MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

February 7, 2017

TO: File for 1,8-Diazabicyclo(5.4.0)undec-7-ene (CAS No. 6674-22-2)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

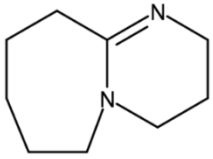
The Initial Threshold Screening Level (ITSL) for 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) is 25 µg/m^3 with an annual averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), the California Office of Environmental Health Hazard Assessment (Cal OEHHA), National Library of Medicine's TOXNET and TOXLINE, Toxic Substance Control Act (TSCA) Test Submissions (TSCATS), EPA's Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV), European Chemicals Agency (ECHA) Risk Assessment (REACH) database, Chemical Abstract Service (CAS) SciFinder database (20-Jan-2017) and US EPA (epa.gov).

SciFinder Data (ACS, 2017)

IUPAC Name: 2,3,4,6,7,8,9,10-octahydro-pyrimido[1,2-a]azepine
Molecular Formula: C9 H16 N2
Liquid
Molecular Weight: 152.24g
Boiling Point (Experimental): 97-98 ℃ @ Pressure: 3 Torr
Density (Experimental): 1.0378 g/cm^3 @ Temp: 20 ℃
pKa (Predicted): 13.28±0.20 @ Temp: 25 ℃
vapor pressure: 0.055 mm Hg @ 25℃ (NLM, 2017)

Figure 1. Molecular Structure of DBU



Additional Note: DBU has a very high pH >12. Corrosive[1]
At 23℃ the pH of a 10.1 g/100g solution in water w as found to be 12.6, the pH of a 50.1 g/100g solution in water was found to be 13.9, the pH of a 89.1 g/100g solution in water was found to be 15.8. (REACH, 2017a)

1,8-Diazabicyclo[5.4.0]undec-7-ene, or more commonly DBU, is a chemical compound and belongs to the class of amidine compounds. It is used in organic synthesis as a catalyst, a complexing ligand, and a non-nucleophilic base (Wikipedia, 2016).

According the EPA's Chemistry Dashboard (EPA, 2017), DBU has been extensively studied in cellular assays (>10,000) as a protein agonist/antagonist for intracellular signaling.

Military Exposure Guidelines (MEGs) were available for DBU (see Tables 1 and 2 below). However, the experimental and methodological basis for the derivation of these values were not available. Therefore, the MEGs for DBU were not used to derive health protective benchmarks for the general public, including sensitive individuals.

Table 1. Military Exposure Guideline (MEG)(U.S. Army, 2013)

MEG Value	UNITS	BASIS	MEDIA	SEVERITY	TIME FRAME
5	mg/m^3	TEEL1[2]	Air	Negligible	1hour
35	mg/m^3	TEEL2	Air	Marginal	1hour
150	mg/m^3	TEEL3	Air	Critical	1hour

Table 2. Definitions of MEG Severity Categories (U.S. Army, 2013)

Negligible 1hr Air MEG	A continuous exposure to airborne concentrations (for 1 hour) above this MEG (but below the Marginal MEG) could begin to produce mild, non-disabling, transient, reversible effects. Such effects, if any, will typically be mild irritant types of effects and/or initially be expected in personnel with underlying susceptibility factors (e.g., asthmatics). Effects are not expected to impair performance.
Marginal 1hr Air MEG	A continuous exposure to airborne concentrations (for 1 hour) above this MEG (but below the Critical MEG) could begin to produce effects that may result in some performance degradation, especially for tasks requiring extreme mental/visual acuity or physical dexterity/strength amongst a portion of individuals.
Critical 1hr Air MEG	A continuous exposure to airborne concentrations (for 1 hour) above the MEG (but below the Catastrophic MEG) could begin to result in serious health effects. This MEG is a conservative population threshold estimate of potential life-threatening or lethal effects; whereby, these effects are expected initially in personnel with underlying susceptibility factors.

[1] Code of Federal Regulations (CFR): 40CFR§261.22: Characteristic of corrosivity. (a) A solid waste exhibits the characteristic of corrosivity if a representative sample has the following property: (1) It is aqueous and has a pH less than or equal to 2 or greater than or equal to 12.5.
[2] Temporary Emergency Exposure Limit (TEEL). Derived by the U.S. Department of Energy (DOE), Office of Emergency Management (OEM), Subcommittee on Consequence Assessment and Protective Actions (SCAPA), TEEL Advisory Group (TAG).

Animal Toxicity Studies

An acute oral toxicity study was performed in groups of five male and five female Wistar rats with three doses: 215, 681 and 2000 mg/kg/bodyweight (mg/kgBW). After the 14-day observation period there were 0 (zero) of 10 deaths at 215 mg/kgBW, 9 of 10 deaths at 681 mg/kgBW, and 10 of 10 deaths at 2000 mg/kgBW. A lethal dose 50% was not calculated based on the idiosyncratic death rates; instead, it was stated that the LD50 was > 215 mg/kgBW and < 681 mg/kgBW (i.e., between 215 and 681 mg/kgBW) (REACH, 2017b).

A 14-day range-finding study was performed in groups of 3 Wistar rats at gavage doses of 0, 15, 40, 100 and 200 mg/kgBW/day (7-days/per week) (REACH, 2017c). There were no effects on body weight (except at the 200 mg/kgBW dose), food consumption, organ weight, hematology, clinical chemistry, and water consumption. Gross pathology was observed in the stomach (reddish foci) of the highest dose tested at 200 mg/kgBW/day. The effects on the stomach were attributed to the high alkalinity of the substance.

In an oral gavage study groups of 5 male and female Wistar-Han (Crl:WI-Han) rats were exposed 7-days per week to 0, 15, 50 or 150 mg/kg-body weight (BW) per day (REACH, 2017d). The pH of the gavage dose was reported as 12.8. During the reproductive phase of the study, males were exposed for 29 days and females exposed for 43-57 days. After a minimum of 14 days after start of exposure, males were placed in cages with females; one male and one female per cage. After mating, males and females were separated. Males continued to receive dosing until day 28. Females who delivered were necropsied between days 5-7 of lactation. Females who did not deliver were necropsied on day 21 post-coitum. Organ weight, histopathology, clinical chemistry and hematology parameters were examined on all adult rats. Reproductive effects that were measured included mating index, fertility index, conception index, gestation index and viability index. All adult rats received neurobehavioral examination that included: hearing ability, pupillary reflex, static righting reflex and grip strength. Statistically elevated absolute and relative (to body weight) kidney weight were found in the female rats at 150 mg/kgBW. Microscopic examination of the kidney revealed no treatment-related findings at the 150 mg/kgBW dose level. The authors stated that the increase kidney weights were not considered biologically relevant. The lowest-observed-adverse-effect-level (LOAEL) was 150 mg/kgBW based on macroscopic and microscopic effects on the stomach. No reproductive or developmental toxicity (mortality, clinical signs, body weight and macroscopic examination) was observed at the highest dose level. Therefore, a reproductive/developmental no-observed-adverse-effect-level (NOAEL) was identified as 150 mg/kgBW (highest dose tested). The adult rat NOAEL was identified as 50 mg/kgBW, with a LOAEL at 150 mg/kgBW.

Derivation of the Screening Level

Repeated dose studies showed macroscopic and microscopic corrosive damage to the stomach mucosa. These effects were most likely indicative of chemical burns due to the high alkalinity of pH of 12 – 15.8 (REACH, 2017a). Increased absolute and relative

kidney weights in the high dose female rats, but without evidence of pathology at the microscopic level, were considered an adverse effect. The 50 mg/kgBW dose level was considered adequate to derive a screening level. However, due to the highly corrosive nature of DBU and the likelihood of a portal-of-entry effect on the respiratory tract, the use of oral study to derive a screening level protective of inhalation effects contributes to a substantial amount of uncertainty. In spite of the toxicological database shortcomings, the reproductive/developmental study provides the best information with which a screening level can be derived. The effects observed were both portal-of-entry (stomach) and increased kidney weight.

Pursuant to Rule 232(1)(e) the ITSL can be calculated from a 7-day subacute oral toxicity study as:

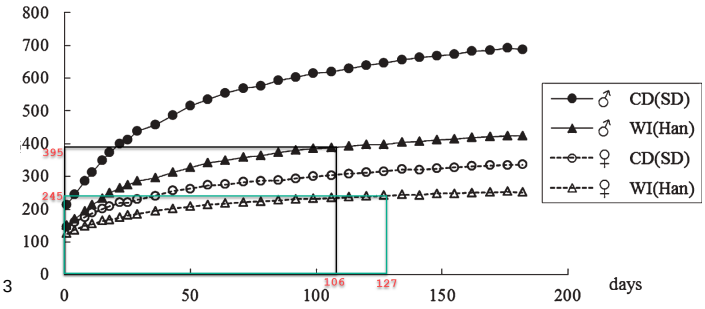
$$ITSL = NOAEL/(35 \times 100) \times W_a/I_a$$

Where W_a is the weight of the animal in kilograms (kg), and I_a is the daily inhalation rate of the animal in cubic meters per day (m^3/day). However, since the study was considerably longer than 7 days of exposure (i.e., 29 days for males, and an average of 50 days for females), the uncertainty factor of 35 was reduced to 20 to account for the decrease in subacute to subchronic duration extrapolation. The equation used for calculating the ITSL is as follows:

$$ITSL = NOAEL/(20 \times 100) \times W_a/I_a$$

The W_a and I_a were not provided in the summary of the REACH (2017d) study. The body weight can be estimated from a graph[3] of weight and ages for this particular stain of Wistar-Hannover rat. The age of the male rats was determined to be 106 days (77 days old when study started plus 29 days of exposure) and the females rats was determined to be 127 days (77 days old when the study started plus 50 days of exposure; midpoint between 43 and 57 days of exposure). The body weights for males and females were determined from the graph to be 395g (0.395kg) and 245g (0.245kg) , respectively.

Inhalation rates were determined by EPA (1988) as 0.919 and 0.995 m^3/kgBW/day for male and female rats, respectively. The resulting inhalation rates were calculated to be:



3

From: Hayakawa, et al., (2013)

Inhalation rate for male rats = 0.395kg x (0.919 m^3/kgBW/day)
Inhalation rate for male rats = 0.363 m^3/day

Inhalation rate for female rats = 0.245kg x (0.995 m^3/kgBW/day)
Inhalation rate for female rats = 0.244 m^3/day

Using the equation for a 7-day oral study from Rule 232(1)(e), with decreased uncertainty factor of 35 to 20 (see explanation above):

Potential male rat ITSL = (50 mg/kg)/(20x100) x 0.395kg/0.363 m^3/day
Potential male rat ITSL = 0.027 mg/m^3 x 1000µg/mg = 27 µg/m^3

Potential female rat ITSL = (50 mg/kg)/(20x100) x 0.245kg/0.243 m^3/day
Potential female rat ITSL = 0.025 mg/m^3 x 1000µg/mg = 25 µg/m^3

The male rat-derived ITSL would not be expected to protect the female rat-derived ITSL; therefore, the female rat-derived ITSL was used as the final screening level.

The ITSL for DBU is 25 µg/m^3. Pursuant to Rule 232(2)(c) the averaging time is annual.

References

ACS. (2017) Chemical Abstract Service Number: 6674-22-2. Substance Identifier. Key Physical Properties. Copyright © 2017 American Chemical Society. <accessed January 20, 2017>.

EPA (1988). Recommendations for and documentation of biological values for use in risk assessment. EPA/600/6-87/008. Environmental Criteria And Assessment Office, Office Of Health And Environmental Assessment, Office Of Research And·Development, U.S. Environmental Protection Agency, Cincinnati. OH 45268 P88-179874.

EPA. (2017) Chemistry Dashboard: 1,8-Diazabicyclo[5.4.0]undec-7-ene. Chemical Activity Summary. National Center for Computational Toxicology, Office of Research & Development, 109 T.W. Alexander Drive, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711. Version 1.1 updated January 03, 2017 at 9:56:19 AM. <accessed 23 Jan, 2017> https://comptox.epa.gov/dashboard

Hayakawa K, Mimura Y, Tachibana S, Furuya M, Kodama T, Aoki T, Hosokawa S, Fukui M, Shibata S, Yoshida M, Masuyama T, Narita T, Kuwagata M, Hisada S, Maki E. (2013) Study for collecting background data on Wistar Hannover [Crl:WI(Han)] rats in general toxicity studies--comparative data to Sprague Dawley rats. J Toxicol Sci. 2013;38(6):855-73.

National Library of Medicine (NLM). (2017) ChemIDplus Substance: 6674-22-2. TOXNET. NLM. 8600 Rockville Pike, Bethesda, MD 20894. National Institutes of Health, U.S. Department of Health & Human Services. <accessed January 20, 2017>.

REACH. (2017a) Physical Properties for 1,8-Diazabicyclo[5.4.0]undec-7-ene Registration Dossier. European Chemicals Agency (ECHA). http://echa.europa.eu/information-on-chemicals/registered-substances

REACH. (2017b) Acute Toxicity for 1,8-Diazabicyclo[5.4.0]undec-7-ene Registration Dossier. European Chemicals Agency (ECHA).

REACH. (2017c) Subacute range-finding study for 1,8-Diazabicyclo[5.4.0]undec-7-ene Registration Dossier. European Chemicals Agency (ECHA).

REACH. (2017d) Toxicity to Reproduction for 1,8-Diazabicyclo[5.4.0]undec-7-ene Registration Dossier. European Chemicals Agency (ECHA).

U.S. Army (2013). Environmental Health Risk Assessment and Chemical Exposure Guidelines for Deployed Military Personnel. 2013 Revision. U.S. Army Public Health Command (USAPHC) Technical Guide (TG) 230. Environmental Health Risk Assessment Program, Aberdeen Proving Ground, Maryland. https://phc.amedd.army.mil/PHC%20Resource%20Library/TG230.pdf <accessed January 23, 2017>

Wikipedia (2016). "1,8-Diazabicyclo(5.4.0)undec-7-ene," Wikipedia, The Free Encyclopedia, authored by Wikipedia contributors updated 21 Oct. 2016 https://en.wikipedia.org/w/index.php?title=1,8-Diazabicyclo(5.4.0)undec-7-ene&oldid=745560703 <accessed January 20, 2017>.