MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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July 16, 2018

To: File for Bis(4-amino-3-methylcyclohexyl)methane (CAS No. 6864-37-5)

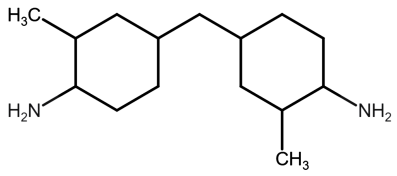
From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Derivation

The initial threshold screening level (ITSL) for bis(4-amino-3-methylcyclohexyl) methane is 2 µg/m³ with annual averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), ECHA (European Chemical Agency) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), EPA Acute Exposure Guideline Levels (AEGLs), National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs), U.S. EPA Provisional Peer Reviewed Toxicity Values (PPRTVs) for Superfund, International Agency for Research on Cancer (IARC) Monographs, California Office of Environmental Health Hazard Assessment (OEHHA), Chemical Abstract Service (CAS) - SciFinder (1967 – May, 2018), National Library of Medicine (NLM) Toxline, and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration for bis(4-amino-3-methylcyclohexyl)methane. The ACGIH has not derived a TLV.

Figure 1. Molecular Structure of 1,2-Diaminocyclohexane



Molecular Formula: C15-H30-N2
Molecular Weight: 238.42g
Vapour pressure: 0.08 Pa @ 20 °C (ECHA, 2018a)
Physical state at 20°C and 1013 hPa: Liquid (ECHA, 2018a)

Bis(4-amino-3-methylcyclohexyl)methane is an amine curing agent for epoxy resin.

Figure 1. Excerpts from International Chemical Safety Card (ICSC) for 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (NIOSH, 2018)

ROUTES OF EXPOSURE: The substance can be absorbed into the body by inhalation of its aerosol, through the skin, and by ingestion.
INHALATION RISK: A harmful contamination of the air will not or will only very slowly be reached on evaporation of this substance at 20°C; on spraying or dispersing, however, much faster.
EFFECTS OF SHORT-TERM EXPOSURE: The substance is severely corrosive to the eyes and the skin. The substance is corrosive to the respiratory tract. Corrosive on ingestion. Inhalation of the aerosol at high levels may cause lung edema (see Note).
EFFECTS OF LONG-TERM OR REPEATED EXPOSURE: The substance may have effects on the skin resulting in chronic disease (scleroderma). The substance may have effects on the blood, cardiovascular system, kidneys and liver, resulting in anemia, cardiac disorders, kidney impairment and liver impairment.

Note: The symptoms of lung edema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation is therefore essential.

Acute Toxicity

Table 1. Fifty Percent Lethal Concentration (LD50)(ChemIDplus, 2018)

Organism	Test Type	Route	Dose	Source
rat	LC50	inhalation	420mg/m³/4hrs	National Technical Information Service. Vol. OTS0539620-1

Table 2. Occupational Exposure Limits (U.S. EPA, 2018)

Value (mg/m³)	Type
0.28	DOE: Protective Action Criteria (PAC) (PAC-1, transient effects)
3.1	DOE: Protective Action Criteria (PAC) (PAC-2, irreversible or serious effects)
19	DOE: Protective Action Criteria (PAC) (PAC-3, life-threatening effects)
150	US Army Military Exposure Guidelines (MEGs) for 1 hour Critical effects
35	US Army Military Exposure Guidelines (MEGs) for 1 hour Marginal effects
5	US Army Military Exposure Guidelines (MEGs) for 1 hour Negligible effects

There were no specific toxicity data or study references concerning the derivation of the inhalation limit values shown in Table 2. Therefore, these values are shown for information purposes only. However, the MEG for negligible effects could be considered a short-term value similar to a Threshold Limit Value. If a short-term screening level was necessary for evaluation of short-term exposures and health effects, the MEG-negligible would be divided by 100, pursuant to the equation in Rule 232(1)(c):

Surrogate ITSL = OEL/100 = (5 mg/m³)/100
Surrogate ITSL = 0.05 mg/m³ × 1000µg/mg
Surrogate ITSL = 50 µg/m³ (with 1-hour averaging time).

Long-term Repeated Dose Toxicity Studies

In a subchronic oral toxicity study, groups of ten male and female Wistar rats were exposed to 0, 2.5, 12 and 60 mg/kg bw/day by gavage five days per week over 3 months (ECHA, 2018b). Deaths occurred in the low dose (one female after 37 exposures) and mid dose group (one male, 47 exposures). No other specific substance-related effect was however noted in the dead rats. At the high dose level (60 mg/kg bw/day) body weight development/food consumption were clearly impaired (body weight -42 % in males, -20 % in females) and the general state of health was poor. At 60 mg/kg there was a significant increase in males ($p < 0.01$) in relative weights of liver, kidney, adrenals, and testes. At 60 mg/kg there was a significant increase in males in absolute weights of adrenals ($p < 0.01$) and decrease in absolute weight of testes (-18 %, $p < 0.05$) and liver ($p < 0.01$). At 60 mg/kg in males there was no change in absolute kidney weight. At 60 mg/kg there was an increase of the lymphocyte values with changed nuclear structure in both sexes. At 60 mg/kg there was an increase of the alanine aminotransferase, aspartate aminotransferase, leukocyte and lymphocyte values in both sexes. At 12 mg/kg there was an increase of the aspartate aminotransferase values in the males. In all high dose males there was atrophy of the seminiferous tubuli (4/10 focal, 2/10 diffuse) and reduced contents of the seminal vesicles. These changes as well as the decreased absolute weight of testes were interpreted as consequence of the marked impairment on body weight. As the body weight was reduced more than the testes weight, the relative testes weight was increased. HISTOPATHOLOGY: At 60 mg/kg there was microvacuolar degeneration of the liver of most animals. The lesion was qualitatively more distinct in the female than in the male animals. Vacuolar tubulopathy was seen in the kidneys of all rats dosed at 60 mg/kg. At 60 mg/kg there was vacuolar myocardial degeneration observed in the heart of all male and female animals. The adrenal glands of all male and female animals showed the picture of a progressive transformation. At 12 mg/kg there was vacuolar tubulopathy in the kidneys of some male and female animals. The heart of most animals was found to show vacuolar myocardial degeneration. Conclusion: The pathological examinations exhibited hepatic, nephrotoxic and myocardial toxic findings at both 12 mg/kg and 60 mg/kg. Based on vacuolar myocardial degeneration in the rats at both 12 and 60 mg/kg, the 12 mg/kg dose level was deemed a lowest-observed-adverse-effect-level (LOAEL). The no-observed-adverse-effect-level (NOAEL) was 2.5 mg/kg.

In a subchronic inhalation study, groups of ten male and ten female Wistar rats were exposed by nose/head only to 2, 12, or 48 mg/m³ of bis(4-amino-3-methylcyclohexyl)methane for 6 hours/day, 5 days/week, for three months (ECHA, 2018b). This report was also summarized by OECD SIDS (2005) which referenced the original study results as BASF AG (1992). **Results of the Subchronic Inhalation Study:** CLINICAL SIGNS AND MORTALITY: There were no mortalities in the control and high dose groups (48 mg/m³). One female at 2 mg/m³ and one male at 12 mg/m³ died after 37 and 48 exposures, respectively. Deaths were judged to be of spontaneous nature. Scattered occurrence of observations throughout all test groups without relation to dose were noted. No specific substance-related effect was noted. BODY WEIGHT AND WEIGHT GAIN: Compared to control animals, statistically reduced mean body weight gain ($p<0.01$) and reduced body weight from day 50 onwards ($p<0.01$) were seen in high dose male rats. Body weight was reduced by approximately 14% compared to controls on day 85. In high dose females, body weight change was significantly reduced ($p<0.05$) from day 71 onwards. Terminal body weight in females was reduced by 8% and statistically different from control animals. No other statistically significant effects on body weight parameters were noted. OPHTHALMOSCOPIC EXAMINATION: no changes in

any of the dose groups noted. HAEMATOLOGY: Significant ($p<0.05$) reductions in hemoglobin, hemoglobin per erythrocyte, and in mean corpuscular hemoglobin concentration (MCHC) were noted in the male high dose rats only. Polychromatosis was noted. Clotting test: statistically significant clotting time increase was seen in females but not in males. The authors stated that this effect was not considered to be treatment related. The dose level at which the increased clotting time occurred was not given. CLINICAL CHEMISTRY: Animals at 12 mg/m³: statistically significant, but marginal increase of alkaline phosphatase (5.658 µkat/l vs. 4.949 µkat/l in controls) and GPT (glutamate pyruvate transaminase; 1.043 µkat/l vs. 0.845 µkat/l in controls) in male rats. GOT (glutamate oxalo-acetate transaminase) was not changed in male rats. Increase of alkaline phosphatase was only seen in this test group. No other change was noted in male or female animals. Animals at 48 mg/m³: statistically significant increase of GOT and GPT (but not alkaline phosphatase) compared with controls in male rats, but not in female rats. Activity of GPT in serum was 1.081 µkat[1]/l vs. 0.845 µkat/l in control animals ($p<0.01$). A significant ($p<0.01$) decrease of serum triglycerides in high dose males was considered to result from a decreased food consumption which was assumed because of the reduced body weight development in this group. The authors stated that this finding was therefore regarded to be a secondary effect. ORGAN WEIGHTS: Relative organ weight of liver, lung, and kidney was significantly increased in high dose male and female animals on the 1% or 5% level of significance. Relative weight of adrenals ($p<0.05$) and testes ($p<0.01$), and absolute lung weight (1.41 g vs. 1.18 g in controls) were significantly increased only in high dose male rats. HISTOPATHOLOGY: NON-NEOPLASTIC: No effects in low and medium dose animal groups. Effects in high dose animals (48 mg/m³) included: Local irritative effects on the skin and slight hyperkeratosis in 7/10 male rats. Minimal to slight vacuolization of the craniodorsal olfactory epithelium in both male (2/10) and female (1/10 animals) rats. At 48 mg/m³ there was significantly increased incidence of slight tubulonephrosis noted in male rats only (6/10 vs. 1/10 in male controls; 9/10 females vs. 7/10 controls), and extramedulary hematopoesis in spleen noted only in female rats (9/10). Hemosiderin was noted in spleen of all high dose animals.

Derivation of Screening Level

As noted in the ninety-day inhalation study (ECHA, 2018b), the high exposure group (48 mg/m³) showed local irritative effects on skin (slight hyperkeratosis in 7/10 animals) and upper airways (nasal mucosa, slight vacuolization of olfactory epithelium in 2/10 high dose males, and in 1/10 high dose females). The increase of GPT (glutamic-pyruvate transaminase; also called alanine aminotransferease or ALT) in mid dose (12 mg/m³) males was marginal (1.043 µkat/l vs. 0.845 µkat/l in controls) and was not accompanied by increase liver weight or histopathology effects. Therefore, the high-dose group of 48 mg/m³ was found to be a LOAEL. The mid dose of 12 mg/m³ was considered a NOAEL, and the point of departure for deriving a screening level.

The NOAEL was adjusted to account for continuous exposure as follows:

$$NOAEL_{adj} = NOAEL_{exp} \times 6hrs/24/hours \times 5days/7days$$

[1] The katal (symbol: kat) is the International System of Units (SI) unit of catalytic activity. It is a derived SI unit for quantifying the catalytic activity of enzymes (measuring the enzymatic activity level in enzyme catalysis) and other catalysts. https://en.wikipedia.org/wiki/Katal

Where the $NOAEL_{adj}$ is the NOAEL adjusted from intermittent to continuous exposure, and $NOAEL_{exp}$ is the exposure concentration used in the study.

$NOAEL_{adj} = 12\ mg/m^3 \times 6hrs/24/hours \times 5days/7days$
$NOAEL_{adj} = 2.14\ mg/m^3$

The ITSL was derived as follows:

$ITSL = NOAEL_{adj}/(UF1 \times UF2 \times UF3) \times unit\ conversion$

Where the Uncertainty Factor (UF1) is 10 for the extrapolation of animal to human, UF2 is 10 for sensitive individuals, and UF3 is 10 for extrapolation of subchronic (90-days) to chronic duration.

$ITSL = (2.14\ mg/m^3)/(10 \times 10 \times 10) \times 1000\mu g/mg$
$ITSL = 2.14\ \mu g/m^3 \approx 2\ \mu g/m^3$ (rounding to one significant figure)

The ITSL for bis(4-amino-3-methylcyclohexyl)methane is 2 $\mu g/m^3$ with annual averaging time (averaging time is specified in Rule (232(2)(c)).

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