a $NOAEL_{HEC}$ of 1.07 mg/m^3 for respiratory effects in male rats) are identified in this study. A $LOAEL_{HEC}$ of 2.93 mg/m^3 got extrarespiratory effects due to increased relative liver weight in female rats and a $NOAEL_{HEC}$ of 1.10 mg/m^3 are considered" (EPA, 2012).

Chronic ITSL Derivation:

Table 2. Significant Changes in Wistar Rats Exposed to Diethanolamine

		Concentration mg/m^3 (HEC)	**Incidence/number of animals tested (% of control)**	
		Study 1		
		Male Rat		
Critical Effect	**0 (0)**	**15 (5.6)**	**150 (55.4)**	**400 (146.2)**
Body Weight at Termination	433 ± 51	407 ± 45 (97%)	396 ± 30 (91%)	376 ± 27 (87%)
Relative Kidney Weight	652 ± 58	674 ± 45 (103%)	716 ± 45 (110%)	734 ± 58 (113%)
Larynx: Squamous Metaplasia	NR	10/10	10/10	10/10
		Female Rat		
Critical Effect	**0 (0)**	**15 (6.8)**	**150 (68.1)**	**400 (181.7)**
Relative Liver Weight	3171 ± 157	3191 ± 161 (101%)	3488 ± 215 (110%)	3771 ± 204 (119%)
Relative Kidney Weight	795 ± 40	811 ± 51 (102%)	891 ± 39 (112%)	922 ± 72 (116%)
Hemoglobin (mmol/l)	9.0 ± 0.3	9.3 ± 0.4 (103%)	8.7 ± 0.3 (97%)	7.9 ± 0.2 (88%)
Larynx: Squamous Metaplasia	NR	10/10	10/10	10/10
		Study 2		
		Male Rat		
Critical Effect	**0**	**1.5 (1.07)**	**3 (2.15)**	**8 (5.66)**
Larynx: Squamous Metaplasia	NR	0/10	3/10	9/10

Female Rat				
Critical Effect	**0**	**1.5 (0.86)**	**3 (1.71)**	**8 (4.61)**
Larynx: Squamous Metaplasia	NR	0/10	0/10	9/10

Table 3. Model Predictions for Significant Changes in Wistar Rats Exposed to Diethanolamine

Critical Effect	Model	p-Value	Scaled Residual	AIC	BMDL
Male rat Larynx Squamous Metaplasia	Dichotomous - Multistage	0.8302	-0.895	22.3385	0.631169
Female rat Relative Liver Weight	Continuous - Power	0.4661	-0.607	497.705012	2.02919

"The critical effect is increased incidence of squamous metaplasia in the epiglottis…and in the larynx…in male rats" (EPA, 2012). EPA performed benchmark dose software [Version 2.14] to model the squamous metaplasia incidence rates in male rats with the Dichotomous-Multistage model, which provided a $BMCL_{10HEC}$ of 0.63 mg/m^3 and a BMC_{10HEC} of 1.25 mg/m^3" (EPA, 2012). "Based on this modeling outcome and the study authors' conclusion that diethanolamine is toxic to the respiratory tract, the $BMCL_{10HEC}$ of 0.63 mg/m^3 is selected as the POD for the derivation of a chronic p-RfC. The $BMCL_{10HEC}$ of 0.63 mg/m^3 as the POD is protective for both respiratory and extra-respiratory effects in both sexes" (EPA, 2012).

The chronic p-RfC for diethanolamine, based on a $BMCL_{10HEC}$ of 0.63 mg/m^3, is derived as follows:

$$Chronic\ p-RfC = \frac{BMCL_{HEC}}{UF_C} = \frac{0.63\ {}^{mg}/_{m^3}}{3000} = 2 \times 10^{-4}\ {}^{mg}/_{m^3}$$

The total uncertainty factor for the chronic p-RfC is 3000: uncertainty of 3 for animal-to-human extrapolation; uncertainty of 10 for lack of reproductive or developmental studies; uncertainty of 10 for susceptible populations of humans; and an uncertainty of 10 for using a subchronic duration study to assess potential effects from chronic exposure.

According to Rule 336.1232(1)(a) in part 2 of Act 451, an ITSL can be derived from an inhalation reference concentration (RfC).

$$ITSL = RfC = 2 \times 10^{-4}\ {}^{mg}/_{m^3} = 0.0002\ {}^{mg}/_{m^3} = 0.2\ {}^{\mu g}/_{m^3}$$

According to Rule 336.1232(2)(b), the averaging time is annual. Therefore, the ITSL for diethanolamine is 0.2 µg/m^3 based on an annual averaging time.

Acute ITSL Derivation:

There are several acute benchmarks for diethanolamine which are summarized in the following table.

Table 4. Diethanolamine non-cancer health benchmarks and candidate ITSLs

Available Inhalation Non-cancer Health Benchmarks	Value (µg/m^3)	Candidate ITSL (µg/m^3)	Candidate ITSL Averaging Time
OSHA PEL	No recommended value		
Cal/OSHA PEL	2000	PEL/100 = 20	8-hour
ACGIH TLV-TWA	1000	TLV/100 = 10	8-hour
NIOSH REL	13000	REL/100 = 130	10-hour
EPA AEGL-1	No recommended value		
DOE PAC-1	3000	PAC-1/100 = 30	8-hour

ACGIH TLV-TWA of 1 mg/m^3 (10 µg/m^3) for the inhalable fraction and vapors of diethanolamine was recommended "to protect against its irritative and systemic effects" in occupational settings. An occupational exposure is used to protect healthy workers exposed during an 8-hour workday over a typical work week. The ITSL is a conservative value which accounts for the differences in susceptibility of the general population, which includes sensitive populations.

According to Rule 232(1)(c), an ITSL can be derived from an occupational exposure level (OEL).

$$ITSL = \frac{OEL}{100} = \frac{1\ {}^{mg}/_{m^3}}{100} = 0.01\ {}^{mg}/_{m^3} = 10\ {}^{\mu g}/_{m^3}$$

Rule 232(2)(a), the averaging time is 8 hours for an ITSL derived from an occupational exposure level. Therefore, the ITSL for diethanolamine (CAS # 111-42-2) is 10 µg/m^3 based on an 8-hour averaging time.

Discussion on Carcinogenicity

The American Conference of Governmental Industrial Hygienists (ACGIH) has classified diethanolamine as a Group A3 carcinogen – "Confirmed Animal Carcinogen with Unknown Relevance to Humans" (ACGIH, 2009). ACGIH made this determination from an NTP (1997) dermal carcinogenic study, which showed dose-related increases in liver tumors in female, but not male, mice and no tumors in rats after dermal exposure. The

International Agency for Research on Cancer (2010) has classified diethanolamine as a Group 2B carcinogen "*possibly carcinogenic to humans"* based on sufficient evidence in carcinogenicity in experimental animals, but inadequate evidence of carcinogenicity in humans. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency added diethanolamine into Proposition 65 list. OEHHA listed diethanolamine as it is known to cause cancer and is listed as a carcinogen by IARC. There are no chronic duration carcinogenicity studies via oral or inhalation exposures. There are no positive genotoxicity tests for this substance, therefore it should be evaluated as a non-genotoxic carcinogen (Uno Y et al., 2015). A dermal study is not sufficient to derive an initial risk screening level for diethanolamine.

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