MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Triethylamine (CAS # 121-44-8)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: August 8, 2016

SUBJECT: Screening Level for Triethylamine (CAS # 121-44-8)

The initial threshold screening level (ITSL) for triethylamine (CAS # 121-44-8) is 7 µg/m^3 based on an annual averaging time. The second initial threshold screening level is 21 µg/m^3 based on an 8-hour averaging time.

Triethylamine, also known as *N,N*-diethylaminoethane, is an aliphatic amine and is a colorless volatile liquid with a strong fishy odor reminiscent of ammonia with a molecular weight of 101.19 g/mol. Triethylamine is used: as a catalytic solvent in chemical syntheses; as an accelerator activator for rubber; as a propellant; in the production of wetting, penetrating, and waterproofing agents of quaternary ammonium compounds for textiles and quaternary ammonium salts for dyes; for the desalination of seawater; for anesthetizing fruit flies and mosquitos in the laboratory; in matrix-assisted laser desorption/ionization (MALDI) matrices to enhance spatial resolution in MALDI mass spectrometric (MS) imaging; and in the determination of active pharmaceutical ingredient in head-space gas chromatography (GC) analysis (EPA, 2016; Sigma-Aldrich, 2016).

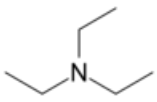

Figure 1. Structure of triethylamine.

A literature review was conducted to determine the screening levels for triethylamine. The following references and databases were searched to derive the above screening levels: Chemical Criteria Database (CCD), United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2014 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 12/2/15), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology

Resource (ACToR) Database, U.S. EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

ITSL Derivation:

EPA (1991) has developed a reference concentration for chronic inhalation exposure (RfC) for trimethylamine of 7E-3 mg/m^3 based on a 28-week rat inhalation study by Lynch et al., (1990). Fischer 344 rats (50/sex/group) inhaled either 0, 25 ppm (103.4 mg/m^3, or 247 ppm (1022.2 mg/m^3) trimethylamine vapors (99% compound purity) for 6 hours/day, 5 days/ week, for 28 weeks. "Body weights were recorded at 2-week intervals. Animals were sacrificed at 30 days, 60 days, and at the end of the 28-week exposure period. Histopathologic examinations were conducted on all major organs including the lungs (following perfusion with formalin), nasal passages (at 5 levels), trachea, and eyes. Clinical parameters measured included BUN, ALT, AST, CPK, creatinine, hemoglobin, and RBC count. Electrocardiograms were performed in 20 (10/sex) rats of each group at the terminal sacrifice. Body weights were not affected by the exposure. Male lung weights were increased in a concentration-dependent manner, although the changes were not statistically significant or accompanied by any histopathology. No treatment-related effects on electrocardiography, hematology, or organ weights (other than lung) were noted. This study established a NOAEL of 247 ppm for inhalation exposure of rats to trimethylamine. The NOAEL(HEC) for extrathoracic effects is 19.5 mg/m^3" (EPA, 1991).

"Subsequent to the above study, the same authors conducted a supplementary inhalation study under the same conditions as above, but at a higher concentration (Virginia Chemicals, 1987). The authors exposed rats (5 males, 5 females) to 1,000 ppm (4139 mg/m^3) 6 hours/day for 10 days. The duration-adjusted concentration of triethylamine is 739 mg/m^3" (EPA, 1991). "All 10 animals had at least moderate (grade 3) necrotizing inflammation of the nasal cavity. Progression of effects deeper into the respiratory tract was indicated by the occurrence of squamous metaplasia (from slight to marked in severity) in the trachea in 7 of 10 animals. Moderate thymic atrophy was present in 7 of 10 animals. Keratitis (graded as slight) was noted in three animals. Two of the males and one of the females died after the seventh day of exposure. Lung effects (perivascular edema) was noted but only in the three animals that died. Although the cause of death is not indicated by the authors, the mortality may be related to the pulmonary edema observed and not due to systemic effects caused by the compound. Based on these effects 1,000 ppm is considered a frank effect level. Dosimetrically adjusted for the extrathoracic region this value would become 79 mg/m^3 = FEL(HEC). Thus, the concentration response curve of triethylamine appears to rise abruptly, with frank effects occurring at levels only 4-fold above a no-effect level" (EPA, 1991).

The EPA derived an RfC of 7E-3 mg/m^3 from the Lynch et al., (1990) NOAEL(HEC) of 19.5 mg/m^3 by converting the NOAEL of 247 ppm by the molecular weight of triethylamine, 101.19 g/mol (assuming 25°C and 760 mmHg). The EPA used a free standing NOAEL of 247 ppm, because the study didn't identify a LOAEL; the EPA determined the NOAEL(HEC) using the following equations:

$$NOAEL\ {}^{mg}/_{m^3} = 247\ ppm \times \frac{101.19\ {}^{g}/_{mol}}{24.45} = 1022.2\ {}^{mg}/_{m^3}$$

The EPA adjusted the NOAEL to account for the intermittent administration of triethylamine in the Lynch et al., (1990) study using the following equation:

$$NOAEL(ADJ) = 1022.2\ {}^{mg}/_{m^3} \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 182.5\ {}^{mg}/_{m^3}$$

"The NOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region (animal to human). MVa = 0.14 m^3/day, MVh = 20 m^3/day, Sa(ET) = 11.6 cm^2, Sh(ET) = 177 cm^2" (EPA, 1991) using the equation below:

$$RGDR(ET) = \frac{(\frac{MVa}{Sa})}{(\frac{MVh}{Sh})} = \frac{(\frac{0.14\ {}^{m^3}/_{day}}{11.6\ cm^2})}{(\frac{20\ {}^{m^3}/_{day}}{177\ cm^2})} = 0.107$$

The EPA used the following equation to determine the NOAEL(HEC).

$$NOAEL(HEC) = NOAEL(ADJ) \times RGDR = 182.5\ {}^{mg}/_{m^3} \times 0.107 = 19.5\ {}^{mg}/_{m^3}$$

An uncertainty factor of 3000 was used (10 for protection of sensitive human populations; 3 for interspecies extrapolation; 10 for the use of a less than chronic study; and 10 for the lack of developmental and reproductive data and lack of data in a second animal species). In general the Michigan Department of Environmental Quality, Air Quality Division does not use the database uncertainty factor, but because the animals study didn't examine eye function (acuity), and the possibility of missing this sensitive endpoint, a database uncertainty factor of 10 should be used in this case. The resulting RfC of 7E-3 mg/m^3 (7 µg/m^3) can be used to derive an ITSL according to Rule 232(1)(a). According to Rule 232(2)(b) a 24-hour averaging time period should be used, but as this ITSL is based on a 28-week rat inhalation study, it is appropriate to utilize a longer averaging time, which would be an annual averaging time. Therefore, the ITSL for triethylamine is 7 µg/m^3 based on an annual averaging time. This chronic ITSL is coupled with an acute ITSL to better ensure health protection.

ACGIH (2015) has established a threshold limit value – time weighted average (TLV-TWA) of 0.5 ppm (2.07 mg/m^3) for triethylamine is recommended to minimize the potential for acute effects in humans. ACGIH has also listed a skin notation based on a dermal LD_{50} dose on rabbits which produced chemical burns on contact with intact skin. "Based on a 2-year drinking water study (Davison et al., 1965), an A4, Not Classifiable as a Human Carcinogen, notation is assigned" (ACGIH, 2015). Triethylamine "is a potent ocular irritant; a single drop in the rabbit eye produced severe injury (Benya and Harbison, 1994; Smyth et al., 1951) attributed to the strong alkalinity (pH = 10 to 11) of aqueous solutions (Grant and Kern, 1968)" (ACGIH, 2015). "Visual acuity and contrast sensitivity were evaluated in four

volunteers exposed in controlled whole-body chambers for 4 hours at concentrations of 0.72, 1.56, and 9.74 ppm. Visual acuity was unchanged at 0.72 and 1.56 ppm and was decreased in three of four subjects exposed to 9.74" (ACGIH, 2015). "Visual disturbances (foggy vision, blue haze, and halo phenomena) were reported on 47 occasions among 19 workers in a polyurethane foam production plant (Akesson et al., 1986)" (ACGIH, 2015).

Rule 232(1)(c) can be used to derive an acute ITSL based on an occupational exposure level (OEL) using the following equation:

$$ITSL = \frac{OEL}{100} = \frac{2.07\ {}^{mg}/_{m^3}}{100} = 0.0207\ {}^{mg}/_{m^3} = 20.7\ {}^{\mu g}/_{m^3} \approx 21\ {}^{\mu g}/_{m^3}$$

Rule 232(2)(a) states that an 8-hour averaging time is to be used for an ITSL derived from an occupational exposure level. Therefore, the acute ITSL for triethylamine is 21 µg/m^3 based on an 8-hour averaging time.

Discussion:

The irritation effects of triethylamine were observed at 1,000 ppm in animals with a NOAEL of 247 ppm after 28 weeks. As referenced by ACGIH, humans had ocular irritation effects resulting in decreased visual acuity at approximately 10 ppm, after a 4-hour exposure. The animal study was inadequate to identify an effect level because the visual acuity effects noted in human studies were not examined in the animal study. It is appropriate to use the animal study for protection from inflammation of nasal passages over long-term exposures coupled with the ocular effects from short-term exposures. The use of both ITSLs provides adequate public health protection. Therefore, the initial threshold screening level (ITSL) for triethylamine (CAS# 121-44-8) is 7 µg/m^3 based on an annual averaging time. The second initial threshold screening level is 21 µg/m^3 based on an 8-hour averaging time.

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