MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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August 10, 2015

To: File for Bis (2-Dimethylaminoethyl) Ether (CAS# 3033-62-3)

From: Michael Depa, Toxics Unit

Subject: Screening Level

The initial threshold screening level (ITSL) for bis(2-dimethylaminoethyl)ether is 0.3 µg/m^3 (based on an annual averaging time).

The following references or databases were searched to identify data to determine the screening level: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), 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, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online, National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) or reference dose (RfD). There are no occupational exposure limits for bis (2-dimethylaminoethyl) ether. The molecular weight is 160.26 g and the vapor pressure is 0.28 mmHg.

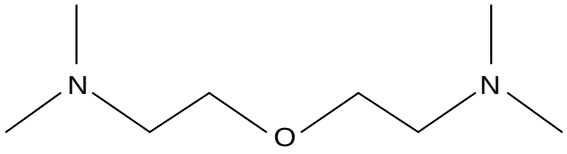

Figure 1. Molecular Formula for Bis(2-dimethylaminoethyl) Ether

Animal Toxicity

A well performed acute oral LD50 study was reported by Ballantyne (1997) in male rats as 909 mg/kg (95% confidence limit = 654-1274).

Groups of 10 male and female Sprague-Dawley rats were exposed to 0, 68, 149, 200, or 248 ppm bis-(2-dimethylaminoethyl)ether for 6-hours then observed for 14 days (Bushy Run, 1992). Clinical signs of ocular and respiratory irritation were observed in all exposed rats. The LC50 was calculated as 166 ppm (95% confidence limit = 155 – 178 ppm).

In an acute inhalation pharmacokinetics study, groups of 4 male Fischer 344 rats were exposed to 5.2 ppm for 4-hours and observed for 48 hours after exposure (Jensen et al., 1997). Absorption was studied in one experiment (5.2 ppm) and elimination and tissue distribution in two further experiments (5.5 and 5.6 ppm). Minimal peripheral sensory irritation was observed during exposure with respiratory rate decreased at the end of exposure period ranging from 13 to 30%. During the absorption phase, plasma 14C-derived radioactivity increased linearly with time during exposure, and did not reach steady-state conditions. Data from the postexposure period showed a log plot of plasma radioactivity versus time was linear and consistent with a first-order elimination. The

pharmacokinetic parameters, derived using a one-compartmental model, gave a plasma half-life of 17.39 – 24.15 h. The major route of elimination of radioactivity was in urine (52.87 – 57.58% of the recovered dose). Less than 1% of the radioactivity was in tissues and organs, with no evidence for preferential accumulation. The authors concluded that bis(2-dimethylaminoethyl)ether was readily absorbed at a constant rate, slowly eliminated mainly by urinary excretion, and without preferential specific organ/tissue accumulation.

In an acute inhalation study, groups of 5 New Zealand white rabbits were exposed for 2-hours to a mean concentration of bis(2-dimethylaminoethyl)ether of 0.1, 0.9, 4.6, 8.8, 12.2, 14.9, 21.1 and 24.8 ppm (Chun and Ballantyne, 1997). A control group was exposed to air alone. Corneal thickness was measured by an ultrasonic pachymeter before and immediately following exposure and at approximately 30 minutes, 3, 5, 24, 48 and 72 hours postexposure, and thereafter as necessary. Eyes were inspected for signs of conjunctival and corneal inflammation. No irritation or corneal dullness was seen at 0.1 or 0.9 ppm bis(2-dimethylaminoethyl)ether vapor, but at 4.6 ppm and above, exposure-related conjunctivitis and corneal dullness occurred with no clear dose-response relationship. Corneal thickness was slightly, although not statistically significantly increased at 4.6 ppm, and not until about 48 hour postexposure. At 8.8 ppm and above increases in corneal thickness were measured immediately. The authors stated that the no-observable-effect-level (NOEL) is between 0.9 and 4.6 ppm and for objectively assessed increased corneal thickness between 4.6 and 8.8 ppm.

Another acute inhalation study was performed where groups of 10 male and female Sprague-Dawley rats were exposed to 0, 1, 8 or 17 ppm bis(2-dimethylaminoethyl)ether (6.54, 52.35 and 111.2 mg/m^3) for 6 hours per day, 5 days per week for 9 days (Bushy Run, 1992). There were no mortalities. Clinical signs of ocular and respiratory irritation were common in the 17 ppm group. Decreased body weight was observed in the rats of the 17 ppm dose group. Increased numbers of neutrophils and leukocytes and a decrease in platelets were observed in rats of the 17 ppm group. At necropsy, treatment related gross lesions included swollen eyelids, corneal cloudiness, and perinasal encrustation (8 and 17 ppm exposure groups). Changes in organ weights in the 17 ppm groups were considered to result from body weight losses. A noteworthy microscopic lesion in exposed rats was vacuolar cytoplasmic swelling of epithelial cells of the nasal cavities. The severity of this finding was concentration related as was the distribution of the lesion within the nasal passages. Rhinitis and epithelial cell necrosis were observed in several rats of the 17 ppm group, and atrophy of the olfactory epithelium was present in rats of both the 8 and 17 ppm groups. Rats of the 1 and 8 ppm exposure groups had statistically significant changes in urinalysis measurements. The authors state that several of these alterations were not concentration related. Examples of statistically significant changes in serum chemistry values for rats of the 8 and 17 ppm groups were increases in alanine aminotransferase (males and females), aspartate aminotransferase (females) and urea nitrogen (females), and decreases in albumin (males and females), phosphorus (males and females), and chloride (males and females). There were no alterations in organ weight for the 1 or 8 ppm rats. All exposed rats had statistically increased incidence of nasal epithelial vacuolation. The 1 ppm dose group was identified as a lowest-observed-adverse-effect-level (LOAEL) based on nasal epithelial vacuolation.

In a subchronic inhalation study, groups of 15 male and female Sprague rats were exposed to 0, 0.23, 1.25 or 5.8 ppm (0, 1.51, 8.18 or 37.96 mg/m^3) bis(2-dimethylaminoethyl)ether for 6 hours per day, 5 days per week for 14 weeks (Losco et al., 1996). Ten rats/sex/group were euthanized after the exposure regimen, and 5 rats/sex/group were euthanized after a 6-week recovery period. Weights were taken of all the major organs and many tissues were examined for histopathology. The 5.8 ppm (37.96 mg/m^3) dose group had reduced body weight gain throughout the exposure regimen. Periocular swelling was observed in all exposure groups, and keratitis was observed in 6 of 10 female rats exposed to 1.25 ppm (8.18 mg/m^3) bis(2-dimethylaminoethyl)ether. The authors stated that no biologically or toxicologically significant findings on hematology, clinical chemistry, or urinalysis were observed in this study. Nasal cavity lesions were present in rats from all exposure groups including the recovery period, while lesions in other respiratory tract tissues were observed only in the 5.8 ppm

group at the 14-week sacrifice. The primary lesion seen in all dose groups was cytoplasmic vacuolation of the nasal mucosa ($p<0.01$). In more severe cases, lesions extended to involve the submucosal glands and interstitial tissue in the female exposed groups ($p<0.05$). Olfactory epithelial hyperplasia/dysplasia was statistically increased even after the 6-week recovery period in males and females ($p<0.05$) at 1.25 and 5.8 ppm, as was epithelial vacuolation in all dose groups ($p<0.01$). Olfactory epithelial necrosis was statistically increased ($p<0.01$) in female rats exposed to 1.25 ppm (8.18 mg/m^3) and 5.8 ppm (37.96 mg/m^3) for 14 weeks. A LOAEL of 0.23 ppm (1.51 mg/m^3) was identified from this study based on nasal epithelial vacuolation and periocular swelling.

Discussion

There were no occupational exposure limits for bis(2-dimethylaminoethyl)ether. However, there is a warning in the NIOSH Pocket Guide (NIOHS, 1997) for NIAX Catalyst and its components, one of which is bis(2-dimethylaminoethyl)ether. NIOSH stated

> Exposures should be limited to as few workers as possible, while minimizing workplace exposure concentrations with effective work practices and engineering controls. Exposed workers should be carefully monitored for potential disorders of the nervous and genitourinary system.

A no-observable-effect-level (NOEL) was not identified in the toxicity database. The lowest dose tested of 0.23 ppm (1.51 mg/m^3) was found to cause nasal epithelial cell vacuolation and periocular swelling in rats exposed for 14 weeks (Losco et al., 1996). This study was well performed and thoroughly examined the respiratory tract. It was concluded that the LOAEL identified in Losco et al., (1996) was adequate for developing a screening level.

Development of Screening Level

A reference concentration (RfC) was developed according to EPA (1994; 2012) methodology. Since bis(2-dimethylaminoethyl)ether is completely water soluble (Losco et al., 1996) it was determined that it is a category 1 gas. There were two critical effects from bis(2-dimethylaminoethyl)ether: periocular swelling and nasal epithelial vacuolation. The EPA (2012) RfC methodology specifies that the dosimetric adjustment factor is "1" for gases that have extrathoracic (ET) effects (e.g., nasal) in rodents. This means that the dose in animals equals the dose in humans.

The lowest-observed-adverse-effect-level (LOAEL) was then adjusted to account for the intermittent exposure.

$LOAEL_{ADJ}$ = LOAEL x (6 hours)/(24 hours) x (5 days)/(7 days)

$LOAEL_{ADJ}$ = 1.51 mg/m^3 x 6/24 x 5/7

$LOAEL_{ADJ}$ = 0.26964 mg/m^3

Since the dose in animals equals the dose in humans:

$LOAEL_{HEC} = LOAEL_{ADJ}$

$LOAEL_{HEC}$ = 0.26964 mg/m^3

The RfC was then calculated as follows:

$$RfC = \frac{LOAEL_{HEC}}{UF_1 \times UF_2 \times UF_3 \times UF_4}$$

Where, UF_1 is an uncertainty factor of 3 to account for the difference between animals and humans [1],
UF_2 is 10 to account for sensitive individuals,
UF_3 is 10 to convert from a subchronic to chronic duration,
UF_4 is 3 to account for the LOAEL to NOAEL conversion [2].

$$RfC = \frac{0.26964\ mg/m^3}{3 \times 10 \times 10 \times 3}$$

$$RfC = 0.0003\ mg/m^3$$

$$RfC = 0.3\ \mu g/m^3$$

In order to develop an RfC based on extrarespiratory (ER) effects (i.e., periocular swelling) the ratio of the animal to human blood gas partition coefficient ($H_{b/g}$) is used. However, if there is no information about the blood gas partition coefficient then the ratio of "1" is used as the default. Since there was no information on $H_{b/g}$, either animal or human, the default ratio of 1 was used. The RfC for extrarespiratory effects is calculated as follows.

$$LOAEL_{HEC} = LOAEL_{ADJ} \text{ (same as above) } \times (H_{b/g})_a/(H_{b/g})_h$$

$$LOAEL_{HEC} = 0.26964\ mg/m^3 \times 1$$

Then the RfC was calculated the same as for the ET effects of nasal lesions:

$$RfC = \frac{0.26964\ mg/m^3}{3 \times 10 \times 10 \times 3}$$

$$RfC = 0.0003\ mg/m^3$$

$$RfC = 0.3\ \mu g/m^3$$

Since both the nasal and periocular swelling effect endpoints produce the same RfC of 0.3 µg/m³, this value will be used to calculate the ITSL. Pursuant to Rule 232(1)(a) the ITSL shall equal the RfC; therefore, the ITSL for bis(2-dimethylaminoethyl)ether is 0.3 µg/m³. The averaging time is annual based on an explicit conversion of the experimental exposure to chronic lifetime exposure (i.e., UF = 10 for subchronic to chronic), pursuant to Rule 229(2)(b).

[1] The LOAEL to NOAEL conversion is usually 10 but the effects observed in the nasal epithelium were considered mild.
[2] The animal to human UF of 3 was used because of the decreased uncertainty in dosimetry (EPA, 1994).

References

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